AN INVESTIGATION OF THE RELATIONSHIP BETWEEN THE SYSTEMIC INFLAMMATORY RESPONSE, BODY COMPOSITION AND OUTCOMES IN PATIENTS WITH CANCER

By

Ross D. Dolan

MBChB (Dundee) MRCS (Glas) MSc (Ed) MA (TCD)

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) to the University of Glasgow

From Research conducted in the University Department of Academic Surgery, Royal Infirmary, Faculty of Medicines, University of Glasgow

Abstract

Globally cancer remains one of the leading causes of mortality. Overall, it has been estimated that one in three people will develop cancer in their lifetime, and one in four will die from it. While a curative intent will always be the aim of any surgical or oncological treatment a significant proportion of patients will go on to develop locally advanced or metastatic disease. Patient outcomes are not solely determined by host or tumour factors but rather by a complex interaction of both. Indeed, the systemic changes associated with cancer including reduced appetite, weight loss and poorer performance can significantly impact on both the quality and quantity of life in patients with cancer. As a result, accurate and realistic prognostication is vitally important and can guide clinical decision making.

In its simplest form the systemic inflammatory response is a reaction to tissue injury brought on by ischaemia, necrosis, trauma, hypoxia or cancer. It is increasingly clear that cancer progression and outcomes are dependent on a complex interaction between both tumour and host characteristics including the systemic inflammatory response. Clinically, the commonest means of measuring the systemic inflammatory response in patients with cancer is with the use of biochemical or haematological markers. In practice this means an elevated C-reactive protein (CRP), hypoalbuminaemia or increased white cells (WCC), neutrophil and platelet counts.

The work presented in this thesis further examines the relationship between the systemic inflammatory response, body composition, tumour metabolic activity and outcomes in patients with cancer. The effect of the systemic inflammatory response on outcomes in patients with cancer was examined directly. The relationship between the systemic inflammatory response and changes in body composition and their relationship to outcomes was then examined with cross-sectional and longitudinal studies. Finally, the question of the driving force behind the relationship between the systemic inflammatory response and

changes in body composition was examined by looking at tumour metabolic activity in patients with cancer.

The results of the two large meta-analyses in both operable and advanced cancers can be seen in Chapter 3 and 4. In operable cancer the systemic inflammatory response had independent prognostic value, across tumour types and geographical locations. On meta-analysis there was a significant relationship between an elevated Neutrophil Lymphocyte Ratio (NLR) and both overall ($p<0.00001$) and cancer specific survival ($p<0.00001$), between an elevated Lymphocyte Monocyte Ratio (LMR) and both overall ($p<0.00001$) and cancer specific survival ($p<0.00001$), between an elevated Platelet Lymphocyte Ratio (PLR) and both overall ($p<0.00001$) and cancer specific survival ($p=0.005$) and between an elevated Glasgow Prognostic Score (GPS)/modified Glasgow Prognostic Score (mGPS) and both overall ($p<0.00001$) and cancer specific survival ($p<0.00001$). In advanced cancer the systemic inflammatory response also had prognostic value, across tumour types and geographical locations. On meta-analysis there was a significant relationship between an elevated NLR and both overall survival ($p<0.00001$) and cancer specific survival (CSS) ($p<0.00001$), between an elevated PLR and overall survival ($p=0.0003$) and between an elevated GPS/mGPS and both overall ($p<0.00001$) and cancer specific survival ($p=0.0001$).

The majority of studies in these two meta-analyses were retrospective in nature, however the results of a further large systematic review focusing solely on randomised control trials can be seen in Chapter 5. In this review the GPS/mGPS was shown to have prognostic value in Non-Small Cell Lung Cancer (NSCLC), oesophageal cancer, pancreatic cancer, prostate cancer and breast cancer. While the NLR was shown to have prognostic value in nasopharyngeal cancer, oesophageal cancer, pancreatic cancer, biliary cancer, prostate cancer and multiple cancer types. Therefore, the prognostic strength of the systemic inflammatory response has been confirmed across over 400 papers including 36 prospective randomised control trials.

However, the question still remained about the level of systemic inflammation in cancer patients as a whole. In order to answer this a further systematic review was undertaken in Chapter 6. This examined the prevalence of cancer associated systemic inflammation as measured by the GPS/mGPS and its implications for the ongoing care of patients with cancer. In this review which contained 140 studies including 40,893 patients the percentage of patients who were systemically inflamed varied from 28% to 63% according to tumour type. The most commonly studied cancer overall was colorectal cancer in which 40% of patients were systemically inflamed. In operable disease the percentage of patients who were systemically inflamed varied from 21% to 38% in gastroesophageal and colorectal cancer respectively. Again, the most commonly studied cancer was colorectal cancer and 38% were systemically inflamed. In inoperable disease the percentage of patients who were systemically inflamed varied from 29% to 79% in prostate and haematological cancers respectively. This confirmed that the systemic inflammatory response was common in both operable and inoperable cancers and could prove to be a fruitful target for therapeutic interventions in the future.

The results of Chapter 3-5 show that the two most widely validated methods of monitoring the systemic inflammatory response are the GPS/mGPS and NLR. These are considered to be cumulative scores and composite ratios respectively. The results of Chapter 7 focuses on comparing the prognostic value of both cumulative scores and composite ratios in patients undergoing surgery for colon cancer (n=801). When adjusted for Tumour Node Metastasis (TNM) stage, NLR>5 ($p<0.001$), Neutrophil Lymphocyte Score (NLS, $p<0.01$), Platelet Lymphocyte Score (PLS, $p<0.001$), LMR<2.4 ($p<0.001$), Lymphocyte Monocyte Score (LMS, $p<0.001$), Neutrophil Platelet Score (NPS, $p<0.001$), CRP Albumin Ratio (CAR, $p<0.001$) and mGPS ($p<0.001$) were significantly associated with cancer specific survival. In patients undergoing elective surgery (n=689) the majority of the composite ratios/scores correlated with age ($p<0.01$), BMI ($p<0.01$), T-stage ($p<0.01$), venous invasion ($p<0.01$) and

peritoneal involvement ($p<0.01$). When NPS (myeloid) and mGPS (liver) were directly compared their relationship with both overall and cancer specific survival was similar. These results suggest that both composite ratios and cumulative scores had prognostic value, independent of TNM stage, in patients with colon cancer. However, cumulative scores, based on normal reference ranges, were simpler and more consistent for clinical use.

The importance of the relationship between the systemic inflammatory response and changes in physical function have long been reported particularly in the setting of patients with advanced cancer. This relationship was examined further in Chapter 8 which was a post hoc analysis of a previously completed randomised control trial assessing the effect of corticosteroid use on analgesic requirements in patients with advanced disease (n=40). It showed that patients with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 2 and an mGPS of 2 had a higher Interleukin-6 (IL-6, $p=0.017$) level and poorer overall survival ($p<0.001$) when compared to patients with an ECOG-PS of 0/1 and an mGPS of 0. This work provides supporting evidence for the potential therapeutic targeting of IL-6 in patients with advanced cancer which is currently being explored with the use of immunomodulatory agents such as tocilizumab.

These results suggest that there is considerable merit in combining monitoring of the systemic inflammatory response using acute phase proteins and other factors such as performance status in patients with cancer. Indeed this method of prognostication is given greater weight by the results of Chapter 10 which show in 730 patients with advanced cancer that on multivariate cox regression analysis ECOG-PS (HR 1.61 95%CI 1.42-1.83, $p<0.001$), mGPS (HR 1.53, 95%CI 1.39-1.69, $p<0.001$) and Body mass index/Weight Loss (BMI/WL) grade (HR 1.41, 95%CI 1.25-1.60, $p<0.001$) remained independently associated with overall survival. In patients with a BMI/WL grade 0/1 both ECOG and mGPS remained independently associated with overall survival. This further suggests that the ECOG/mGPS

framework may form the basis of risk stratification of survival in patients with advanced cancer.

The use of CT scanning to determine the quantity and quality of skeletal muscle in patients with cancer is an increasing area of research and clinical interest. The two most commonly used software packages for image analysis are ImageJ and Slice-O-Matic. In Chapter 2 the differential impact of the use of these software packages is examined in patients undergoing surgery for colorectal cancer (n=341). In this study, Bland-Altman analysis showed that ImageJ gave consistently higher values for all body composition parameters ($p<0.001$), resulting in more patients classified as having a high subcutaneous fat index (SFI, $p<0.001$) and visceral fat index (VFI, $p<0.001$) and fewer patients being classified as having a low skeletal muscle index (SMI, $p<.0001$) and skeletal muscle density (SMD, $p<0.001$). In addition, SFI, VFI, SMI and SMD were significantly associated with shorter overall survival when calculated with ImageJ (all $p<0.05$). These results suggest that with the drive towards the incorporation of CT derived body composition analysis to standard clinical practice there must be a concurrent drive towards standardisation irrespective of the software package used.

Skeletal muscle is a very physiologically active tissue and the quantity and quality of skeletal muscle can have a direct impact on outcomes in patients with cancer. In Chapter 9 the effect of the systemic inflammatory response on body composition and outcomes in patients with operable colorectal cancer (n=650) is examined. In this study on univariate survival analysis, age, ASA, TNM stage, mGPS, BMI, SFI, visceral obesity (VO), SMI and SMD were significantly associated with overall survival (all $p<0.05$). Furthermore, a low SMI and SMD were significantly associated with an elevated mGPS (<0.05). On multivariate analysis, SMI (HR 1.50, 95%CI 1.04-2.18, p=0.031), SMD (HR 1.42, 95%CI 0.98-2.05, p=0.061) and mGPS (HR 1.44, 95%CI 1.15-1.79, p=0.001) remained independently associated with overall survival. This study therefore delineates the relationship between the loss of quantity

and quality of skeletal muscle mass, the systemic inflammatory response and survival in patients with operable colorectal cancer.

The results of Chapter 11 add further weight to the prognostic relationship between markers of the systemic inflammatory response, physical function and body composition in patients with advanced cancer (n=289). In this study ECOG-PS, mGPS, timed up and go (TUG), 2 minute walk test (2MWT), hand grip strength (HGS), combined objective performance tests (COPT), SMI and SMD had prognostic value (all $p<0.05$). However, none of these factors, with the exception of HGS (HR 1.63, 95%CI 1.03–2.59, $p=0.04$), displaced the prognostic value of ECOG-PS within the ECOG-PS/mGPS framework. These results validate the clinical utility of the ECOG-PS/mGPS framework in the assessment of patients with advanced cancer.

Furthermore, in Chapter 12 the results of the longitudinal monitor of body composition in patients with operable colorectal cancer (n=470) have shown that the majority of patients did not change their SMI (81%) or SMD (72%) status on follow-up. In male patients those who maintained a low SMI were older ($p<0.001$), received less adjuvant chemotherapy ($p<0.05$), had a higher mGPS/NLR (both $p<0.05$), had a BMI≥25, had pre-op VO and follow up VO (all $p<0.01$). In female patients those who maintained a low SMI were older ($p<0.01$), had more open surgery ($p<0.05$), had a higher mGPS ($p<0.05$), had a BMI≥25, had pre-op VO and follow up VO (all $p<0.01$). On Cox-regression analysis patients who maintained a low SMI and SMD on follow up had worse overall survival ($p<0.05$). However, when adjusted for age, sex, TNM stage and mGPS neither a maintained low SMI nor SMD was independently associated with survival. This suggests that a low skeletal muscle mass and quality are established early in the disease course, maintained following resection of the primary tumour and associated with VO and the presence of a systemic inflammatory response.

The relationship between tumour metabolic activity and the systemic inflammatory response was examined in Chapter 13. This systematic review contained twelve studies including 2,588 patients and showed that the majority of studies showed a direct relationship between the tumour and bone marrow glucose uptake as measured by positron emission tomography CT (PET-CT) scanning and the host systemic inflammatory responses as measured by CRP (n=2), albumin (n=2), WCC (n=3), neutrophils (n=2) and platelets (n=2). The majority of the studies (n=8) also showed a direct relationship between tumour and bone marrow glucose uptake and poor outcomes. This suggests a direct relationship between the tumour and bone marrow glucose uptake and host systemic inflammation. This may suggest new approaches for more optimal therapeutic targeting and monitoring strategies in patients with cancer.

Furthermore, Chapter 14 showed in patients undergoing curative radiotherapy for lung cancer (n=119) that on univariate survival analysis, lung cancer stage ($p<0.01$), mGPS ($p<0.05$), NLR ($p<0.01$), SMD ($p<0.05$) and Total Lesion Glycolysis (TLG, $p<0.001$) were associated with overall survival. An elevated TLG was associated with sex ($p<0.05$), TNM stage ($p<0.001$), mGPS ($p<0.01$) and maximized standardised uptake values (SUVmax, $p<0.001$). On multivariate survival analysis only a TLG>68.89 (HR:2.03, 95%CI 1.35-3.07, $p<0.001$) remained independently associated with OS. This suggests that Tumour glucose uptake was associated with activation of the systemic inflammatory response but not lower skeletal muscle mass in patients with lung cancer. This suggests that the early targeting of the systemic inflammatory response could provide a fruitful treatment strategy aimed at maintaining skeletal muscle mass and function while also improving quality of life and outcomes in patients with cancer.

In summary, the systemic inflammatory response has a direct relationship with changes in body composition and outcomes in patients with cancer. Interestingly this association would seem to be independent of tumour metabolic activity and potentially tumour stage. Cancer related changes in body composition and their associated effect on performance status seem

to be established early in the disease process and maintained despite treatments targeting the tumour specifically, be they oncological or surgical. Given that an elevated systemic inflammatory response is not currently targeted, the present results would suggest that the die is cast in these patients. However, it may be that new treatment strategies targeting the inflammatory response as early as possible in the disease progression may arrest or reverse any skeletal muscle loss and improve outcomes in patients with cancer.

Table of Contents

List of Tables

List of Figures

Acknowledgement

Thank you to my friends and family, especially my partner Gillian and daughter Mirren, for putting up with me during this period of research.

Further thanks to my partner Gillian for giving her time and expertise in proofreading this work.

Thanks to Professor Paul Horgan for allowing me to complete this period of research and for providing me with a salary during it.

Thanks to Professor Donald McMillan for providing, in abundance, his time, guidance, and expert editorial eye during the creation of this thesis.

Thanks to Dr Barry Laird for his guidance and assistance in drafting the text of the papers resulting from several of the chapters of this thesis focusing on advanced disease. In addition, Dr Laird was the chief investigator responsible for the clinical component of the IPAC study which formed part of chapters 10 and 11 of this thesis.

Thanks to Mr Jason Lim for his assistance in the systematic review and meta-analysis in chapter 4 of this thesis.

Thanks to Dr Douglas Black for his assistance in training and validation of my CT- derived body composition analysis.

Thanks to Miss Yu Tzu Tien for her assistance in the analysis of the scans contained in chapter 2 of this thesis.

Thanks to Miss Ly Dieu for her assistance in the analysis of the scans contained in chapter 9 of this thesis.

Thanks to Miss Arwa Almasaudi for her assistance in the analysis of the scans contained in chapter 9 of this thesis.

Thanks to Mr Wei MJ Sim for his assistance in the analysis of the scans contained in chapter 12 of this thesis.

Thanks to Dr Louise Daly for her assistance in the analysis of the scans contained in chapter 11. In addition, Dr Daly was the chief investigator responsible for collecting clinical information on the patients with advanced cancer from Cork included in chapters 10 and 11 of this thesis.

Thanks to Miss Naomi McLees and Mr Ahmer Irfan for their assistance in the systematic review in chapter 13 of this thesis.

Thanks to Dr John Maclay who was the chief investigator responsible for collecting clinical information on the patients with advanced lung cancer included in chapters 14 of this thesis.

Thanks to Dr David Colville for his assistance with the PET-CT analysis included in chapter 14 of this thesis.

Thanks to my colleagues and the other research fellows within our team who were a constant source of help and encouragement.

Final thanks should go to the clinicians and patients of the Glasgow Royal Infirmary and the Beatson West of Scotland Cancer, without whom there would be no such research.

Author's Declaration

The work presented in this thesis was undertaken between 2015 and 2018 in the Academic Unit of Colorectal Surgery at Glasgow Royal Infirmary. I declare that the work presented herein was undertaken by me, except where indicated below:

Assistance with the systematic reviews and meta-analysis was provided by Mr Jason Lim (Chapter 4), Ms Naomi McLees (Chapter 13) and Mr Ahmer Irfan (Chapter 13)

Assistance with scan analysis was provided by Miss Yu Tzu Tien (Chapter 2), Dr Arwa Almasaudi (Chapter 9 & 11), Louise Daly (Chapter 11), Mr Wei Sim (Chapter 11 & 12), Ms Ly Bui Dieu (Chapter 12)

Assistance with data collection was provide by Ms Louise Daly (Chapter 11)

Assistance with data collection was provided by Dr John Maclay (Chapter 14)

Assisting with PET-CT scan analysis was provided by Dr David Colville (Chapter 14)

Ethical approval for the work contained in this thesis was provided by:

- West of Scotland Ethics Committee: GN170N474 and 18/WS/0001
- Greater Manchester East Research Ethics Committee: 17/NW/0190
- Regional Committee for Medical Research Ethics Central Norway: 4.2007.846
- Norwegian Directorate of Health: NCT00676936, EudraCT No 2007–005617-19
- Cork Research Ethics Committee Ireland: ECM 4 (g) (03/03/2015)

Publications

The work presented in this thesis has resulted in the following publications:

1. **Neutrophil-to-lymphocyte ratio as a bladder cancer biomarker: Assessing prognostic and predictive value in SWOG 8710**.

   Dolan R, McMullan DC

   Cancer. 2017 Jun 30. doi: 10.1002/cncr.30872

2. **The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: Systematic review and meta-analysis**

   Dolan R, McSorley S, McMillan D, Horgan P.

   Critical Reviews in Oncology/Hematology Volume 116, August 2017, Pages 134–146

3. **Attitudes of surgical trainees and consultants to the use of postoperative markers of the systemic inflammatory response [SIR] following elective surgery**

   Dolan R, McSorley S, McMillan D, Horgan P.

   Ann Med Surg (Lond). 2017 Sep; 21: 14–19.

4. **The role of the systemic inflammatory response in predicting outcomes in patients with operable cancer: Systematic review and meta-analysis**

   Dolan R, Lim J, McSorley S, McMillan D, Horgan P.

   Sci Rep. 2017 Dec 1;7(1):16717

5. **Determinants of lymph node count and positivity in patients undergoing surgery for colon cancer.**

   Dolan R, Lim J, McSorley S, McMillan D, Horgan P.

   Medicine (Baltimore). 2018 Mar;97(13):e0185

6. **The prognostic value of systemic inflammation in patients undergoing surgery for colon cancer: Comparison of composite ratios and cumulative scores**

   Dolan R, McSorley S, Park J, Watt D, Roxburgh C, Horgan P, McMillan D.

Br J Cancer. 2018 Jul;119(1):40-51

7. **The relationship between tumour glucose metabolism and host systemic inflammatory responses in patients with cancer: A systematic review**

   Dolan R, McLees N, Irfan A, McSorley S, Horgan P, Colville D, McMillan D.

   J Nucl Med. 2018 Aug 30. pii: jnumed.118.216697. doi: 10.2967/jnumed.118.216697

8. **The prognostic value of the systemic inflammatory response in randomised clinical trials in cancer: A systematic review**

   Dolan R, Laird B, Horgan P, McMillan D.

   Crit Rev Oncol Hematol. 2018 Dec;132:130-137. doi:10.1016/j.critrevonc.2018.09.016

9. **The relationship between body composition, the systemic inflammatory response and survival in colorectal cancer**

   Dolan R, Almasaudi A, Dieu L, Horgan P, McSorley S, McMillan D.

   Journal of Cachexia, Sarcopenia and Muscle. 2018 Nov 20. doi: 10.1002/jcsm.12357

10. **The relation between Malnutrition Universal Screening Tool (MUST), computed tomography-derived body composition, systemic inflammation, and clinical outcomes in patients undergoing surgery for colorectal cancer.**

    Almasaudi AS, McSorley ST, Dolan RD, Edwards CA, McMillan DC.

    Am J Clin Nutr. 2019 Sep 16. pii: nqz230. doi: 10.1093/ajcn/nqz230. [Epub ahead of print]

11. **An exploratory study examining the relationship between performance status, systemic inflammation and cytokine profiles in patients with advanced cancer**

    Dolan R, Laird B, Klepstad P, Kaasa S, Horgan P, Paulsen O, McMillan D.

    Medicine (Baltimore). 2019 Sep;98(37):e17019. doi: 10.1097/MD.0000000000017019.

12. **Comparison of the prognostic value of ECOG-PS, mGPS and BMI/WL Grade in patients with advanced cancer: Implications for a clinically important framework for assessment and treatment of cancer**

Dolan R, Daly L, Sim W, Fallon M, Ryan A, McMillan D, Laird B

Clin Nutr. 2019 Dec 27;S0261-5614(19)33212-1. doi: 10.1016/j.clnu.2019.12.024.

13. **The relationship between longitudinal changes in body composition, clinicopathological characteristics and systemic inflammation in patients with colorectal cancer**

Dolan R, Sim W, Almasaudi A, Dieu L, Horgan P, McSorley S, McMillan D

Submitted to press

14. **The relationship between tumour metabolism, body composition and systemic inflammation in patients with lung cancer**

Dolan R & Maclay J, Colville D, Buali F, MacLeod N, McSorley S, Horgan P, McMillan D

Submitted to press

15. **Determinants of quality of life in patients with incurable cancer.**

Dolan R & L Daly, Power D, Ní Bhuachalla E, Sim W, Cushen S, Fallon M, Simmons C, McMillan D, Laird B, Ryan A.

Cancer. 2020 Jun 15;126(12):2872-2882. doi: 10.1002/cncr.32824. Epub 2020 Apr 8.

16. **The relationship between ECOG-PS, mGPS, BMI/WL grade and body composition and physical function in patients with advanced cancer**

Dolan R, Daly L, Simmons C, Ryan A, Sim W, Fallon M, Power D, Wilcock A, Maddocks M, Ni Bhuachalla E, Bennett M, Cushen S, Usborne C, Laird BJ, McMillan D.

Cancers (Basel). 2020 May 8;12(5):E1187. doi: 10.3390/cancers12051187.

17. **The relationship between CT-derived body composition and survival in colorectal cancer: The effect of image software**

    Dolan RD & Tien YT, Horgan PG, Edwards CA, McMillan DC

    JCSM Rapid Communications (2020) Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/rco2.1

18. **The prognostic value of systemic inflammation in patients undergoing surgery for rectal cancer: Comparison of composite ratios and cumulative scores**

    Dolan RD, McSorley ST, Park JH, Roxburgh CS, Horgan PG, McMillan DC

    Submitted to press

19. **The prevalence of cancer associated systemic inflammation and its implications: Observations from prognostic studies using the Glasgow Prognostic Score.**

    Dolan RD, McMillan DC

    Crit Rev Oncol Hematol. 2020 Jun;150:102962.doi:10.1016/j.critrevonc.2020.102962. Epub 2020 Apr 18.

Presentations

The work presented in this thesis has resulted in the following presentations:

1. **The relationship between imaging derived tumour metabolic activity, body composition and the systemic inflammatory response in patients with lung cancer treated with radical radiotherapy**

   ASGBI Conference, Glasgow (June 20) - *poster presentation*

2. **The relationship between longitudinal changes in body composition, clinicopathology and systemic inflammation in colorectal cancer**

   ASGBI Conference, Glasgow (June 20) - *poster presentation*

3. **Evaluation of techniques of assessing body composition in patients with colorectal cancer.**

   ASCO GI Conference, San Francisco (Jan 20) - *poster presentation*

4. **The relationship between CT-derived body composition, host systemic inflammatory response and survival in patients undergoing surgery for colorectal cancer**

   ACPGBI Conference, Birmingham (July 18) - *poster presentation*

5. **The prognostic value of systemic inflammation in patients undergoing surgery for rectal cancer: Comparison of composite ratios and cumulative scores.**

   ASCO GI Conference, San Francisco (Jan 18) - *poster presentation*

6. **Evaluation of systemic inflammation based prognostic scores in patients with advanced oesophageal cancer receiving palliative radiotherapy.**

   ASCO GI Conference, San Francisco (Jan 18) - *poster presentation*

7. **Ongoing systemic inflammatory response (SIR) at diagnosis is not associated with lower lymph node retrieval and higher node positivity in patients undergoing surgery for colonic cancer.**

   ACPGBI Conference, Glasgow (July 17) - *oral presentation*

8. **Does the CRP/Albumin ratio offer additional prognostic value to the Glasgow Prognostic Score in patients with primary operable in colorectal cancer?**

   ACPGBI Conference, Glasgow (July 17) - *oral presentation*

9. **Evaluation of systemic inflammation based prognostic scores in patients with advanced colorectal cancer receiving palliative pelvic radiotherapy**

   ACPGBI Conference, Glasgow (July 17) - *oral presentation*

10. **Ongoing systemic inflammatory response (SIR) at diagnosis is not associated with lower lymph node retrieval and higher node positivity in patients undergoing surgery for colonic cancer.**

    ASCO GI Conference, San Francisco (Jan 17) - *poster presentation*

11. **Evaluation of systemic inflammation based prognostic scores in patients with advanced colorectal cancer receiving palliative pelvic radiotherapy**

    ASCO GI Conference, San Francisco (Jan 17) - *poster presentation*

Definitions/Abbreviations

2MWT	2 Minute Walk Test
18FDG	^{18}F-2-fluoro-2-deoxy-d-glucose
ASA	America Society of Anaesthesiologist Physical Status Classification
BLR	Bone Marrow to Liver Ratio
CAR	C-reactive protein/albumin ratio
CDSR	Cochrane Database of Systematic Reviews
CNP	Combined NLR and PLR
COP-NLR	Preoperative Platelet Count and Neutrophil-Lymphocyte Ratio
COPT	Combined Objective Performance Test
CRP	C-Reactive Protein
CSS	Cancer Specific Survival
CT	Computed Tomography
DEXA	Dual-energy X-ray absorptiometry
ECPG-PS	Eastern Cooperative Oncology Group Performance Status
ESR	Erythrocyte Sedimentation Rate
FOLFOX-A	Folinic Acid, Fluorouracil, Oxaliplatin and nab-Paclitaxel
GPS	Glasgow Prognostic Score
H&E	Hematoxylin and Eosin
HGS	Hand Grip Strength
IGF	Insulin Growth Factor
IL	Interleukin
IMAT	Intramuscular Adipose Tissue
JAK/STAT	Janus/Kinase/Signal Transducer and activator of transcription
KM	Klintrup-Makinen
LMR	Lymphocyte Monocyte Ratio
LMS	Lymphocyte Monocyte Score
MeSH	Medical Subject Heading
MIP	Macrophage Inflammatory Protein
MRI	Magnetic Resonance Imaging
dNLR	Derived Neutrophil Lymphocyte Ratio
NLR	Neutrophil Lymphocyte Ratio
NLS	Neutrophil Lymphocyte Score
NPS	Neutrophil Platelet Score

NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
mGPS	Modified Glasgow Prognostic Score
MIF	Macrophage Inhibitory Factor
MTV	Metabolic Tumour Volume
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression Free Survival
PINI	Prognostic Inflammatory and Nutritional Index
PLR	Platelet Lymphocyte Ratio
PLS	Platelet Lymphocyte Score
PS	Performance Status
US	Ultrasound Scan
RCT	Randomised Control Trial
RECIST	Response evaluation criteria in solid tumors
ROI	Region Of Interest
SAT	Subcutaneous Adipose Tissue
SIR	Systemic Inflammatory Response
SFA	Skeletal Fat Area
SFI	Subcutaneous Fat Index
SMA	Skeletal Muscle Area
SMD	Skeletal Muscle Density
SMI	Skeletal Muscle Index
BMSUV	Bone Marrow Standardized Uptake Value
SUV	Standardized Uptake Value
TSUV	Tumour Standardized Uptake Value
TFA	Total Fat Area
TFI	Total Fat Index
TLG	Total Lesion Glycolysis
TGF	Transforming Growth Factor
TNF	Tumour Necrosis Factor
TME	Tumour Microenvironment
TNM	Tumour, Node, Metastasis
TUG	Timed Up and Go
TSP	Tumour Stroma Percentage

VAT	Visceral Adipose Tissue
VFA	Visceral Fat Area
VFI	Visceral Fat Index
VAT	Visceral Adipose Tissue
VO	Visceral Obesity
WCC	White Cell Count
WHO	World Health Organization

Dedication

To my partner Gillian who has provided enduring support and encouragement throughout. To my daughter Mirren whose birth has highlights to me the importance of clinical research for generations yet to come. And to my parents, who have always stood by me and supported me in everything I have done.

1. INTRODUCTION

1.1 HOST IMMUNE RESPONSE

The immune response is the protective mechanism of detecting and removing organisms such as bacteria, yeasts, fungi, and helminths identified as non-self. In addition, it targets host cells which are displaying non-self antigens including those infected with viruses and cancer cells. However, at times the immune surveillance and destruction of cancer cells is not complete. In this case the cancer cells can reach a stable equilibrium with the host immune system (1, 2). Subsequent evasion of the immune system allows growth of the primary cancer and eventual development of disseminated disease (1, 2). The immune system is divided into two broad constituent parts: the innate or non-specific immune system and the adaptive or acquired immune system.

The innate immune system generates a non-specific response to pathogens and tissue injury. The initial barrier defence consists of epithelium lined body surfaces including the skin, gastrointestinal tract, respiratory tract and genitourinary tract. Should this be breached then the innate non-specific immune system is activated. Specifically, this consists of circulating humoral factors in the complement cascade, and cellular components including phagocytes (neutrophils and macrophages), granulocytes (basophils, eosinophils, and mast cells), and directly cytotoxic natural killer cells (NK).

The innate immune response is initiated and coordinated by the interaction of pro and anti-inflammatory cytokines and chemokines (3, 4). In the initial acute response, pro-inflammatory cytokines such as IL-1 and IL-6 predominate (4). Once the acute insult is dealt with anti-inflammatory cytokines such as IL-10 and TGF-β begin to predominate allowing restoration of normal tissue structure and function (4).

In the majority of cases activation of the innate response in turn leads to activation of the adaptive immune response through the presentation of antigens by phagocytic cells. The adaptive immune system provides a more specific response to pathogens and other non-self antigens/cancer cells which can be stored providing immunological memory.

Lymphocytes are the predominant cell of the adaptive immune response. Lymphocytes mature in the bone marrow (B cells) or thymus (T cells) and become activated by presentation of non-self antigens by antigen presenting cells such as neutrophils and macrophages. B cells form part of the humoral immune system and, following activation, produce antibodies against the specific antigens. Antibodies can directly target pathogens while also recruiting and potentiating the innate immune response following antibody-antigen binding through the compliment cascade and by encouraging phagocytosis. The action of T cells is mediated by the binding of non-self antigens to T cell receptors. Cytotoxic T cells (CD8+) are the predominant cell of the T-cell mediated adaptive immune response and act via the production of cytotoxins. In addition, several other subsets of T cells exist, each with specific roles including antigen presentation (CD4+ helper T cells), antigen memory (CD45R0+ memory T cells), and regulation of the adaptive immune response (FOXP3+ T regs).

Generally, the adaptive immune system is regarded as the most important for cancer immunoediting. Indeed, it is thought that innate immune response related inflammation promotes tumour progression at least in part by suppression of the adaptive immune response (5).

1.2 THE LOCAL INFLAMMATORY RESPONSE

It is now recognised that the pathogenicity of cancer is due to a complex interaction between both host and tumour factors (6, 7). For a considerable amount of time the importance of the extent and specific type of intra and peri-tumour infiltration has been recognised in patients with cancer (8). Recently, there has been an increasing appreciation of the importance of the interaction between tumour cells, the local inflammatory infiltrate, and the tumour microenvironment in terms of both prognosis and as a potential therapeutic target. It has been reported that a high level of lymphocytic tumour infiltrate is associated with better outcomes in patients with cancer (9). Interestingly and in contrast to the above, local infiltration by cells of the innate response such as macrophages and neutrophils produce a local pro-tumour environment which aids in tumour progression and is associated with a poorer outcome (10).

1.3 THE SYSTEMIC INFLAMMATORY RESPONSE

Inflammation in its simplest form is a reaction to tissue injury brought on by ischaemia, necrosis, trauma, hypoxia or cancer or as a response to an active infection. The acute phase of inflammation may resolve after the removal of the causal stimulus or it may persist and become chronic. There are multiple inflammatory stimuli including prostaglandins, and leukotrienes released by damaged cells and pro-inflammatory cytokines (IL-1. IL-6 and TNF-α) released by macrophages and neutrophils. These pro-inflammatory factors act on target cells to release a cascade of mediators which initiate and maintain the inflammatory response. The acute phase of the inflammatory response is characterised by local and systemic changes in vasculature, metabolism and plasma protein composition and the promotion of the initial non-specific immune response with the influx of neutrophils, complement and antibodies.

Acute phase proteins whose concentration changes by at least 25% in the presence of an inflammatory stimuli are produced within the liver (11). These proteins undergo substantial metabolic alterations across several organ systems resulting in the behavioural, psychological, biochemical and nutritional changes associated with systemic inflammation (12). Pro-inflammatory cytokines, in particular IL-6 which acts on hepatocytes, are believed to mediate the acute phase response and both serum C-reactive protein and amyloid have been shown to be highly specific markers of the systemic inflammation(13). If the causative inflammatory stimulus is not removed inflammation can become chronic with profound multisystemic consequences including alteration in the protein production of hepatic cells, hematopoietic changes, metabolic changes and alterations in the hypothalamic-pituitary-adrenal axis.

1.3.1 The Systemic Inflammatory Response and Cancer:

It is increasingly clear that cancer progression is dependent in a complex interaction between both tumour and host characteristics and in particular the host systemic inflammatory response(14-16). Indeed, there is increasing evidence that in addition to an elevated systemic inflammatory response that other host factors such as weight loss and performance status have an impact on outcomes in patients with cancer (17-24). In particular the systemic inflammatory response has been associated with increased weight loss and reduced performance status and may be an important contributing factor in the nutritional and functional decline seen in patients with advanced cancer (17, 25).

Indeed, recently there has been an increase in interest in the prognostic impact of the systemic inflammatory response in patients with advanced and metastatic disease. This interest was further heightened by recent cohort studies which show that inappropriate anticancer treatment in patients with metastatic disease does not improve quality of life or

survival, has increased costs associated with end-of-life care, and has been directly related to death within 30 days of initiating treatment (26-28). As mentioned above Temel and co-workers have further validated these results in a recent randomised control trial reporting longer median survival and improved quality of life in patients with metastatic non-small cell lung cancer who received early best supportive care (29). These studies have reported that markers of the systemic inflammatory response have an independent prognostic value, across tumour types and geographical locations, in patients with advanced cancer (30, 31). Indeed, the mGPS has been shown in several studies to provide additional prognostic determination when combined performance status in patients with advanced cancer (17, 32).

In healthy patients the inflammatory response is short lived however in patients with cancer the presence of the systemic inflammatory response bears striking similarities to chronic inflammation. In his setting the normal inflammatory homeostasis is altered in favour of a pro-inflammatory phenotype. In this setting the normal endogenous anti-inflammatory mechanisms mediated by interleukin- 10 (IL-10), transforming growth factor (TGF) -β, prostaglandins and lipoxins are impaired by pro-inflammatory cytokines such as IL-1, IL-6, tumour necrosis factor (TNF) α and IGF-1(33). This alteration of haemostasis increased the likelihood of the development of malignancy. Indeed, in animal models it has been shown the inhibition of IL-6 by TGF-β inhibits tumour growth (34). In addition, the deletion of IL-10 in mice has been shown to lead to the development of colorectal cancers (35).

Furthermore, the importance of the systemic inflammatory response in patients with cancer can be seen by the effect that targeting it has on patient care. Indeed, clinical studies including RTCs have shown that NSAIDs improve global quality of life scores in patients with advanced cancer (23). Additionally, more targeted therapy with the JAK inhibitor ruxolitinib in patients with myeloproliferative disease, has been shown to improve quality of life (36).

1.3.2 Measurement of the systemic inflammatory response

Clinically, the most common means of measuring the systemic inflammatory response in patients with cancer is with the use of biochemical or haematological markers. In practice this means an elevated C-reactive protein, hypoalbuminaemia or increased white cells, neutrophils and platelet counts. A clear relationship between individual markers of the systemic inflammatory response and outcomes has been demonstrated in both inoperable and inoperable disease (37, 38). In addition these individual factors can be used to construct cumulative scores and composite ratios such as the modified Glasgow Prognostic score (mGPS), Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte ratio (PLR) (37, 38). The prognostic value of these individual factors and the scores and ratios constructed from them in both operable and inoperable cancers and in the setting of randomised control trials are outlined below.

1.3.2.1 C-reactive protein

C-reactive protein (CRP) is a pentraxin protein which was discovered in 1930 and received its name due to its reactivity with the pneumococcal C-polysaccharide (12). It is classed as a positive acute phase protein and its prevalence in the acute phase response is seen in Figure 1.1. CRP is produced by hepatocytes after pathogen induced IL 6 secretion by both macrophages and T cells. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dying or damaged cells and some bacterial cell membranes. It acts as an opsonin while also potentiating the action of the complement cascade and the innate immune response. The presence of a raised CRP has been shown to be a poor prognostic indicator in patients with both operable and inoperable cancers (37, 38). Furthermore, its close association with IL-6 production has led to its use as a surrogate marker of IL-6 production and activation of the JAK/STAT signalling pathway in patients with cancer.

1.3.2.2 Albumin

Albumin is globular protein produced in the liver. It is the most prevalent plasma transport protein and has a negative impact on the acute phase response as can be seen in Figure 1.1. Low serum albumin levels are associated with activation of the acute phase of the innate immune response. Furthermore, low serum albumin concentrations have been shown to be poor prognostic indicator in patients with both operable and inoperable cancers (37, 38).

1.3.2.3 The Glasgow Prognostic Scores

A combination of both CRP and albumin readings in the form of the Glasgow Prognostic Scores (GPS) and the modified Glasgow Prognostic Score (mGPS) have been shown to be prognostic in patients with cancer independent of stage and tumour type (37, 38). The makeup of both the GPS and mGPS is summarised in Table 1.1. Both use the widely accepted cut of values of >10mg/L for CRP and <35g/L for albumin to build a cumulative prognostic score. The basis of the prognostic value of both the GPS and mGPS is in their relationship to the innate immune response and the acute phase of it in particular. As can be seen in Figure 1.1 a high CRP and a low albumin are associated with the initial acute response and the activation of the JAK/STAT pathway with its potentiation of the innate immune response. In the case of patients with cancer this response can become established chronically leading to the alteration of both local and systemic homeostasis in favour of disease progression.

1.3.2.4 The Differential White Cell Count and Associated Cumulative Scores and Composite Ratios

The total count of white blood cells is a common laboratory measure of the systemic inflammatory response and has been shown to be prognostic in patients with cancer (37, 38). In addition, the different constituent part of the white cell count have been shown to be

prognostic in patients with cancer while also directly relating back to activation of the immune response. Neutrophils make up the majority of the circulating white cell population and are the key effector cells of the innate immune system. Furthermore, platelets and monocytes have been shown to be important markers of acute inflammation. Lymphocytes are the predominant cell type of the adaptive immune system. As a result, ratios and scores comparing neutrophils, platelets, monocytes and lymphocytes can show the preponderance of the innate immune response over the adaptive immune response in patients with cancer (Table 1.1). The most commonly used composite ratio in both operable and inoperable disease is the Neutrophil Lymphocyte Ratio (NLR) (37, 38). While several cumulative scores using different components of the differential white cell count have been constructed including the Neutrophil Platelet Score (NPS) and the Neutrophil Lymphocyte Score (NLS) both of which have been shown to be prognostic in patients with cancer (39, 40).

1.4 THE SYSTEMIC INFLAMMATORY RESPONSE, BODY COMPOSITION AND TUMOUR METABOLIC ACTIVITY IN PATIENTS WITH CANCER

1.4.1 The Systemic Inflammatory Response and Anorexia, Weight Loss and Physical Function in Patients with Cancer

The progression of cancer is often associated with anorexia, weight loss and loss of skeletal muscle (cancer cachexia) all of which are associated with poor outcomes (41) (42). However, the basis for this change in body composition is not fully understood. Indeed, the level of cancer cachexia varies according to tumour type with lung and gastrointestinal cancers being particularly associated with weight loss and a loss of muscle mass.

The presence of an elevated systemic inflammatory response has been shown to be associated with lower quantity and quality of skeletal muscle in patients with cancer. Indeed in some longitudinal studies it has been shown that an elevated inflammatory response can

lead to a progressive decline in skeletal muscle even after treatment has been instigated (20, 43, 44). As a result it has been speculated that the systemic inflammation may be a key underlying mechanism driving skeletal muscle catabolism in patients with cancer (45).

Preservation of skeletal muscle quantity and quality has been shown to have a central role in maintaining physical function and outcomes in patients with cancer. Furthermore, the central role for the systemic inflammatory response in driving cancer related catabolism can be seen in a recent randomised clinical trial by Lundholm and co-workers which showed a significant improvement in ECOG-PS in patients treated with the NSAID indomethacin, when compared to placebo (46). Indeed this association between the control of the systemic inflammatory response and physical function was given further weight by Maddedu and co-workers who showed in the setting of another randomised control trial a significant improvement in 6min walk test performance and an improvement in ECOG-PS in patients treated with celecoxib, when compared to baseline (47).

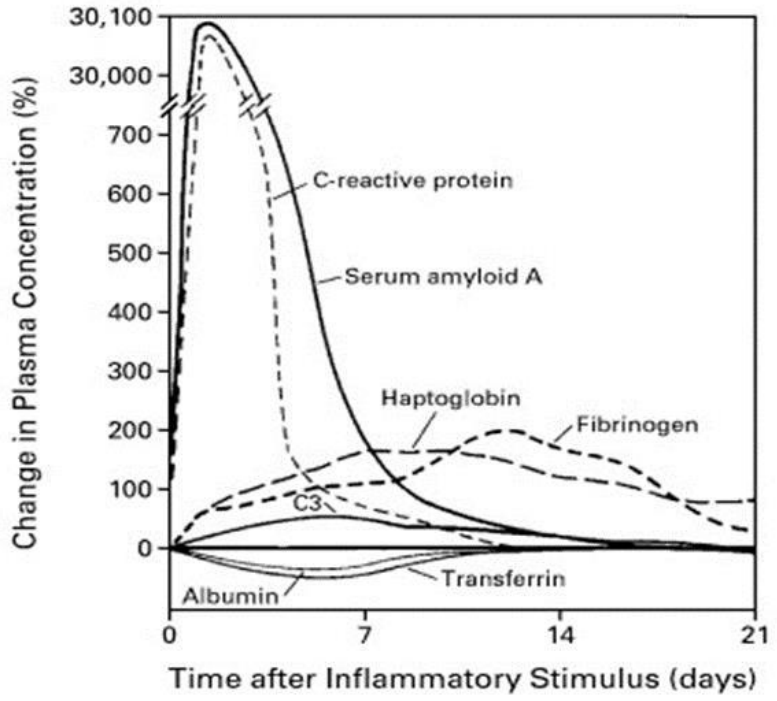


Figure 1.1: Change in plasma concentrations of some acute phase proteins after a moderate inflammatory stimulus (adapted from Gabay and Kushner 1999) (12)

Table 1.1: Systemic inflammation based prognostic ratios and scores based of acute phase proteins and the constituent part of the differential white blood cell count

Ratio/ Score	Ratio/Score
Neutrophil Lymphocyte Ratio (NLR):	
Neutrophil count: lymphocyte count	≤3
Neutrophil count: lymphocyte count	3-5
Neutrophil count: lymphocyte count	>5
Platelet Lymphocyte Ratio (PLR):	
Platelet count: lymphocyte count	≤150
Platelet count: lymphocyte count	>150
Lymphocyte Monocyte Ratio (LMR):	
lymphocyte count: monocyte count	≥2.40
lymphocyte count: monocyte count	<2.40
Neutrophil Platelet Score (NPS):	
Neutrophil Count ≤ 7.5 x 10^9/l and platelet count ≤ 400 x 10^9/l	0
Neutrophil Count > 7.5 x 10^9/l and platelet count ≤ 400 x 10^9/l	1
Neutrophil Count ≤ 7.5 x 10^9/l and platelet count > 400 x 10^9/l	1
Neutrophil Count > 7.5 x 10^9/l and platelet count > 400 x 10^9/l	2
Glasgow Prognostic Score (GPS):	
C-reactive protein ≤ 10mg/l and Albumin ≥35 g/l	0
C-reactive protein > 10mg/l and Albumin ≥35 g/l	1
C-reactive protein ≤ 10mg/l and Albumin <35 g/l	1
C-reactive protein > 10mg/l and Albumin <35 g/l	2
modified Glasgow Prognostic Score (mGPS):	
C-reactive protein ≤ 10mg/l and Albumin ≥35 g/l	0
C-reactive protein > 10mg/l and Albumin ≥35 g/l	1
C-reactive protein > 10mg/l and Albumin <35 g/l	2

1.4.2 Body Composition Assessment in Patients with Cancer

In the past, body mass index (BMI) was used as a means of assessing malnutrition and cancer cachexia. However, BMI is a very non-specific means of assessing body composition and does not take account the amount of adipose tissue or lean muscle mass. As a result, various

techniques have been used to better define body composition in patients with cancer including as bioelectric impedance analysis, whole body potassium, and air displacement plethysmography.

These techniques had some merit in the research setting but their application to clinical work was fraught with difficulties. As a result, image-based approaches such as Dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), ultrasound scan (USS) and computed tomography (CT), have been increasingly utilized. In particular due to its routine used in cancer staging, CT is now being widely used to measure body composition, providing new clinically useful information about both pre and post treatment body composition in patients with cancer.

There are currently several software packages available which allow for the calculation of body composition based on staging or post treatment CT scans. These are both manual and semi-automated depending on the package used. The majority of studies use a single CT slice at the L3 level to calculate the quantity and quality of skeletal muscle as well as the quantity of visceral, intra-muscular and subcutaneous fat in patients with cancer (48). These can then be related to specific outcomes such as post-operative complications, performance status and survival in patients with cancer.

1.4.3 Tumour Metabolic Activity in Patients with Cancer

Prognostication in patients with cancer involves a close interaction between host factors such as the systemic inflammatory response and tumour factors. Indeed, the importance of both has been highlighted in recent studies by Park and co-workers on the importance of staging both the tumour and the host (7).

The driving force behind the skeletal muscle loss seen in patients with cancer with the associated loss in physical function and poorer outcomes is likely to follow a similar pattern.

The metabolic activity of both the primary tumour and metastatic deposits are now being assessed using Positron Emission Tomography (PET) scanning in patients with multiple solid organ tumours including lung, gastro-oesophageal and colorectal cancers. This often forms part of the standard pre-operative or pre-oncological treatment workup for patients to assess the size and metabolic activity of the primary tumour as well as for the presence of any metastatic disease.

PET is an established nuclear imaging technique based on the uptake of glucose using the tracer ^{18}F-2-fluoro-2-deoxy-d-glucose (18FDG) in order to examine the metabolic activities of tumours (49). Recently PET scanning has been combined with CT imaging to give information about the anatomical location as well as tumour physiological activity (49). In addition to highlighting the primary tumour or any metastatic deposits PET-CT scanning has highlighted areas of increased metabolic activity in patients with cancer including the bone marrow. This provides invaluable information about the potential connections between tumour physiological activity, the host systemic inflammatory response and body composition in patients with cancer.

1.5 Summary and Aims

1.5.1 Summary

Cancer remains one of the leading causes of mortality worldwide and while a curative intent is the aim of any surgical or oncological treatment many patients either present with or go onto develop disseminated disease requiring systemic anti-cancer therapy and best supportive care (38). In this case and given that patients with advanced cancer have a limited life expectancy, appropriate treatment selection becomes of the utmost importance. Indeed, there is increasing evidence that inappropriate anti-cancer treatments can negatively affect both the quality and quantity of life of patients with cancer (50).

The systemic inflammatory response has been implicated as a unifying mechanism for the systemic symptoms associated with cancer such as pain, nausea, anorexia, weight loss and reduced physical function (51). Furthermore, the systemic inflammatory response has been implicated as the driving force behind the deterioration in both skeletal muscle quantity and quality in patients with both operable and advanced cancers (52). This loss of skeletal muscle mass is associated with both poorer outcomes in patients with operable and inoperable cancers and with increased complications of both surgical and oncological treatments.

The driving force behind this physiological and functional decline seen in patients with cancer is of some debate. It has been postulated that the tumour itself is the primary furnace behind this deterioration. However, recent studies have shown that the host factors including the systemic inflammatory response in particular are equally as important at predicting outcomes in patients with cancer. Indeed, recent studies using PET-CT scanning have shown a direct relationship between tumour and bone marrow metabolic activity and the systemic inflammatory response in patients with cancer (53). However, it remains to be seen if tumour metabolic activity has a direct impact on skeletal muscle loss or if the systemic inflammatory response is driving this physiological and functional decline. Taken together these proposed

relationships, if proven, could provide novel therapeutic targets and monitoring strategies to improve outcomes for patients with both operable and inoperable cancers.

1.5.2 Aims

1. To definitively establish the relationship between the systemic inflammatory response and outcomes in patients with both operable and inoperable cancer.
2. To compare the prognostic value of systemic inflammatory response markers, in particular that of composite ratios and cumulative scores, in patients with cancer.
3. To determine the effect of software packages on CT derived body composition.
4. To determine the relationship between the systemic inflammatory response and CT derived body composition measurements and outcomes in patients with cancer
5. To determine the relationship between longitudinal changes in CT derived body composition, clinicopathological characteristics, the systemic inflammatory response and outcomes in patients with cancer.
6. To compare and contrast the clinical utility of the ECOG-PS/ mGPS framework and the BMI/WL grade in patients with cancer.
7. To determine the relationship between the ECOG-PS/ mGPS framework, CT-derived body composition, physical function tests and outcomes in patients with advanced cancer
8. To determine the relationship between imaging derived tumour metabolic activity, body composition, the systemic inflammatory response and outcomes in patients with cancer.

2. METHODS FOR ASSESSMENT OF THE SYSTEMIC INFLAMMATORY RESPONSE, CT-DERIVED BODY COMPOSITION AND PET-CT DERIVED TUMOUR METABOLIC ACTIVITY

2.1 Assessment of the Systemic Inflammatory Response

The monitoring of the systemic inflammatory response in this thesis was carried out by using either acute phase proteins i.e. CRP and albumin or the constituent parts of the differential white blood cell count i.e. neutrophils, lymphocytes, platelets and monocytes (37, 38, 54, 55). The results of two recent systematic reviews and meta-analyses have shown that the majority of studies now use composite ratios constructed from the differential white blood cell count such as the Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR) and the Lymphocyte Monocyte Ratio (LMR) or acute phase proteins such as the CRP/Albumin Ratio (CAR) (37, 38).

In addition, cumulative scores constructed using normal reference ranges of the different components of the white blood cell count such as the neutrophil lymphocyte score (NLS), platelet lymphocyte score (PLS), lymphocyte monocyte score (LMS), Neutrophil Platelet Score (NPS) or acute phase proteins such as the Glasgow Prognostic Score/modified Glasgow Prognostic Score (GPS/mGPS) are widely used (37, 38, 40, 55). Both methods have been shown to be prognostic in patients with both operable and advanced cancer and their means of construction is given in Table 2.1 below.

2.1.1 Tables and Footnotes

Table 2.1: Systemic inflammation based prognostic ratios and scores

Ratio/ Score	Ratio/Score
Neutrophil Lymphocyte Ratio (NLR):	
Neutrophil count: lymphocyte count	≤3
Neutrophil count: lymphocyte count	3-5
Neutrophil count: lymphocyte count	>5
Neutrophil Lymphocyte Score (NLS):	
Neutrophil Count ≤ 7.5 x 10^9/l and lymphocyte count ≥1.5 x 10^9/l	0
Neutrophil Count > 7.5 x 10^9/l and lymphocyte count ≥1.5 x 10^9/l	1
Neutrophil Count ≤ 7.5 x 10^9/l and lymphocyte count <1.5 x 10^9/l	1
Neutrophil Count > 7.5 x 10^9/l and lymphocyte count <1.5 x 10^9/l	2
Platelet Lymphocyte Ratio (PLR):	
Platelet count: lymphocyte count	≤150
Platelet count: lymphocyte count	>150
Platelet Lymphocyte Score (PLS):	
Platelet Count ≤ 400 x 10^9/l and lymphocyte count ≥1.5 x 10^9/l	0
Platelet Count > 400 x 10^9/l and lymphocyte count ≥1.5 x 10^9/l	1
Platelet Count ≤ 400 x 10^9/l and lymphocyte count <1.5 x 10^9/l	1
Platelet Count > 400 x 10^9/l and lymphocyte count <1.5 x 10^9/l	2
Lymphocyte Monocyte Ratio (LMR):	
Lymphocyte count: monocyte count	≥2.40
Lymphocyte count: monocyte count	<2.40
Lymphocyte Monocyte Score (LMS):	
Lymphocyte count ≥1.5 x 10^9/l and monocyte count ≤ 0.80 x 10^9/l	0
Lymphocyte count <1.5 x 10^9/l and monocyte count ≤ 0.80 x 10^9/l	1
Lymphocyte count ≥1.5 x 10^9/l and monocyte count > 0.80 x 10^9/l	1
Lymphocyte count <1.5 x 10^9/l and monocyte count > 0.80 x 10^9/l	2
Neutrophil Platelet Score (NPS):	
Neutrophil Count ≤ 7.5 x 10^9/l and platelet count ≤ 400 x 10^9/l	0
Neutrophil Count > 7.5 x 10^9/l and platelet count ≤ 400 x 10^9/l	1
Neutrophil Count ≤ 7.5 x 10^9/l and platelet count > 400 x 10^9/l	1
Neutrophil Count > 7.5 x 10^9/l and platelet count > 400 x 10^9/l	2
C-reactive protein Albumin Ratio (CAR):	
C-reactive protein: Albumin	≤0.22
C-reactive protein: Albumin	>0.22
Glasgow Prognostic Score (GPS):	
C-reactive protein ≤ 10mg/l and Albumin ≥35 g/l	0
C-reactive protein > 10mg/l and Albumin ≥35 g/l	1
C-reactive protein ≤ 10mg/l and Albumin <35 g/l	1
C-reactive protein > 10mg/l and Albumin <35 g/l	2
modified Glasgow Prognostic Score (mGPS):	
C-reactive protein ≤ 10mg/l and Albumin ≥35 g/l	0
C-reactive protein > 10mg/l and Albumin ≥35 g/l	1
C-reactive protein > 10mg/l and Albumin <35 g/l	2

2.2 Systematic Review and Meta-analysis methods

2.2.1 Systematic Review

All systematic reviews and meta-analysis of published literature in this thesis were undertaken according to a pre-defined protocol described in the PRISMA-P statement. The primary outcomes to be assessed are defined in individual Chapters. Wide-ranging literature searches were carried out using specified medical subject heading (MeSH) terms defined in each Chapter in the US National Library of Medicine (MEDLINE), the Excerpta Medica database (EMBASE) and the Cochrane Database of Systematic Reviews (CDSR) to identify articles.

On completion of the online search, the title and abstract of each identified study was examined for relevance. Studies not in cancer patients, studies not available in English and those published in abstract form only were excluded. Where there were multiple publications from the same cohort the most recent paper was included. Full texts were obtained for all studies deemed potentially relevant. Once further exclusions outlined below were carried out, the bibliographies of all included articles were subsequently hand searched to identify any additional studies.

Only articles that reported survival analysis and gave hazard ratios (HR) with associated confidence intervals were included in any final meta-analysis. Articles reporting survival analysis in relative risk (RR) and odds ratio (OR) were also included but not in the meta-analysis. All potentially eligible papers were reviewed in full by two authors independently and graded according to GRADE recommendations.

2.2.2 Meta-analysis:

The HRs and 95 % CIs were directly retrieved from the article. If several estimates were reported for the same marker, the multivariate estimate was used in preference to the

univariate analysis. Data was assessed for heterogeneity using the I2 statistic and $\chi 2$ test interpreted using the guidance from the Cochrane Handbook for Systematic Reviews of Interventions (56). The degrees of heterogeneity were defined as minimal between 0% and 30%, moderate between 30% and 50%, substantial between 50% and 80% and considerable between 80% and 100%. Given the likely differences in methodology of the studies included, meta-analysis was performed using the random- effects (DerSimonian – Laird method) model unless stated otherwise. The Z test was used to assess the overall impact of systemic inflammation based scores on overall and cancer specific survival. All P values were 2-sided and $P < 0.05$ were considered statistically significant. Evidence of publication bias was evaluated using visual inspection of funnel plots. All analyses were performed using Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014.

2.3 CT-Derived Body Composition

2.3.1 Definitions and Nomenclature

Cancer is predominantly a disease of old age. As a result, often cancer related muscle loss may be a combination of age-related muscle decline or sarcopenia and disease related cachexia. Age related muscle loss or sarcopenia can begin from the age of 40 and can progress at a rate of 6% per decade until the age of 70 when it can increase to 25-40% per decade (57-59). The precise definition of sarcopenia remains the subject of some debate. However it has generally been accepted to constitute a level of loss of muscle mass greater than two standard deviations below that of a healthy young reference population (59, 60).

Cancer cachexia is a multifactorial syndrome which is characterised by the loss of muscle mass either with or without the loss of adipose tissue leading to a progressive functional and physiological decline (61). Systemic inflammation is one of the central components of cancer cachexia and can increase the baseline metabolic rate and catabolic rate of muscle tissue while also supressing food intake, therefore driving weight loss (61-63).

Skeletal muscle is a highly physiologically active organ and accounts for about 40-45% of body weight. Skeletal muscle is highly plastic and can respond to a variety of stimuli. As a result, skeletal muscle mass has been closely related to morbidity and mortality leading to a significant increase in interest in skeletal muscle when investigating frailty and cachexia (59, 64).

In addition to skeletal muscle mass and fat mass, their respective densities have been associated with outcomes in patients with cancer. Two recent studies reported that patients with elevated visceral fat had lower functional capacity, greater treatment-related toxicities and poorer overall survival (65, 66).

The recent advent of CT-derived measurements of muscle radiodensity have potentially allowed for assessment of muscle quality (i.e. the degree of fat infiltration) to be assessed without the need for tissue sampling (59). Such muscle radiodensity has been associated with myopenia or a clinically relevant muscle wasting associated with reduced performance status (67).

While muscle wasting in cancer may be due to a combination of both sarcopenia and cancer cachexia the term sarcopenia is now widely used to define low CT-derived muscle mass in patients with cancer (59). Similarly, low skeletal muscle radiodensity and myosteatosis have been used interchangeably. The variation in this nomenclature was highlighted in a recent editorial by Skipworth and needs to be standardised along with the assessment for CT-derived measurement of muscle quantity and quality to enter routine clinical practice (68).

For the purpose of this thesis the abbreviation SMI has been used interchangeably with sarcopenia. Specifically, this refers to height and/or BMI and sex adjusted measurement of CT derived skeletal muscle volume (66). Similarly, the abbreviation SMD has been used interchangeably with myosteatosis. Specifically, this refers to height and/or BMI and sex adjusted measurement of CT-derived skeletal muscle radiodensity (66). The abbreviation SFI has been used to refer to sub cutaneous fat. Specifically, this refers to sex adjusted measurement of CT derived subcutaneous fat mass (69). Finally, visceral obesity refers to sex adjusted measurements of CT-derived visceral fat mass (66, 70).

2.3.2 CT Images Analysis

CT scans were conducted at a tube voltage of 120kV, with 5mm slice thickness, and a 512 × 512 image resolution (71). An individual CT slice was acquired at the level of the third lumbar vertebra. Patients whose scans were taken 3 months or more prior to their surgery/treatment were excluded from the study. The two most commonly used image analysis software packages are ImageJ and Slice-O-Matic. The specific methodology for using both software packages is described below. Measurements were performed by two individuals for each Chapter. Initial training was undertaken on a cohort of training scans before test measurement of 30 scans was carried out with each scorer being blinded to the others results. Inter-rater reliability was assessed using inter-class correlation coefficients with a correlation of ≥0.8 being required before joint scoring could be commenced. The investigators were blind to patient's demographic and clinico-pathological status

ImageJ

ImageJ is a Java-based image processing and analysis program developed by NIH and is free to be downloaded from their website (version 1.52, https://imagej.nih.gov/ij/download.html). ImageJ is able to evaluate the density of each pixel, and with the latest advances in the package, density has been calibrated to reflect true HU values (72). Region of interest measurements include Total Fat Area (TFA), Visceral Fat Area (VFA) and Skeletal Muscle Area (SMA) with an attenuation threshold from -190 to +150 HU (i.e. -190 to -30 for adipose tissue, -29 to +150 for skeletal muscle). Specifically, TFA was quantified by depicting the outer contours of the abdominal wall, while VFA was performed by outlining the inner contour of the psoas and abdominal wall muscles (Figure 2.1). Similarly, SMA was measured by manually delineating muscle areas included quadratus lumborum, psoas, rectus abdominus, erector spinae muscles, internal transverse

and external oblique muscle groups (Figure 2.2). SFA calculated by subtracting VFA from TFA (Figure 2.1). Skeletal muscle radiodensity (SMD) was measured from the same region of interest used to calculate SMI, as its mean HU (Figure 2.2).

Slice-O-Matic

Slice-O-Matic version 5.0 (TomoVision, Magog, Canada; 64 bit; available at https://www.tomovision.com/index.html) was used to perform CT image segmentation process within different body composition regions. The adipose tissue was segmented to distinguish between intramuscular adipose tissue (IMAT), visceral (intra-abdominal) adipose tissue (VAT) and subcutaneous adipose tissue (SAT) using pre-defined thresholds. Skeletal muscle areas included quadratus lumborum, psoas, rectus abdominus, erector spinae muscles, internal transverse and external oblique muscle groups (Figure 2.3). Every tissue cross-sectional area was initially tagged with standard HU ranges using set thresholds for IMAT of -190 to -30HU, for VAT of -150 to -50 HU, for SAT of -190 to -30 HU and for SMA of -29 to +150 HU (Figure 2.3). Once the appropriate threshold HU ranges were set, compartmental segmentation was computed.

Body composition measurements

All results of body composition parameters (TFA, VFA, SFA, SMA) were later divided by the patient's height in meters squared to generate total fat index (TFI, cm^2/m^2), visceral fat index (VFI, cm^2/m^2), subcutaneous fat index (SFI, cm^2/m^2) and skeletal muscle index (SMI, cm^2/m^2). These indices were then adjusted for sex and BMI and compared with established thresholds for body composition status (Table 2.2). Skeletal muscle radiodensity (SMD, HU) was measured from the same region of interest used to calculate SMI, as its mean HU (Table 2.2). These radiodensities were then adjusted for sex and BMI and compared with established thresholds for body composition status (Table 2.2).

2.3.3 Tables and Footnotes

Table 2.2: CT derived body composition measures and thresholds used

Body Composition Measurement
High SFI (69):
Males>50.0 cm^2m^2 and Females>42.0 cm^2m^2
Visceral obesity (66, 70):
VFA: Males >160 cm2 and Females >80 cm2
Sarcopenia
SMI (Dolan) (52):
Males: BMI≤25kg/m^2 and SMI<45 cm^2m^2 or BMI>25kg/m^2 and SMI<53 cm^2m^2 Females: BMI≤25kg/m^2 and SMI<39 cm^2m^2 or BMI>25kg/m^2 and SMI<41 cm^2m^2
SMI (Martin) (66):
Males: BMI≤25kg/m^2 and SMI<43 cm^2m^2 or BMI>25kg/m^2 and SMI<53 cm^2m^2 Females: BMI≤25kg/m^2 and SMI<41 cm^2m^2 or BMI>25kg/m^2 and SMI<41 cm^2m^2
Myosteatosis
SMD (Dolan) (52):
BMI≤25kg/m^2 and SMD<34 HU or BMI>25kg/m^2 and SMD<32HU
SMD (Martin) (66):
BMI≤25kg/m^2 and SMD<41 HU or BMI>25kg/m^2 and SMD<33HU

2.3.4 Figures and Legends

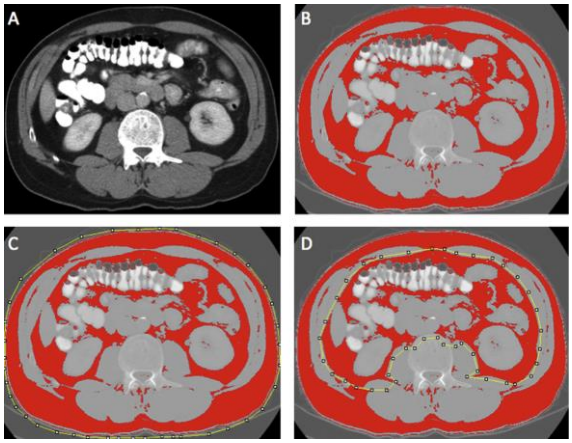


Figure 2.1: Example of selection of CT body composition fat areas using ImageJ software; (A) mid-L3 vertebra axial slice from preoperative portal venous phase CT, (B) threshold selection of adipose tissue using automatic selection of pixels of radiodensity ranging -190 to -30 Hounsfield units (HU), (C) region of interest (ROI) selection for total fat area (TFA,cm2), (D) ROI selection for visceral fat area (VFA, cm2). Adapted from McSorley et al 2017 (71) .

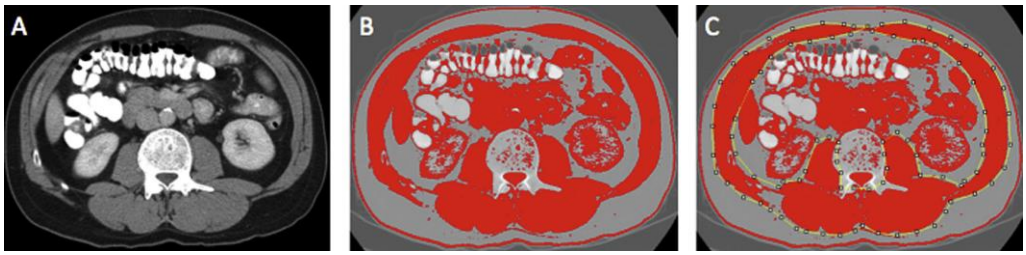


Figure 2.2: Example of selection of CT body composition skeletal muscle area using ImageJ software; (A) mid-L3 vertebra axial slice from preoperative portal venous phase CT, (B) threshold selection of skeletal muscle tissue using automatic selection of pixels of radiodensity ranging _29 to 150 Hounsfield units (HU), (C) region of interest (ROI) selection for skeletal muscle area (SMA, cm2). Adapted from McSorley et al 2017 (71).

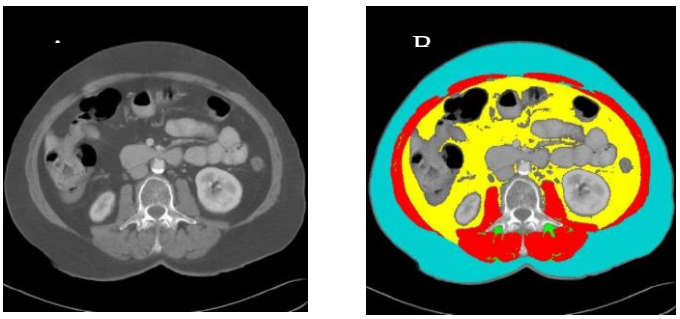


Figure 2.3: Example of selection of CT body composition fat areas using Slice-O-Matic; (A) mid-L3 vertebra axial slice from preoperative portal venous phase CT, (B)threshold selection of intramuscular adipose tissue (IMAT, -190 to -30 Hounsfield units (HU), green), visceral (intra-abdominal) adipose tissue (VAT, -150 to -50 Hounsfield units (HU), yellow), subcutaneous adipose tissue (SAT, -190 to -30 Hounsfield units (HU), blue) and skeletal muscle area (SMA, -29 to +150 Hounsfield units (HU), red) (73).

2.4 Direct comparison of Image J and Slice-O-Matic CT-derived body composition in patients with colorectal cancer

2.4.1 Introduction

Currently there are several software programs that calculate CT derived body composition at the 3rd lumbar vertebrae. The two most commonly used software packages are ImageJ (National Institutes of Health, Bethesda, USA) and Slice-O-Matic 5.0 (TomoVision, Montreal, Canada). ImageJ requires the manual analysis of areas of interest including the quadratus lumborum, psoas, rectus abdominus, erector spinae muscles, internal transverse and external oblique muscle groups whereas Slice-O-Matic carried out the same analysis in a semi-automated manner. Irving and co-workers directly compared the values generated for adipose tissue and skeletal muscle cross-sectional areas from these software packages in 26 patients with a mean percentage difference of less than 2% (72). Teigen and co-workers directly compared the values generated from these software packages in 51 patients with a mean percentage difference of less than 1% (74).

Therefore, in small cohort studies CT-derived body composition parameters analyzed by ImageJ and Slice-O-Matic give similar but not identical results. The aim of this direct comparison was, for the first time, to compare body composition analysis using both ImageJ and Slice-O-Matic and their relationship with survival in a large cohort of patients undergoing surgery for colorectal cancer.

2.4.2 Patients and Methods

CT-derived body composition was carried out using both Image J and Slice-O-Matic as outlined above in Section 2.3. For each parameter comparison, normality of the data was assessed by Shapiro-Wilk normality tests. Spearman's rank correlation coefficient was used to examine the strength of the inter-relationship between ImageJ and Slice-O-Matic for each body composition parameter. In addition, the difference between ImageJ and Slice-O-Matic for each body composition parameter was tested using Wilcoxon-test. The determination of proportional bias between two software programs (ImageJ and Slice-O-Matic) was carried out using Bland-Altman analysis.

Mortality within 30 days of the index procedure or during the index admission results in exclusion from subsequent survival analysis. The time between the date of surgery and the date of death of any cause was used to define overall survival (OS). Survival data were analysed using univariate and multivariate Cox regression. Those variables associated to a degree of $p<0.1$ were entered into a backward conditional multivariate model. Kaplan-Meier curves for overall survival were constructed over a 60-month period. Missing data were excluded from analysis on a variable by variable basis. Two tailed p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 21.0. SPSS Inc., Chicago, IL, USA).

2.4.3 Results

A total of 341 colorectal cancer patients were selected for CT scans

Association between ImageJ and Slice-O-Matic

The overall mean TFI was significantly correlated between ImageJ and Slice-O-Matic (R^2 = 0.996, p<0.001). The overall mean SFI was significantly correlated between ImageJ and Slice-O-Matic (R^2 = 0.969, p<0.001, Table 2.3). The overall mean VFI was significantly correlated between ImageJ and Slice-O-Matic (R^2 = 0.919, p<0.001, Table 2.3). The overall mean SMI was significantly correlated between ImageJ and Slice-O-Matic (R^2 = 0.927, p<0.001, Table 2.3). The overall mean SMD was significantly correlated between ImageJ and Slice-O-Matic (R^2 = 0.971, p<0.001, Table 2.3).

The mean percentage difference for TFI calculated using ImageJ and Slice-O-Matic (+9.3% (0.56), p<0.001). The mean percentage difference for SFI calculated using ImageJ and Slice-O-Matic (+7.9% (0.17), p<0.001, Table 2.3). The mean percentage difference for VFI calculated using ImageJ and Slice-O-Matic (+20.3% (0.21), p<0.001, Table 2.3). The mean percentage difference for SMI calculated using ImageJ and Slice-O-Matic (+2.9% (0.49), p<0.001, Table 2.3). The mean percentage difference for SMD calculated using ImageJ and Slice-O-Matic (+1.2% (0.09), p<0.001, Table 2.3).

Bland-Altman analysis between ImageJ and Slice-O-Matic

The mean difference of TFI using ImageJ and Slice-O-Matic was 13.1 (-10.1% to +36.3%) respectively and 1.17% (4/341) of patients were outside the 95% CI (p<0.001). The mean difference of VFI using ImageJ and Slice-O-Matic was 5.4 (-22.9% to +48.9) respectively and 3.23% (11/341) of patients were outside the 95% CI (p<0.001). The mean difference of SFI using ImageJ and Slice-O-Matic was 5.4 (-39.5% to +50.3%) respectively and 3.23% (11/341) of patients were outside the 95% CI (p<0.001). The mean difference of SMI using

ImageJ and Slice-O-Matic was 2.3 (-6.5% +11.7%) respectively and 2.64% (9/341) of patients were outside the 95% CI (p<0.001). The mean difference of SMD using ImageJ and Slice-O-Matic was 0.5 (-3.8% to +4.8%) respectively and 1.76% (6/341) of patients were outside the 95% CI (p<0.001).

Body composition and overall survival between ImageJ and Slice-O-Matic

In total 256 (75.1%) patients were classified as having visceral obesity using ImageJ compared to 210 (61.6%) patients using Slice-O-Matic (Table 2.3). In total 271 (79.5%) were classified as having an elevated SFI using ImageJ compared to 245 patients (71.8%) using Slice-O-Matic.

In total 157 (46%) were classified as sarcopenic (Dolan) using Image J compared to 209 (61.3%) using Slice-O-Matic. In total 131 (38.4%) were classified as having myosteatosis (Dolan) using Image J compared to 141 (41.3%) using Slice-O-Matic. In total 157 (46%) were classified as sarcopenic (Martin) using Image J compared to 203 (59.5%) using Slice-O-Matic. In total 191 (56%) were classified as having myosteatosis (Martin) using Image J compared to 1813 (53.1%) using Slice-O-Matic.

On univariate Cox regression survival analysis, visceral obesity (VO) when analysed with Image J, was significantly associated with overall survival (HR: 0.58, 95%CI 0.40-0.86, p = 0.007, Table 2.4). In contrast, on univariate Cox regression survival analysis, VO when analysed with Slice-O-Matic was not significantly associated with overall survival (p=0.084, Table 2.4). On multivariate Cox regression analysis VO when analysed with Image J remained independently associated with overall survival (HR: 0.58, 95%CI 0.40-0.86, p=0.007, Table 2.4)

On univariate Cox regression survival analysis SFI was significantly associated with overall survival when analysed with Image J (HR: 0.48, 95%CI 0.32-0.70, p<0.001, Table 2.4). On

univariate Cox regression survival analysis SFI was significantly associated with overall survival when analysed with Slice-O-Matic (HR: 0.54, 95%CI 0.37-0.79, p<0.001, Table 2.4). On multivariate Cox regression analysis SFI when analysed with Image J remained independently associated with overall survival (HR: 0.48, 95%CI 0.32-0.70, p<0.001, Table 2.4).

On univariate Cox regression analysis Sarcopenia (Dolan) was significantly associated with overall survival when analysed with Image J (HR: 1.92, 95%CI 1.32-2.80, p=0.001, Table 2.4). On univariate Cox regression analysis Sarcopenia (Dolan) was significantly associated with overall survival when analysed with Slice-O-Matic (HR: 2.04, 95%CI 1.34-3.10, p=0.001, Table 2.4). On multivariate Cox regression analysis Sarcopenia (Dolan) when analysed with Slice-O-Matic remained independently associated with overall survival (HR: 2.04, 95%CI 1.34-3.10, p=0.001, Table 2.4).

On univariate Cox regression analysis Sarcopenia (Martin) was significantly associated with overall survival when analysed with Image J (HR: 1.75, 95%CI 1.21-2.55, p=0.003, Table 2.4). On univariate Cox regression analysis Sarcopenia (Martin) was significantly associated with overall survival when analysed with Slice-O-Matic (HR: 1.66, 95%CI 1.11-2.48, p=0.012, Table 2.4). On multivariate Cox regression analysis Sarcopenia (Martin) when analysed with Image J remained independently associated with overall survival (HR: 1.75, 95%CI 1.21-2.55, p=0.003, Table 2.4).

On univariate Cox regression analysis Myosteatosis (Dolan) was significantly associated with overall survival when analysed with Image J (HR: 1.62, 95%CI 1.12-2.34, p=0.01, Table 2.4). On univariate Cox regression analysis Myosteatosis (Dolan) was significantly associated with overall survival when analysed with Slice-O-Matic (HR: 1.73, 95%CI 1.20-2.50, p=0.004, Table 2.4). On multivariate Cox regression analysis Myosteatosis (Martin)

when analysed with Slice-O-Matic remained independently associated with overall survival (HR: 1.73, 95%CI 1.20-2.50, p=0.004, Table 2.4).

On univariate Cox regression analysis Myosteatosis (Martin) was not significantly associated with overall survival when analysed with Image J (p=0.689, Table 2.4). On univariate Cox regression analysis Myosteatosis (Martin) was significantly associated with overall survival when analysed with Slice-O-Matic (HR: 2.07, 95%CI 1.40-3.06, p<0.001, Table 2.4). On multivariate Cox regression analysis Myosteatosis (Martin) when analysed with Slice-O-Matic remained independently associated with overall survival (HR: 2.07, 95%CI 1.40-3.06, p<0.001, Table 2.4).

2.4.4 Discussion

The present study showed that ImageJ and Slice-O-Matic derived values for TFI, SFI, VFI and SMI were strongly associated. However, ImageJ consistently gave higher values for all body composition parameters. As a consequence, these higher values resulted in more patients being classified as viscerally obese (~14%) and fewer patients being classified as sarcopenic (~14%) using standard thresholds previously described. Finally, such differences between the software packages' estimates altered the relationship of the body composition indices with overall survival. Therefore, CT-derived body composition is not only dependent on the age, sex, BMI and the systemic inflammatory response- it would appear to be also dependent on the software package used (75).

There was a consistent proportional systematic bias in the values calculated by the two software packages for TFI, VFI, SFI and SMI. The lower values from the Slice-O-Matic analysis may be explained by the semi-automated procedure such that there was an underestimation relative to the manual Image J procedure. For example, Image J requires the user to draw around the areas of interest on the CT scan whereas Slice-O-Matic automatically selects the areas of interest to calculate the total area. With reference to fat and muscle tissue, Slice-O-Matic may classify areas as part of adjacent structures. Indeed, this limitation is acknowledged for some CT scans in the Slice-O-Matic manual and an additional image editing component to the software is included to allow for fine tuning of automated images based on expert clinical and anatomical knowledge (74).

Several limitations associated with this study should be acknowledged. This study was carried out on retrospectively collected CT-scans and both ImageJ and Slice-O-Matic image analysis was carried out once for each scan. Nevertheless, the present study reflects the real-world use of these software packages.

In conclusion, the present study showed that ImageJ, compared with Slice-o-Matic, gave higher values of different body composition parameters. The impact of different software programs on the appropriate classification thresholds should be taken into account when carrying out CT-derived body composition analysis in patients with colorectal cancer. As a result of this study a decision was made to use ImageJ for all CT-derived body composition analysis in this thesis.

.

2.4.5 Tables and Footnotes

Table 2.3: Mean (SD) CT body composition parameters measurements and correlation coefficient test using ImageJ and Slice-O-Matic. Body composition parameters included VFI, SFI, SMI.

Body composition parameters	Software program	N	Mean (SD)	R^2 (*P*-value)	Mean Percentage Difference (SD)	*P*-value
VFI (cm^2/m^2)	ImageJ	341	70.6 (39.6)	0.919 (<0.001[a])	+20.3% (0.21)	<0.001[b]
	Slice-O-Matic	341	57.7 (36.4)			
SFI (cm^2/m^2)	ImageJ	341	86.1 (50.2)	0.969 (<0.001[a])	+7.9% (0.17)	<0.001[b]
	Slice-O-Matic	341	81.0 (54.8)			
SMI (cm^2/m^2)	ImageJ	341	46.5 (9.7)	0.927 (<0.001[a])	+2.9% (0.49)	<0.001[b]
	Slice-O-Matic	341	44.0 (9.6)			
SMD (cm^2/m^2)	ImageJ	341	34.5 (8.3)	0.971 (<0.001[a])	+1.2% (0.09)	<0.001[b]
	Slice-O-Matic	341	34.1 (8.3)			

Abbreviations: SD, standard deviation; CT, computed tomography; VFI, visceral fat index; SFI, subcutaneous fat index; SMI; skeletal muscle index.[a.] Calculated with one sample *t*-test. [b.] Calculated with Wilcoxon-test.

Table 2.4: The relationship between body composition and overall survival in patients with colorectal cancer using ImageJ and Slice-O-Matic.

Body composition	Software program	Threshold value (N, %)	Univariate Cox Regression		Multivariate Cox regression	
			HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Visceral obesity	ImageJ	256 (75.1)	0.58 (0.40-0.86)	0.007	0.58 (0.40-0.86)	0.007
	Slice-O-Matic	210 (61.6)	0.72 (0.50-1.04)	0.084	_	0.636
High SFI	ImageJ	271 (79.5)	0.48 (0.32-0.70)	<0.001	0.48 (0.32-0.70)	<0.001
	Slice-O-Matic	245 (71.8)	0.54 (0.37-0.79)	0.001	_	0.683
Sarcopenia (Dolan)	ImageJ	157 (46.0)	1.92 (1.32-2.80)	0.001	_	0.154
	Slice-O-Matic	209 (61.3)	2.04 (1.34-3.10)	0.001	2.04 (1.34-3.10)	0.001
Sarcopenia (Martin)	ImageJ	157 (46.0)	1.75 (1.21-2.55)	0.003	1.75 (1.21-2.55)	0.003
	Slice-O-Matic	203 (59.5)	1.66 (1.11-2.48)	0.012	_	0.595
Myosteatosis (Dolan)	ImageJ	131 (38.4)	1.62 (1.12-2.34)	0.010	_	0.992
	Slice-O-Matic	141 (41.3)	1.73 (1.20-2.50)	0.004	1.73 (1.20-2.50)	0.004
Myosteatosis (Martin)	ImageJ	191 (56.0)	0.93 (0.64-1.34)	0.689	_	0.474
	Slice-O-Matic	181 (53.1)	2.07 (1.40-3.06)	<0.001	2.07 (1.40-3.06)	<0.001

2.5 PET-CT Images Analysis

2.5.1 PET-CT

Positron Emission Tomography (PET) is an established nuclear imaging technique based on the uptake of glucose that reflects the metabolic activity of tumours and combined with CT scanning gives both anatomic and metabolic assessment of the tumour and metastases (49), commonly using the tracer ^{18}F-2-fluoro-2-deoxy-D-glucose (18FDG) (76). The PET-CT parameters included in this thesis were maximum standardised tumour uptake value (SUVmax), mean standardized tumour uptake (SUVmean) and metabolic tumour volume (MTV). Tumour derived glucose uptake was then calculated as total lesion glycolysis (TLG) using the following formula: TLG= SUVmean x MTV. An example of a PET-CT scan in a patients with squamous cell lung cancer is included below (Figure 2.4) (77).

2.5.2 18F FDG-PETCT

18F FDG-PETCT scanning was performed according to departmental standard procedures based on the EANM guidelines (78) on one of the two multimodality PETCT scanners (Discovery-690 or 710, General Electric System, Milwaukee, WI, USA). Patients were fasted for at least 6 hours before and 1 hour after the IV injection of 400MBq 18F-FDG. Blood glucose levels were measured before 18F-FDG injection to ensure concentrations <11mmol/l. Unenhanced CT images were acquired using a 120kV automatic mA modulation range of 15-240mAs. The torso CT covered from the skull base to the mid-thigh, with reconstructions performed at 2.5 mm increments. This was followed by PET images, encompassing the same transverse field of view as the CT. PET acquisition time was 3-4 minutes per bed position. PET attenuation correction was based on the CT data and images were corrected for scatter and iteratively reconstructed using Time of Flight and SharpIR on a 192x192 matrix.

PETCT images were analysed on GE Advantage Workstation using a SUVmax of 7g/ml threshold level to view the PET images. SUVmean and MTV were obtained from 3D isocontour at 42% of the maximal pixel value (VOL42). TLG was calculated according to the following formula: TLG= SUVmean x MTV. PETCT data were measured from the region of interest (ROI) placed over the dominant sites.

2.5.3 Figures and Legends

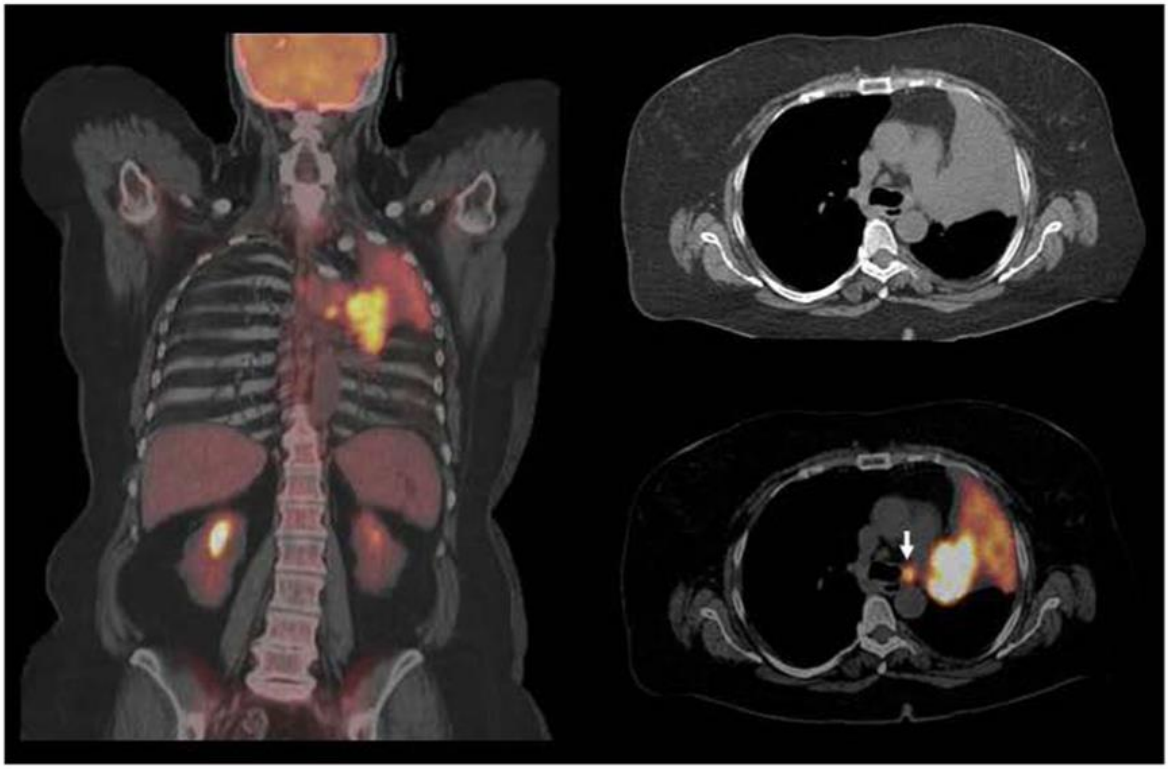


Figure 2.4: Squamous cell carcinoma in left upper lobe with associated atelectasis. Adapted from Lee et al 2012 (77)

3. THE ROLE OF THE SYSTEMIC INFLAMMATORY RESPONSE IN PREDICTING OUTCOMES IN PATIENTS WITH ADVANCED INOPERABLE CANCER: SYSTEMATIC REVIEW AND META-ANALYSIS

3.1 Introduction

As mentioned above in Chapter 2 cancer is a leading cause of both morbidity and mortality globally (79). Furthermore, while a curative intent is the aim of any surgical treatment many patients either present with or go onto develop disseminated disease requiring systemic anti-cancer therapy with a palliative intent. Given that patients with advanced cancer have a limited life expectancy appropriate treatment selection becomes vital. Indeed, the paradigm of precision medicine (right treatment, right patient, right time) is in the vanguard of oncology treatment, and if applied outcomes for all patients would improve irrespective of new treatment availability.(80)

However, optimal allocation of treatment remains elusive. There is increasing evidence that inappropriate anti-cancer treatment does not improve quality of life or survival (26-28, 50). A National Clinical Enquiry into Patient Outcome and Death (NCEPOD) reported that chemotherapy hastened or directly caused the death of over 25% of patients who died within 30 days of receiving treatment (26). This need for caution has been further illustrated by a randomised control trial comparing early palliative and standard oncological care in patients with metastatic non-small cell lung cancer conducted by Temel *et al* (50). In this randomised trial patients who received palliative care early not only maintained better quality of life scores but also had a significantly longer median survival (50). These reports provide a persuasive argument for optimising the stratification of anti-cancer therapy in patients with advanced cancer. Therefore, it is important to examine the criteria that may be used to effectively stratify patients as to their likely survival prior to the allocation of treatment in patients with advanced cancer.

In the setting of patients with advanced cancer, Tumour, Node, Metastasis (TNM) staging has little discriminatory prognostic value and other patient related measures such as weight loss, performance status and quality of life have superior prognostic value. Therefore, the decision to proceed with systemic therapy is frequently based on these parameters by an oncologist and primarily on the basis of subjective clinical observation. More recently, measurement of skeletal muscle mass made from CT scans has been proposed to be useful in this context (66). Nevertheless, it is clear that the potential for sub-optimal allocation of anti-cancer therapy is considerable.

Recently, in a systematic review of prognostic tools in patients with advanced cancer, it was reported that a number of prognostic tools had been validated in different centres (32). It was striking that the majority of these validated tools were based on subjective criteria, in particular the assessment of physical function. Only one validated prognostic tool the GPS, assessing the magnitude of the systemic inflammatory response, was based exclusively on objective criteria. Indeed, there is now strong evidence that the chronic systemic inflammatory response results in classical features of cancer cachexia, including the preferential loss of lean muscle mass (81-83). Indeed, studies have shown a direct relationship between systemic inflammation measured by the GPS and NLR and elevation of inflammatory cytokines, adipokines and other biochemical disturbances associated with loss of lean muscle mass and reduced performance status (81, 84-87). Recently, Laird and co-workers showed that in a large cohort study in two international bio banks, the combination of performance status and the systemic inflammatory response as measured by the mGPS improved the prediction of outcomes of patients with advanced cancer (17). Furthermore, they showed that quality of life was independently associated with both performance and the GPS (25).

Therefore, from the above and with the introduction of immunotherapeutic agents for advanced inoperable cancer the aim on this systematic review and meta-analysis is to assess

the role of the markers of systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer.

3.2 Patients and Methods

The present systematic review and meta-analysis of published literature was undertaken as outlined in Chapter 2. The primary outcome was to assess the prognostic value of the systemic inflammatory response in patients with advanced inoperable cancer treated with chemotherapy, immunotherapy, radiotherapy, best supportive care or a combination of these treatment strategies. This was carried out by a wide-ranging literature search to identify studies carried out up to December 2015. The medical subject heading (MeSH) terms used were Advanced Cancer, CRP, Albumin, White Cell Count, Neutrophil Count, Lymphocyte Count, Monocyte Count, Platelet Count and Red Blood Cell Count. As stated in Chapter 2 only articles that reported survival analysis were included in the review. Studies with patients who had failed resections and patients who underwent palliative symptom control procedures were also included.

Statistical Analysis

A meta-analysis was carried out as outlined in Chapter 2.

3.3 Results

Study selection process

Initial search strategy identified 9546 articles whose titles and abstracts were reviewed (Figure 3.1). Articles were excluded if initial curative surgery formed part of the treatment regimen (n=3114), where survival was not the primary outcome measure (n=1225), full articles were not available (n=1195), articles examining response to bacterial and viral infection (n=924), articles not carried out in humans (n=2021), articles not published in English (n=219), and those that were a systematic review/meta-analysis (n=149).

This led to a review of the full text of 699 articles. Further articles were excluded if surgery was part of the treatment regimen being examined (n=421), progression free survival (PFS) was the only outcome measured (n=62) and if survival was not expressed as HR (95%CI; n=47). The remaining 169 articles had their bibliographies reviewed in a systematic manner and this identified a further 29 articles to be included in the final analysis leading to a final total of 198 articles.

Studies of the prognostic value of C-reactive protein (CRP) in patients with advanced cancer:

Sixty-three articles with both OS and/or CSS as their primary outcome measures were identified comprising data on 13,498 patients (8,466 deaths) (Table 17.1). Fifty-four studies were carried out in a retrospective manner while eight were prospective with one study having both prospective and retrospective arms (Table 17.1). Fifty-four studies used multivariate and nine used univariate survival analysis (Table 17.1). On meta-analysis of the 55 retrospective studies including 11,761 patients (7,316 deaths) there was a significant association between elevated CRP and survival (HR: 1.97 95%CI 1.76-2.21, $p<0.00001$) with a considerable degree of heterogeneity ($I^2=92\%$). On meta-analysis of the 9 prospective

studies including 1,598 patients (1,009 deaths) there was a significant association between elevated CRP and survival (HR: 1.72 95%CI1.31-2.26, p<0.00001) with a considerable degree of heterogeneity (I^2=88%).

Fifty-six studies examined the relationship with overall survival including 11,787 patients (7,477 deaths), as the primary outcome measure. On meta-analysis, there was a significant association between CRP and overall survival (HR: 1.47 95%CI 1.40-1.54, p<0.00001) with a considerable degree of heterogeneity (I^2=90%,Figure 3.2). There was variation in the threshold of CRP used in the studies, the most common being >10 mg/L (n=19) followed by >5 mg/L (n=5). Other thresholds (n=32) were used in <5 studies and therefore meta-analysis was not carried out.

On meta-analysis those studies with a threshold of >10mg/L (n=19), including 3,883 patients (3,458 deaths), there was a significant association between CRP and overall survival (HR: 1.73 95%CI 1.55-1.93, p<0.00001) with a moderate degree of heterogeneity (I^2 = 35%). These included studies on cancer of the pancreas (n=6), lung (n=5), lymphoma (n=2), HCC (n=1), osteosarcoma (n=1), prostate (n=1), oesophagus (n=1), multiple cancers (n=1) and renal cells (n=1).

On meta-analysis of those studies with a threshold of >10mg/L and pancreatic cancer (n=6) 1,510 patients (1,446 deaths) there was a significant association between CRP and overall survival (HR: 1.64 95%CI 1.28-2.10, p<0.0001) with substantial heterogeneity (I^2=73%). In these six studies, there was a variation in their geographical locations including Japan (n=2), Korea (n=2), Germany (n=1) and Australia (n=1). The proportion of patients who had a CRP level >10mg/L with pancreatic cancer was 90% in Japan, 65% in Korea, 63% in Australia and 19% in Germany.

On meta-analysis of those studies with a threshold of >10mg/L and lung cancer (n=5) including 996 patients (960 deaths) there was a significant association between CRP and

overall survival (HR: 1.58 95%CI 1.37-1.84, p<0.00001) with no heterogeneity (I^2=0%). In these 5 studies, there was a wide variation in their geographical locations including the Czech Rep (n=1), UK (n=1), Sweden (n=1), China (n=1) and Japan (n=1). The proportion of patients who had a CRP level >10mg/L and lung cancer was 98% in the Czech Rep, 80% in the UK, 71% in Sweden, 43% in China and 33% in Japan. Remaining cancer types and geographical locations had <5 studies therefore further meta-analysis was not carried out.

On meta-analysis those studies with a threshold of >5mg/L (n=5), including 961 patients (515 deaths), there was a significant association between CRP and overall survival (HR: 1.66 95%CI 1.15-2.38, p=0.007) with a substantial degree of heterogeneity (I^2 = 83%). These included studies on cancer of the pancreas (n=2), prostate (n=1), renal cells (n=1) and colorectal (n=1). These included studies carried out in Japan (n=3), Belgium (n=1) and Sweden (n=1). The proportion of patients who had a CRP>5mg/L was 100% in Sweden, 66% in Belgium and 50% in Japan. Remaining cancer types and geographical locations had <5 studies therefore further meta-analysis was not carried out.

Ten studies examined the relationship with cancer specific survival including 1711 patients (989 deaths), as its primary outcome measure. On meta-analysis, there was a significant association between CRP and cancer specific survival (HR: 2.93 95%CI 2.14-4.01, p<0.00001) with a substantial degree of heterogeneity (I^2=66%). The most common thresholds used on the CSS group were >10 mg/L (n=4) including cancer of the prostate (n=1), breast (n=1), renal cells (n=1) and urothelial (n=1). All thresholds had <5 studies and therefore meta-analysis was not carried out. In the >10mg/L group studies were carried out in the UK (n=3) and Italy (n=1). The proportion of patients who had a CRP level >10mg/L was 64% in the UK and 50% in Italy.

Studies of the prognostic value of albumin (Alb) in patients with advanced cancer:

Thirty-three articles with both OS (n=29) and/or CSS (n=5) as their primary outcome measures were identified comprising data on 10,288 patients (8,740 deaths) (Table 17.2). Twenty-eight studies were conducted in a retrospective manner while five were prospective. Twenty-nine articles used multivariate and four univariate survival analysis (Table 17.2).

Thirty-one studies examined the relationship with overall survival including 9,753 patients (8,493 deaths), as its primary outcome measure. On meta-analysis, there was a significant association between low albumin and overall survival (HR: 1.77 95%CI 1.54-2.03, p<0.00001) with a considerable degree of heterogeneity (I^2=84%, Figure 3.3). There was variation in the threshold of albumin examined. The most common thresholds examined were <35g/L (n=13) and <30 mg/L (n=5). Other thresholds were used in <5 studies (n=15) and therefore meta-analysis was not carried out.

On meta-analysis those studies with a threshold of <35g/L (n=13), including 2,127 patients (1,831 deaths), there was a significant association between low albumin and overall survival (HR: 2.21 95%CI 1.60-3.06, p<0.00001) with a considerable degree of heterogeneity (I^2 = 79%). These included studies on cancer of the pancreas (n=5), biliary tract (n=2), multi anatomical sites (n=1), breast (n=1), lung (n=1), HCC (n=1), colorectal (n=1) and multiple myeloma (n=1). These included studies carried out in Korea (n=6), Japan (n=3), Singapore (n=1), Canada (n=1), Belgium (n=1), France (n=1), Spain (n=1), Australia (n=1), and the UK (n=1). The proportion of patients who had an albumin <35g/L was 51% in Korea, 49% in Spain, 31% in Belgium, 26% in the UK and 16% in France.

On meta-analysis of those studies with a threshold of <35g/L and pancreatic cancer (n=5) 910 patients (834 deaths) there was a significant association between reduced albumin and overall survival (HR: 1.96 95%CI 1.04-3.69, p=0.04) with substantial heterogeneity (I^2=85%). In these five studies, there was a variation in their geographical locations including

Korea (n=2), Japan (n=1), Australia (n=1) and Belgium (n=1). The proportion of patients who had an albumin level <35g/L with pancreatic cancer was 31% in Belgium and 42% in Australia.

On meta-analysis of those studies with a threshold of <30g/L (n=5), including 1,319 patients (1,192 deaths), there was a significant association between low albumin and overall survival (HR: 1.57 95%CI 1.26-1.95, p<0.0001) with a minimal degree of heterogeneity (I^2 =14%). These included studies on cancer of the lung (n=2), gastric (n=1), renal cells (n=1), and multiple anatomical sites (n=1). These included studies carried out in the US (n=1), Taiwan (n=1), Japan (n=1), Turkey (n=1) and Sweden (n=1). The proportion of patients who had an albumin <30g/L was 49% in Taiwan, 39% in Japan, 20% in Turkey and 17% in Sweden.

Studies of the prognostic value of white cell count (WCC) in patients with advanced cancer:

Four articles with both OS (n=3) and/or CSS (n=1) as their primary outcome measures were identified comprising data on 1,593 patients (1,440 deaths) (Table 17.3). All four were retrospective multivariate survival studies carried out in cancer of the lung (n=2), renal cells (n=1) and multiple anatomical sites (n=1). There was variation in the level of WCC used between different papers including >$10x10^9$/L (n=2), >$10.2x10^9$/L for males and >$10.6x10^9$ /L for females (n=1), and >11 x 10^9 /L for both sexes (n=1). Geographically studies were carried out in the UK (n=2), US (n=1) and Italy (n=1). The proportion of patients who had an elevated WCC was 24% in the US, 28% in the UK and 28% in Italy. Due to the small number of studies, meta-analysis was not carried out.

Studies of the prognostic value of neutrophils in patients with advanced cancer:

Nine articles with both OS (n=7) and/or CSS (n=2) as their primary outcome measures were identified comprising data on 2,870 patients (2,266 deaths) (Table 17.4). Seven studies were conducted in a retrospective manner while two were prospective. (Table 17.4). Five articles reported significance on multivariate and two articles reported significance on univariate survival analysis. There was variation in the levels of neutrophils used in individual papers including neutrophil count ≥ upper limit of normal (ULN) without defining it explicitly (n=3), neutrophil count >$7.5x10^9$ cells/ml (n=1), neutrophil count >$3.41x10^9$ cells/ml (n=1), absolute neutrophil count (ANL) >4.7×10^9 L (n=1), ANC≥7500 (n=1), log of readings above normal which was defined as >$7x10^9$/L (n=1) and >$8x10^9$/L (n=1).

Seven studies examined the relationship with overall survival including 2,364 patients (1,999 deaths), as its primary outcome measure. On meta-analysis, there was a significant association between elevated neutrophils and overall survival (HR: 1.89 95%CI 1.25-2.85, p=0.002) with a considerable degree of heterogeneity (I^2=87%). Studies were in melanoma (n=2), renal (n=1), lung (n=1), breast (n=1), mesothelioma (n=1) and lung (n=1) cancer. Geographically studies were carried out in France (n=2) and Italy (n=2), USA (n=1), China (n=1) and Australia (n=1). The proportion of patients who had elevated Neutrophils was 32% in Australia, 28% in France, 19% in the USA and 12% in Italy.

Two studies examined the relationship with cancer specific survival including 506 patients (267 deaths), as its primary outcome measure. Due to the small number of studies, meta-analysis was not carried out.

Studies of the prognostic value of lymphocytes in patients with advanced cancer:

Eleven articles with OS as their primary outcome measures were identified comprising data on 2,517 patients (2,148 deaths) (Table 17.5). Ten studies were conducted in a retrospective

manner and one prospectively. Nine studies reported significance on multivariate survival analysis and two on univariate survival analysis. (Table 17.5). On meta-analysis, there was a significant association between lower lymphocyte levels and overall survival (HR: 1.68 95%CI 1.35-2.09, p<0.00001) with a substantial degree of heterogeneity (I^2=68%).

There was considerable variation in the lymphocyte thresholds used in each study including continuous readings (n=1), <0.5x10^9/L (n=1), <0.7x10^9/L (n=1), >2x10^9/L (n=2), <1x$10^{9/}$L (n=2), ≥0.45x10^9/L (n=1), <2.25x10^9/L (n=1), <1.4x1x$10^{9/}$L (n=1), and 2.70x10^9/L (n=1). These included studies on cancer of the pancreas (n=3), lymphoma (n=1), lung (n=1), nasopharyngeal (n=1), mesothelioma (n=1), colorectal (n=1), cervical (n=1), melanoma (n=1) and multiple cancer types (n=1). Geographically studies were carried out in China (n=3), US (n=3), France (n=2), Japan (n=2) and Korea (n=1), The proportion of patients who had low lymphocytes was 75% in Korea, 48% in US, 47% in China, 45% in Japan and 32% in France. All eleven studies used chemotherapy as the treatment modality. No specific lymphocyte thresholds had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of monocytes in patients with advanced cancer:

Five articles with OS as their primary outcome measures were identified comprising data on 1,367 patients (1,152 deaths) (Table 17.6). All five studies were conducted in a retrospective multivariate manner, used chemotherapy as the treatment regime of choice and conducted their analysis in a multivariate manner. On meta-analysis of there was a significant association between elevated monocytes and survival (HR: 1.40 95%CI 1.05-1.87, p=0.02) with a substantial degree of heterogeneity (I^2=66%). There was considerable variation in the levels of monocytes used including >0.8x10^9/L (n=1), ≥0.64x10^9/L (n=1), ≥0.45x10^9/L (n=1), ≥0.35x10^9/L (n=1) and ≥0.55x10^9/L (n=1). There was also variation in the types of

cancer examined including lung (n=2), lymphoma (n=1), nasopharyngeal (n=1) and colorectal metastasis (n=1). In terms of geographical locations, the studies were carried out in China (n=3), Korea (n=1) and Italy (n=1). The proportion of patients who had high monocytes was 57% in China, 50% in Korea, and 23% in Italy. No specific monocyte thresholds had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of platelets in patients with advanced cancer:

Eight articles with both OS (n=7) and/or CSS (n=1) as their primary outcome measures were identified comprising data on 4,850 patients (2,422 deaths) (Table 17.7). Seven studies were conducted in a retrospective manner while one was prospective (Table 17.7). All eight articles reported multivariate survival analysis.

Seven studies examined the relationship with overall survival including 4,653 patients (2,293 deaths), as its primary outcome measure. On meta-analysis of there was a significant association between elevated platelets and survival (HR: 1.47 95%CI 1.12-1.93, p=0.006) with a considerable degree of heterogeneity (I^2=92%). There was variation in the thresholds of platelets examined including a platelet count >300 × 10^9 /L (n=1), >360 x 109 /L (n=1), <130 g/L (n=1), >350 × 10^9 /L (n=1), >450 × 10^9 /L (n=1), ≥ULN (n=1) and continuous readings (n=1). There was also variation in the type of cancers being examined including lung (n=1), oropharyngeal (n=1), pleural mesothelioma (n=1), nasopharyngeal (n=1), pancreatic (n=1), renal (n=1) and multiple cancers (n=1). Geographically studies were carried out in US (n=3), China (n=2), France (n=1) and Sweden (n=1). The proportion of patients who had elevated platelet counts was 30% in Sweden, 24% in the US, 15% in China and 11% in France. However, no specific platelet thresholds had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of the Glasgow Prognostic Score (GPS/mGPS) in patients with advanced cancer:

Forty-four articles with both OS (n=37) and/or CSS (n=9) as their primary outcome measures were identified comprising data on 12,578 patients (10,745 deaths) (Table 17.8). Thirty-two studies were conducted in a retrospective manner while twelve were prospective (Table 17.8). Forty studies reported multivariate and four reported univariate survival analysis (Table 17.8). On meta-analysis of the 32 retrospective studies including 9,472 patients (7,936 deaths) there was a significant association between elevated GPS/mGPS and survival (HR: 1.93 95%CI 1.76-2.13, p<0.00001) with a moderate degree of heterogeneity (I^2=42%). On meta-analysis of the 12 prospective studies including 3,244 patients (2,809 deaths) there was a significant association between elevated GPS/mGPS and survival (HR: 2.09 95%CI 1.69-2.57, p=0.0001) with a substantial degree of heterogeneity (I^2=69%).

Thirty-six studies examined the relationship with overall survival including 11,441 patients (10,022 deaths), as its primary outcome measure. On meta-analysis, there was a significant association between GPS and overall survival (HR: 2.06 95%CI 1.86-2.28, p<0.00001) with a substantial degree of heterogeneity (I^2=56%, Figure 3.4). These included studies on cancer of multiple anatomical sites (n=7), gastric (n=7), lung (n=5), pancreas (n=5), colon (n=3), lymphoma (n=1), biliary tract (n=1), bladder (n=1), haematological (n=1), prostate (n=1), renal cell (n=1), oesophagus (n=1), HCC (n=1) and cervix (n=1).

On meta-analysis those studies carried out in multiple anatomical sites (n=7), including 5,804 patients (5,139 deaths), there was a significant association between elevated GPS/mGPS and overall survival (HR: 2.22 95%CI 1.81-2.71, p<0.00001) with a moderate degree of heterogeneity (I^2 = 65%). These included studies carried out in the UK (n=2), Australia (n=2), Japan (n=1), Norway (n=1) and Brazil (n=1). The proportion of patients

who had an elevated GPS was 93% in Japan, 77% in the UK, 69% in Norway, 46% in Australia and 20% in Brazil.

On meta-analysis those studies carried out in gastric cancer (n=7), including 1,283 patients (5139 deaths), there was a significant association between elevated GPS/mGPS and overall survival (HR: 2.08 95%CI 1.58-2.74, p<0.00001) with a moderate degree of heterogeneity (I^2 = 40%). These included studies carried out in the Japan (n=2), Korea (n=2), Taiwan (n=1), UK (n=1) and Czech Rep (n=1). The proportion of patients who had an elevated GPS was 74% in Taiwan, 73% in the UK, 52% in the Czech Rep, 49% in Japan and 42% in Korea.

On meta-analysis those studies carried out in lung cancer (n=5), including 1,104 patients (708 deaths), there was a significant association between elevated GPS and overall survival (HR: 2.05 95%CI 1.52-2.77, p<0.00001) with a substantial degree of heterogeneity (I^2 = 55%). These included studies carried out in the UK (n=2), China (n=2) and Greece (n=1). The proportion of patients who had an elevated GPS was 76% in the UK, 33% in China and 29% in Greece.

On meta-analysis those studies carried out in pancreatic cancer (n=5), including 735 patients (719 deaths), there was a significant association between elevated GPS and overall survival (HR: 1.91 95%CI 1.29-2.83, p=0.001) with a substantial degree of heterogeneity (I^2 = 70%). These included studies carried out in the Japan (n=3), Australia (n=1) and the UK (n=1). The proportion of patients who had an elevated GPS was 70% in the UK, 63% in Australia and 36% in Japan.

Nine studies examined cancer specific survival including 1,137 patients (723 deaths), as its primary outcome measure. On meta-analysis, there was a significant association between elevated GPS and cancer specific survival (HR: 1.69 95%CI 1.48-1.92, p<0.00001) with a minimal degree of heterogeneity (I^2=4%). These included studies on cancer of the colon (n=3), lung (n=2), gastro-oesophageal (n=2), breast (n=1) and renal cells (n=1). These

included studies carried out in the UK (n=5), Japan (n=2) and China (n=2). The proportion of patients who had an elevated GPS was 77% in China, 65% in the UK and 43% in Japan. However, since no cancer type or country had more than four studies further meta-analysis was not carried out.

Studies of the prognostic value of Neutrophil Lymphocyte Ratio (NLR) in patients with advanced cancer:

Fifty-nine articles with both OS (n=58) and/or CSS (n=2) as their primary outcome measures were identified comprising data on 16,921 patients (12,801 deaths) (Table 17.9). Forty-three of these were conducted in a retrospective manner while sixteen were prospective. Fifty-five studies reported multivariate and four reported univariate survival analysis (Table 17.9). On meta-analysis of the 43 retrospective studies including 10,870 patients (8,044 deaths) there was a significant association between elevated NLR and survival (HR: 1.78 95%CI 1.59-1.98, p<0.00001) with a considerable degree of heterogeneity (I^2=77%; Figure 3.5). On meta-analysis of the 16 prospective studies including 5,898 patients (4,733 deaths) there was a significant association between elevated NLR and survival (HR: 1.63 95%CI 1.41-1.88, p<0.00001) with a substantial degree of heterogeneity (I^2=67%; Figure 3.5).

Fifty-eight studies examined the relationship with overall survival including 16,405 patients (12,675 deaths) as its primary outcome measure. On meta-analysis, there was a significant association between NLR and overall survival (HR: 1.71 95%CI 1.57-1.86, p<0.00001) with a substantial degree of heterogeneity (I^2=79%, Figure 3.5). The most common NLR thresholds used were ≥5 (n=19), ≥4 (n=5) and ≥3 (n=12). Other thresholds were used in <5 studies and therefore meta-analysis was not carried out (n=23).

On meta-analysis those studies with a threshold of ≥5 (n=19), including 5,506 patients (4,613 deaths) there was a significant association between elevated NLR and overall survival (HR:

1.64 95%CI 1.42-1.89, p<0.00001) with a substantial degree of heterogeneity (I^2 = 57%). These included cancer of the pancreas (n=5), lung (n=4), colorectal (n=3), multiple anatomical sites (n=2), mesothelioma (n=1), prostate (n=2), cholangiocarcinoma (n=1) and HCC (n=1).

On meta-analysis of those studies with a threshold of ≥5 and pancreatic cancer (n=5) 1009 patients (942 deaths) there was a significant association between an NLR≥5 and overall survival (HR: 1.78 95%CI 1.30-2.44, p=0.0003) with substantial heterogeneity (I^2=56%). In these five studies, there was a variation in their geographical locations including Japan (n=2), Australia (n=1), Korea (n=1) and China (n=1). The proportion of patients who had an NLR≥5 with pancreatic cancer 48% in Australia, 29% in Korea, and 20% in Japan. No country had more than 4 studies and therefore no further meta-analysis was carried out.

On meta-analysis those studies with a threshold of ≥4 (n=5), including 834 patients (588 deaths), there was a significant association between elevated NLR and overall survival (HR: 2.08 95%CI 1.45-3.00, p<0.0001) with a substantial degree of heterogeneity (I^2 = 57%). These included cancer of the lung (n=1), colorectal (n=1), B-cell lymphoma (n=1), T-cell lymphoma (n=1) and gastric (n=1). In these five studies, there was a variation in their geographical locations including Japan (n=2), UK (n=1), Peru (n=1) and Austria (n=1). The proportion of patients who had an NLR≥4 was 40% in Japan, 35% in Peru, 32% in the UK and 19% in Austria.

On meta-analysis those studies with a threshold of ≥3 (n=12), including 4,195 patients (3,130 deaths), there was a significant association between elevated NLR and overall survival (HR: 1.75 95%CI 1.53-2.01, p<0.00001) with a substantial degree of heterogeneity (I^2=56%). These included cancer of the renal cells (n=3), prostate (n=3), gastric (n=3), melanoma (n=1), colorectal (n=1) and multiple anatomical sites (n=1). These included studies carried out in the Korea (n=2), US/Israel (n=2), China (n=2), Italy (n=2), Australia (n=1), Canada

(n=1), Taiwan (n=1) and the UK (n=1). The proportion of patients who had an NLR≥3 was 71% in the US/Israel, 53% in Korea, 52% in Australia, 51% in Taiwan, 47% in the UK, 42% in China and 30% in Italy. No tumour site had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of lymphocyte monocyte ratio (LMR) in patients with advanced cancer:

Eleven articles with both OS (n=11) and/or CSS (n=1) as their primary outcome measures were identified comprising data on 5,043 patients (3,842 deaths) (Table 17.10). All 11 studies were retrospective and multivariate analysis was carried out. On meta-analysis, there was a significant association between a low LMR and overall survival (HR: 1.84 95%CI 1.64-2.07, p<0.00001) with minimal heterogeneity (I^2=8%, Figure 3.6). There was a variety of LMR thresholds used in each study including ≤2.6 (n=1), <2.8 (n=1), ≥2.475 (n=1), <2.11 (n=1), >5.22 (n=1), ≤4.56 (n=1), ≤5.07 (n=1), ≤3.4 (n=1), ≤2.11 (n=1), ≤3.11 (n=1) and low LMR but no figures given (n=1). These included studies on lung cancer (n=2), lymphoma (n=2), nasopharyngeal cancer (n=3) Hodgkin's lymphoma (n=2), and colorectal (n=2). Geographically the studies were carried out in China (n=5), Korea (n=3), Taiwan (n=1), Hungary (n=1) and Italy (n=1). The proportion of patients who had low LMRs was 53% in Italy, 52% in Korea 45% in China and 41% in Taiwan. No specific LMR thresholds had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of platelet lymphocyte ratio (PLR) in patients with advanced cancer:

Twelve articles with both OS (n=12) and/or CSS (n=2) as their primary outcome measures were identified comprising data on 5,733 patients (2,611 deaths) (Table 17.11). Ten studies

were conducted in a retrospective manner and two prospectively. Eleven studies were also conducted in a multivariate and one in a univariate manner (Table 17.11). On meta-analysis, there was a significant association between an elevated PLR on overall survival (HR: 1.49 95%CI 2.10-1.84, p=0.0003) with considerable heterogeneity (I^2=82%, Figure 3.7). There was a variety of PLR thresholds used in each study including >111.23 (n=1), ≥190 (n=1), >153.44 (n=1), >322 (n=1), >146 (n=1), >200 (n=1), ≥152.6 (n=1), ≥250 (n=1), >119.50 (n=1), ≥150 (n=1), >162 (n=1) and one study which simply stated elevated PLR without given a numerical value. These included studies on cancer of the lung (n=5), nasopharynx (n=1), cervix (n=1), prostate (n=1), pancreas (n=2), colorectal (n=1) and liver (n=1). Geographically studies were located in China (n=6), Japan (n=2), Turkey (n=1), Austria (n=1), Australia (n=1) and the US (n=1). The proportion of patients who had an elevated PLR was 61% in Australia, 59% in Japan, 50% in Turkey, 31% in China, 29% in Austria and 20% in the US. No specific PLR thresholds had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of other markers/scores of the systemic inflammatory response in patients with advanced cancer:

During the course of this review several studies (n=6) were identified which could not be assigned to one of the above groupings (Table 17.12). Two studies focused on the CRP/Albumin ratio (CAR). The first such study was by Zhou et al(88) from China. In this multivariate survival analysis on patients with small cell lung cancer a CRP/Alb ratio ≥0.441 was shown to be related to a statistically significant worse OS (HR: 1.34 95%CI 1.04-1.73 p=0.025). The second such study by Yamashita et al(89) from Japan. In this multivariate survival analysis on patients with prostate cancer a CRP/Alb ratio ≥7 was shown to be related to a statistically non-significant worse overall survival (HR: 2.34 95%CI 0.91-6.05 p=0.08).

Two further studies focused on the relationship between globulin, albumin and survival. Shibutani et al(90) in Japan reported that the albumin/globulin ratio predicted overall survival (HR: 2.247, 95%CI 1.069-4.722, p=0.033) independent of the NLR. Yao et al(91) in China reported that in patients with advanced NSCLC, the globulin/albumin ratio (GAR) >0.58 and an Alb<35g/L was associated with poorer OS (GAR HR: 1.65, 95%CI 1.20-2.26, p=0.002, Alb HR 1.92, 95%CI ,1.10-3.36, p=0.022). Chan et al(92) in China reported that, in patients with HCC, the albumin-to-alkaline phosphatase ratio (AAPR) >0.68 predicted poorer OS (HR 2.185, 95%CI, 1.780-2.683, p<0.001).

Finally, Zhou et al(88) in China reported that, in patients with SCLC, the CRP/Globulin ratio ≥1.29 predicted poorer OS in both the testing (HR: 1.35, 95%CI, 1.61-1.81, p=0.046) and validated (HR: 1.43, 95%CI, 1.052-1.95, p=0.022) cohorts. Due to the small number of these studies meta-analysis was not carried out.

3.4 Discussion

The results of the present systematic review and meta-analysis show clearly that the systemic inflammatory response, as evidenced by a number of markers at clinical thresholds, have independent prognostic value, across tumour types and geographical locations, in patients with advanced cancer. In particular, CRP, albumin and neutrophil count and the scores derived from them (GPS and NLR) have been consistently validated worldwide. There was considerable variation in the thresholds reported to have prognostic value when CRP, albumin and neutrophil counts were examined. There was less variation in the thresholds reported for NLR and still less for the GPS. The majority of studies were retrospective and therefore further prospective studies are warranted. In particular, there is a need to determine their clinical utility in the context of randomised clinical trials and thereby inform the appropriate treatment selection for patients with advanced cancer.

In the present review, the majority of studies reported overall survival as the endpoint. However, for some markers of the systemic inflammatory response such as CRP and GPS there were also multiple studies using cancer specific survival as an endpoint. It was of interest therefore that, on meta-analysis, the degree of heterogeneity appeared to be greater for overall survival as an endpoint compared with cancer specific survival (CRP 90% vs. 66% and GPS 56% vs. 4% respectively). This observation may be explained by previous observations that markers of the systemic inflammatory response have a stronger relationship with the cancer survival compared with the overall survival (93, 94). Therefore, the optimal prognostic utility of markers of the systemic inflammatory response such as CRP and the GPS are in the prediction of cancer specific survival.

With reference to overall survival as an end-point, heterogeneity was greater in studies with a variety of thresholds compared to those with a standard threshold (e.g. CRP 90% (all) vs. 35% (>10mg/l), albumin 84% (all) vs. 79% (<35g/l) and NLR 79% (all) vs. 57% ($\geq$5)

respectively). In studies with these specific thresholds (e.g. in CRP threshold >10mg/l), compared with all tumour types, heterogeneity was less in specific tumour types (e.g. lung cancer heterogeneity was lower, 0% vs. 35% for all). Therefore, the threshold used, and the specific cancer studied influence the consistency of the association between markers of the systemic inflammatory response and overall survival in patients with advanced cancer. This has implications for the routine clinical application of markers such as CRP and NLR where several different thresholds have been reported in the literature. However, the GPS/mGPS have internationally recognised thresholds and are the preferred measure of the systemic inflammatory response amongst those investigators active in the field (95) and therefore are likely to have reproducible clinical utility in the context of randomised trials in patients with advanced cancer.

In the present review it was of interest that, across different markers of the systemic inflammatory response, when comparing using the same threshold and tumour type, the geographical prevalence of an elevated systemic inflammatory response varied. There was a trend towards a greater proportion of patients who had elevated markers in Western countries compared with Eastern Asian countries. Given the objective nature of these measurements there may be genetic or environmental causes of such a consistent difference. Indeed, as was mentioned in Chapter 2 there are well known ethnic differences in the normal range of neutrophils and lymphocytes (96-98). Given that the most common thresholds used for NLR were >5 and >3 it is likely that a combination of genetic and environmental factors are responsible for such consistent East/West differences. To date, similar data for the GPS/mGPS has not appeared in the literature. Therefore, differences in the magnitude of systemic inflammatory responses may explain, in part, the East/West split often observed in overall survival independent of tumour stage alone. Irrespective, the present results point to the value of not only staging the tumour but also the host systemic inflammatory response (99) in patients with advanced disease.

As mentioned above while IL-6 would appear to be an ideal marker for the systemic inflammatory response its strong correlation with CRP, and the relative expense of IL-6 measurement has resulted in IL-6 not being routinely measured despite its central position in the systemic inflammatory cascade. Furthermore, IL-6 is produced in most tissues including the tumour meaning that compared with CRP and albumin (produced in the liver only) and neutrophils and platelets (myeloid tissue only), its use as a marker of the systemic inflammatory responses is perhaps suboptimal.

While little work has focused on the use of systemic inflammatory response monitoring to track treatment response in the setting of advanced disease this is not the case in the neoadjuvant and adjuvant settings (100-102). Carruthers *et al* (2012) showed a direct relationship between an NLR ≥ 5 and decreased time to local recurrence (HR: 3.8 95%CI 1.3–11.2 p=0.014) in patients with locally advanced rectal cancers receiving chemoradiotherapy (102). Dreyer *et al* (2016) showed that an elevated mGPS was associated with a poorer pathological response (p=0.022) in patients treated with neoadjuvant chemoradiotherapy (101), while Crozier *et al* (2006) showed that a CRP≥10mg/l was associated with worse survival in patients receiving adjuvant chemotherapy following surgery for colorectal cancer (HR: 5.57 95%CI 1.32–23.51 p=0.019) (100). It has been widely reported that the toxicity caused by chemotherapy and/or radiotherapy has its basis in the inflammatory response (51). This suggests that immune system modulation could be the key mechanism in their therapeutic activity and a potential therapeutic target (51, 103, 104).

Furthermore, there is increasing evidence that the systemic inflammatory response is a central mediator of the negative symptoms associated with both chemotherapy and radiotherapy (51, 105). Animal models have suggested that the administration of chemotherapeutic agents induces IL-6 production and illness behaviours in mice (51, 106). Several common chemotherapeutic agents have been shown to be associated with the

production of proinflammatory cytokines and the presence of natural killer (NK) cells, and activated T cell in patients with cancer (51, 107-109). In a recent observational study in patients being treated with chemoradiotherapy for advanced disease there was a dose-dependent rise in IL 6, IL 10, and TNF, correlating with symptoms such as pain, fatigue, and anorexia (51, 110).

The development of immune-oncology medications such as ipilimumab provides a potential means to target the activated inflammatory cascades to treat patients (111, 112). Indeed in a recent study in pancreatic cancer ruxolitinib, a strong down regulator of the inflammatory JAK/STAT pathway, was shown to increase median survival from 1.8 to 2.7 months in patients with high CRP readings (113). This suggests a possible innovative means to treat patients with advanced cancers (113).

The present systematic review and meta-analysis has a number of limitations. While it was the aim to only include the most recent paper where multiple publications from the same cohort where available, due to the practice of combining databases from different geographical locations under different lead institutions some double counting has occurred. Intrinsic to the process and the high proportion of retrospective studies is the potential for publication bias. However, the volume of studies examined in the present review would mitigate, in part, against such publication bias. In the meta-analysis there was considerable heterogeneity that could be accounted for in part by differing thresholds and tumour type. It may be that as there is greater threshold standardisation in prospective studies the degree of heterogeneity will be reduced in subsequent meta-analysis of prospective studies.

In summary, the present systematic review and meta-analysis shows clearly that the systemic inflammatory response, as evidenced by a number of markers, has independent prognostic value in patients with advanced cancer. Of these markers, the GPS and NLR have been consistently validated worldwide. Therefore, it can be concluded that the systemic

inflammatory response is an important predictor of outcome and is likely to inform treatment decisions in patients with advanced cancer. Further prospective studies are warranted.

3.5 Figures and Legends

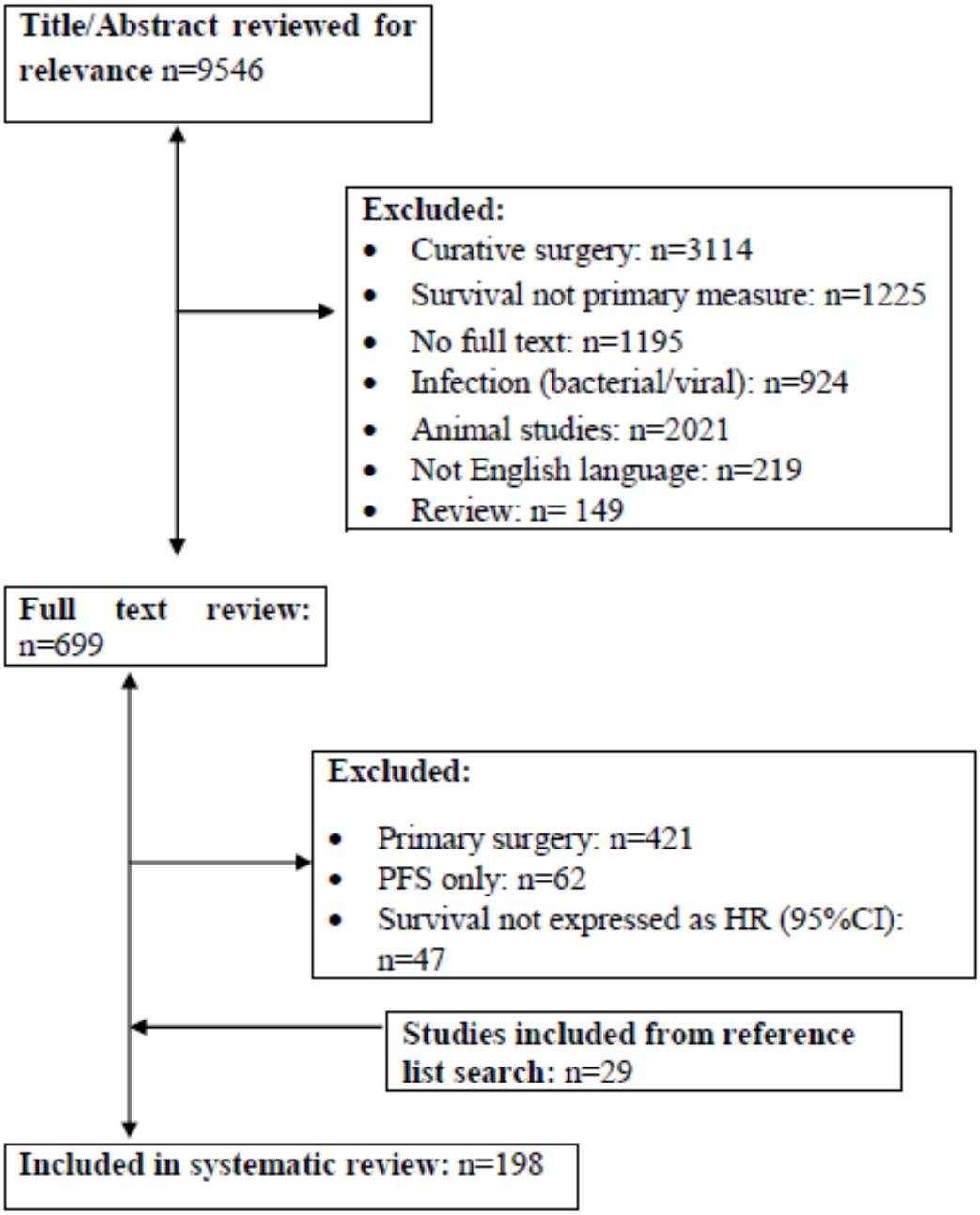


Figure 3.1: PRISMA flowchart demonstrating study selection

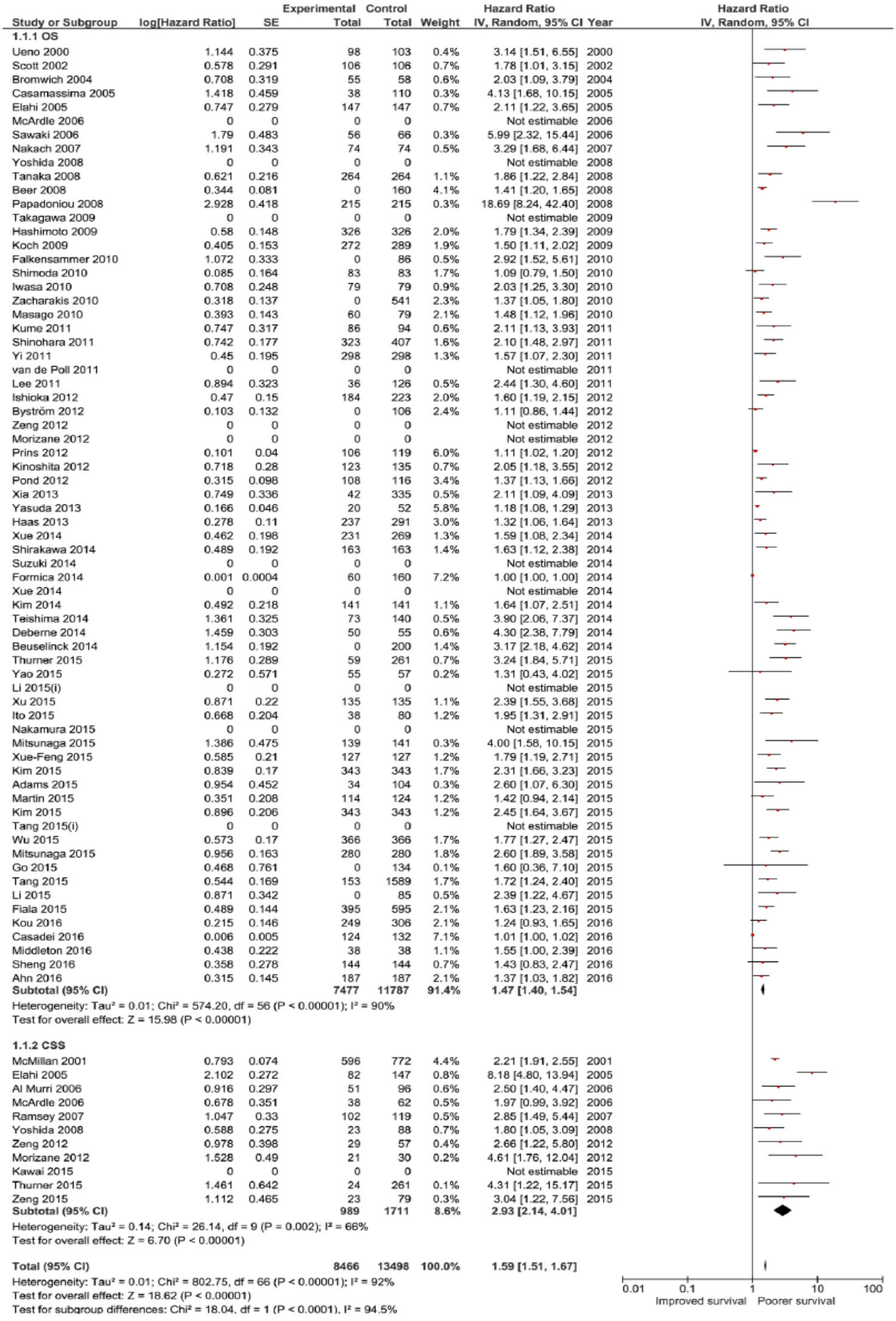


Figure 3.2: Forrest Plot of Studies investigating the prognostic value of CRP in an unselected cohort of patients with advanced cancer

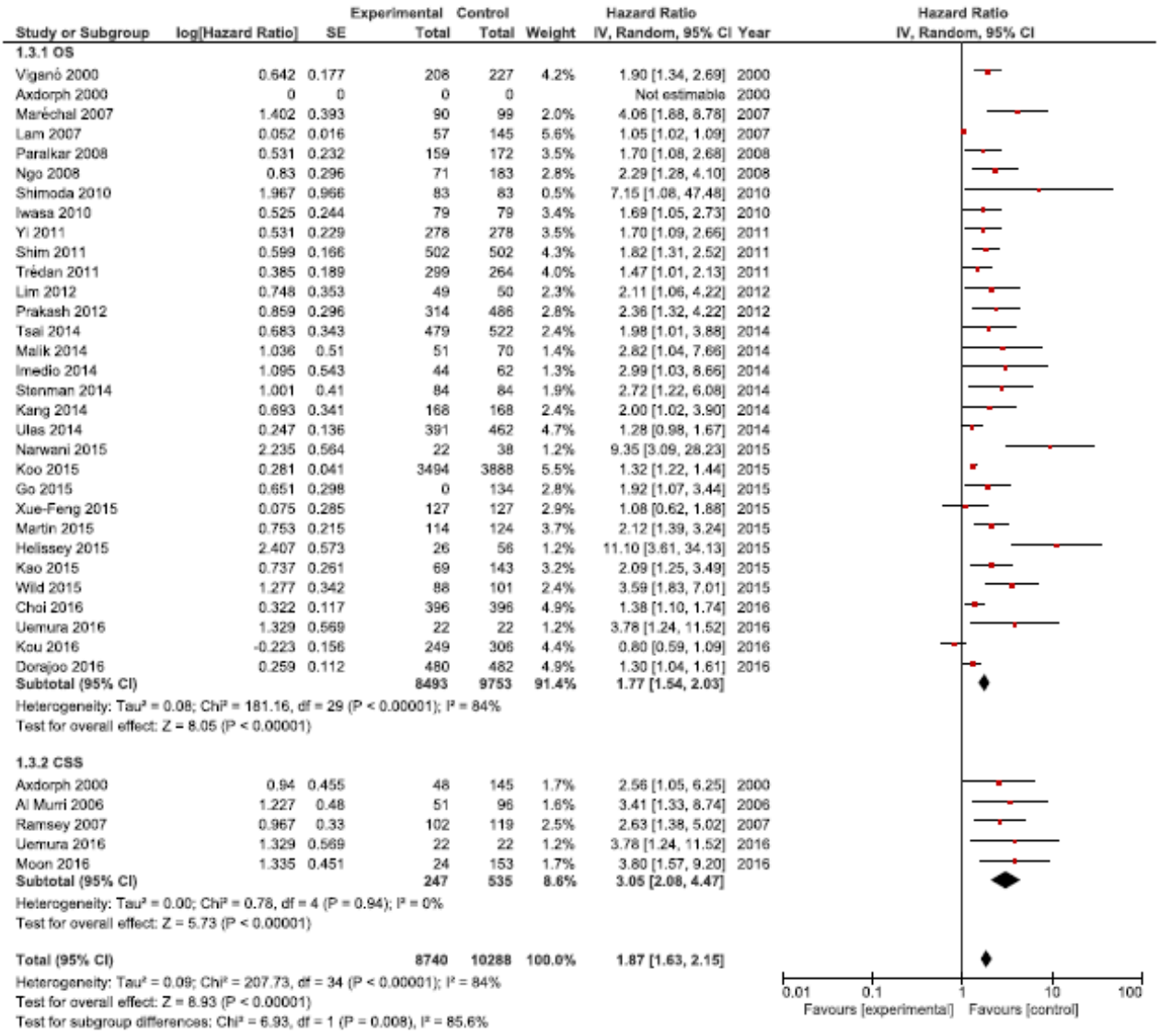


Figure 3.3: Forrest Plot of Studies investigating the prognostic value of Albumin in an unselected cohort of patients with advanced cancer

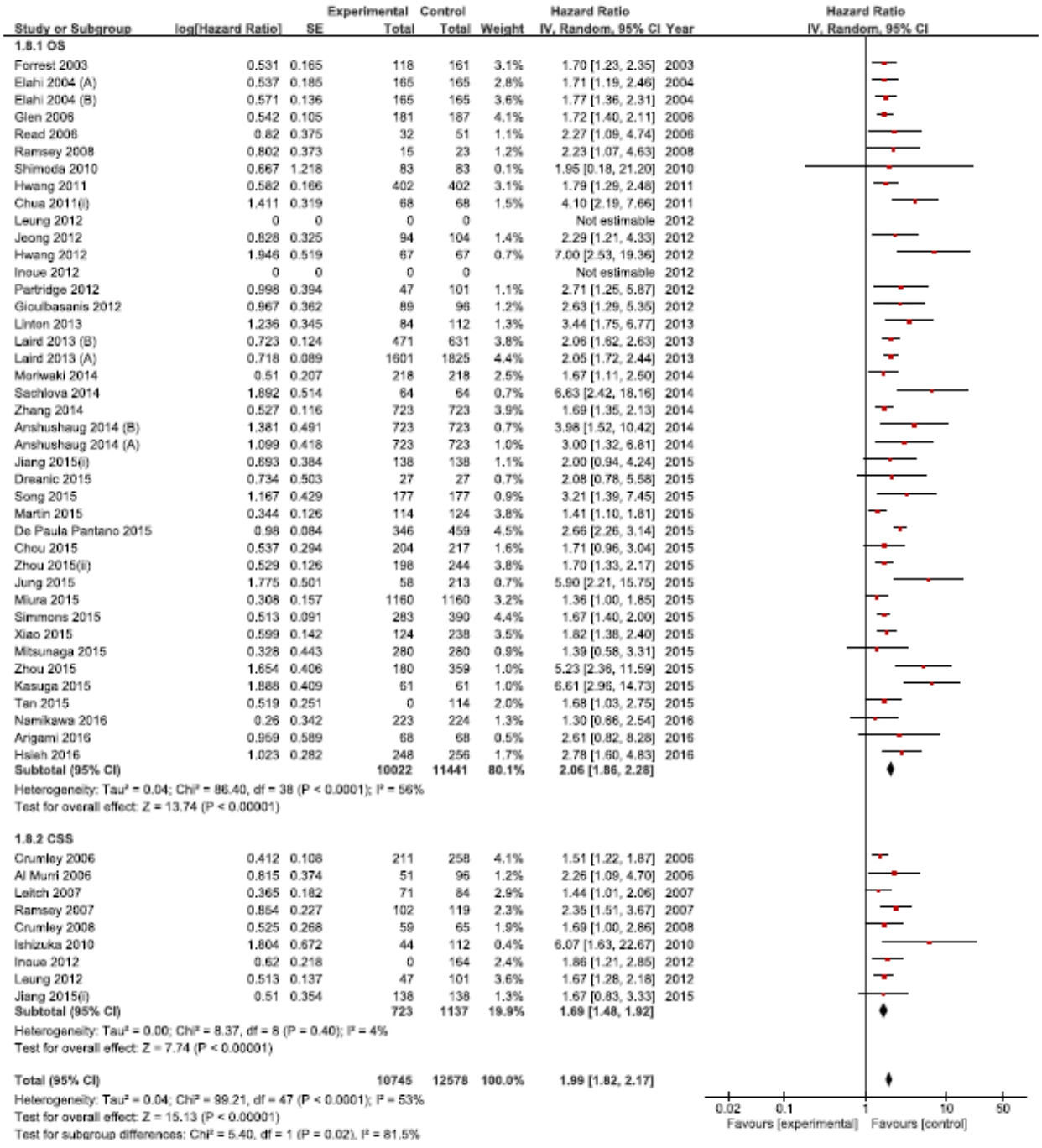


Figure 3.4**:** Forrest Plot of Studies investigating the prognostic value of GPS/mGPS in an unselected cohort of patients with advanced cancer

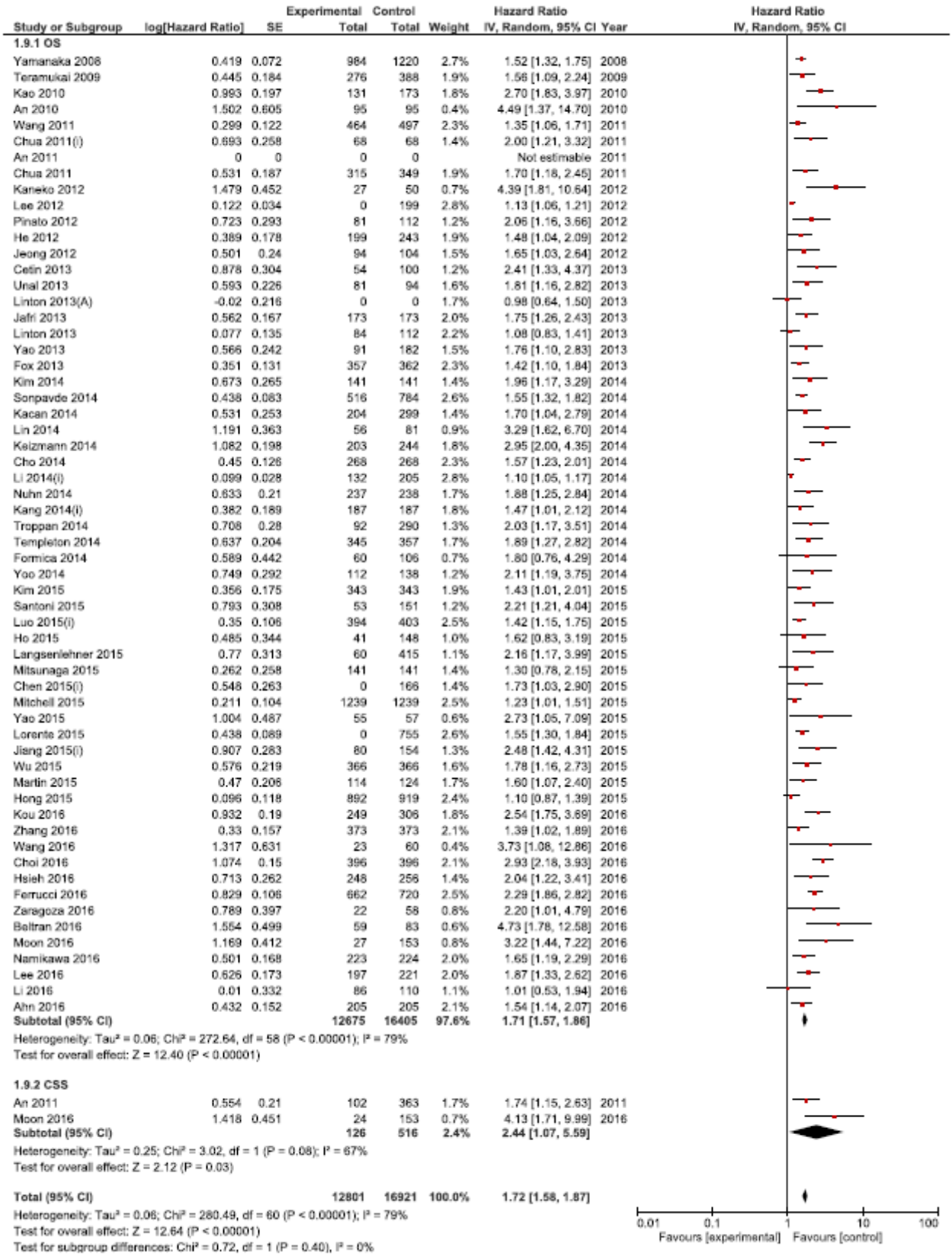


Figure 3.5**:** Forrest Plot of Studies investigating the prognostic value of NLR in an unselected cohort of patients with advanced cancer

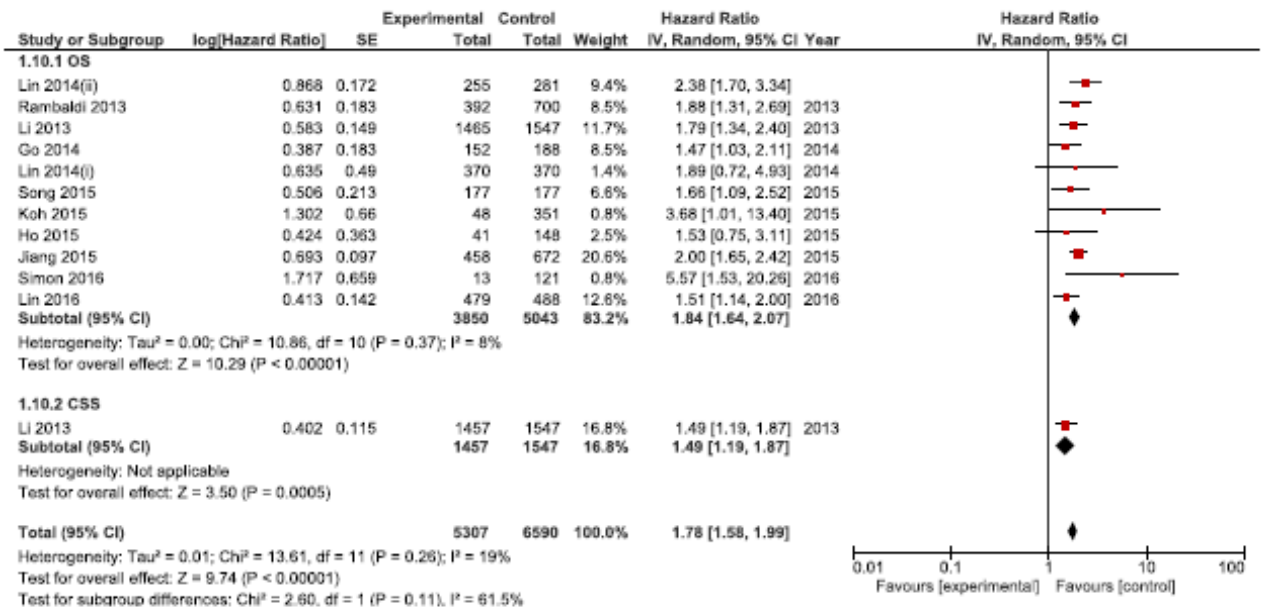


Figure 3.6: Forrest Plot of Studies investigating the prognostic value of LMR in an unselected cohort of patients with advanced cancer

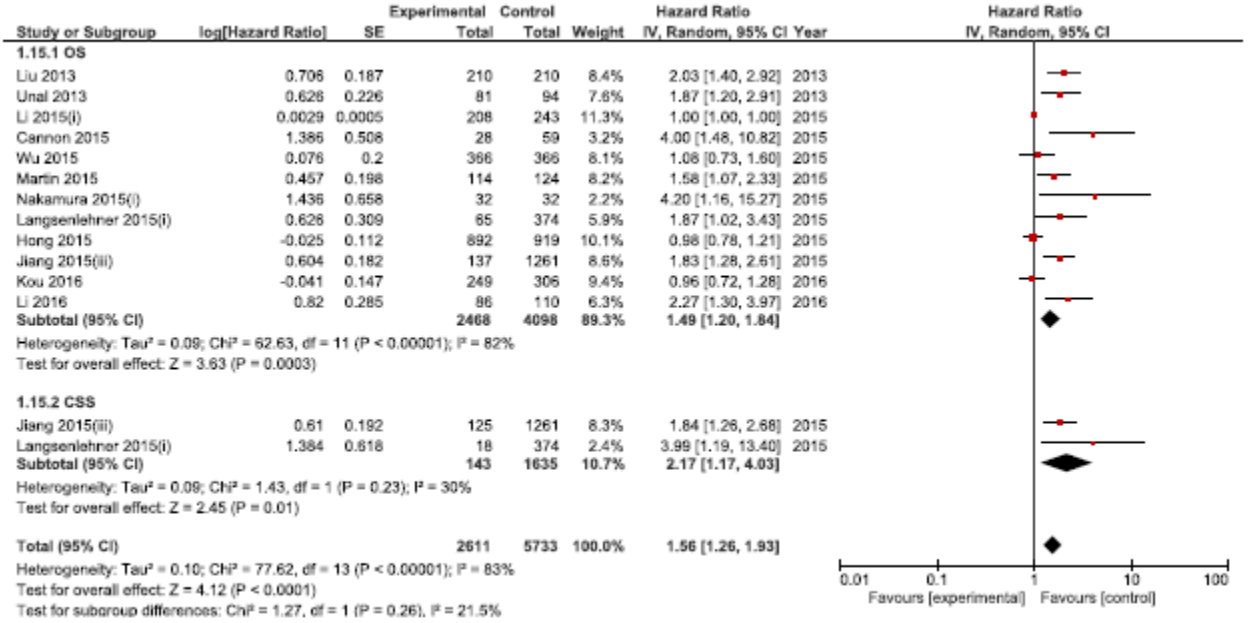


Figure 3.7: Forrest Plot of Studies investigating the prognostic value of PLR in an unselected cohort of patients with advanced cancer

4. THE ROLE OF THE SYSTEMIC INFLAMMATORY RESPONSE IN PREDICTING OUTCOMES IN PATIENTS WITH OPERABLE CANCER: SYTEMATIC REVIEW AND META-ANALYSIS

4.1 Introduction

Cancer remains one of the leading causes of mortality worldwide and is responsible for 8.8 million deaths per year (79). Overall, it has been estimated that one in three people will develop cancer in their lifetime, and one in four will die from it (114, 115).Indeed, in the UK alone it is estimated that 150,000 people die because of cancer each year (79, 115). Such a large burden of disease accounts for a significant proportion of the healthcare budgets of the UK, US and worldwide medical care (79, 115, 116).

Four cancers: lung, colorectal, breast and prostate account for approximately half of all new cases and deaths (114). For a range of solid organ malignancies including colorectal, lung, breast and prostate cancers, definitive local therapy in the form of surgical resection remains the cornerstone of treatment (114).

The genetic composition of many different types of cancer has been widely reported, however there is also increasing evidence that the host inflammatory response plays an important role in the development and progression of cancer (7, 14, 115, 117). In 2010 Roxburgh and McMillan published the first comprehensive review of the role of the systemic inflammatory response in predicting survival in patients with primary operable cancer (114). They identified 80 studies where the systemic inflammatory response was related to either overall, and cancer specific survival (114). However the majority of studies used singular markers of the inflammatory response such as CRP, albumin neutrophil, lymphocyte and platelet counts, indeed just 18 studies reported combined prognostic scores to improve prediction of survival (114). These included eight that reported the prognostic value of the GPS, and nine studies that reported the prognostic value of NLR. While these studies

reported a significant relationship between the systemic inflammatory response and survival there were variable thresholds used for the single or combined markers resulting in considerable variability in the magnitude of the effect reported (114).

However, since this review there has been a marked increase in the number of studies reporting the prognostic value of combined scoring systems based on the systemic inflammatory response. The majority reported have principally been ratios of components of the white cell count such as the neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), lymphocyte monocyte ratio (LMR) but also acute phase proteins such as C-reactive protein/albumin ratio (CAR). Another approach is to combine scores of the acute phase proteins such as GPS/mGPS (85, 115, 118). The presence of an elevated systemic inflammatory response as shown by the presence of circulating white cells and acute phase proteins is an important unifying host characteristic in patients with cancer. The prognostic ability of the combined scores has been widely reported and there have been reviews of NLR (85) and mGPS (87) and in advanced cancer (38). The present review is the first since 2010 to focus on primarily operable cancer and to include all recognised systemic inflammation based prognostic scores. This will rationalise the evidence for the role of systemic inflammation based prognostic scores in patients with primary operable cancers.

4.2 Patients and Methods

The present systematic review and meta-analysis of published literature was undertaken as outlined in Chapter 2. The primary outcome was to assess the prognostic value of the validated combined scores of the systemic inflammatory response (NLR, PLR, LMR, GPS and mGPS) in patients with primary operable cancer. This was carried out by a wide-ranging literature search to identify studies carried out up to December 2016. The medical subject heading (MeSH) terms used were Cancer, GPS, Glasgow Prognostic Score, mGPS, modified Glasgow Prognostic Score, NLR, Neutrophil Lymphocyte Ratio, LMR, Leucocyte Monocyte Ratio, PLR and Platelet Lymphocyte Ratio. As stated in Chapter 2 only articles that reported survival analysis were included in the review. Studies that did not follow the majority of other studies in terms of score or ratio direction interpretation were excluded from the final meta-analysis. Studies with patients who had chemotherapy and/ or radiotherapy before or after surgery were also included.

Statistical Analysis

A meta-analysis was carried out as outlined in Chapter 2.

.

4.3 Results

Study selection process

The study selection process is summarised in Figure 4.1. Initial search strategy identified 4780 articles whose titles and abstracts were reviewed. Articles were excluded if the treatment regime was chemotherapy/ radiotherapy only (n=659), where survival was not the primary outcome measure (n=2811), full articles were not available (n=372), and those that were a systematic review/meta-analysis (n=374).

This led to a review of the full text of 564 articles. A further 351 articles were excluded if progression free survival (PFS) was the only outcome measured (n=112), if the treatment regime was chemotherapy/ radiotherapy only (n=58) and if survival was not expressed as HR/ OR/ RR (95%CI; n=181). The remaining 213 articles had their bibliographies reviewed in a systematic manner and this identified a further 31 articles to be included in the final analysis leading to final figure of 244 articles considered in the present systematic review and meta-analysis.

Studies of the prognostic value of Glasgow Prognostic Score (GPS) or modified Glasgow Prognostic Score (mGPS) in patients with primary operable cancer:

Eighty articles with both overall survival (OS) and/or cancer specific survival (CSS) as their primary outcome measures were identified (Table 18.1). This comprised data on 25,207 patients (9,361 deaths) reporting the significant prognostic value of GPS/mGPS in cohorts of patients with primary operable cancer (Table 18.1). Seventy two studies were carried out in a retrospective manner while eight were prospective (Table 18.1). Seventy two studies used multivariate and eight used univariate survival analysis (Table 18.1).

After exclusion forty eight studies examined the relationship with overall survival including 16,160 patients (6,051 deaths), as the primary outcome measure. On meta-analysis there was a significant association between GPS/mGPS and overall survival (HR 1.86 95%CI 1.68-2.07, p<0.00001) with a substantial degree of heterogeneity (I^2=61%, Figure 4.2). These included studies on colorectal (n=12), oesophageal (n=7), liver (n=6), gastric (n=6), pancreatic (n=5), lung (n=4), gallbladder (n=2), colorectal liver metastases (n=1), renal (n=1), bladder (n=1), cholangiocarcinoma (n=1), oral (n=1) and vulval cancers (n=1).

On meta-analysis of those studies carried out in colorectal cancer (n=12), including 4,739 patients (1,883 deaths), there was a significant association between elevated GPS/ mGPS and overall survival (HR: 1.62 95%CI 1.42-1.84, p< 0.00001) with a substantial degree of heterogeneity (I^2 = 51%, Figure 4.3). These included studies carried out in the UK (n=8), Japan (n=2), Korea (n=1) and Australia (n=1). The proportion of patients who had an elevated GPS/ mGPS was 60% in Australia, 39% in Japan, 37% in the UK and 21% in Korea.

On meta-analysis of studies involving oesophageal cancer (n=7), including 1,918 patients (669 deaths), there was a significant association between GPS/mGPS and overall survival (HR: 1.73 95%CI 1.31-2.29, p<0.0001) with a minimal degree of heterogeneity (I^2 = 34%, Figure 4.4). These included studies carried out in Japan (n=4), Germany (n=1), China (n=1) and Ireland (n=1). The proportion of patients who had an elevated GPS/mGPS was 19% in Japan, 46% in Germany, 28% in China and 22% in Ireland.

On meta-analysis of studies involving liver cancer (n=6), including 2,142 patients (801 deaths), there was a significant association between GPS/mGPS and overall survival (HR: 2.87 95%CI 1.79-4.60, p<0.0001) with a substantial degree of heterogeneity (I^2 = 71%, Figure 4.5). These included studies carried out in Japan (n=3) and China (n=3). The proportion of patients who had an elevated GPS/ mGPS was 20% in Japan and 12% in China.

On meta-analysis of studies involving gastric cancer (n=6), including 2,471 patients (753 deaths), there was a significant association between GPS/mGPS and overall survival (HR: 1.95 95%CI 1.36-2.79, p=0.0003) with a substantial degree of heterogeneity (I^2 = 70%, Figure 4.6). These included studies carried out in Japan (n=4), China (n=1) and Italy (n=1). The proportion of patients who had an elevated GPS/mGPS was, 30% in Japan, 23% in China and 52% in Italy.

On meta-analysis those studies carried out in pancreatic cancer (n=5), including 549 patients (501 deaths), there was a significant association between GPS/ mGPS and overall survival (HR: 1.70 95%CI 1.21-2.38, p=0.002) with a substantial degree of heterogeneity (I^2 = 60%, Figure 4.7). These included studies carried out in the UK (n=2), Japan (n=1), Italy (n=1) and Austria (n=1). The proportion of patients who had an elevated GPS/mGPS was 45% in the UK, 23% in Japan, 68% in Italy and 34% in Austria.

After exclusion twenty nine studies examined CSS including 9,053 patients (2,686 deaths), as its primary outcome measure. On meta-analysis there was a significant association between GPS/mGPS and cancer specific survival (HR 2.08 95%CI 1.82-2.39, p<0.00001) with a substantial degree of heterogeneity (I^2=68%, Figure 4.8). These included studies on colorectal (n=16), oesophageal (n=4), oesophago-gastric (n=2), gastric (n=2), renal cell (n=2), colorectal liver metastases (n=1), oral (n=1) and bladder cancers (n=1).

On meta-analysis of studies involving colorectal cancer (n=16), including 5121 patients (1300 deaths), there was a significant association between GPS/mGPS and cancer specific survival (HR: 1.75 95%CI 1.55-1.98, p<0.00001) with a moderate degree of heterogeneity (I^2 = 42%, Figure 4.9). These included studies carried out in the UK (n=15) and Japan (n=1). The proportion of patients who had an elevated GPS/mGPS was 39% in the UK and 8% in Japan.

Studies of the prognostic value of Neutrophil Lymphocyte Ratio (NLR) in patients with primary operable cancer:

One hundred and fifty eight articles with both OS and/or CSS as their primary outcome measures were identified (Table 18.2). This comprised data on 63,837 patients (22,681 deaths) reporting the significant prognostic value of NLR in cohorts of patients with primary operable cancer. All one hundred and fifty eight studies were carried out in a retrospective manner (Table 18.2). One hundred and twenty eight studies used multivariate and thirty used univariate survival analysis (Table 18.2). After exclusion one hundred and nineteen studies examined the relationship with overall survival including 49,664 patients (18,542 deaths), as the primary outcome measure. On meta-analysis there was a significant association between NLR and overall survival (HR 1.73 95%CI 1.56-1.91, p<0.00001) with a considerable degree of heterogeneity (I^2=98%, Figure 4.10). The most common NLR threshold examined was ≥5 (n=29). Other thresholds were ≥3 (n=9), ≥2.5 (n=7), NLR as continuous variable (n=7), ≥4 (n=7) and ≥2 (n=5). Other thresholds were used in <5 studies and thus, meta-analysis was not carried out (n=55).

On meta-analysis of those studies with a threshold of ≥5 (n=29), including 9,997 patients (4,012 deaths) there was a significant association between elevated NLR and overall survival (HR: 1.92 95%CI 1.67-2.20, p<0.00001) with a moderate degree of heterogeneity (I^2 = 47%, Figure 4.11). These included colorectal (n=8), lung (n=4), colorectal liver metastases (n=4), oesophageal (n=3), gastric (n=2), soft tissue sarcoma (n=2), liver (n=2), pancreatic (n=1), renal (n=1), pleural mesothelioma (n=1) and hepato-pancreatico-biliary cancers (n=1).

On meta-analysis of those studies with a threshold of ≥5 and colorectal cancer (n=8), including 3,379 patients (825 deaths) there was a significant association between an NLR≥5 and overall survival (HR: 1.80 95%CI 1.37-2.37, p<0.0001) with moderate heterogeneity (I^2=45%, Figure 4.12). In these eight studies, there was a variation in their geographical

locations including the UK (n=2), Korea (n=2), Taiwan (n=1), Austria (n=1), US (n=1) and Australia (n=1). The proportion of patients who had an NLR≥5 with colorectal cancer was 25% in the UK, 5% in Korea, 25% in Taiwan, 11% in US and 30% in Australia. 29% in Korea and 20% in Japan. No country had more than 4 studies and therefore no further meta-analysis was carried out.

On meta-analysis of those studies with a threshold of ≥3 (n=9), including 2,638 patients (835 deaths) there was a significant association between elevated NLR and overall survival (HR: 1.83 95%CI 1.48-2.27, p<0.00001) with a moderate degree of heterogeneity (I^2 = 44%, Figure 4.13). These included gastric (n=2), liver (n=1), biliary tract (n=1), bladder (n=1), breast (n=1), colorectal (n=1), pleural mesothelioma (n=1) and endometrial cancers (n=1). In these nine studies, there was a variation in their geographical locations including Japan (n=4), Canada (n=2), China (n=1), Belgium (n=1) and Australia (n=1). The proportion of patients who had an NLR≥3 was 28% in Japan, 47% in Canada, 33% in China, 31% in Belgium and 52% in Australia. No tumour site had more than four studies and therefore no further meta-analysis was carried out.

On meta-analysis of those studies with a threshold of ≥2.5 (n=7), including 1,888 patients (475 deaths) there was a significant association between elevated NLR and overall survival (HR: 1.78 95%CI 1.29-2.44, p=0.0004) with a moderate degree of heterogeneity (I^2 = 42%, Figure 4.14). These included lung (n=3), oesophageal (n=1), colorectal (n=1), soft tissue sarcoma (n=1) and liver cancers (n=1). In these seven studies, there was a variation in their geographical locations including Japan (n=5), China (n=1) and US (n=1). The proportion of patients who had an NLR≥2.5 was 30% in Japan, 28% in China and 50% in US. No tumour site had more than four studies and therefore no further meta-analysis was carried out.

On meta-analysis those studies with NLR as continuous variable (n=7), including 2,472 patients (1,466 deaths) there was a moderate association between elevated NLR and overall

survival (HR: 1.05 95%CI 1.02-1.08, p=0.001) with a substantial degree of heterogeneity (I^2 = 63%, Figure 4.15). These included pancreatic (n=2), renal (n=2), colorectal (n=1), lung (n=1) and bladder cancers (n=1). In these seven studies, there was a variation in their geographical locations including the UK (n=2), US (n=2), China (n=1), Austria (n=1) and Australia (n=1). No tumour site had more than four studies and therefore no further meta-analysis was carried out.

On meta-analysis those studies with a threshold of ≥4 (n=7), including 2,195 patients (697 deaths) there was a significant association between elevated NLR and overall survival (HR: 1.36 95%CI 1.01-1.84, p=0.04) with a substantial degree of heterogeneity (I^2 = 73%, Figure 4.16). These included glioblastoma (n=2), gastric (n=1), oesophageal (n=1), ovarian (n=1), breast (n=1) and colon cancers (n=1). In these seven studies, there was a variation in their geographical locations including Japan (n=2), China (n=1), the UK (n=1), Belgium (n=1), Austria (n=1) and Ireland (n=1). The proportion of patients who had an NLR≥4 was 15% in Japan, 32% in China, 22% in Belgium and 36% in Ireland. No tumour site had more than four studies and therefore no further meta-analysis was carried out.

On meta-analysis those studies with a threshold of ≥2 (n=5), including 3,065 patients (1,068 deaths) there was a significant association between elevated NLR and overall survival (HR: 1.48 95%CI 1.28-1.72, p<0.00001) with minimal heterogeneity (I^2 = 0%, Figure 4.17). These cancers included gastric (n=2), colorectal (n=1), liver (n=1) and pancreatic (n=1). In these five studies, there was a variation in their geographical locations including China (n=3) and Korea (n=2). The proportion of patients who had an NLR≥2 was 60% in China and 39% in Korea. No tumour site had more than four studies and therefore no further meta-analysis was carried out.

After exclusion forty one studies examined the relationship with cancer specific survival including 17,539 patients (4,617 deaths), as its primary outcome measure. On meta-analysis

there was a significant association between NLR and cancer specific survival (HR 1.32 95%CI 1.24-1.41, p<0.00001) with a considerable degree of heterogeneity (I^2=81%, Figure 4.18). The most common NLR thresholds used was≥5 (n=7), ≥3 (n=6) and NLR as continuous variable (n=5). Other thresholds did not have more than four studies and therefore meta-analysis was not carried out (n=19).

On meta-analysis those studies with a threshold of ≥5 (n=7), including 1,283 patients (531 deaths) there was a significant association between elevated NLR and cancer specific survival (HR: 1.89 95%CI 1.53-2.34, p<0.00001) with minimal heterogeneity (I^2 = 0%, Figure 4.19). These included colorectal (n=2), liver only colorectal metastases (n=1) and soft tissue sarcoma (n=1), adrenal (n=1), pancreatic (n=1) and renal cancers (n=1). In these seven studies, there was a variation in their geographical locations including the UK (n=3), Austria (n=2), US (n=1) and South Korea (n=1). The proportion of patients who had an NLR≥5 was 19% in the UK, 35% in US and 7% in South Korea. No tumour site had more than four studies and therefore no further meta-analysis was carried out.

On meta-analysis those studies with a threshold of ≥3 (n=6), including 2,367 patients (525 deaths) there was a significant association between elevated NLR and cancer specific survival (HR: 1.81 95%CI 1.42-2.30, p<0.00001) with a moderate degree of heterogeneity (I^2 = 32%, Figure 4.20). These included renal (n=2), bladder (n=1), colorectal (n=1), oesophageal (n=1) and gastric cancers (n=1). In these six studies, there was a variation in their geographical locations including Japan (n=2), Korea (n=1), China (n=1), Taiwan (n=1) and Canada (n=1). The proportion of patients who had an NLR≥3 was 25% in Japan, 20% in Korea, 20% in China, 40% in Taiwan and 51% in Canada. No tumour site had more than four studies and therefore no further meta-analysis was carried out.

On meta-analysis those studies with NLR as continuous variable (n=5), including 3,686 patients (1,312 deaths) there was a significant association between elevated NLR and cancer

specific survival (HR: 1.06 95%CI 1.01-1.10, p=0.008) with a substantial degree of heterogeneity (I^2 = 80%, Figure 4.21). These included renal (n=1), bladder (n=1), colorectal (n=1), liver only colorectal metastases (n=1) and gastric cancers (n=1). In these six studies, there was a variation in their geographical locations including the US (n=3), the UK (n=1) and Australia (n=1). No tumour site had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of platelet lymphocyte ratio (PLR) in patients with primary operable cancer:

Sixty eight articles with both OS and/or CSS as their primary outcome measures were identified (Table 18.3). This comprised data on 29,273 patients (10,729 deaths) reporting the significant prognostic value of PLR in cohorts of patients with primary operable cancer (Table 18.3). All sixty eight studies were conducted in a retrospective manner. Forty three studies were conducted in a multivariate and twenty five in a univariate manner (Table 18.3).

After exclusions fifty five studies examined the relationship with overall survival including 25,601 patients (9,258 deaths), as the primary outcome measure. On meta-analysis there was a significant association between an elevated PLR and overall survival (HR 1.09 95%CI 1.06-1.11, p<0.00001) with a substantial degree of heterogeneity (I^2=80%, Figure 4.22). The most common PLR thresholds examined were ≥300 (n=10) and ≥150 (n=7). Other thresholds did not have more than four studies and therefore meta-analysis was not carried out (n=58).

On meta-analysis those studies with a threshold of ≥300 (n=10), including 3,713 patients (HR: 1.61 95%CI 1.20-2.18, p=0.002) with a substantial degree of heterogeneity (I^2 = 75%, Figure 4.23). These included colorectal (n=3), lung (n=2), gastric (n=2), colorectal liver metastases (n=1), oesophageal (n=1) and ovarian cancers (n=1). In these ten studies, there

was a variation in their geographical locations including the UK (n=3), Korea (n=2), China (n=2), Hungary (n=1), Italy (n=1) and Japan (n=1). The proportion of patients who had a PLR≥300 was 20% in the UK, 4% in Korea, 10% in China, 13% in Italy and 5% in Japan. No tumour site had more than four studies and therefore no further meta-analysis was carried out.

On meta-analysis those studies with a threshold of ≥150 (n=7), including 1,315 patients (667 deaths) there was a significant association between elevated PLR and overall survival (HR: 1.59 95%CI 1.29-1.97, p<0.0001) with a minimal degree of heterogeneity (I^2 = 29%, Figure 4.24). These included oesophageal (n=2), pancreatic (n=2), liver (n=1), colorectal liver metastases (n=1) and colorectal cancers (n=1). In these seven studies, there was a variation in their geographical locations including China (n=2), Japan (n=2), the UK (n=1), Hong Kong (n=1) and Australia (n=1). The proportion of patients who had a PLR≥150 was 43% in China, 49% in Japan, 41% in the UK, 27% in Hong Kong and 75% in Australia. No tumour site had more than four studies and therefore no further meta-analysis was carried out.

After exclusions fifteen studies examined the relationship with cancer specific survival including 4,489 patients (1,769 deaths), as the primary outcome measure. On meta-analysis there was a significant association between an elevated PLR and cancer specific survival (HR 1.21 95%CI 1.06-1.38, p=0.005) with a substantial degree of heterogeneity (I^2=63%, Figure 4.25). The most common PLR threshold examined was ≥300 (n=4). Other thresholds used were >150 (n=1), ≥25.4 (n=1), >103 (n=1), ≥132 (n=1), ≥176 (n=1), >190 (n=1), ≥200 (n=1), ≥240 (n=1), ≥292 (n=1), PLR as continuous variable (n=1) and PLR per 100 units (n=1). These included studies on oesophageal (n=3), colorectal (n=3), gastric (n=2), colorectal liver metastases (n=1), adrenal (n=1), renal (n=1), endometrial (n=1), bladder (n=1), soft tissue sarcoma (n=1) and breast cancers (n=1). Geographically studies were located in the UK (n=5), China (n=4), Austria (n=2), Japan (n=1), US (n=1), South Korea

(n=1) and Canada (n=1). The proportion of patients who had an elevated PLR was 12% in the UK, 55% in China, 23% in Japan, 38% in US and 3% in South Korea. No specific PLR thresholds had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of lymphocyte monocyte ratio (LMR) in patients with primary operable cancer:

Twenty one articles with both OS and/or CSS as their primary outcome measures were identified (Table 18.4). This comprised data on 15,386 patients (4,298 deaths) reporting the significant prognostic value of LMR in cohorts of patients with primary operable cancer (Table 18.4). All 21 studies were retrospective. Nineteen studies used multivariate and two used univariate survival analysis (Table 18.4).

After exclusion twelve studies examined the relationship with overall survival including 11,913 patients (3,106 deaths), as the primary outcome measure. On meta-analysis there was a significant association between an elevated LMR and overall survival (HR 0.69 95%CI 0.63-0.74, $p<0.00001$) with a substantial degree of heterogeneity ($I^2=61\%$, Figure 4.26). There was a variety of LMR cut-offs used in each study including ≥2, (n=1), ≥2.14 (n=1), >2.35 (n=1), >2.38 (n=1), >2.83 (n=1), ≥2.85 (n=1), >2.87 (n=1), >3.23 (n=1), ≥3.80 (n=1), ≥4 (n=1), ≥4.32 (n=1) and ≥4.95 (n=1). These included studies on colorectal (n=3), bladder (n=2), liver only colorectal metastases (n=1), gastric (n=1), renal (n=1), liver (n=1), breast (n=1), soft tissue sarcoma (n=1) and cervical cancers (n=1). Geographically the studies were carried out in China (n=6), Austria (n=3), the UK (n=1), Canada (n=1) and Australia (n=1). The proportion of patients who had high LMRs was 71% in China, 68% in Japan, 64% in the UK, 49% in Australia and 48% in Austria. No specific LMR thresholds had more than four studies and therefore no further meta-analysis was carried out.

After exclusion five studies examined the relationship with cancer specific survival including 1,627 patients (697 deaths), as the primary outcome measure. On meta-analysis there was a significant association between an elevated LMR and cancer specific survival (HR 0.70 95%CI 0.60-0.82, p<0.00001) with a moderate degree of heterogeneity (I^2=47%, Figure 4.27). There was a variety of LMR cut-offs used in each study including >2.35 (n=1), ≥2.85 (n=1), >2.93 (n=1) and ≥4.95 (n=1). One study expressed LMR in terms of log. These included studies on liver only colorectal metastases (n=1), gastric cancer (n=1), oesophageal cancer (n=1), bladder cancer (n=1) and soft tissue sarcoma (n=1). Geographically the studies were carried out in the China (n=2), UK (n=1), Austria (n=1), and Canada (n=1). The proportion of patients who had high LMRs was 68% in Japan, 64% in the UK, 50% in Austria and 40% in China. No specific LMR thresholds had more than four studies and therefore no further meta-analysis was carried out.

Studies of the prognostic value of other scores of the systemic inflammatory response in patients with primary operable cancer:

Thirty five articles reported a variety of other scores reported in less than 10 studies each. These included the PNI (Prognostic Nutritional Index), COP-NLR (combined platelet count and NLR), NLR/PLR combination, CAR (CRP/albumin ratio), SI (systemic inflammatory score), SII (systemic inflammatory index), NLR/CRP combination, (HALP) haemoglobin, albumin, lymphocyte and platelet, NLR/ESR (erythrocyte sedimentation rate) combination, (WLR) white cell count to lymphocyte count ratio, (APRI) AST-platelet ratio index, PI/CRP/WCC combination, Canton score, (AGR) albumin/ globulin ratio, CRP/Neutrophil combination, (PIS) Prognostic Inflammation Score, and the CONUT score.

Eight articles with both OS and/or CSS as their primary outcome measures were identified (Table 18.5). This comprised data on 2,666 patients (1,387 deaths) reporting the significant

prognostic value of PNI in cohorts of patients with primary operable cancer. All eight studies were carried out in a retrospective manner (Table 18.5). Six studies used multivariate and two used univariate survival analysis (Table 18.5).

After exclusion seven studies examined the relationship with overall survival including 2,087 patients (1,087 deaths), as the primary outcome measure. On meta-analysis there was a significant association between PNI and overall survival (HR 1.76 95%CI 1.52-2.04, p<0.00001) with minimal heterogeneity (I^2=0%, Figure 4.28). The most common PNI threshold examined was ≤45 (n=3), ≤50 (n=1), ≤50.5 (n=1), 48.5 (n=1), 48.2 (n=1). These included hepatocellular (n=3), gastric (n=2), lung (n=1) and colorectal liver metastases (n=1). In these eight studies, there was a variation in their geographical locations including Japan (n=2), UK (n=1), Hong Kong (n=1), China (n=1), US (n=1) and Italy (n=1).The proportion of patients who with an elevated PNI was 74% in Hong Kong, 59% in Japan, 59% in Italy, 52% in China and 17% in the UK. No tumour site had more than four studies and therefore no further meta-analysis was carried out. Two studies examined the relationship with cancer specific survival including 579 patients (300 deaths), as the primary outcome measure. Both of these studies used a PNI threshold of ≤45. No threshold was used in ≥4 studies and thus, meta-analysis was not carried out.

Four studies reported the COP-NLR score. The first such study was by Ishizuka and co-workers(119) from Japan. In this multivariate survival analysis on patients with colorectal cancer, low COP-NLR was shown to be related to a statistically better cancer specific survival (OR: 0.464 95% CI 0.267-0.807 p=0.007). The second such study was also by Ishizuka and co-workers(120) from Japan. In this multivariate survival analysis on patients with gastric cancer, elevated COP-NLR was shown to be related to a statistically significant worse overall survival (HR: 1.781 95% CI 1.094-2.899 p=0.020). The third such study was by Zhang and co-workers(121) from China. In this multivariate survival analysis on patients with lung cancer, elevated COP-NLR was shown to be related to a statistically significant

worse overall survival (HR: 1.810 95% CI 1.587-2.056 p<0.001). The fourth such study was by Neal and co-workers(122) from the UK. In this univariate survival analysis on patients with colorectal liver metastases, elevated COP-NLR was shown to be related to a statistically significant worse overall survival (HR: 1.230 95% CI 1.005-1.505 p=0.045) and worse cancer specific survival (HR: 1.243 95% CI 1.003-1.541 p=0.047).

Three studies reported the combination of the NLR and PLR. The first such study was by Feng and co-workers(123) from China. The combination of NLR and PLR is collectively named the CNP. The CNP was calculated based on data obtained on the day of admission, where patients with both elevated NLR (>3.45) and PLR (>166.5) were allocated a score of 2, and patients showing one or neither were allocated a score of 1 or 0, respectively. In this multivariate survival analysis on patients with oesophageal cancer, CNP 1 or 2 was shown to be related to a statistically worse overall survival (HR: 1.964 95% CI 1.371-2.814 p<0.001). The second such study was by Cummings and coworkers (124) from the UK. In this multivariate survival analysis on patients with endometrial cancer, both high NLR and PLR was shown to be related to a statistically significant worse overall survival (HR: 2.54 95% CI 1.61-4.01 p<0.001) and worse cancer specific survival (HR: 2.26 95% CI 1.24-4.13 p=0.008). The third such study was by Chuan Li and co-workers(125) from China. In this multivariate survival analysis on patients with liver cancer, elevated postoperative NLR-PLR was shown to be related to a statistically significant worse overall survival (HR: 2.894 95% CI 1.992-4.2 p<0.001).

Two studies reported the CAR. The first such study was by Ishizuka and coworkers (126) from Japan. In this multivariate survival analysis on patients with colorectal cancer, CAR >0.038 was shown to be related to a statistically worse overall survival (HR: 2.613 95% CI 1.621-4.212 p<0.001). The second such study was by Xu and coworkers (127) from China. In this multivariate survival analysis on patients with oesophageal cancer, CRP/ Albumin

ratio >0.50 was shown to be related to a statistically significant worse overall survival (HR: 2.44 95% CI 1.82-3.26 p<0.0001).

One study reported the SI, a score involving leucocyte count, serum albumin and haemoglobin level. High leucocyte count (>9,500 µl), low serum albumin level (3.5 g/dl) and low haemoglobin level (<12.5 mg/dl) was each allocated a score of 1.The study was conducted by Miyata and coworkers (128) from Japan. In this multivariate survival analysis on patients with oesophageal cancer, SI score of 2/3 was shown to be related to a statistically significant worse overall survival (HR: 3.17 95% CI 1.74-5.78 p=0.0002).

One study reported on the SII which was determined as neutrophil x platelet / lymphocyte. The study was conducted by Ha and coworkers (129) from South Korea. In this multivariate survival analysis on patients with ampulla of vater cancer, SII ≤ 780 was shown to predict better overall survival (HR: 0.924 95% CI 0.44-1.93 p=0.833).

One study reported on the combination of the NLR and CRP. The study was conducted by Tomita and coworkers (130) from Japan. In this multivariate survival analysis on patients with lung cancer, low NLR and low CRP (compared to both high) was shown to predict better overall survival (RR: 0.403 95% CI 0.240-0.689 p=0.0012).

One study reported on preoperative HALP. The study was conducted by Chen and coworkers (131) from China. In this multivariate survival analysis on patients with gastric cancer, HALP ≥ 56.8 was shown to predict better overall survival (HR: 0.700 95% CI 0.496-0.987 p=0.042).

One study reported on the combination of the NLR and ESR. The study was conducted by Hyun and coworkers (132) from Korea. Patients were divided into three groups: those with ESR and NLR in the normal range (group 0), those with either elevated ESR or elevated NLR (group I), and those with both elevated ESR and elevated NLR (group II). In this multivariate survival analysis on patients with renal cancer, both elevated ESR and NLR was

shown to predict worse overall survival (HR: 3.521 95% CI 1.888-6.567 p<0.001) and worse cancer specific survival (HR: 4.367 95% CI 1.987-9.597 p<0.001).

One study reported on the WLR. The study was conducted by East and coworkers (133) from the UK. In this multivariate survival analysis on patients with colon cancer, WLR ≥ 3.4 was shown to predict worse overall survival (HR: 4.10 95% CI 3.13-7.42 p=0.03).

One study reported on the APRI. The study was conducted by Shen and coworkers (134) from China. In this multivariate survival analysis on patients with liver cancer, APRI ≥ 0.62 was shown to predict worse overall survival (HR: 1.508 95% CI 1.127-2.016 p=0.006).

One study reported on the combination of the PI, CRP and white cell count (0 if both low, 1 if either high, 2 if both high). The study was conducted by Aurello and co-workers(135) from Italy. In this multivariate survival analysis on patients with gastric cancer, PI 2 was shown to predict worse overall survival (HR: 0.37 95% CI 0.16-0.82 p=0.01).

One study reported on the Canton score involving PNI, NLR and platelet. The study was conducted by Sun and coworkers (136) from China. In this multivariate survival analysis on patients with gastric cancer, elevated Canton score was shown to predict worse overall survival (HR: 1.643 95% CI 1.142-2.364 p=0.007).

One study reported on the AGR. The study was conducted by Li and coworkers (137) from China. In this multivariate survival analysis on patients with colorectal cancer, AGR ≥ 1.50 was shown to predict better overall survival (HR: 0.646 95% CI 0.543-0.767 p<0.001).

One study reported on the combination of CRP and neutrophils. The study was conducted by Christina and coworkers (138) from Austria. In this multivariate survival analysis on patients with oral cancer, high CRP/ neutrophil was shown to predict worse overall survival (HR: 2.7 95% CI 0.68-10.75 p=0.16).

One study reported on the PIS involving a combination of NLR and serum albumin. PIS was defined as follows: patients with increased NLR and decreased serum albumin were assigned score 0; patients with either increased NLR or decreased serum albumin were assigned score 1; patients with decreased NLR and increased serum albumin were assigned score 2. The study was conducted by Wang and coworkers (139) from China. In this multivariate survival analysis on patients with ovarian cancer, PIS 2 was shown to predict better overall survival (HR: 0.18 95% CI 0.09-0.38 $p<0.001$).

Finally, the last study reported on the CONUT score involving serum albumin concentration, total lymphocyte counts and total cholesterol concentration. The study was conducted by Toyokawa and coworkers (140) from Japan. In this multivariate survival analysis on patients with oesophageal cancer, high CONUT score was shown to predict worse overall survival (HR: 2.303 95% CI 1.191-4.455 $p=0.013$).

Assessment of bias using funnel plot analysis of studies carried out in patients with primary operable cancer:

Funnel plot analysis containing ten or more studies revealed bias towards studies reporting a relationship between an increased systemic inflammatory response as evidenced by the GPS/GPS (multiple tumour types Figure 4.2 and Figure 4.8; colorectal cancer Figure 4.3 and Figure 4.9), NLR (multiple tumour types Figure 4.10 and Figure 4.18; NLR$\geq$5 Figure 4.11), PLR (multiple tumour types Figure 4.22 and 25; PLR>300 Figure 4.23), LMR (multiple tumour types Figure 4.26) and poorer survival. The funnel plots also showed that a clear majority of studies had high patient numbers. This is particularly true for studies focusing on GPS/mGPS (Figure 4.2 and Figure 4.9), NLR (Figure 4.10 and Figure 4.18), PLR (Figure 4.22) and LMR (Figure 4.26).

4.4 Discussion

In the present review 244 reports of the prognostic value of systemic inflammation based prognostic scores were identified. This is in contrast to the initial review by Roxburgh and McMillan (2010) where 18 such studies were identified. In particular, those scores based on the ratio of components of a white cell count have been the subject of intense interest with, over the intervening 7 years, 158 studies reporting the value of the NLR, 68 reporting PLR and 21 reporting LMR. Also, the cumulative GPS/mGPS has been the subject of 80 reports. The majority of these studies have been carried out in lung and gastrointestinal cancer. For example, the GPS/mGPS had prognostic value in lung (5 studies), gastric cancer (7 studies), pancreatic (5 studies), and colon cancer (3 studies). A feature of this up to date review of systemic inflammation based prognostic scores is the identification of the proliferation of new scores derived from routinely available markers of the systemic inflammatory response. Most notable among these that have been validated in several studies are PINI (7 studies), COP-NLR (4 studies) and CNP (3 studies). It remains to be established whether any of the scores will have prognostic value in addition to the GPS/mGPS and NLR. Irrespective, there is increasing recognition and acceptance of the clinical utility of systemic inflammation based prognostic scores prior to surgery for cancer.

It is perhaps surprising that, given apparent the superior prognostic value of the GPS/ mGPS (115) the relatively larger numbers of reports of the prognostic value of ratios based on components of the white cell count. However, the pre-operative differential white cell count is part of the standard pre-operative workup for the majority of cancer resections as it is used to help identify patients who may have an infection prior to surgery. Also, the white cell count is used to identify any pre-existing conditions that may affect the surgical procedure such as the hypercoagulability of thrombocytosis. Thus, these results are routinely available for retrospective studies. This might also explain the variety of prognostic thresholds reported for NLR, PLR and LMR. In contrast, reports on the prognostic value of the

GPS/mGPS, not routinely assessed as part of the standard pre-operative workup, were more likely to be examined in prospective studies. This might explain the consistent adherence to the original thresholds reported for GPS/ mGPS. From the above there is a strong case for the GPS/mGPS to be incorporated into pre-operative workup of patients undergoing surgery for cancer.

It is of interest that while there is general uniformity of thresholds used in the GPS/mGPS studies, with most adhering to the original abnormal thresholds (CRP >10mg/l and albumin <35g/l), studies in East Asia particularly Japan have used thresholds of 7.5mg/l (141), 5mg/l (142, 143) and 3mg/l (144-146). Such lower CRP thresholds are above the normal reference ranges in Japan/ East Asia cohorts and results in fewer patients breaching the CRP>10mg/l threshold. This observation of a greater proportion of patients with elevated systemic inflammation markers in Western countries compared with Eastern Asian countries is also apparent in white cell derived ratios. Given the objective and reproducible nature of systemic inflammation based prognostic scores it is likely that such observations are real. Indeed, there are recognized ethnic differences in the normal range of neutrophils and lymphocytes (96-98). For example, Azab and co-workers recently reported that, in more than 9,000 patients in the United States, there were ethnic differences in the NLR (97). Specifically, in the cohort as a whole the mean NLR was 2.15. In contrast, black Americans had a mean NLR of 1.76, Hispanic Americans had a mean NLR of 2.08 and white Americans had a mean NLR of 2.24 (97). Also, within ethnicities, patients who had diabetes, cardiovascular disease, a high BMI and were smokers had a significantly higher NLR (97). Although, similar data for the GPS/mGPS has not yet appeared in the literature it is likely that there would be a similar effect on the GPS/ mGPS. Therefore, given that the most common abnormal thresholds used for NLR are >5 and >3 it is likely that a combination of tumour and host genetic and environmental factors are responsible for such consistent East/West differences. These and the present results emphasise the importance of not only

staging the tumour but also the host systemic inflammatory response in patients with operable disease (7).

Recently, studies have directly compared the prognostic value of the two most common combined markers of the systemic inflammatory response, the NLR and the GPS/ mGPS. Guthrie and co-workers (2013) reported a comparison in both the preoperative and follow-up settings in patients with resectable colorectal cancer. In this study of 206 patients undergoing a surgical resection at a single institution it was reported that both preoperative mGPS (HR: 1.97, CI 1.16-3.34, $p<0.005$) and NLR (HR: 3.07, CI 1.23-7.63, $p<0.05$) were independently associated with cancer specific survival (147). However, in the postoperative follow-up only mGPS (HR: 4.81, CI 2.13-10.83, $p<0.001$) maintained its significance in terms of cancer specific survival (147). In contrast, Wang and co-workers (2012) reported that, in 177 patients with pancreatic cancer treated with surgery and palliative chemotherapy, although NLR and mGPS predicted overall survival, only NLR was independently associated with overall survival (HR: 2.54 CI 1.31-4.90, $p=0.006$) (148). Finally, Okuno and co-workers (2016) reported that, in 534 patients with perihilar cholangiocarcinoma, both the NLR and mGPS had prognostic value (149). However, on multivariate analysis, only the mGPS was independently associated with overall survival (HR: 1.58 CI 1.21-2.06, $p=0.001$) (149).

The present review and meta-analysis has a number of limitations. While it was the aim to only include the most recent paper where multiple publications from the same cohort where available, due to the practice of combining databases from different geographical locations under different lead institutions some double counting has occurred. In addition, funnel plot analysis, even after fixed effect analysis, showed that there was for all systemic inflammation based prognostic scores some asymmetry. This would suggest that there may be some reporting bias. The basis of this bias is not clear. Other than statistically significant results being more likely to be published other possible contributors may be that the studies included

in the analysis were English language only publication, had small study size, included multiple tumour types and included multiple thresholds. Nevertheless, the consistency of prognostic value over a variety of systemic inflammation based prognostic scores and across larger studies, single tumour types and single thresholds would indicate that although there was evidence of bias in the meta-analysis, such scores do indeed have prognostic value. Similarly, when only univariate analysis was available it was entered into the analysis. The majority of studies had HR derived from multivariate analysis (181 studies) and therefore harmonisation of HR results was not attempted. In the present meta-analysis, there was considerable heterogeneity in the HR of some of the markers of the systemic inflammatory response. However, this was less when a consistent threshold for the marker was used. There are other potential contributors to such heterogeneity including geographical location. Such sub-analysis was limited by the number of studies available for meta-analysis. The strength of this present review is its comprehensive nature.

In summary, the results of this review consolidate the prognostic value of combined markers of the systemic inflammatory response including GPS/mGPS NLR, PLR and LMR in patients with resectable cancers. This is particularly true for the GPS/mGPS and NLR and in lung and GI cancers. These should form part of the routine preoperative workup and follow-up for all such patients undergoing resection for cancer.

4.5 Figures and Legends

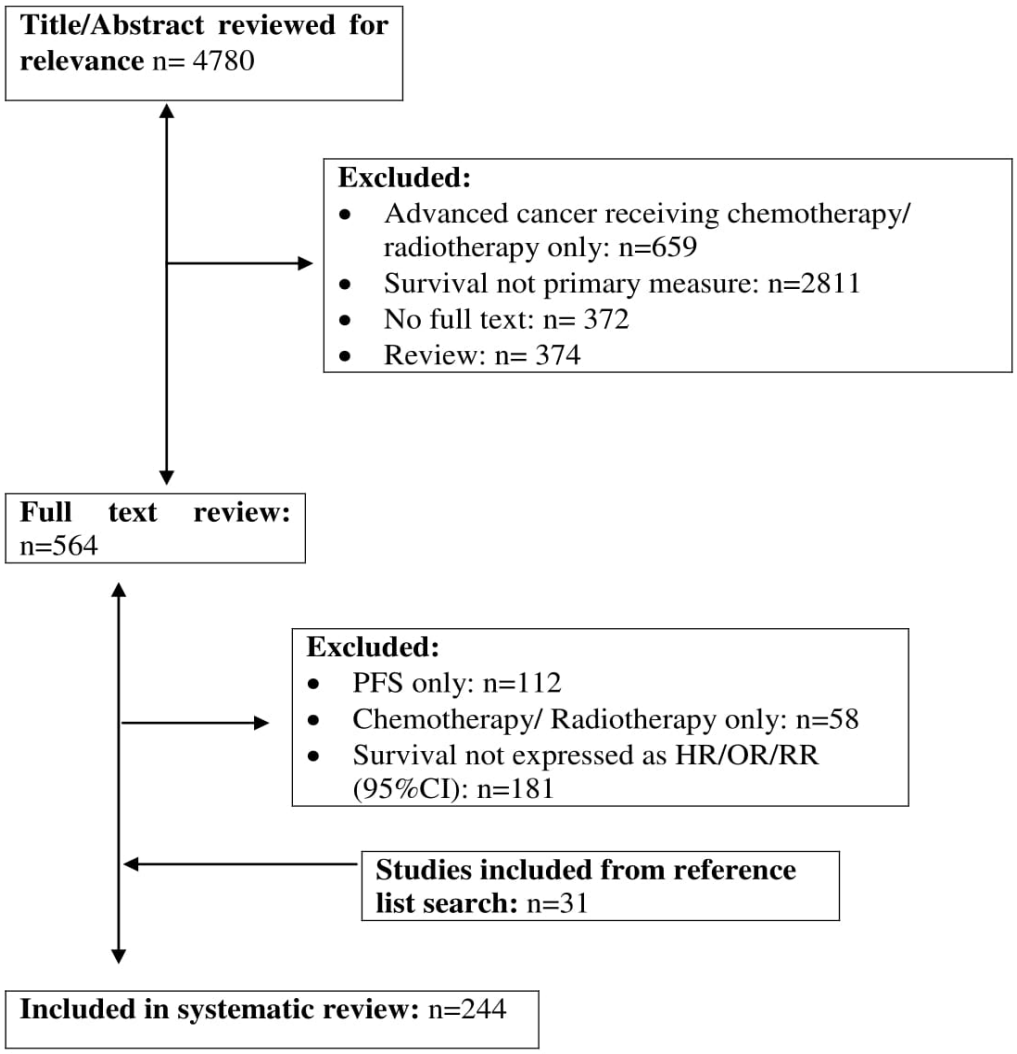


Figure 4.1: PRISMA flowchart demonstrating study selection

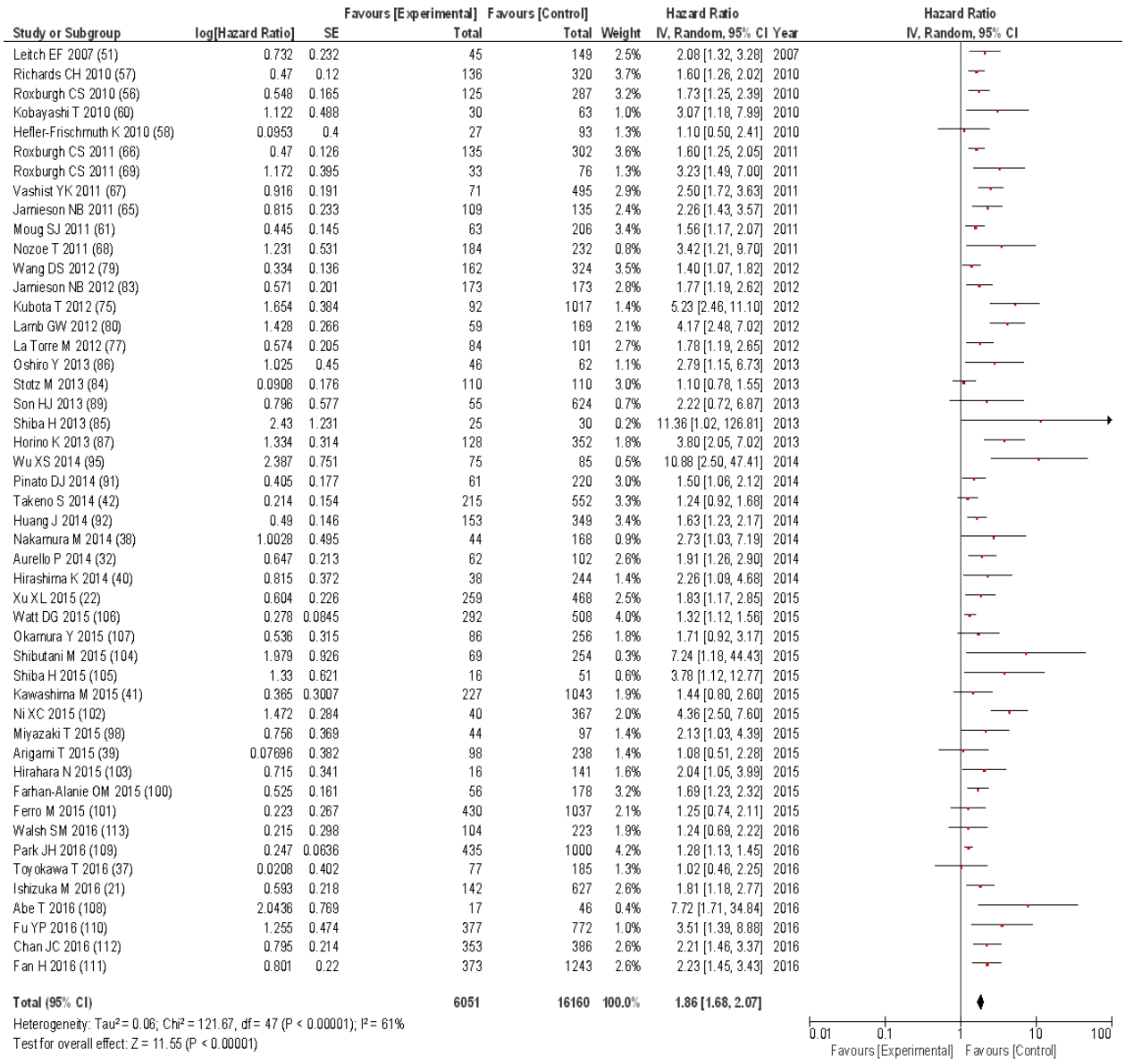


Figure 4.2: Forrest and Funnel Plot of Studies investigating the prognostic value of GPS/mGPS in terms of OS in an unselected cohort of patients with operable cancer

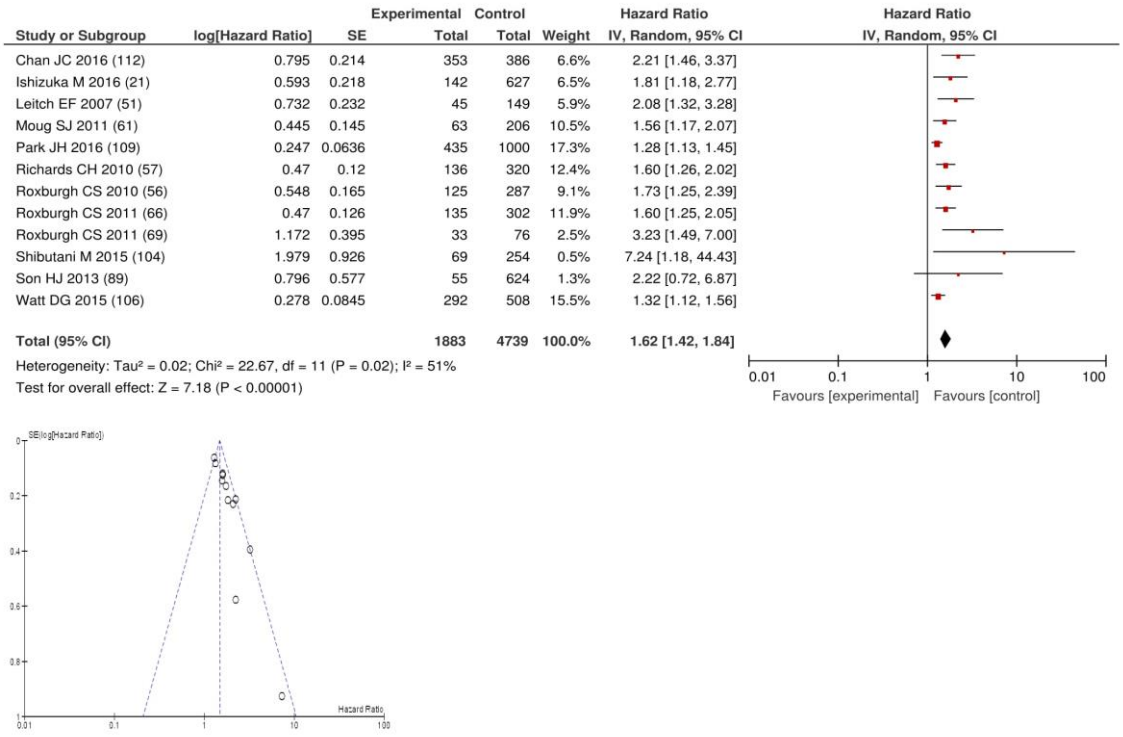


Figure 4.3: Forrest and Funnel Plot of Studies investigating the prognostic value of GPS/mGPS in terms of OS in patients with operable colorectal cancer

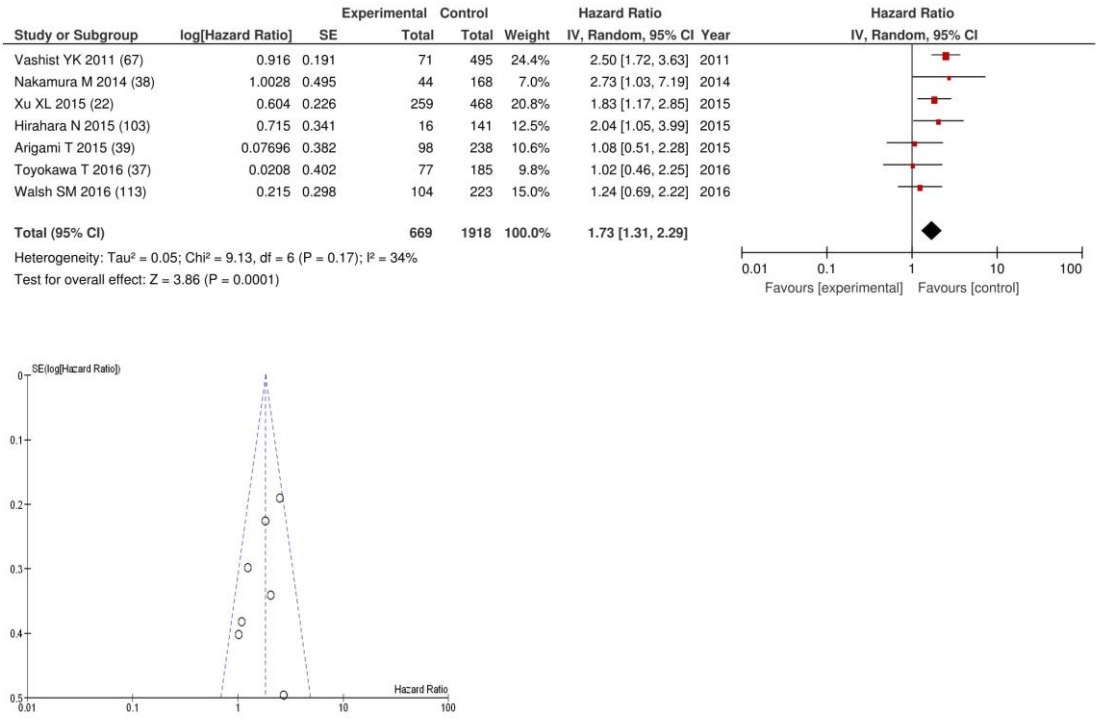


Figure 4.4: Forrest and Funnel Plot of Studies investigating the prognostic value of GPS/mGPS in terms of OS in patients with operable oesophageal cancer

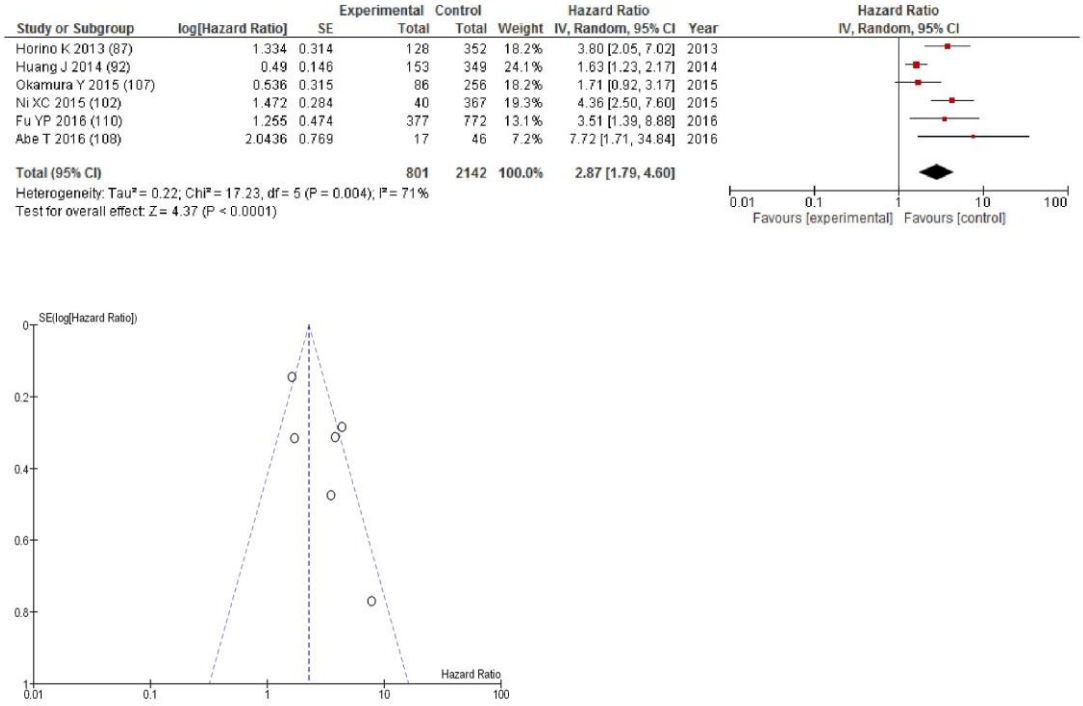


Figure 4.5: Forrest and Funnel Plot of Studies investigating the prognostic value of GPS/mGPS in terms of OS in patients with operable liver cancer

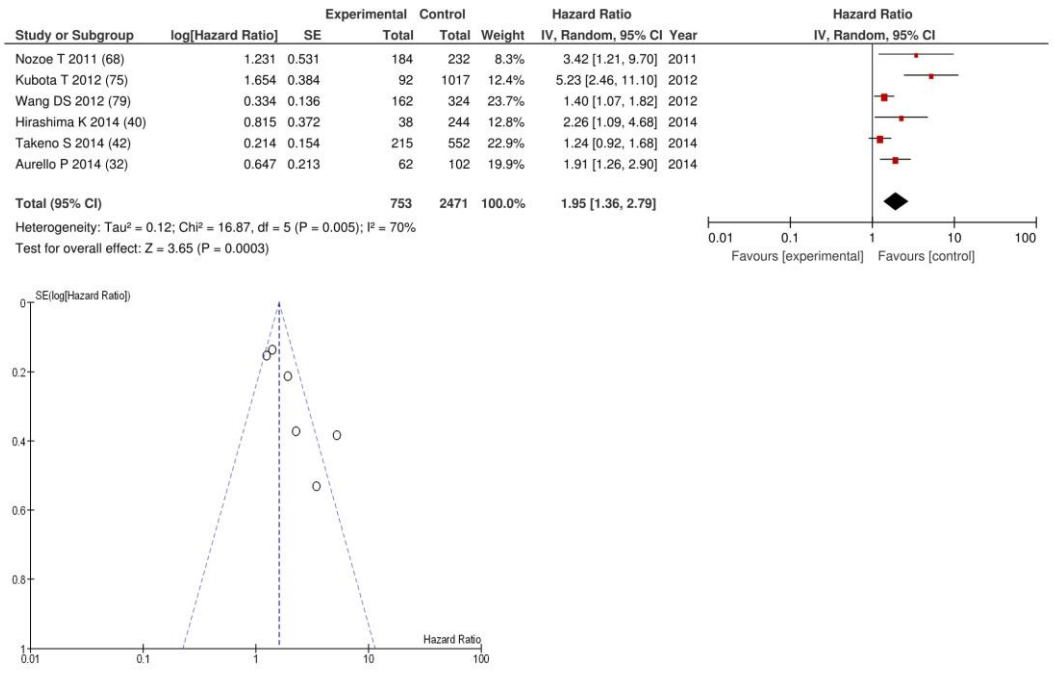


Figure 4.6: Forrest and Funnel Plot of Studies investigating the prognostic value of GPS/mGPS in terms of OS in patients with operable gastric cancer

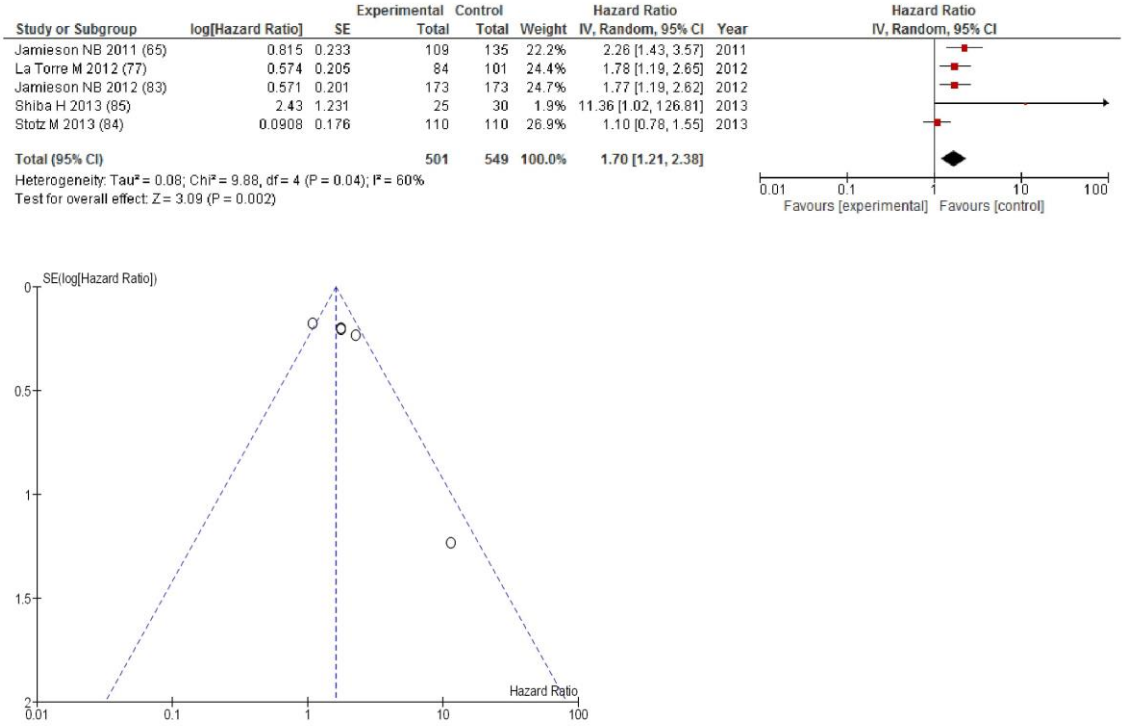


Figure 4.7: Forrest and Funnel Plot of Studies investigating the prognostic value of GPS/mGPS in terms of OS in patients with operable pancreatic cancer

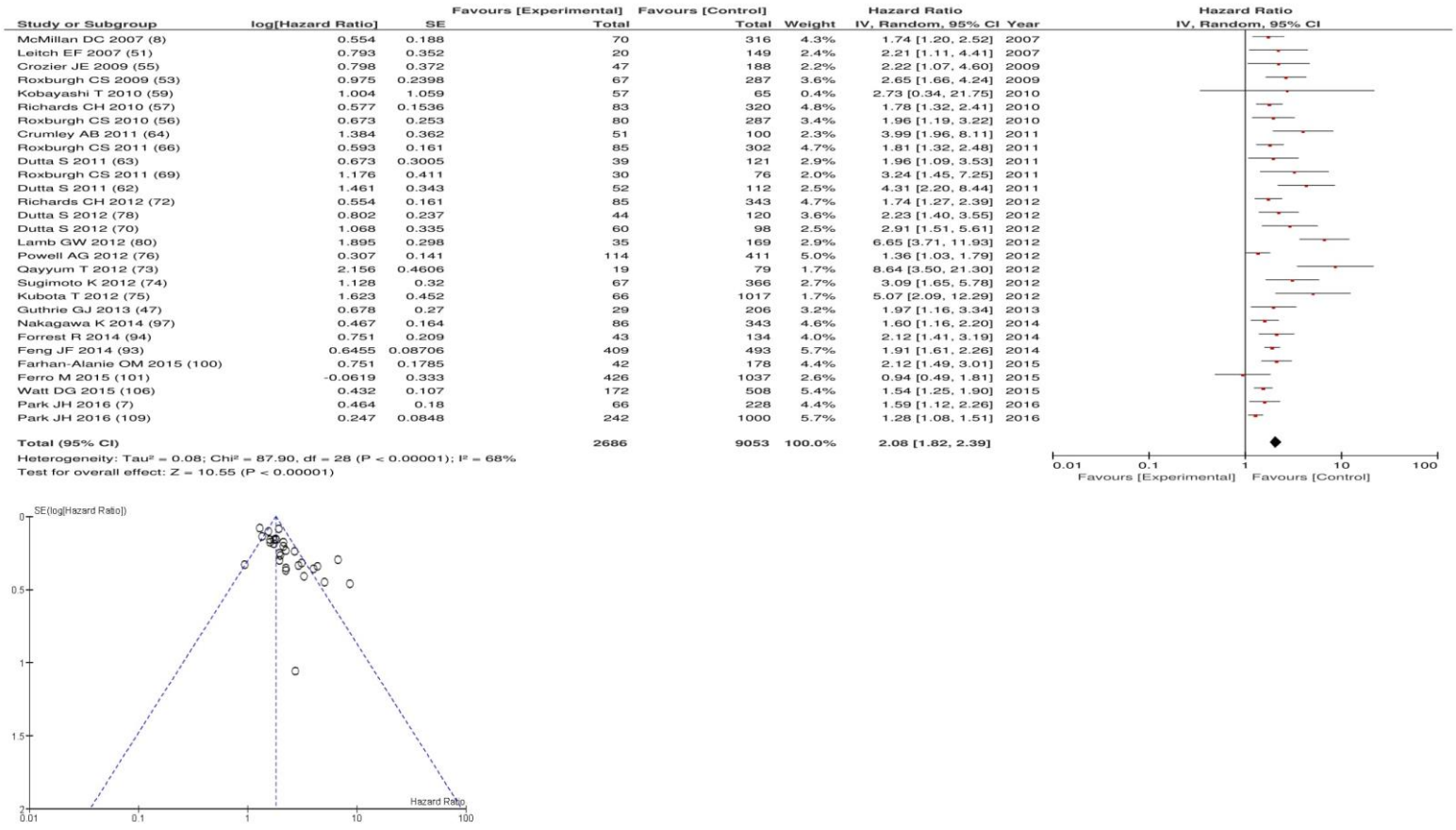


Figure 4.8: Forrest and Funnel Plot of Studies investigating the prognostic value of GPS/mGPS in terms of CSS in an unselected cohort of patients with operable cancer

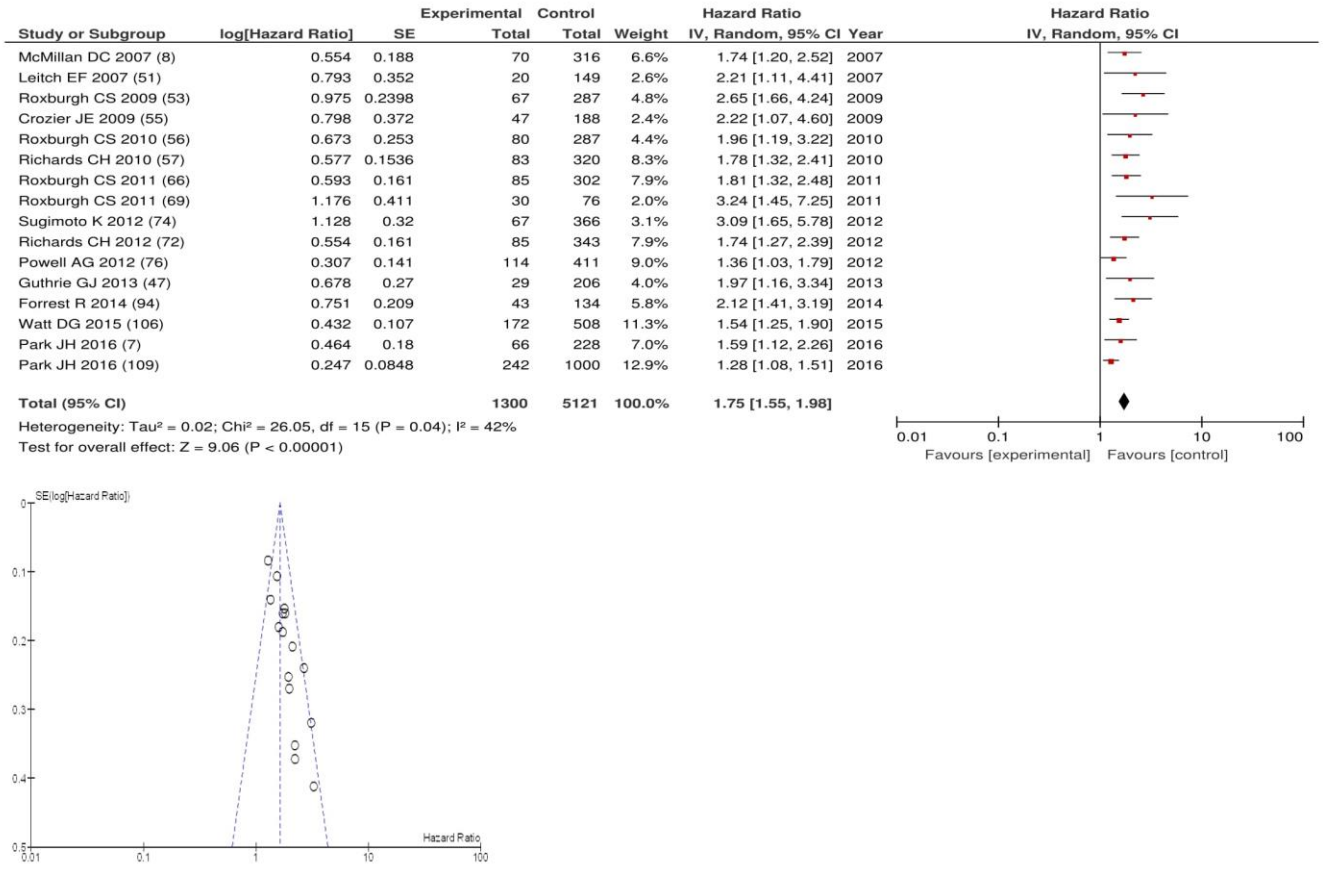
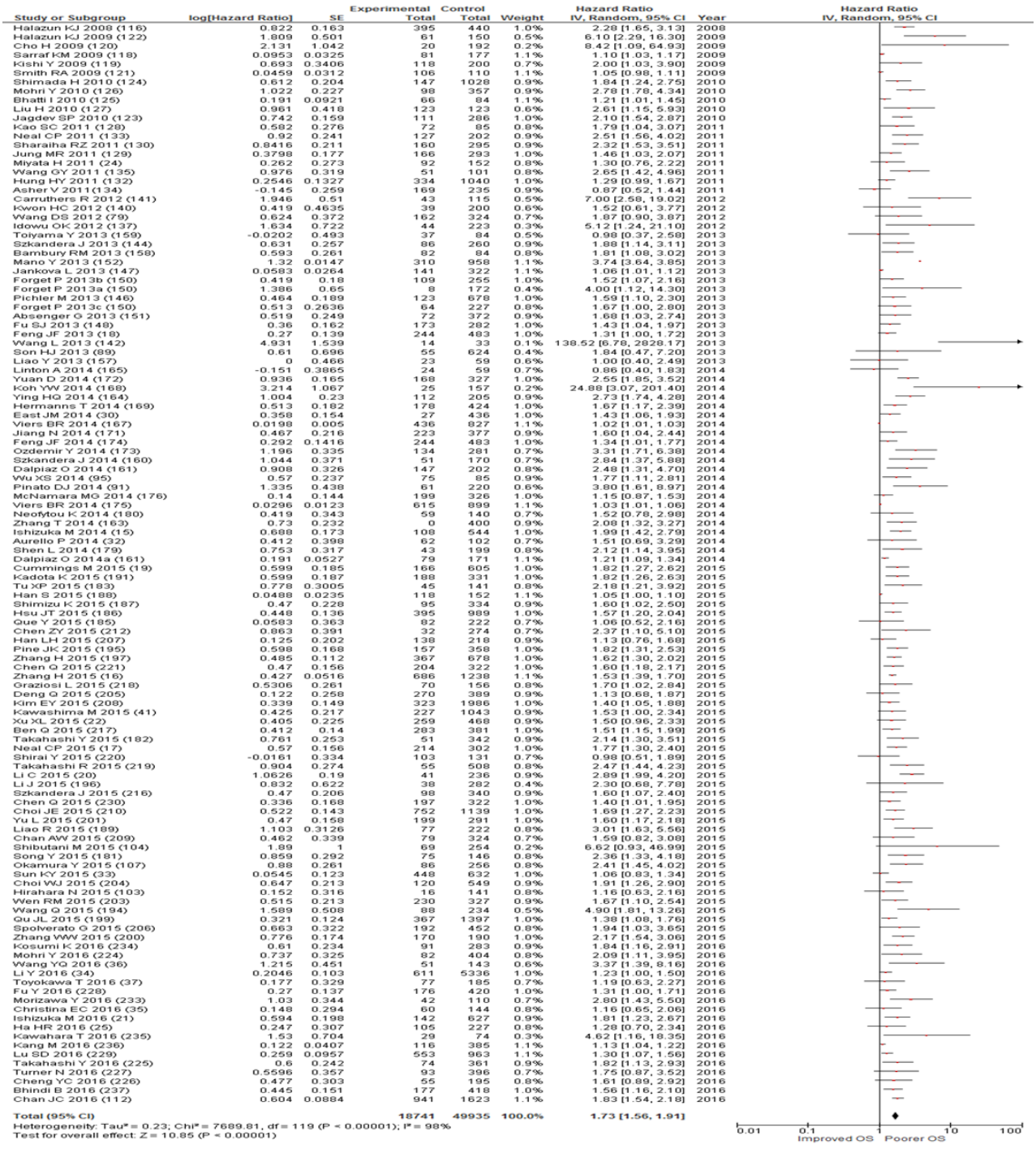


Figure 4.9: Forrest and Funnel Plot of Studies investigating the prognostic value of GPS/mGPS in terms of CSS in patients with operable colorectal cancer



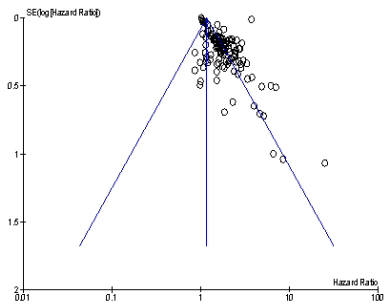
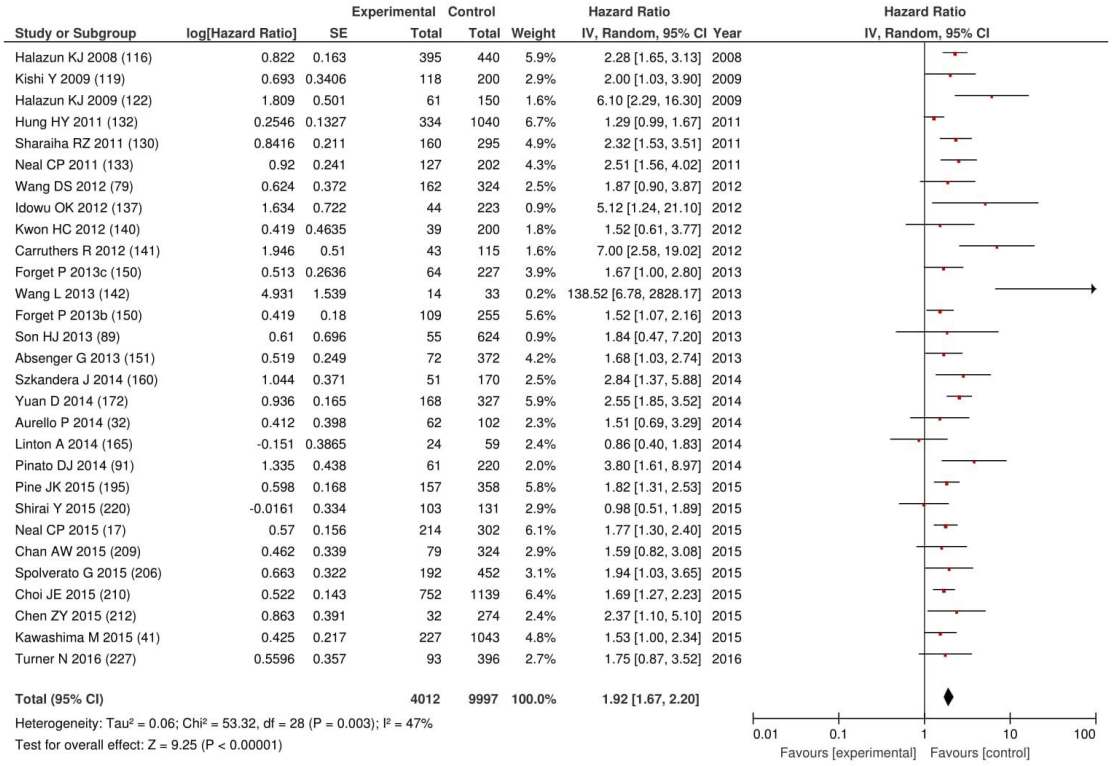


Figure 4.10: Forrest and Funnel Plot of Studies investigating the prognostic value of NLR in terms of OS in an unselected cohort of patients with operable cancer



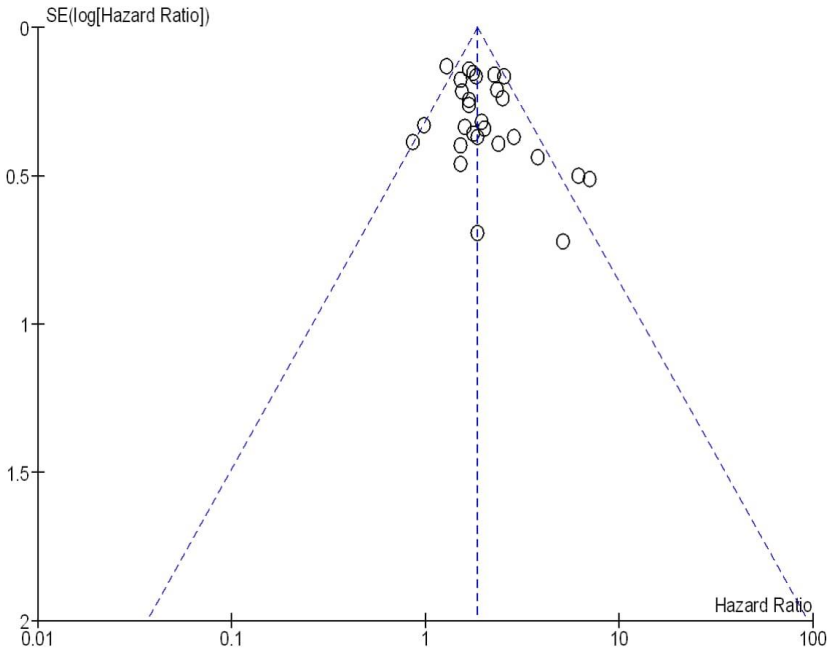


Figure 4.11: Forrest and Funnel Plot of Studies investigating the prognostic value of NLR≥5 in terms of OS in an unselected cohort of patients with operable cancer

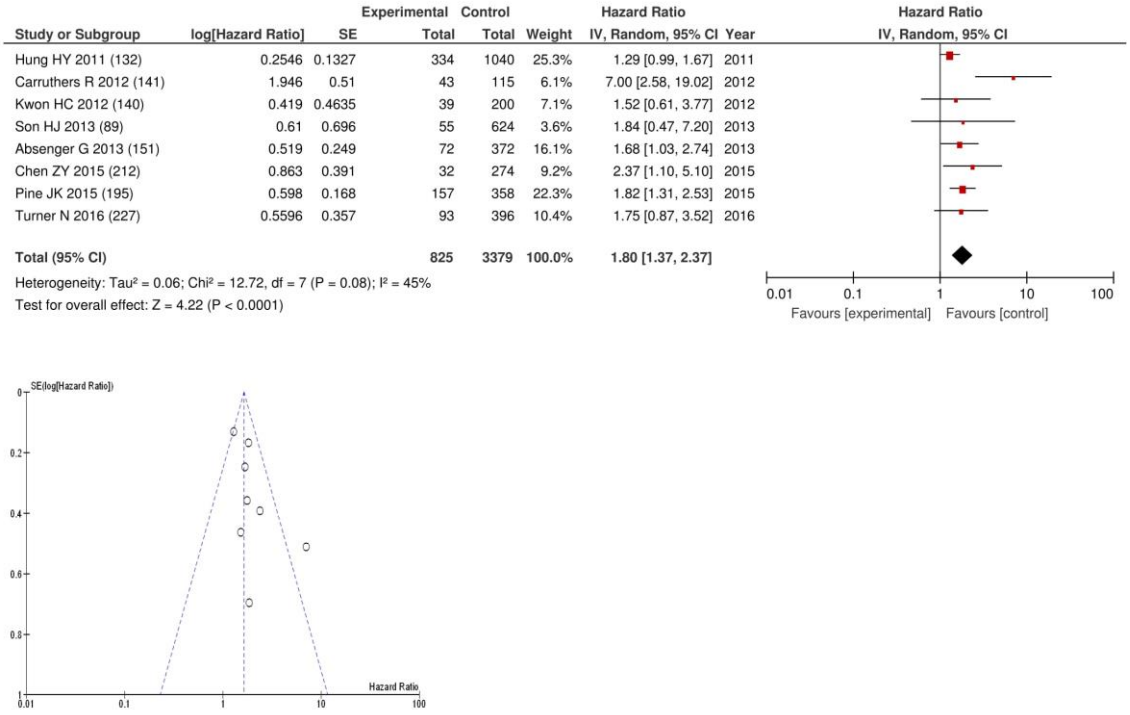


Figure 4.12: Forrest and Funnel Plot of Studies investigating the prognostic value of NLR≥5 in terms of OS in patients with operable colorectal cancer

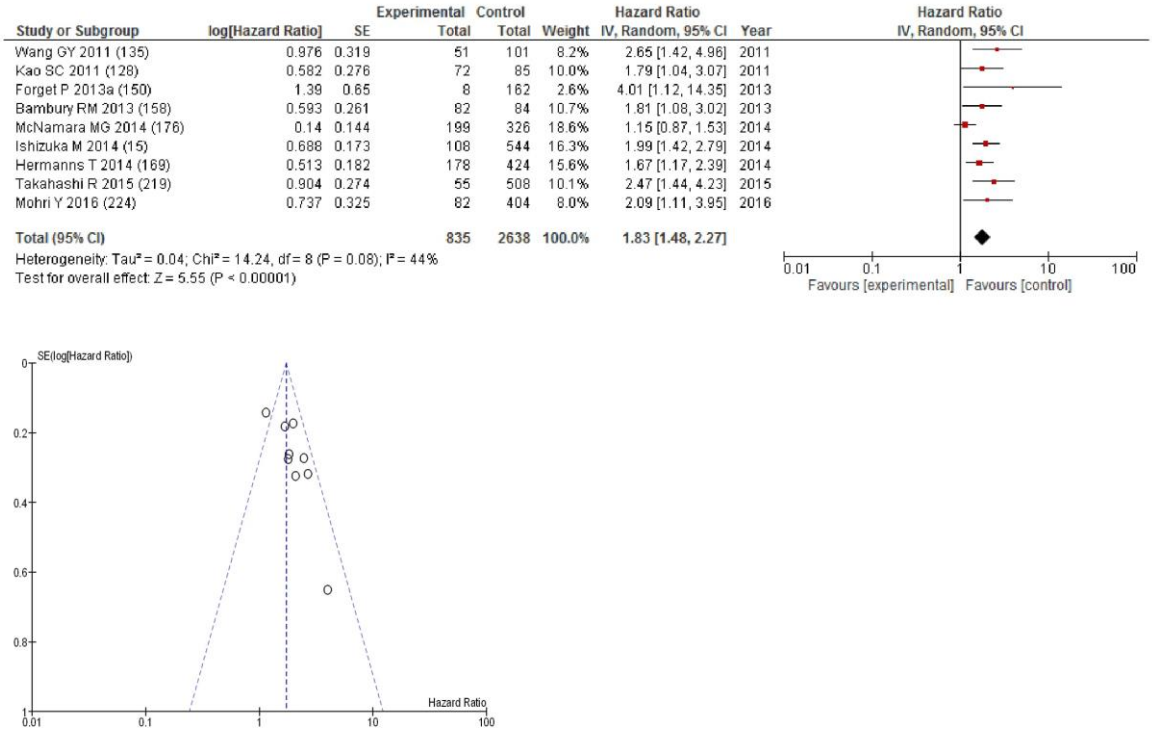


Figure 4.13: Forrest and Funnel Plot of Studies investigating the prognostic value of NLR≥3 in terms of OS in an unselected cohort of patients with operable cancer

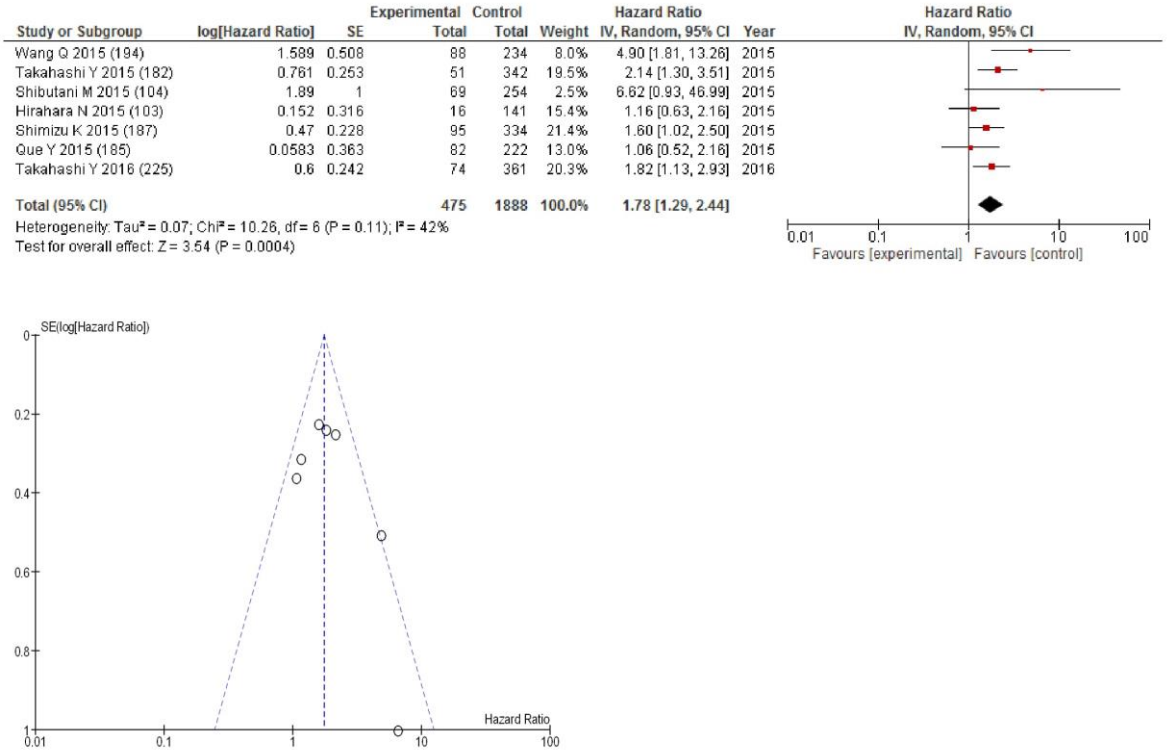


Figure 4.14: Forrest and Funnel Plot of Studies investigating the prognostic value of NLR≥2.5 in terms of OS in an unselected cohort of patients with operable cancer

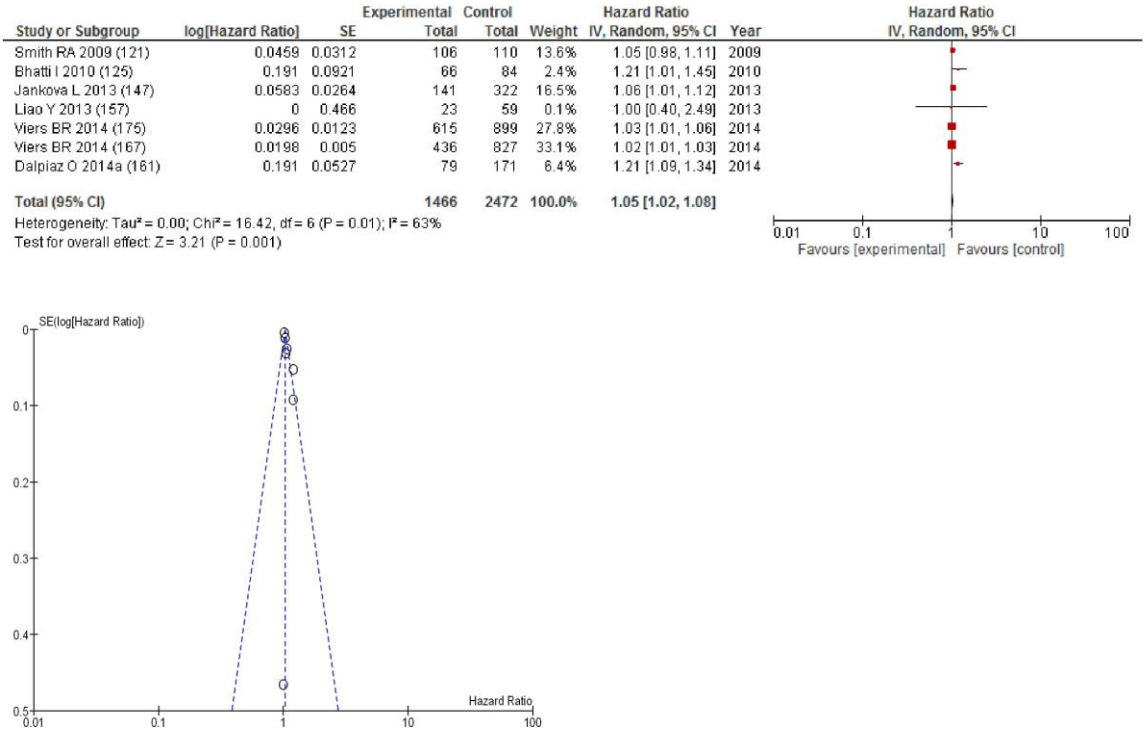


Figure 4.15: Forrest and Funnel Plot of Studies investigating the prognostic value of NLR as a continuous variable in terms of OS in an unselected cohort of patients with operable cancer

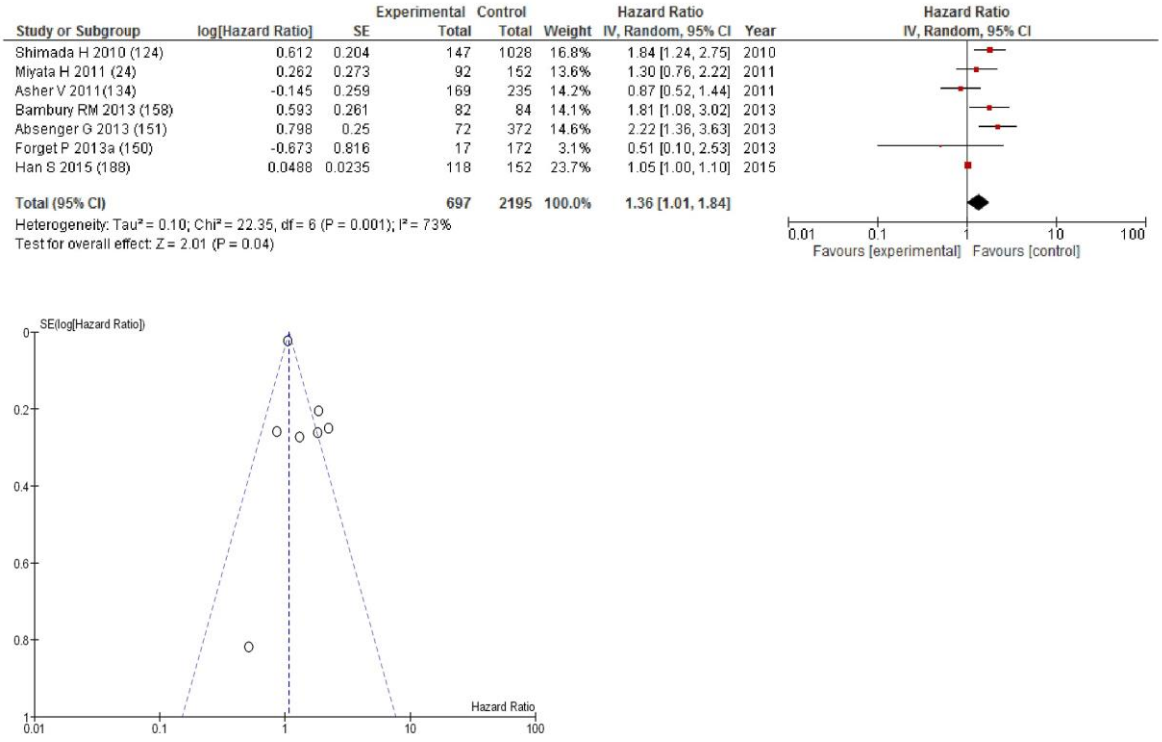


Figure 4.16: Forrest and Funnel Plot of Studies investigating the prognostic value of NLR≥4 in terms of OS in an unselected cohort of patients with operable cancer

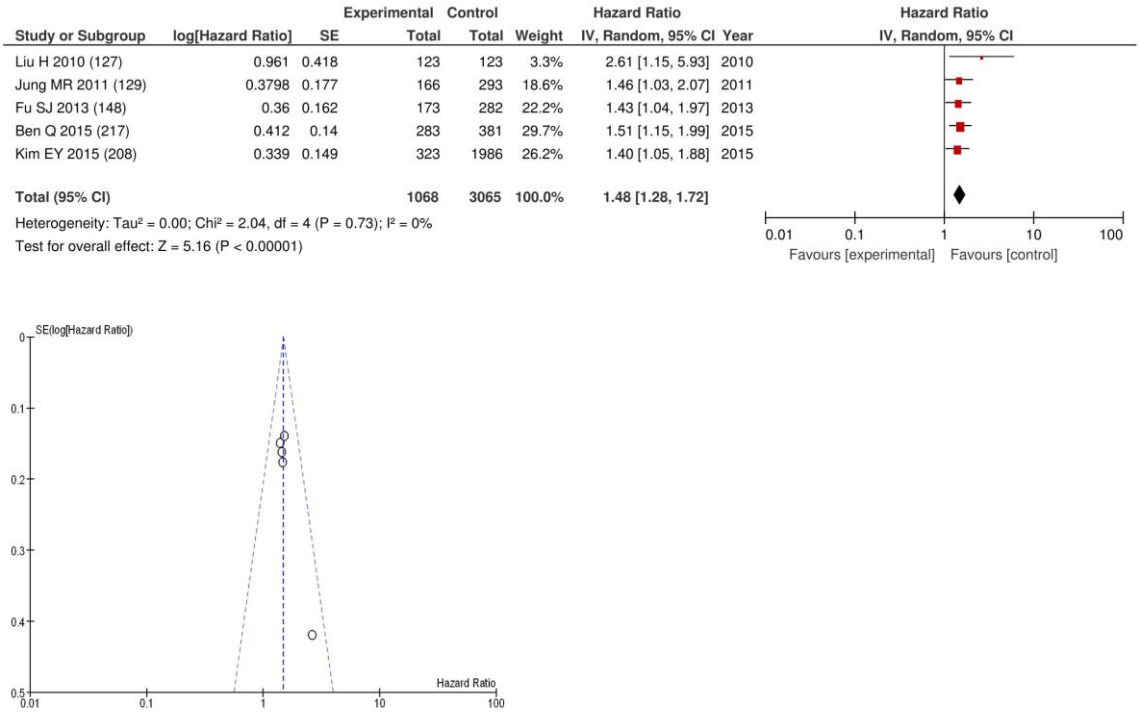
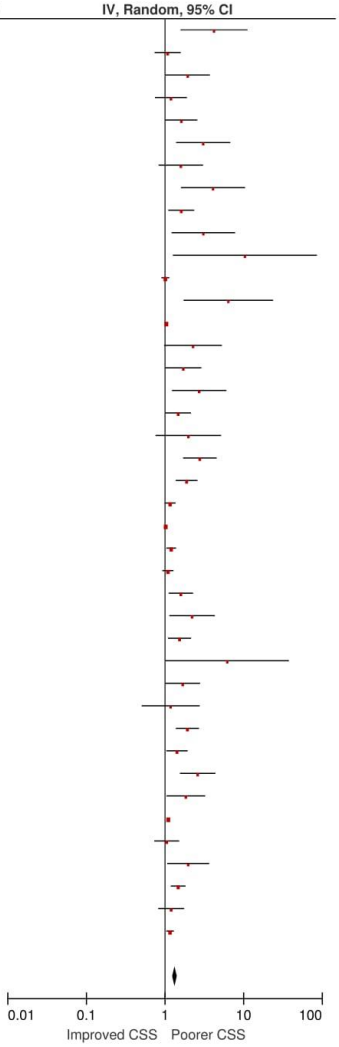


Figure 4.17: Forrest and Funnel Plot of Studies investigating the prognostic value of NLR≥2 in terms of OS in an unselected cohort of patients with operable cancer

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Jagdev SP 2010 (123)	1.435	0.492	63	286	0.4%	4.20 [1.60, 11.02]	2010
Dutta S 2011 (62)	0.07696	0.187	52	112	2.1%	1.08 [0.75, 1.56]	2011
Gondo T 2012 (139)	0.666	0.322	54	189	0.9%	1.95 [1.04, 3.66]	2012
Dutta S 2012 (78)	0.174	0.2297	44	120	1.6%	1.19 [0.76, 1.87]	2012
Stotz M 2013 (84)	0.477	0.231	110	110	1.5%	1.61 [1.02, 2.53]	2013
Azuma T 2013 (153)	1.118	0.397	54	137	0.6%	3.06 [1.40, 6.66]	2013
Pichler M 2013 (146)	0.464	0.324	59	678	0.9%	1.59 [0.84, 3.00]	2013
Noh H 2013 (156)	1.406	0.471	25	442	0.4%	4.08 [1.62, 10.27]	2013
Shibutani M 2013 (149)	0.476	0.186	136	674	2.1%	1.61 [1.12, 2.32]	2013
Guthrie GJ 2013 (47)	1.122	0.4656	29	206	0.4%	3.07 [1.23, 7.65]	2013
Perisanidis C 2013 (155)	2.339	1.068	17	97	0.1%	10.37 [1.28, 84.12]	2013
Jankova L 2013 (147)	0.00995	0.0502	86	322	6.7%	1.01 [0.92, 1.11]	2013
Luo HL 2014 (162)	1.853	0.661	24	234	0.2%	6.38 [1.75, 23.30]	2014
Viers BR 2014 (175)	0.0392	0.0171	345	899	7.8%	1.04 [1.01, 1.08]	2014
Forrest R 2014 (94)	0.82	0.423	43	134	0.5%	2.27 [0.99, 5.20]	2014
Kubo T 2014 (166)	0.536	0.262	74	524	1.2%	1.71 [1.02, 2.86]	2014
Dalpiaz O 2014 (161)	0.9999	0.398	58	202	0.6%	2.72 [1.25, 5.93]	2014
Tanaka N 2014 (170)	0.385	0.183	129	665	2.2%	1.47 [1.03, 2.10]	2014
Szkandera J 2014 (160)	0.683	0.481	22	170	0.4%	1.98 [0.77, 5.08]	2014
Ying HQ 2014 (164)	1.019	0.243	100	205	1.4%	2.77 [1.72, 4.46]	2014
Hermanns T 2014 (169)	0.631	0.154	110	424	2.8%	1.88 [1.39, 2.54]	2014
Dalpiaz O 2014a (161)	0.148	0.074	54	171	5.6%	1.16 [1.00, 1.34]	2014
Viers BR 2014 (167)	0.0198	0.00747	233	827	8.0%	1.02 [1.01, 1.04]	2014
Neofytou K 2015 (192)	0.182	0.0636	60	140	6.1%	1.20 [1.06, 1.36]	2015
Lee SK 2015 (211)	0.0862	0.0747	300	3116	5.6%	1.09 [0.94, 1.26]	2015
Duan H 2015 (202)	0.464	0.174	192	371	2.4%	1.59 [1.13, 2.24]	2015
Bagante F 2015 (193)	0.793	0.331	50	84	0.8%	2.21 [1.16, 4.23]	2015
Deng Q 2015 (205)	0.425	0.164	235	389	2.6%	1.53 [1.11, 2.11]	2015
Shin JS 2015 (184)	1.823	0.913	5	269	0.1%	6.19 [1.03, 37.06]	2015
Cummings M 2015 (19)	0.519	0.251	96	605	1.3%	1.68 [1.03, 2.75]	2015
Kim M 2015 (215)	0.165	0.426	73	277	0.5%	1.18 [0.51, 2.72]	2015
Neal CP 2015 (17)	0.656	0.164	204	302	2.6%	1.93 [1.40, 2.66]	2015
Fu Y 2016 (228)	0.351	0.15	171	420	2.9%	1.42 [1.06, 1.91]	2016
Morizawa Y 2016 (233)	0.956	0.257	32	110	1.3%	2.60 [1.57, 4.30]	2016
Kosumi K 2016 (234)	0.61	0.28	65	283	1.1%	1.84 [1.06, 3.19]	2016
Wang SC 2016 (231)	0.0953	0.0187	588	1498	7.8%	1.10 [1.06, 1.14]	2016
Chen PC 2016 (214)	0.0488	0.178	221	323	2.3%	1.05 [0.74, 1.49]	2016
Mohri Y 2016 (224)	0.678	0.306	65	404	1.0%	1.97 [1.08, 3.59]	2016
Bhindi B 2016 (237)	0.385	0.103	107	418	4.4%	1.47 [1.20, 1.80]	2016
Xie X 2016 (223)	0.179	0.185	147	317	2.2%	1.20 [0.83, 1.72]	2016
Kang M 2016 (236)	0.148	0.0481	85	385	6.8%	1.16 [1.06, 1.27]	2016
Total (95% CI)			**4617**	**17539**	**100.0%**	**1.32 [1.24, 1.41]**	

Heterogeneity: Tau² = 0.01; Chi² = 208.77, df = 40 (P < 0.00001); I² = 81%
Test for overall effect: Z = 8.83 (P < 0.00001)



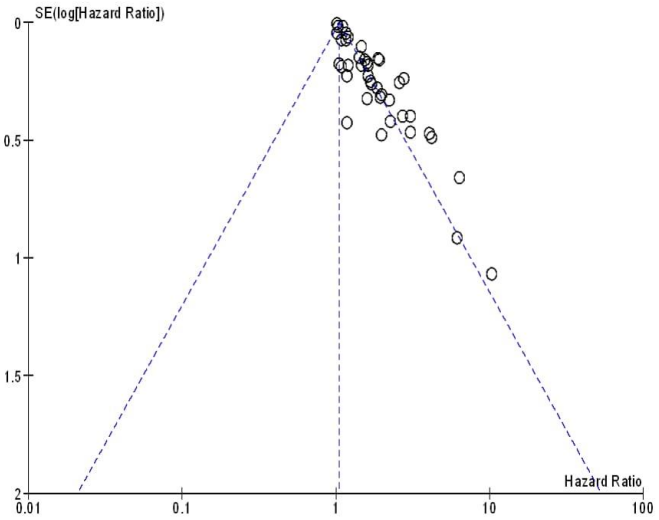


Figure 4.18: Forrest and Funnel Plot of Studies investigating the prognostic value of NLR in terms of CSS in an unselected cohort of patients with operable cancer

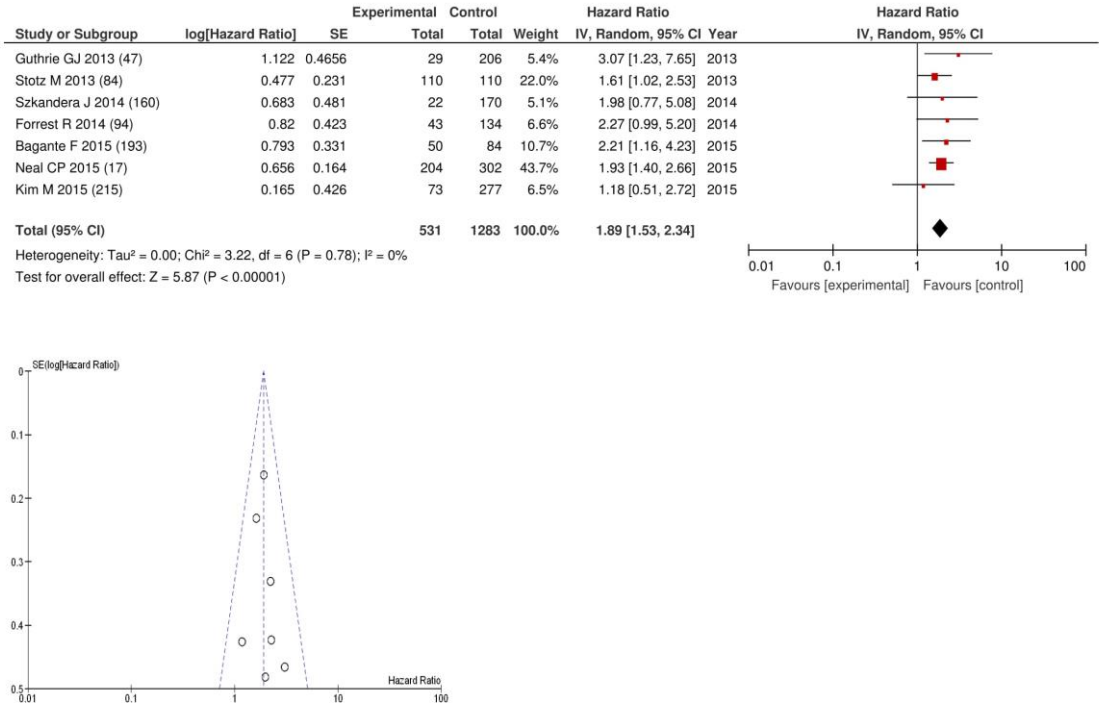


Figure 4.19: Forrest and Funnel Plot of Studies investigating the prognostic value of NLR≥5 in terms of CSS in an unselected cohort of patients with operable cancer

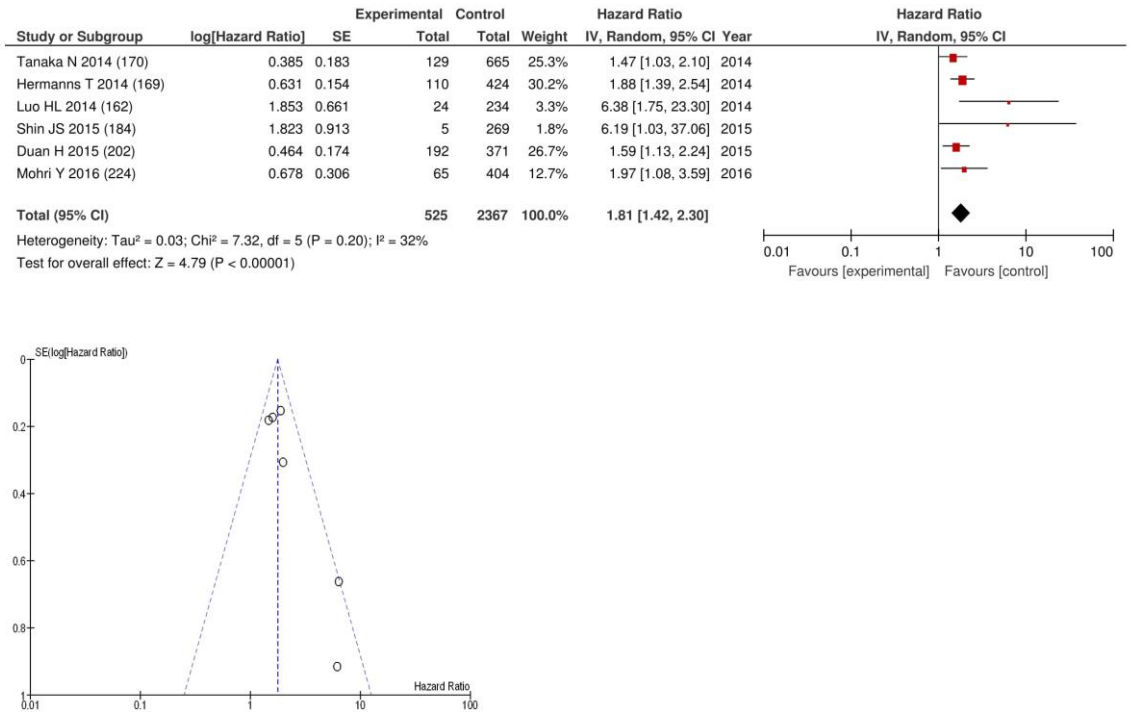


Figure 4.20: Forrest and Funnel Plot of Studies investigating the prognostic value of NLR≥3 in terms of CSS in an unselected cohort of patients with operable cancer

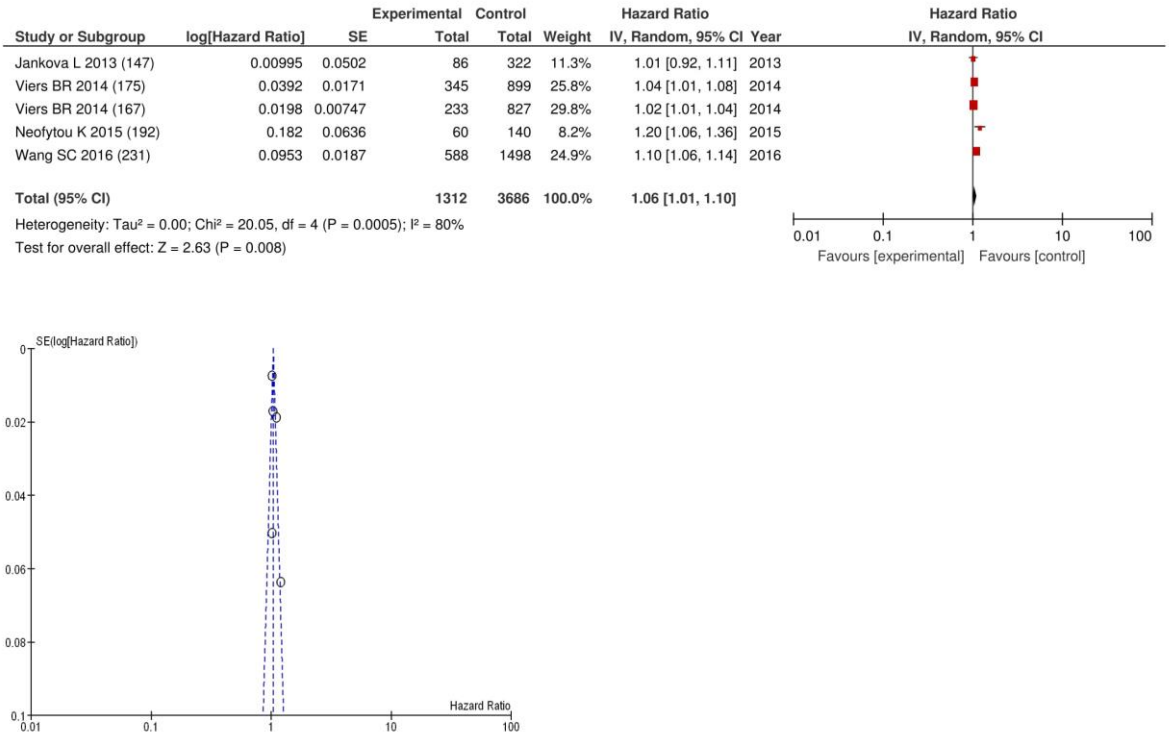


Figure 4.21: Forrest and Funnel Plot of Studies investigating the prognostic value of NLR as a continuous variable in terms of CSS in an unselected cohort of patients with operable cancer

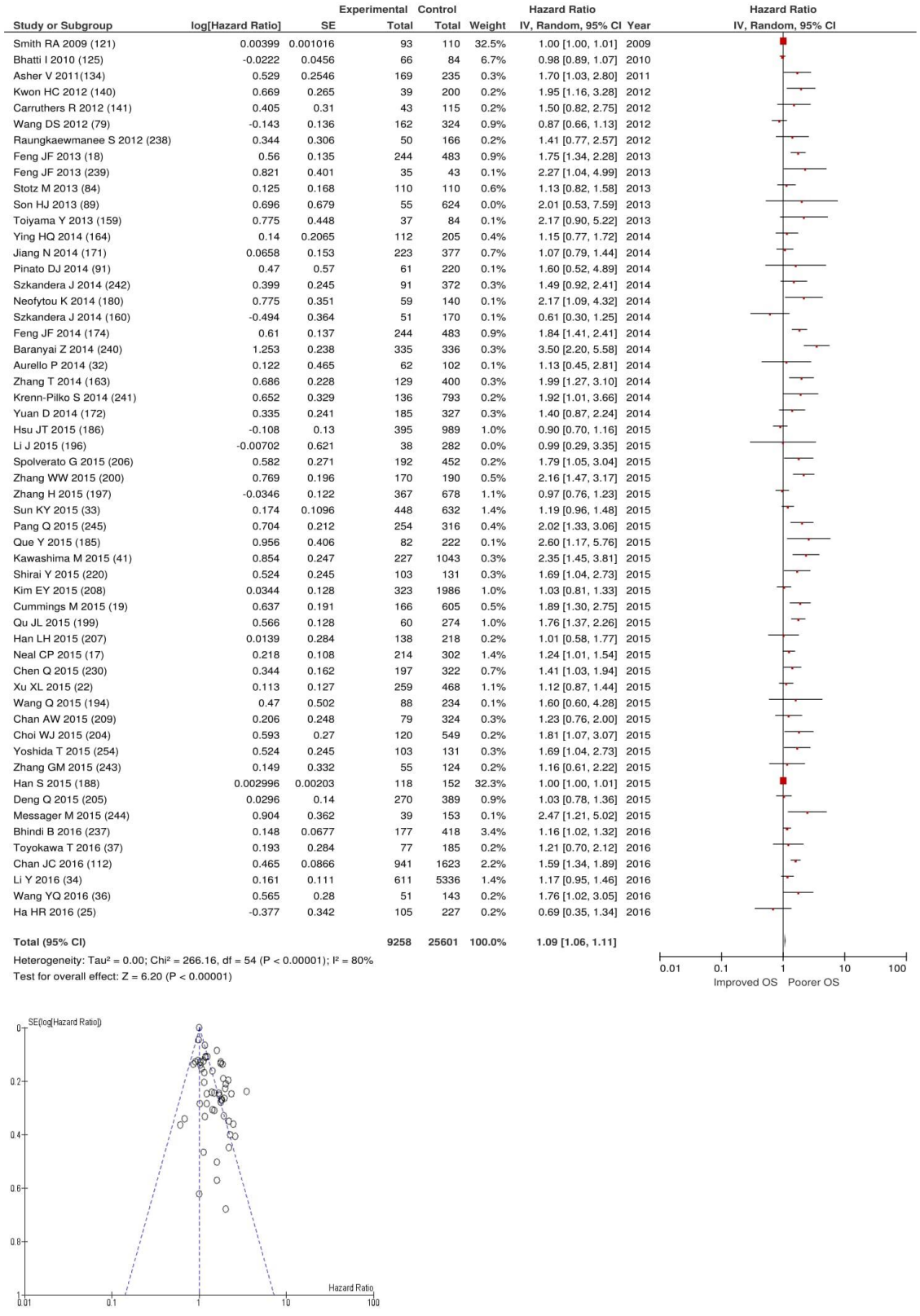


Figure 4.22: Forrest and Funnel Plot of Studies investigating the prognostic value of PLR in terms of OS in an unselected cohort of patients with operable cancer

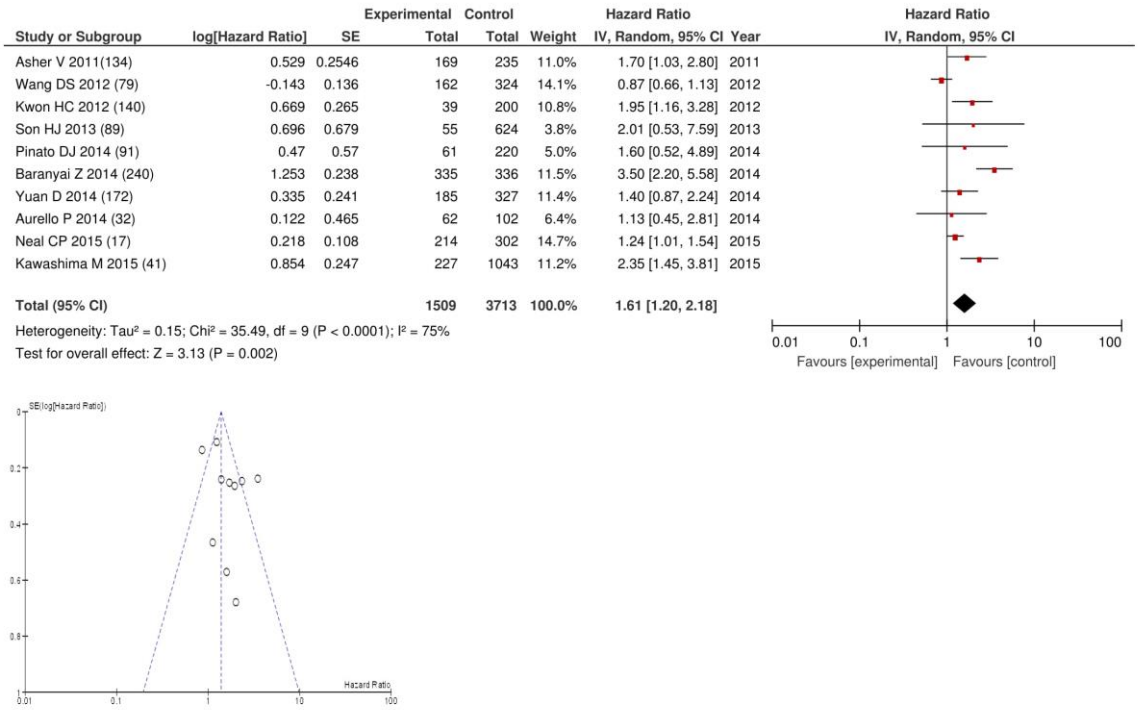


Figure 4.23: Forrest and Funnel Plot of Studies investigating the prognostic value of PLR≥300 in terms of OS in an unselected cohort of patients with operable cancer

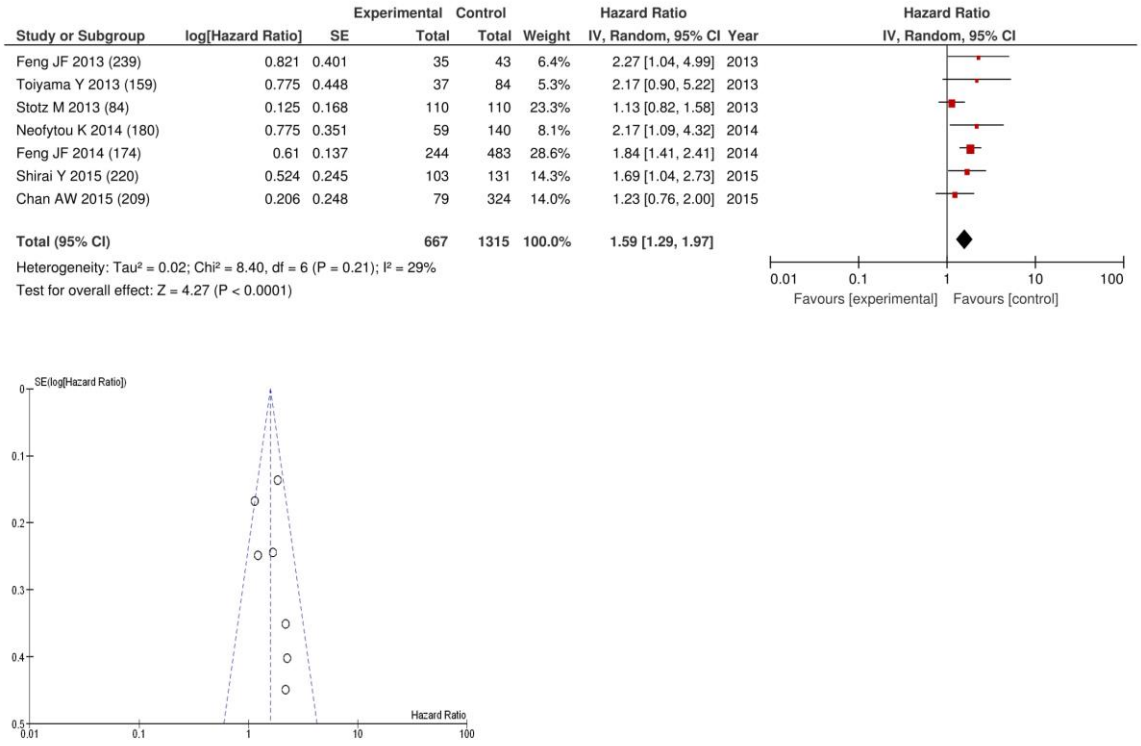


Figure 4.24: Forrest and Funnel Plot of Studies investigating the prognostic value of PLR≥150 in terms of OS in an unselected cohort of patients with operable cancer

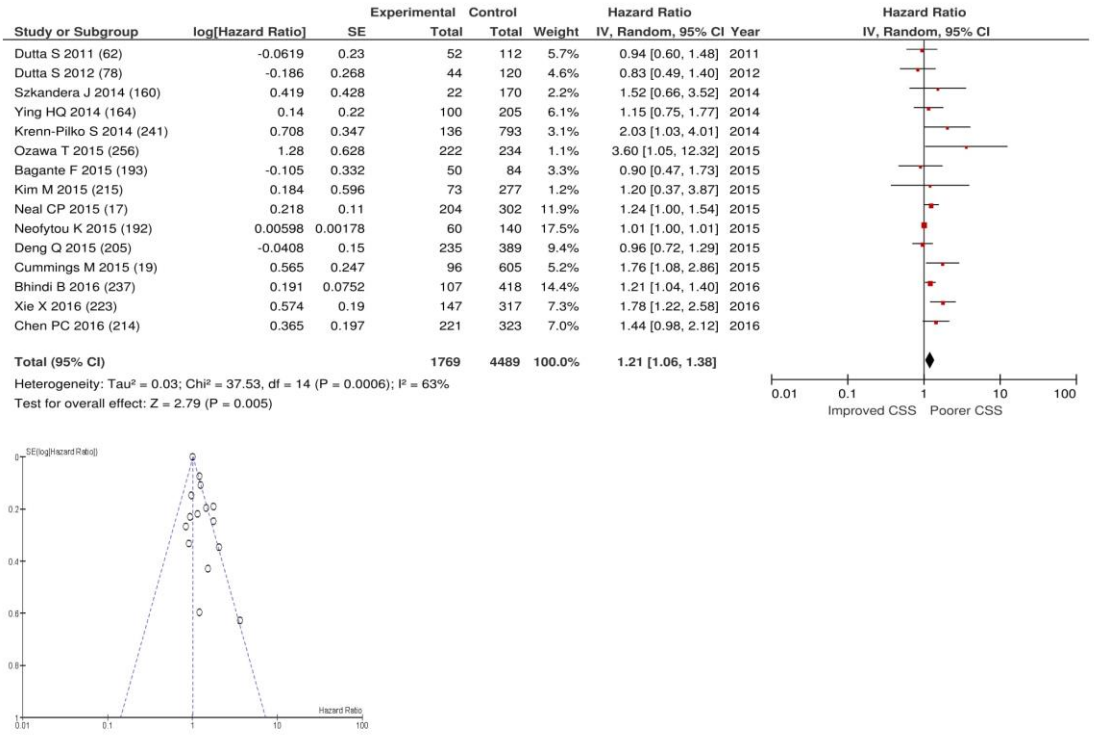


Figure 4.25: Forrest and Funnel Plot of Studies investigating the prognostic value of PLR in terms of CSS in an unselected cohort of patients with operable cancer

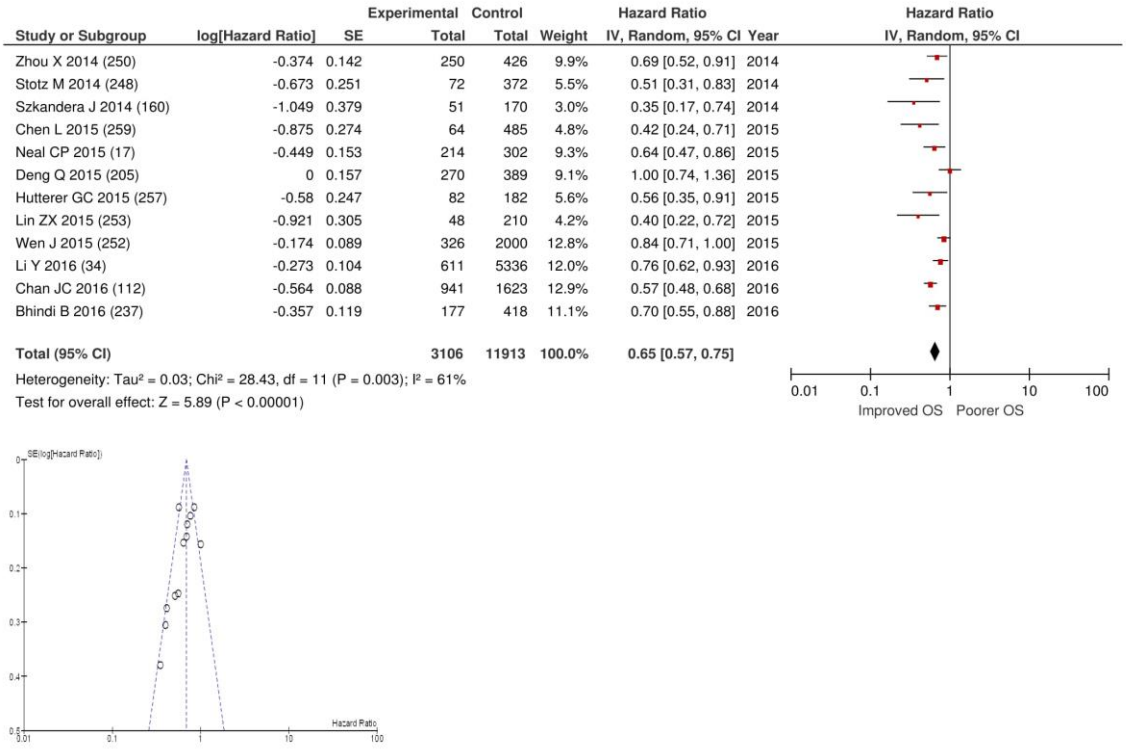


Figure 4.26: Forrest and Funnel Plot of Studies investigating the prognostic value of LMR in terms of OS in an unselected cohort of patients with operable cancer

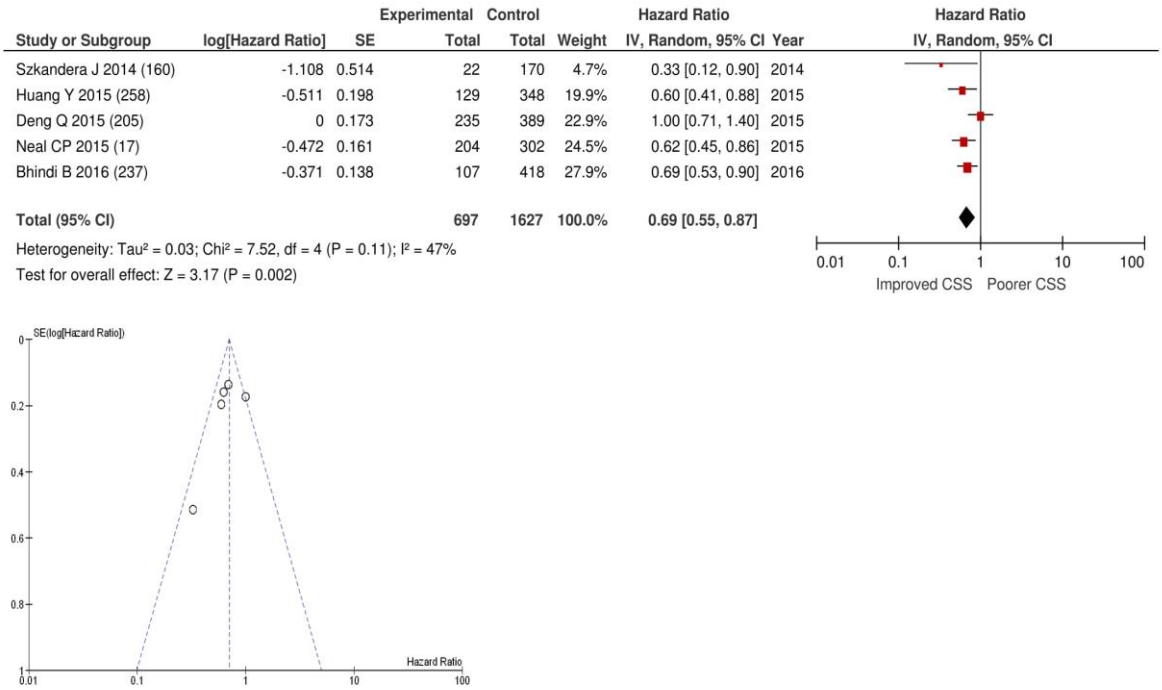


Figure 4.27: Forrest and Funnel Plot of Studies investigating the prognostic value of LMR in terms of CSS in an unselected cohort of patients with operable cancer

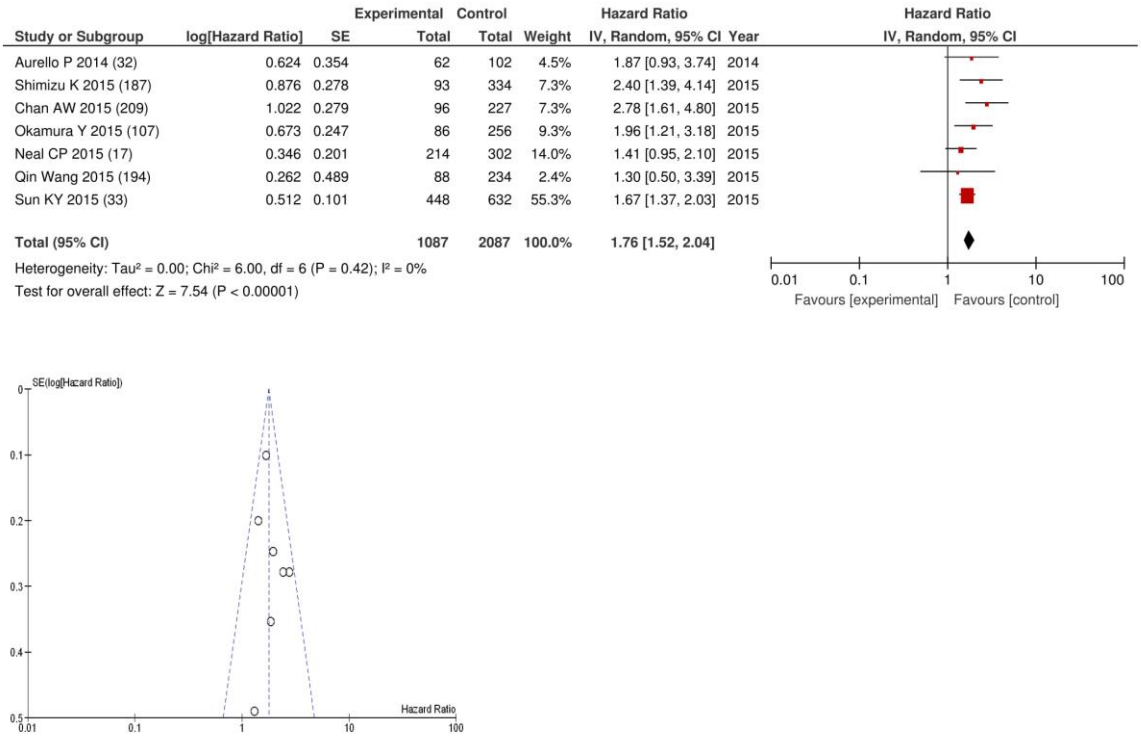


Figure 4.28: Forrest and Funnel Plot of Studies investigating the prognostic value of PNI in terms of OS in an unselected cohort of patients with operable cancer

5. THE PROGNOSTIC VALUE OF THE SYSTEMIC INFLAMMATORY RESPONSE IN RANDOMISED CLINICAL TRIALS IN CANCER: A SYSTEMATIC REVIEW

5.1 Introduction

As mentioned above in Chapter 3 and 4 the prognostic value of the systemic inflammatory response in cancer has been well established in observational studies. Over the course of the last 30 years multiple markers of the systemic inflammatory response such as CRP, albumin, neutrophil count, lymphocyte count and that of other white cells have been reported to have prognostic value in patients with cancer, at all stages of disease (85, 87). In the last 15 years there has been a movement towards the use of combined prognostic scores such as the GPS/mGPS (CRP and albumin) and ratios such as the NLR (neutrophils and lymphocytes) to standardise and maximise prognostic value (37, 38).

Despite the proven utility of these prognostic tools there has been an ongoing reluctance by the oncology community to incorporate these into routine clinical trial design. In 2012, MacDonald commented, "The seminal observation by McMillan and colleagues that the presence of a dysregulated state as evidenced by a high CRP connotes a dire prognosis has been generally ignored to date and not used to stratify patients in oncology clinical trials. Particularly in the more aggressive tumour types (e.g. pancreas and lung), the future of patients with elevated mGPS scores is so grim that they should be given precachexia status and offered multimodal therapy which may delay the onset of cachexia and/or death (150)." More recently, Laird and co-workers in large prospective cohorts of patients with advanced cancer have added weight to this assertion (17, 25).

Based on work to date and the sound rationale for the use of prognostic tools in oncology trials, the aim of this systematic review was to examine and rationalise the evidence for the

role of systemic inflammation based prognostic scores in the setting of randomised control trials.

5.2 Patients and Methods

The present systematic review and meta-analysis of published literature was undertaken as outlined in Chapter 2. Inclusion criteria consisted of randomised controlled clinical trials carried out in adult patients (aged 18-99) with curable and incurable cancer treated with any systemic anti-cancer therapy using validated combined scores of the systemic inflammatory response in both prospective and retrospective analysis with a primary outcome measure of survival. The primary aim was to assess the prognostic value of the validated combined scores of the systemic inflammatory response (NLR, PLR, LMR, GPS and mGPS) in the setting of randomised controlled clinical trials. This was carried out by a wide-ranging literature search to identify trials carried out from January 1947 to 31st January 2018. The medical subject heading (MeSH) terms used were Cancer, Randomised Control Trial, GPS, Glasgow Prognostic Score, mGPS, modified Glasgow Prognostic Score, NLR, Neutrophil Lymphocyte Ratio, LMR, Leucocyte Monocyte Ratio, PLR and Platelet Lymphocyte Ratio.

Only articles that reported survival were included. Results were reported in terms of (1) cancer type and (2) combined markers of the systemic inflammatory response used. No meta-analysis was carried out.

5.3 Results

The study selection process is summarised in Figure 5.1. Initial search strategy identified 382 papers and abstracts whose titles and abstracts were reviewed. Trials were excluded as they were not clinical trials (n=173) and as survival was not their primary measure (n=72). This led to a review of the full text of 137 articles. A further 106 articles were excluded as they were not in English (n=51), were animal studies (n=32), were not carried out in patients with cancer (n=20) and were carried out in duplicate datasets (n=3). The remaining 31 articles, had their bibliographies reviewed in a systematic manner and this identified a further 5 articles to be included in the final analysis leading to final figure of 36 reports containing data on 40,354 patients considered in the present systematic review (Table 5.1 and Table 5.2).

There were 28 trials containing data on 36,549 patients presented in full paper form and 8 trials containing data on 3,805 patients presented in abstract form. Most trials were published within the last three years. Seven trials containing data on 6,044 patients were published in 2015. Seven trials containing data on 3,913 patients were published in 2016. Twelve trials containing data on 27,228 patients were published in 2017. In all 36 trials the predominant treatments being investigated was chemotherapy and radiotherapy. The majority of trials were in advanced inoperable cancer and colorectal cancer was most common cancer type with 10 articles containing data on 27,438 patients.

The prognostic utility of the GPS/mGPS was assessed in 7 trials with data on 1,284 patients and NLR/dNLR was assessed in 33 trials with data on 39,313 patients. All 36 trials were analysed in a post hoc manner. The thresholds used for GPS/mGPS were the same in all trials. The GPS/mGPS was shown to have prognostic value in randomised clinical trials in NSCLC (151), oesophageal cancer (152), pancreatic cancer (153), prostate cancer (154) and breast cancer (155). The thresholds for NLR varied between 3 to 6 and for dNLR between 2

to 5. The most common threshold for NLR was ≥3 and was used in 9 trials containing data on 4,042 patients. The most common threshold for dNLR was 2 and was used in 3 trials containing data on 3,810 patients. The NLR/dNLR was shown to have prognostic value in randomised clinical trials in nasopharyngeal cancer (156), oesophageal cancer (157), pancreatic cancer (158), biliary cancer (159), prostate cancer (160) and multiple cancer types (161). A combination of both GPS/mGPS and NLR/dNLR were measured in 2 trials containing data on 461 patients (162, 163). Thomsen and colleagues showed that both mGPS (HR: 2.16, 95%CI 1.52-3.06, p<0.001) and dNLR (HR: 1.68, 95%CI 1.35-2.08, p<0.001) were prognostic in 68 patients with multiple cancer types (162). Chua and colleagues showed that both GPS (HR: 4.1, 95%CI 2.2-7.7, p<0.0001) and NLR (HR: 2.0, 95%CI 1.2-3.3, p=0.010) were prognostic in 393 patients with colorectal cancer (163).

5.4 Discussion

The results of the present systematic review are consistent with previous observational studies and confirm the clinical utility and prognostic value of systemic inflammation based prognostic tools in the randomised control trial setting. Therefore, we propose that the time has now come for the universal incorporation of measures of the systemic inflammatory response into the design of randomised clinical trials in patients with cancer. Monitoring of both tumour and host responses will enable a more reliable estimate of benefit from oncological treatment. This will in turn highlight opportunities not only to target the tumour but also host systemic inflammatory responses.

Despite supportive meta-analysis of hundreds of reports of the prognostic value of markers of the systemic inflammatory response (37, 38) , one of the main reasons for the lack of incorporation on monitoring of the systemic inflammatory response into standard randomised control trial protocols has been the apparent lack of prospective data and also the lack of a clear biological rationale behind their clinical utility. Therefore, the present review has only included prospective randomised trials, and these confirm the prognostic value of the systemic inflammatory response. Moreover, with the explosion of interest in immunological treatments in patients with cancer, including several dedicated journals, the biological rationale for such systemic inflammation based prognostic scores has now become clear (164, 165). It remains to be established which of the markers of the systemic inflammatory response will be used in the RCT setting. However, compared with a ratio such as the NLR with its variable and poorly defined cut-off, a score such as the GPS with its well defined cut-off has a clear advantage (40).

In the present systematic review only two small RCTs reported two measures of the systemic inflammatory response and in both trials the GPS/mGPS and the NLR/dNLR were shown to have independent prognostic value (162, 163).

Therefore, in the context of the large preponderance of RCTs using NLR/dNLR it would suggest that NLR/dNLR should become the tool of choice for the measurement of the systemic inflammatory response in randomised trials. However, recently the NLR/ dNLR ratio approach to combining markers of the systemic inflammatory response as a prognostic tool has been questioned (40, 166).

In particular it is not clear from a ratio what component is abnormal, what component is the prognostic value derived from and therefore the optimal threshold for prognostic value. This is confirmed in the variety of thresholds that have been reported for NLR/dNLR both in observational studies and the RCT setting. In contrast, the cumulative score approach such as the GPS/mGPS uses consistent thresholds and have been successfully applied to the RCT setting. Although, in many centres in the USA CRP has not been routinely measured either in clinical oncology practice or in the randomised control trial setting, recently CRP, albumin, and NLR have been listed as mandatory measurements in the first international consensus on mandatory baseline and prognostic characteristics in future trials for the treatment of unresectable pancreatic cancer (167).

The advantage of a differential white cell count on which to base a prognostic score is that currently it is universally examined in clinical practice in patients with cancer. We have recently proposed that a number of scores based on the differential white cell count could be used to replace the ratios currently used (40). For example, the neutrophil lymphocyte score (NLS) could replace the NLR, the platelet lymphocyte score (PLS) could replace the PLR and the lymphocyte monocyte score (LMS) could replace the LMR (40). Indeed, recent analysis of the ARCAD database of >22,000 patients with advanced colorectal cancer confirms the value of the cumulative score approach compared with the ratio approach (168).

In summary, the prognostic value of systemic inflammation-based prognostic scores established extensively in observational studies over the past two decades has now been

confirmed in the randomised controlled setting. The time has now come for prospective incorporation of such scores into randomised controlled trials in patients with cancer.

5.5 Tables and Footnotes

Table 5.1: The relationship between the systemic inflammatory response and survival in randomised clinical trials in patients with cancer (published papers)

Authors	Randomised Clinical Trial	Tumour Type	Country	Patients (n)	Randomised Clinical Trial	Systemic Inflammation	Outcome	Comment
Rinehart et al 2013 (151)	DEX	NSCLC	United States	124	Standard chemotherapy vs. Standard chemotherapy and Dexamethasone	GPS	OS	Univariate analysis: GPS: p< 0.05
Lee et al 2012 (169)	First-SIGNAL NCT00455936	Lung	Korea	199	Gefitinib plus gemcitabine plus cisplatin vs gefitinib monotherapy	NLR	OS	Multivariate Post treatment NLR>2.52 HR 1.13, 95%CI 1.06-1.21, p<0.001
Chua et al 2016 (156)	SQNP01 NCC0901	Naso-pharyngeal	Singapore	221 172	Two-dimensional radiotherapy vs. Two-dimensional radiotherapy and chemotherapy Intensity modulated radiotherapy or concurrent chemotherapy vs. Intensity modulated radiotherapy and chemotherapy	NLR	OS	Multivariate: NLR≥3: HR 1.06, 95%CI 0.76-1.49, p>0.05
Cox et al 2017 (157)	SCOPE1: NCT00509561	Oesophageal	UK	258	Chemoradiotherapy vs Chemoradiotherapy and cetuximab	dNLR	OS	Multivariate dNLR≥2 HR 1.64 95%CI 1.17-2.29, p<0.01
Okuno et al 2017 (152)	JCOG0303: UMIN000000861	Oesophageal	Japan	142	Radiotherapy and standard cisplatin vs. Radiotherapy and low dose cisplatin	GPS	OS	Univariate GPS 2 vs GPS 0 HR 1.95 95%CI 1.19-3.18, p<0.01
Grenader et al 2016 (170)	REAL-2 ISRCTN51678883	Oesophago-gastric	UK	908	Epirubicin and cisplatin and either fluorouracil (ECF) or capecitabine (ECX) vs Epirubicin and oxaliplatin and either fluorouracil (EOF) or capecitabine (EOX)	NLR	OS	Multivariate NLR>3 HR 1.67 95% CI 1.45–1.93 p<0.001
Bruix et al 2017 (171)	Sharp NCT00105443 AP: NCT00492752	Hepatocellular	Multinational	827	Sorafenib vs. Placebo	NLR	OS	Multivariate NLR>3 (Sorafenib group) HR 2.356, p<0.0001

								NLR>3.86 (Placebo group) HR 1.779, p<0.0001
Grenader et al 2015 (159)	ABC-02: NCT00262769 BT-22: UMIN 000001685	Biliary	UK Japan	462	Gemcitabine vs. Gemcitabine and cisplatin Gemcitabine vs. Gemcitabine and cisplatin	dNLR	OS	Multivariate dNLR≥3 HR 1.62, 95% CI 1.32–2.01, p<0.001
Vivaldi et al 2016 (158)	FLAP: NCT02351219	Pancreatic	Italy	137	Neoadjuvant FOLFOXIRI and Surgery vs Neoadjuvant FOLFOXIRI and radiotherapy	NLR	OS	Multivariate NLR ≥4 HR 2.42, 95%CI: 1.38-4.25, p<0.01
Hurwitz et al 2015 (153)	RECAP: NCT01423604	Pancreatic	United States	127	Capecitabine vs Capecitabine and ruxolitinib	mGPS	OS	Univariate mGPS 1/2 vs mGPS 0 HR 0.60, 95%CI 0.35-1.03, p<0.10
Goldstein et al 2015 (172)	MPACT: NCT00844649	Pancreatic	Multinational	861	Gemcitabine vs Gemcitabine and nab-paclitaxel	NLR	OS	Multivariate NLR≤5 HR 0.57, 95%CI 0.48-0.68, p<0.001
Renfro et al 2017 (173)	Multiple in ARCAD database	Colorectal	Multinational	22,654	Multiple chemotherapy trials	dNLR	30 day OS	Multivariate dNLR≥5 HR 1.74, 95%CI 1.25-2.41, p<0.01
Wood et al 2017 (174)	COIN: NCT00182715	Colorectal	UK and Ireland	1630	Oxaliplatin/fluoropyrimidine combination chemotherapy vs oxaliplatin/fluoropyrimidine combination chemotherapy and Cetuximab	dNLR	OS	Univariate dNLR≥2.2 HR 1.35, 95%CI 1.20-1.52, p<0.001
Thomsen et al 2016 (162)	NORDIC-VII: NCT00660582	Colorectal	Norway and Denmark	393	Cetuximab and FLOX vs. Cetuximab and intermittent FLOX	mGPS, dNLR	OS	Univariate mGPS1 vs 0 HR 1.60, 95%CI 1.27-2.01, p<0.001 mGPS 0 vs 2 HR : 2.16, 95%CI 1.52-3.06, p<0.001 dNLR>2.1 HR : 1.68, 95%CI 1.35-2.08, p<0.001

Passardi et al 2016 (175)	ITACa: NCT01878422	Colorectal	Italy	289	Standard chemotherapy vs. either FOLFIRI or FOLFOX4 and bevacizumab.	NLR	OS	Multivariate NLR ≥3 HR:1.78, 95%CI: 1.17-2.70, p<0.01
Correale et al 2014 (176)	GOLFIG-2 EUDRACT: 2005-003458-81	Colorectal	Italy	124	Gemcitabine, Oxaliplatin, Levofolinate, 5-Fluorouracil, Granulocyte-Macrophage Colony-Stimulating Factor, and Interleukin-2 (GOLFIG) Vs. FOLFOX Chemotherapy	NLR	OS	Univariate NLR< 3 HR 0.44, P< 0.001
Hazama et al 2014 (177)	Phase 1 HLA2402 matched	Colorectal	Japan	96	Comparison of five HLA-A*2402-restricted peptides, three derived from oncoantigens and two from vascular endothelial growth factor (VEGF)	NLR	OS	Univariate analysis: NLR≥3: p<0.05
Lorente et al 2015 (178)	Phase III TROPC trial	Prostate	UK	755	Cabazitaxel vs. mitoxantrone	NLR	OS	Multivariate NLR≥3 HR 1.55, 95% CI 1.3– 1.84, p<0.001
Van Soest et al 2015 (160)	VENICE: NCT00519285 TAX327: NCT01487902	Prostate	Multinational	1224 1006	Docetaxel/ prednisone and placebo vs Docetaxel/ prednisone and aflibercept Docetaxel/ prednisone and placebo vs Docetaxel/ prednisone and mitoxantrone	dNLR	OS	Multivariate dNLR ≥2.0 HR 1.29, 95% CI 1.11–1.50, p<0.001 dNLR ≥2.0 HR 1.43, 95% CI 1.20–1.70, p<0.001
Sonpavde et al 2014 (179)	SUN-1120: NCT00676650	Prostate	Multinational	848	Prednisone and sunitinib or placebo following docetaxel monotherpy	NLR	OS	Multivariate NLR Log-transformed HR 1.55, 95%CI 1.32-1.83, p<0.001
Linton et al 2013 (154)	AT-101-CS-205: NCT00571675	Prostate	United States and Russia	220	Docetaxel/prednisone vs Docetaxel/ pednisone and AT101	mGPS	OS	Multivariate mGPS HR 1.87, 95% CI 1.35-2.59, p<0.001 mGPS 2 vs 0 HR 3.44, 95%CI 1.75-6.76, p<0.001
Fox et al 2013 (180)	EGF20001	Renal	Multinational	362	Lapatinib versus hormone therapy	NLR PLR	OS	Multivariate: NLR>3 HR 1.42, 95%CI 1.10-1.84, p=0.008 Univariate: PLR>195

								HR 1.88, 95%CI 1.48-2.37, p<0.0001
Ojerholm et al 2017 (181)	SWOG8710: NCT02756637	Bladder	United States	230	Cystectomy plus neoadjuvant chemotherapy vs. cystectomy alone	NLR	OS	Multivariate NLR (continuous) HR 1.04, 95%CI 0.98-1.11, p=0.24
Honecker et al 2017 (155)	PELICAN: NCT00266799	Breast	Germany	210	First-line pegylated liposomal doxorubicin (PLD) vs. capecitabine.	GPS	OS	Multivariate GPS: p<0.10
Romano et al 2015 (182)	Multiple: GIMEMA MMY-3006, GIMEMA MM03-05, RV-MM-PI209, J0231	Multiple Myeloma	Italy	309	Multiple trials on newly diagnosed multiple myeloma treated with novel therapies	NLR	OS	Univariate analysis: NLR≥2: p=0.0002
Bigot et al 2017 (183)	ICT –Phase 1 trial	Multiple	France	155	Standard treatment vs. Immune checkpoint treatment	NLR	OS	Multivariate NLR≥6 HR 1.75, 95%CI 1.04-2.94, p<0.05
Kumar et al 2015 (161)	Multiple Phase 1 (RMH)	Multiple	UK	1300	Dose and toxicity finding study for chemotherapy in multiple phase 1 chemotherapy trials	NLR	OS	Univariate Test Cohort, NLR>4.45 HR 1.78, 95%CI 1.41-2.87, p<.0001 Validation Cohort, NLR>4.45 HR 1.57, 95%CI 1.42-1.97, p<0.001
Chua et al 2012 (163)	Single Agent Phase 1	Multiple	Australia	68	Docetaxel monotherapy vs. standard treatment	GPS NLR	OS	Multivariate GPS HR 4.1, 95%CI 2.2-7.7, p<0.0001 NLR>5 HR 2.0, 95%CI 1.2-3.3, p=0.010

Table 5.2: The relationship between the systemic inflammatory response and survival in randomised clinical trials in patients with cancer (published abstracts)

Authors	Randomised Clinical Trial	Tumour Type	Country	Patients (n)	Randomised Clinical Trial	Systemic Inflammation	Outcome	Comment
Diakos et al 2016 (184)	CO.17 NCT00640471 CO.20 NCT00079066	Colorectal	Australia and Canada	572 750	CO.17: Cetuximab vs. best supportive care, CO.20: Brivanib (B) vs. placebo	dNLR	OS	Multivariate dNLR≥2 CO.17 HR 1.4, 95% CI 1.1-1.8, p <0.01 CO.20 HR 1.4, 95% CI 1.2-1.6, p<0.0001
Diakos et al 2016 (185)	AGITG MAX	Colorectal	Australia	471	Capecitabine and bevacizumab vs. Capecitabine and bevacizumab and mitomycin C	NLR	OS	Multivariate NLR≥5 HR 1.8, 95%CI 1.3-2.3, p<.0001
Ce Maio et al 2017 (186)	ECRTC 62043/62072	Sarcoma	Belgium	333	Pazopanib vs placebo	NLR	OS	Univariate NLR>3 HR 1.86, 95%CI 1.43-2.41, p<0.001
Coleman et al 2017 (187)	Phase 1 Trial	Recurrent Primary Malignant Brain Tumour	UK	100	Primary corticosteroid vs. best supportive care	NLR	OS	Multivariate NLR≥4 HR 1.73, 95%CI 1.02-2.94, p=0.043
Wang-Gillam et al 2017 (188)	NAPOLI-1: NCT01494506	Pancreatic	Multinational	116	Liposomal irinotecan + 5-fluorouracil and leucovorin vs 5-fluorouracil and leucovorin alone	NLR PLR	OS	Univariate NLR≤5 HR 0.62, 95%CI 0.44-0.86, p=0.005 PLR≤150 HR 0.52, 95%CI 0.32-0.84, p=0.008
Smyth et al 2017 (189)	REAL 3: NCT00824785	Oesphagogastric	UK	553	Epirubicin, Oxaliplatin, Capecitabine (EOC) vs EOC plus panitumumab (EOC-P)	NLR	OS	Univariate NLR: Upper Tertile EOC cohort HR: 9.97, 95%CI 7.43-15.43, p<0.001 ECP-P cohort HR: 5.26, 95%CI 4.28-7.17, p<0.001

Clarke et al 2018 (190)	ASCENT: NCT01588990	Colorectal	Australia	128	First line BEV+XELOX or mFOLFOX6 in phase A (PhA) with planned continuation of BEV+FOLFIRI beyond 1st progression in phase B (PhB).	NLR	OS	Univariate: NLR>5 HR: 1.6, 95% CI 1.0-2.7, p = 0.052
Argiles et al 2018 (191)	RECOURSE: NCT01607957	Colorectal	Multinational	782	Trifluridine/tipiracil (TAS-102) vs placebo	NLR	OS	Multivariate: NLR≥3: p = 0.15

5.6 Figures and Legends

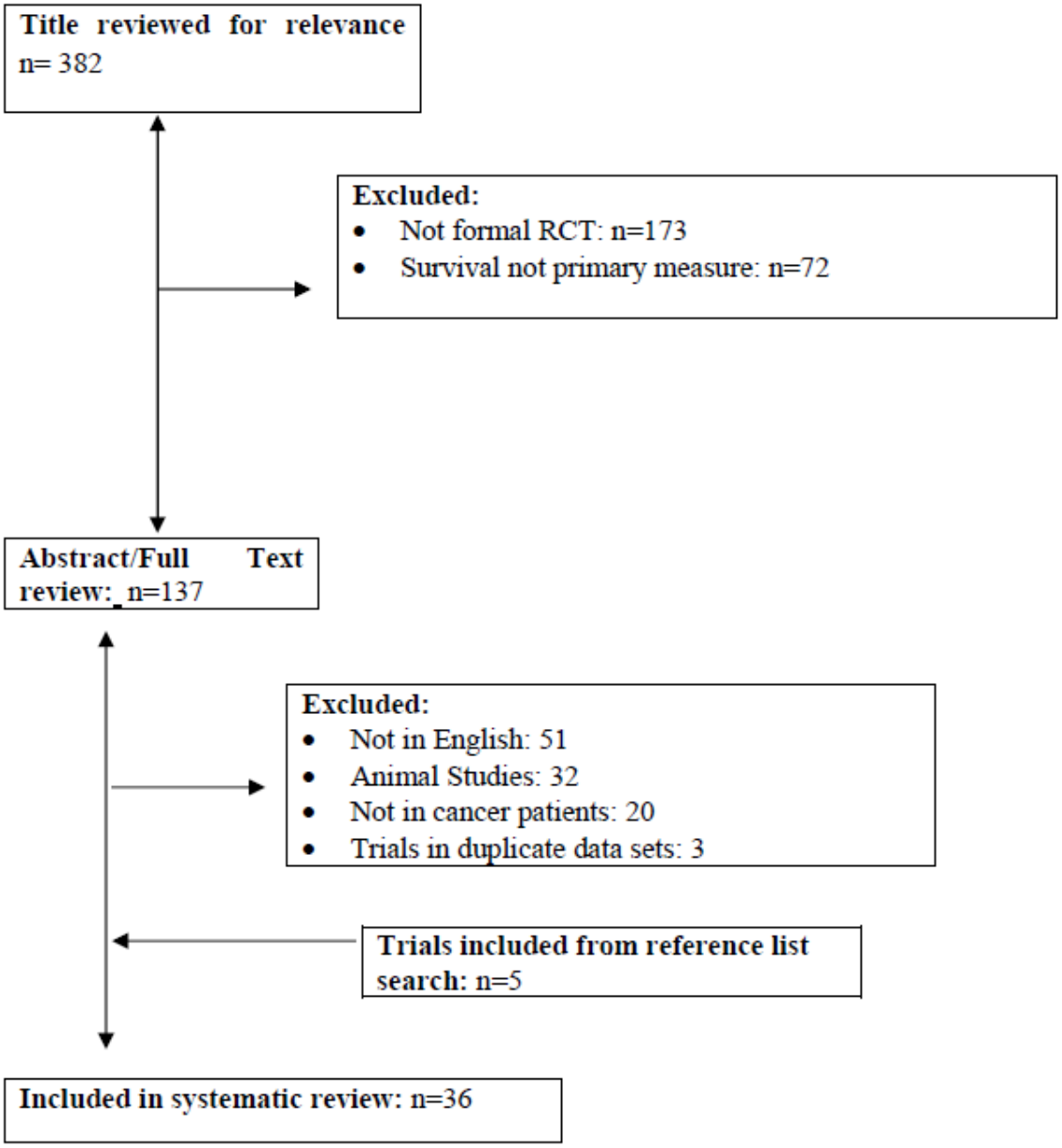


Figure 5.1: PRISMA flowchart demonstrating study selection

6. THE PREVALENCE OF CANCER ASSOCIATED SYSTEMIC INFLAMMATION AND ITS IMPLICATIONS: OBSERVATIONS FROM PROGNOSTIC STUDIES USING THE GLASGOW PROGNOSTIC SCORE

6.1 Introduction

In 2014 McAllister and Weinberg concluded that tumour related systemic inflammation was the "seventh hallmark of cancer" and the "tip of the iceberg" in terms of cancer biology and treatment (117, 192, 193). Furthermore, as can be seen in Chapter 3 and 4 Dolan and co-workers showed that widely used clinical markers of the systemic inflammatory response (CRP, albumin, neutrophils and platelets) had prognostic value in patients with operable and in advanced cancer. Indeed, the activation of the systemic inflammatory response has been strongly implicated in the aggressiveness of the disease and development of cachexia with associated deleterious outcomes (7, 193, 194).

The prognostic application of markers of the systemic inflammatory response in patients with cancer are usually based around composite ratios or scores of different circulating white blood cells or acute phase proteins; representing the systemic responses of two different organs, lymphoid/myeloid tissue and liver respectively (40). The most widely validated example of a composite ratio would be the NLR based on the ratio of circulating neutrophil and lymphocyte counts (37, 38). While it is clear that composite ratios such as the NLR have prognostic value, there is a large variation in the specific threshold levels used which makes comparison of studies difficult (37, 38). The most widely validated example of a cumulative scores is the GPS/mGPS based on the acute phase proteins CRP and albumin (37, 38). The advantage of cumulative scores are that they are based on validated laboratory reference ranges and the advantage of the GPS/mGPS is that consistent thresholds that allow for direct comparison of the systemic inflammatory response across different institutions and geographical locations.

While the prognostic importance of the systemic inflammatory response in patients with both operable and inoperable cancers is widely recognised, the level of systemic inflammation in patients with cancer across the literature has not been formally assessed. Therefore, the aim of this Chapter was to determine the prevalence of systemic inflammation as measured by the GPS/ mGPS in patients with either operable and inoperable cancer.

6.2 Patients and Methods

The present review of published literature was based on that of two previous systematic reviews (37, 38) undertaken according to a pre-defined protocol described in the PRISMA-P statement and outlined in Chapters 2. Only studies that had greater than 100 observations and reported survival were considered in the final analysis.

Statistical Analysis

Studies were reviewed and the number of patients with breast, bladder, gynaecological, prostate, gastrointestinal, haematological, renal, colorectal, head and neck, hepatopancreaticobiliary, pulmonary and multiple types of cancer types were grouped into tables for operable, inoperable and combined studies. The individual number of patients with elevated CRP and albumin readings were also included. No meta analysis was carried out since it could be considered as a narrative review of previous systematic reviews (37, 38).

6.3 Results

Study selection process

The review of existing systematic reviews (37, 38) led to a review of the full text of 104 articles. A further 36 articles were identified from bibliographies and were included in this narrative review leading to a final total of 140 articles. The details of the 140 studies included in the review are shown in Table 6.1.

Studies of the GPS/ mGPS in patients with breast cancer

No articles were identified in patients with operable breast cancer (Table 6.1). Two studies including 181 patients were identified in inoperable breast cancer. These studies included both retrospective (n=1) and prospective studies (n=1). These included studies carried out in the UK (n=1) and Germany (n=1). In total 81 (45%) of patients were systematically inflamed (Table 6.1 and Table 6.2).

Studies of the GPS/ mGPS in patients with bladder cancer

Two studies including 2133 patients were identified in operable bladder cancer. These studies were both retrospective studies (n=2). These included studies carried out in Italy (n=1) and Japan (n=1). In total 723 (34%) of patients were systematically inflamed (Table 6.1 and Table 6.2). A single study was identified in patients with inoperable bladder cancer. This contained 67 patients, was prospective, carried out in the Korea and showed that 34 (51%) of patients were systemically inflamed.

Studies of the GPS/ mGPS in patients with gynaecological cancer

Three studies including 724 patients were identified in operable gynaecological cancer. These studies included both retrospective (n=2) and prospective studies (n=1). These included studies carried out in the Austria (n=1), Japan (n=1) and China (n=1). In total 186 (26%) of patients were systematically inflamed (Table 6.1 and Table 6.2).

Three studies including 870 patients were identified in inoperable gynaecological cancer. These studies included both retrospective (n=2) and prospective studies (n=1). These included studies carried out in the multiple countries (n=1), Austria (n=1) and China (n=1). In total 309 (36%) of patients were systematically inflamed (Table 6.1 and Table 6.2).

Studies of the GPS/ mGPS in patients with prostate cancer

No articles were identified in patients with operable prostate cancer (Table 6.1Table 5.1 and Table 6.2). Two studies including 223 patients were identified in inoperable prostate cancer. These studies included both retrospective (n=1) and prospective studies (n=1). These included studies carried out in multiple countries (n=1) and Japan (n=1). In total 65 (29%) of patients were systematically inflamed (Table 6.1 and Table 6.2).

Studies of the GPS/ mGPS in patients with gastroesophageal cancer

Twenty-five studies including 7,693 patients were identified in operable gastroesophageal cancer. These studies included both retrospective (n=24) and prospective studies (n=1). These included studies carried out in Japan (n=13), UK (n=5), China (n=3), Germany (n=2), Ireland (n=1) and Italy (n=1). In total 1,617 (21%) of patients were systematically inflamed (Table 6.1 and Table 6.2).

Eleven studies including 1,897 patients were identified in inoperable gastroesophageal cancer. These studies included both retrospective (n=10) and prospective studies (n=1). These included studies carried out in the UK (n=3), Japan (n=3), Korea (n=2), China (n=1), Czech Rep (n=1) and Taiwan (n=1). In total 1032 (54%) of patients were systematically inflamed (Table 6.1 and Table 6.3).

Studies of the GPS/ mGPS in patients with haematological cancer

Two studies including 430 patients were identified in inoperable haematological cancer. All studies were retrospective. These included studies carried out in China (n=1) and Korea (n=1). In total 340 (79%) of patients were systematically inflamed (Table 6.1 and Table 6.3).

Studies of the GPS/ mGPS in patients with renal cancer

Seven studies including 2417 patients were identified in operable renal cancer. These studies included both retrospective (n=6) and prospective studies (n=1). These included studies carried out in the UK (n=2), Japan (n=4) and Korea (n=1). In total 717 (30%) of patients were systematically inflamed (Table 6.1 and Table 6.2).

Two studies including 142 patients were identified in inoperable renal cancer. These studies included both retrospective (n=1) and prospective studies (n=1). These studies were both carried out in the UK. In total 101 (45%) of patients were systematically inflamed (Table 6.1 and Table 6.3).

Studies of the GPS/ mGPS in patients with colorectal cancer

Twenty-nine studies including 8,832 patients were identified in operable colorectal cancer. These studies included both retrospective (n=26) and prospective studies (n=3). These included studies carried out in the UK (n=15), Japan (n=11), China (n=1), Korea (n=1) and Australia (n=1). In total 3,356 (38%) of patients were systematically inflamed (Table 6.1 and Table 6.2).

Eight studies including 1166 patients were identified in inoperable colorectal cancer. These studies included both retrospective (n=6) and prospective studies (n=2). These included studies carried out in the UK (n=2), Japan (n=2), France (n=1), Korea (n=1), Australia (n=1) and Norway/Denmark (n=1). In total 622 (53%) of patients were systematically inflamed (Table 6.1 and Table 6.3).

Studies of the systemic inflammatory response in patients with head and neck cancer

A single study was identified in patients with operable head and neck cancer. This contained 178 patients, was retrospective, carried out in the UK and showed that 47 (26%) of patients were systemically inflamed (Table 6.1 and Table 6.2). Three studies including 531 patients were identified in inoperable head and neck cancer. These studies included both retrospective (n=1) and prospective studies (n=1). These included studies carried out in Taiwan (n=2) and China (n=1). In total 251 (47%) of patients were systematically inflamed (and).

Studies of the GPS/ mGPS in patients with Hepatopancreaticobiliary *Cancer*

Sixteen studies including 3,587 patients were identified in operable hepatopancreaticobiliary cancer. These studies included both retrospective (n=14) and prospective studies (n=2). These included studies carried out in Japan (n=8), the UK (n=2), China (n=4), Italy (n=1), and Austria (n=1). In total 1,001 (28%) of patients were systematically inflamed (Table 6.1 and Table 6.2) .

Seven studies including 920 patients were identified in inoperable hepatopancreaticobiliary cancer. These studies included both retrospective (n=5) and prospective studies (n=2). These included studies carried out in Japan (n=3), UK (n=1), USA (n=1), China (n=1) and Australia (n=1). In total 333 (36%) of patients were systematically inflamed (Table 6.1 and Table 6.3).

Studies of the GPS/ mGPS in patients with Pulmonary Cancer

Four studies including 2,579 patients were identified in operable pulmonary cancer. All of these studies were retrospective. These included studies carried out in the Japan (n=2), UK (n=1) and China (n=1). In total 1,001 (27.9) of patients were systematically inflamed (Table 6.1 and Table 6.2).

Seven studies including 1,456 patients were identified in inoperable pulmonary cancer. These studies included were both retrospective (n=4) and prospective studies (n=3). These included studies carried out in the UK (n=2), China (n=2), Greece (n=2) and the USA (n=1). In total 857 (59%) of patients were systematically inflamed (Table 6.1 and Table 6.3).

Studies of the GPS/mGPS in patients with Multiple Cancer Types

No articles were identified in patients with operable multiple types of cancer. Seven studies including 4,867 patients were identified in inoperable multiple cancer types. These studies included both retrospective (n=3) and prospective studies (n=4). These included studies carried out in the UK (n=2), Australia (n=2), USA (n=1), Japan (n=1) and Norway (n=1). In total 3,556 (73%) of patients were systematically inflamed (Table 6.1 and Table 6.3).

Combined Inoperable and Operable Studies:

Inoperable and operable cancer studies are summarised in Table 6.2 and Table 6.3. The percentage of patients (>40,000) who were systemically inflamed varied from 28% to 63% according to tumour type (gastroesophageal and multiple cancers respectively). The most commonly studied cancer was colorectal cancer (~10,000 patients) and 40% were systemically inflamed overall (Table 6.2). The percentage of patients with operable cancer (>28,000) who were systemically inflamed varied from 21% to 38% (gastroesophageal and colorectal cancer respectively, Table 6.3). The most commonly studied cancer was colorectal cancer (>8,500 patients) and 38% were systemically inflamed (Table 6.3). The percentage of patients with inoperable cancer (>12,000) who were systemically inflamed varied from 29% to 79% (prostate and haematological cancers, Table 6.3). Furthermore, a commonly studied cancer was colorectal cancer (>1,100 patients) and 53% were systemically inflamed (Table 6.3).

6.4 Discussion

In the present narrative review of the prevalence of the systemic inflammatory response (as evidenced by GPS/mGPS) in more than 40,000 patients with cancer it was clear that the elevation of the GPS/mGPS was common and the prevalence was greater in advanced cancer compared with operable cancer. In particular, in patients with operable tumours (>500 patients) no tumour type had more than 50% of patients with an elevated GPS/mGPS. In contrast, in patients with inoperable disease (>500 patients) gastro-oesophageal cancer, colorectal cancer, hepatopancreaticobiliary cancer, pulmonary cancer and multiple cancers all had more than 50% of patients with an elevated GPS/mGPS. Therefore, it is clear that the presence of a systemic inflammatory response is a common prognostic feature of established cancer, especially advanced cancer.

The results of the present review are consistent with the report of Procter and colleagues who first studied the prevalence of the mGPS before and after diagnosis in an unselected cohort of patients with cancer and reported that "the proportions of mGPS 1 and 2 were greater following a diagnosis of cancer (195)." Taken together these results would indicate that the systemic inflammatory response is present at the earliest stages of cancer and increases as the cancer progresses. Given the independent prognostic value of the mGPS this may suggest that the systemic inflammatory response reflects or promotes tumour progression. Irrespective, these results have implications for the future stratification and treatment of both operable and inoperable disease in patients with cancer.

The implications for patient stratification are clear and there is now evidence of the GPS/mGPS being used in the randomised clinical trial setting (54). The implications for treatment are less clear in patients with operable cancer. For example, there is increasing interest in the addition of either aspirin or steroids to pre-operative management regimes (196). The implication for treatment in patients with inoperable cancers is likely to focus on

the use of anti-inflammatory regimes to improve the response rates for anticancer therapies (82).

In summary, the systemic inflammatory response, as evidenced by the GPS/mGPS, was common in both primary operable and advanced inoperable cancers particularly in lung and gastrointestinal cancers. Therefore, the systemic inflammation “iceberg” is in plain sight and should be factored into future treatment plans of patients with cancer.

6.5 Tables and Footnotes

Table 6.1: Studies using mGPS to stratify patients undergoing operative and non-operative treatment for cancer.

No: GPS/ mGPS	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	CRP >10mg/l	Albumin <35 g/l	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2	Additional Treatment
Breast cancer Operable												
1					_				_	_	_	
Breast cancer Inoperable												
1.	Al Murri et al 2006 (197)	Retrospective	Breast cancer	UK	96	GPS (0/1/2)	45 (47)	6 (6)	51 (53)	39 (41)	6 (6)	Chemotherapy and endocrine therapy
2.	Honecker et al 2018 (198)	Prospective	Breast cancer	Germany	85	GPS (0/1/2)	36	17	49 (57.6)	22 (25.9)	14 (16.5)	First line chemotherapy
Combined Total					**181**				**100 (55.2)**	**61 (33.7)**	**20 (11.1)**	
Bladder cancer Operable												
1.	Ferro et al 2015 (199)	Retrospective	Bladder cancer	Italy	1037	mGPS (0/1/2)	391 (37.7)	97 (9.4)	646 (62.3)	297 (28.6)	94 (9.1)	77.1% received adjuvant chemotherapy
2.	Kimura et al 2019 (200)	Retrospective	Bladder cancer	Japan	1096	mGPS	_	_	764 (69.7)	299 (27.3)	33 (3.0)	4.0% patients received adjuvant chemotherapy
Bladder cancer Inoperable												
1.	Hwang et al 2012 (201)	Prospective	Bladder cancer	Korea	67	GPS (1&2)	30 (44.8)	21 (31.3)	33 (49.3)	17 (25.4)	17 (25.4)	Treated with chemotherapy
Combined Total					**2200**				**1443 (65.6)**	**613 (27.9)**	**144 (6.5)**	
Gynaecological cancer Operable												
1.	Hefler-Frischmuth et al 2010 (202)	Prospective	Vulval cancer	Austria	93	GPS (0/1/2)	_	_	72 (77.4)	16 (17.2)	5 (5.4)	Adjuvant treatment not specified

2.	Saijo et al 2017 (203)	Retrospective	Endometrial cancer	Japan	431		51 (11.8)	21 (4.9)	376 (87.2)	38 (8.8)	17 (4.0)	Adjuvant chemotherapy in high risk patients
3.	Liu et al 2017 (204)	Retrospective	Ovarian cancer	China	200	mGPS (0/1/2)	41 (20.5)	6 (3.0)	90 (45)	90 (45)	20 (10)	96% patients received chemotherapy
Gynaecological cancer Inoperable												
1.	Xiao et al 2015 (205)	Retrospective	Cervical cancer	China	238	mGPS (0/1/2)	107 (45.0)	29 (12.2)	138 (58.0)	71 (29.8)	29 (12.2)	Chemo and radiotherapy
2.	Roncolato et al 2018 (206)	Prospective	Endometrial cancer	Multinational	516	mGPS (0/1/2)	_	_	282 (54.7)	123 (23.8)	111 (21.5)	Chemotherapy and best supportive care
3.	Seebacher et al 2019 (207)	Retrospective	Cervical cancer	Austria	116	GPS	_	_	41 (35.3)	56 (48.3)	19 (16.4)	Best supportive care for recurrent disease
Combined Total					**1594**				**999 (62.7)**	**394 (24.7)**	**201 (12.6)**	
Prostate cancer Operable												
1.					_				_	_	_	
Total												
Prostate cancer Inoperable												
1.	Linton et al 2013 (154)	Prospective	Prostate cancer	Multinational	112	mGPS (2 vs. 0) (1 vs. 0)	>5: 36 (32.1)	27 (24.1)	76 (67.9)	17 (15.2)	19 (16.9)	Docetaxel and prednisone treatment
2.	Owari et al 2018 (208)	Retrospective	Renal, prostate and urethral cancer	Japan	111	mGPS (0/1/2)	_	_	82 (74)	26 (23)	3 (3)	84% treated with radiotherapy
Combined Total					**223**				**158 (70.9)**	**43 (19.3)**	**22 (9.9)**	
Gastro-oesophageal cancer Operable												
1.	Kobayashi et al 2008 (209)	Retrospective	Oesophageal squamous cell carcinoma	Japan	48	GPS (0/ 1 and 2)	_	_	27 (56.3)	16 (33.3)	5 (10.4)	Neoadjuvant chemoradiotherapy (nCRT)

2.	Kobayashi et al 2010 (210)	Retrospective	Oesophageal Squamous Cell Carcinoma	Japan	65	GPS (0 and 1)	_	_	43 (66.2)	16 (24.6)	6 (9.2)	60% patients received neoadjuvant chemoradiotherapy
3.	Dutta et al 2011 (211)	Retrospective	Oesophageal cancer	UK	112	GPS (0/1/2)	_	_	99 (88.4)	13 (11.6)	0 (0)	27.7% patients received neoadjuvant therapy and 12.5% received adjuvant therapy
4.	Dutta et al 2011 (212)	Retrospective	Gastro-oesophageal cancer	UK	121	GPS (0/1/2)	_	_	99 (81.8)	16 (13.2)	6 (5.0)	55.4% patients received neoadjuvant and 15.7% received adjuvant therapy
5.	Crumley et al 2011(213)	Retrospective	Gastro-oesophageal cancer	UK	100	GPS (0/1/2)	_	_	87 (87)	13 (13)	0 (0)	Adjuvant and neoadjuvant therapy administered
6.	Vashist et al 2011 (214)	Retrospective	Oesophageal cancer	Germany	495	GPS (0/1/2)	_	_	268 (54.1)	166 (33.5)	61 (12.3)	No adjuvant or neoadjuvant therapy
7.	Dutta et al 2012 (215)	Retrospective	Oesophageal cancer	UK	98	GPS (0/1/2)	_	_	87 (88.8)	9 (9.2)	2 (2.0)	48.0% received neoadjuvant therapy and 18.4% received adjuvant therapy
8.	Feng et al 2014 (216)	Retrospective	Oesophageal cancer	China	493	GPS (0/1/2)	_	_	316 (64.1)	121 (24.5)	56 (11.4)	Adjuvant chemo and radiotherapy administered
9.	Nakamura et al 2014 (141)	Retrospective	Oesophageal cancer	Japan	168	mGPS (0/1/2)	_	_	137 (81.6)	19 (11.3)	12 (7.1)	7.7% received neoadjuvant therapy while 36.9% received adjuvant therapy
10.	Matsuda et al 2015 (217)	Retrospective	Oesophageal cancer	Japan	199	GPS (0/1/2)	10 (5.0)	12 (6.0)	108 (54.3)	68 (34.2)	23 (11.5)	49.8% patients received neoadjuvant chemo and radiotherapy
11.	Arigami et al 2015 (142)	Retrospective	Oesophageal cancer	Japan	238	mGPS (0/1/2)	_	_	168 (70.6)	54 (22.7)	16 (6.7)	Adjuvant therapy not specified

12.	Xu et al 2015 (127)	Retrospective	Oesophageal SCC	China	468	GPS/mGPS (0/1/2)	108 (23)	89 (19)	GPS: 336 (71.8) mGPS: 360 (76.9)	GPS: 101 (21.6) mGPS: 77 (16.5)	GPS: 31 (6.6) mGPS: 31 (6.6)	41.9% patient received adjuvant chemo and radiotherapy
13.	Hirahara et al 2015 (218)	Retrospective	Oesophageal cancer	Japan	141	GPS (0/1/2)	18 (12.8)	27 (19.1)	109 (77.3)	23 (16.3)	9 (6.4)	Adjuvant therapy not specified
14.	Walsh et al 2016 (219)	Retrospective	Oesophageal cancer	Ireland	223	mGPS (0 vs. 1/2)	_	_	174 (78.0)	_	mGPS 1&2: 49 (22.0)	48.9% patients received neoadjuvant chemoradiotherapy, 29.6% patients received chemotherapy
15.	Otowa et al 2016 (220)	Retrospective	Oesophageal cancer	Japan	100	Pre-NAC mGPS (0/1-2) Post-NAC mGPS (0/2) NAC=neoadjuvant chemotherapy	_	_	Pre: 82 (82.0) Post: 90 (90.0)	Pre: 7 (7.0) Post: 0 (0)	Pre: 11 (11.0) Post: 10 (10.0)	All patients received neoadjuvant chemotherapy
16.	Toyokawa et al 2016 (140)	Retrospective	Thoracic oesophageal squamous cell carcinoma	Japan	185	GPS (0 vs 1/2)	_	_	171 (92.5)	13 (7.0)	1 (0.5)	24.9% patients received neoadjuvant therapy
17.	Nozoe et al 2011 (221)	Prospective	Gastric cancer	Japan	232	GPS (0/1/2) mGPS (0/1/2)	58 (25.0)	62 (26.7)	140 (60.3)	64 (27.6)	28 (12.1)	Adjuvant therapy not specified
18.	Kubota et al 2012 (222)	Retrospective	Gastric cancer	Japan	1017	GPS (0/1/2)	_	_	956 (94.0)	40 (3.9)	21 (2.1)	Adjuvant therapy not specified
19.	Dutta et al 2012 (223)	Retrospective	Gastric cancer	UK	120	GPS (0/1/2)	_	_	97 (80.8)	18 (15.0)	5 (4.2)	Patients received both adjuvant and neoadjuvant therapy
20.	Wang et al 2012 (224)	Retrospective	Gastric cancer	China	324	GPS (0/1/2)	62 (19.1)	32 (9.9)	248 (76.5)	58 (17.9)	18 (5.6)	64.8% patients received adjuvant chemotherapy

21.	Jiang et al 2012 (225)	Retrospective	Gastric cancer	Japan	1710	mGPS (0/1/2)	145 (8.5)	162 (9.5)	1565 (91.5)	78 (4.6)	67 (3.9)	Adjuvant therapy not specified
22.	Takeno et al 2014 (145)	Retrospective	Gastric cancer	Japan	552	mGPS (0/1/2)	_	_	494 (89.5)	24 (4.3)	34 (6.2)	Adjuvant therapy not specified
23.	Hirashima et al 2014 (143)	Retrospective	Gastric cancer	Japan	294	mGPS (0/1/2)	_	_	174 (59.2)	84 (28.6)	36 (12.2)	3.1% patients received neoadjuvant chemotherapy
24.	Aurello et al 2014 (135)	Retrospective	Gastric cancer	Italy	102	mGPS (0/1/2)	53 (51.9)	55 (53.9)	49 (48.0)	25 (24.5)	28 (27.5)	66.7% patients received adjuvant chemotherapy
25.	Melling et al 2016 (226)	Retrospective	Gastric cancer	Germany	88	GPS (0/1/2)	_	_	42 (47.7)	22 (25.0)	24 (27.3)	Neoadjuvant and adjuvant therapy not specified
Gastro-oesophageal cancer Inoperable												
1.	Crumley et al 2006 (227)	Retrospective	Gastro-oesophageal cancer	UK	258	GPS (0/1/2)	_	_	92 (36)	121 (47)	45 (17)	Palliative Chemo and radiotherapy
2.	Crumley et al 2008 (228)	Retrospective	Gastro-oesophageal cancer	UK	65	GPS (0/1/2)	_	_	26 (40)	31 (48)	8 (12)	Cisplatin based chemotherapy
3.	Zhang et al 2014 (229)	Retrospective	Oesophageal cancer	China	212	mGPS (0,1,2)	122 (57.6)	134 (63.3)	90 (42.5)	78 (36.8)	44 (20.8)	Radiotherapy and cisplatin based chemo
4.	Elahi et al 2004 (230)	Retrospective	Gastric and colorectal cancer	UK	Gastric: 66	GPS (0/1/2)	47 (71.2)	25 (37.9)	Gastric: 17 (25.8)	Gastric: 26 (39.4)	Gastric: 23 (34.8)	Palliative Chemo and Supportive Care
5.	Hwang et al 2011 (231)	Retrospective	Gastric cancer	Korea	402	GPS: (1&2)	140 (34.9)	77 (19.2)	238 (59.2)	111 (27.6)	53 (13.2)	Cisplatin based chemotherapy
6.	Jeong et al 2012 (232)	Retrospective	Gastric cancer	Korea	104	mGPS: (1 & 2)	_	_	58 (55.8)	29 (27.9)	17 (16.3)	Palliative chemo

7.	Sachlova et al 2014 (233)	Retrospective	Gastric cancer	Czech Rep	91 Total 64 (treated with chemo)	GPS (1&2)	_	_	37 (41)	31 (34)	23 (25)	Palliative platinum based chemotherapy
8.	Namikawa et al 2016 (234)	Retrospective	Gastric cancer	Japan	244	GPS (0/1 or 2) mGPS (0/1 or 2)	_ _	_ _	GPS: 150 (61.5) mGPS: 143 (58.6)	GPS: _ mGPS: _	GPS: 1&2: 94 (38.5) mGPS 1&2: 101 (41.4)	Combination chemotherapy including trastuzmab
9.	Arigami et al 2016 (235)	Retrospective	Gastric cancer	Japan	68	GPS: 1&2	_	_	35 (51.5)	27 (39.7)	6 (8.8)	Chemotherapy and chemoradiotherapy
10.	Hsieh et al 2016 (236)	Retrospective	Gastric cancer	Taiwan	256	mGPS (>1)	_	_	66 (26)	100 (39)	90 (35)	Combination Chemotherapy
11.	Okuno et al 2017 (152)	Prospective	Oesophageal cancer	Japan	131	GPS (0/1/2)	_	_	56 (42.8)	48 (36.6)	27 (20.6)	Radiotherapy and standard cisplatin vs. Radiotherapy and low dose cisplatin
Combined Total					**9590**				**6941 (72.4)**	**1670 (17.4)**	**979 (10.2)**	
Haematological cancer Inoperable												
1.	Chou et al 2015 (237)	Retrospective	Haematological cancer	China	217	GPS: (1&2)	181 (83.4)	156 (71.9)	15 (6.9)	56 (30.9)	146 (62.2)	Best supportive palliative care
3.	Jung et al 2015 (238)	Retrospective	B-cell Lymphoma	Korea	213	L-GPS: 1&2	135 (63.4)	43 (20.2)	75 (35.2)	109 (51.2)	29 (13.6)	R-CHOP chemotherapy.
Combined Total					**430**				**90 (20.9)**	**165 (38.4)**	**175 (40.7)**	
Renal cancer Operable												
1.	Qayyum et al 2012 (239)	Prospective	Renal cell cancer	UK	79	GPS (0/1/2)	_	_	57 (72.2)	19 (24.1)	3 (3.7)	Adjuvant therapies not specified
2.	Lamb et al 2012 (240)	Retrospective	Renal cancer	UK	169	GPS (0/1/2)	_	_	117 (69.2)	46 (27.2)	6 (3.6)	Adjuvant therapies not specified

3.	Tsuijino et al 2017 (241)	Retrospective	Renal cancer	Japan	219	mGPS (0/1/2)	_	_	184 (84.0)	20 (9.1)	15 (6.9)	Adjuvant therapies not specified
4.	Fukuda et al 2018 (242)	Retrospective	Renal cancer	Japan	170	GPS (0/1/2)	_	_	56 (33)	67 (39)	47 (28)	Chemo and immunotherapy as part of cryoreductive treatment
5.	Inamoto et al 2017 (243)	Retrospective	Urethral cancer	Japan	574	GPS (0/1/2)	_	_	332 (57.8)	132 (23.0)	110 (19.2)	Adjuvant therapies not specified
6.	Son et al 2018 (244)	Retrospective	Urethelial cancer	South Korea	1137	mGPS (0/1/2)	219 (19.3)	158 (13.8)	918 (80.7)	148 (13.0)	71 (6.2)	30.6% treated with adjuvant chemotherapy
7.	Owari et al 2018 (208)	Retrospective	Renal and urethral cancer	Japan	69	GPS (0/1/2)	_	_	36 (52.2)	19 (27.5)	14 (20.3)	56.5% treated with radiotherapy
Renal cancer Inoperable												
1.	Ramsey et al 2007 (31)	Retrospective	Renal cell cancer	UK	119	GPS: (0/1/2)	84 (71)	16 (14)	33 (28)	72 (60)	14 (12)	Active Immunotherapy
2.	Ramsey et al 2008 (245)	Prospective	Renal cell cancer	UK	23	GPS (0/1/2)	_	_	8 (35)	6 (26)	9 (39)	Palliative immunotherapy
Combined Total					**2559**				**1741 (68.0)**	**529 (20.7)**	**289 (11.3)**	
Colorectal Cancer Operable												
1.	Ishizuka et al 2007 (246)	Retrospective	Colorectal cancer	Japan	315	GPS (0/1/2)	76 (24.1)	100 (21.8)	183 (58.1)	89 (28.3)	43 (13.6)	Neoadjuvant treatments not specified
2.	McMillan et al 2007 (118)	Retrospective	Colorectal cancer	UK	316	mGPS (0/1/2)	101 (32.0)	54 (17.1)	185 (58.5)	93 (29.5)	38 (12.0)	Adjuvant therapy not specified
3.	Leitch et al 2007 (247)	Retrospective	Colorectal cancer	UK	149	mGPS (0/1/2)	61 (40.9)	14 (9.4)	88 (59.1)	48 (32.2)	13 (8.7)	47.7% of patients received adjuvant therapy

4.	Roxburgh et al 2009 (248)	Retrospective	Colorectal cancer	UK	287	mGPS (0/1/2)	_	_	171 (60)	82 (28)	34 (12)	Adjuvant therapy not specified
5.	Ishizuka et al 2009 (249)	Retrospective	Colorectal liver metastases	Japan	93	GPS (0/1/2)	_	_	63 (67.7)	24 (25.8)	6 (6.5)	Neoadjuvant therapy not specified
6.	Crozier et al 2009 (250)	Prospective	Colon cancer	UK	188	mGPS (0/1/2)	_	_	79 (42.0)	80 (42.6)	29 (15.4)	28.7% patients received adjuvant therapy
7.	Roxburgh et al 2010 (251)	Retrospective	Colon cancer	UK	287	mGPS (0/1/2)	_	_	143 (57)	102 (33)	42 (10)	Adjuvant chemotherapy
8.	Richards et al 2010 (252)	Prospective	Colorectal cancer	UK	320	mGPS (0/1/2)	_	_	194 (61)	90 (28)	36 (11)	20.6% had adjuvant therapy
9.	Kobayashi et al 2010 (253)	Retrospective	Colorectal liver metastases	Japan	63	GPS (0/ 1 and 2)	_	_	57 (90.5)	4 (6.3)	2 (3.2)	84.1% patients received adjuvant chemotherapy
10.	Moug et al 2011 (254)	Retrospective	Colorectal cancer	UK	206	GPS (0/1/2)	_	_	113 (54.9)	53 (25.7)	40 (19.4)	4.4% received neoadjuvant and 23.3% received adjuvant therapy
11.	Roxburgh et al 2011 (255)	Retrospective	Colorectal cancer	UK	302	GPS (0/1/2)	115 (38.1)	39 (12.9)	188 (62)	85 (28)	29 (10)	23.5% patients received adjuvant therapy
12.	Roxburgh et al 2011 (256)	Retrospective	Colon cancer	UK	76	mGPS (0/1 or 2)	42 (55.3)	31 (40.8)	34 (44.7)	33 (43.5)	9 (11.8)	100% patients received adjuvant chemotherapy
13.	Richards et sl 2012 (257)	Retrospective	Colorectal cancer	UK	343	GPS (0/1/2)	_	_	194 (56.6)	112 (32.7)	37 (10.7)	Adjuvant therapies not specified
14.	Suigimoto et al 2012 (258)	Retrospective	Colorectal cancer	Japan	366	GPS (0/1/2)	_	_	mGPS 0/1: 335 (91.5)	_	31 (8.5)	Adjuvant chemotherapy

15.	Powell et al 2012 (259)	Prospective	Colorectal cancer	UK	411	mGPS (0/1/2)	181 (44.0)	74 (18.0)	243 (59.1)	125 (30.4)	43 (10.5)	Adjuvant therapies not specified
16.	Ishizuka et al 2012 (260)	Retrospective	Colorectal cancer	Japan	271	GPS (0/1/2)	_	_	176 (64.9)	_	mGPS 1&2: 95 (35.1)	28.1% patients received adjuvant chemotherapy
17.	Guthrie et al 2013 (147)	Retrospective	Colorectal cancer	UK	206	mGPS (0/1/2)	_	_	132 (64)	33 (16)	41 (20)	28.2% patients received adjuvant chemotherapy
18.	Ishizuka et al 2013 (261)	Retrospective	Colorectal stage IV cancer	Japan	108	GPS 2 vs. 0,1	45 (41.7)	55 (50.9)	37 (34.2)	42 (38.9)	29 (26.9)	Adjuvant chemotherapy
19.	Ishizuka et al 2013 (119)	Retrospective	Colorectal cancer	Japan	480	GPS (0/1/2)	_	_	270 (56.3)	150 (31.2)	60 (12.5)	Patients with stage IV received chemotherapy
20.	Son et al 2013 (262)	Retrospective	Colon cancer	Korea	546	mGPS (2 vs. 0-1)	_	_	433 (80.0)	93 (17.0)	20 (3.0)	92.1% patients received chemotherapy
21.	Nozoe et al 2014 (263)	Retrospective	Colorectal cancer	Japan	272	GPS (0/1/2)	_	_	179 (65.8)	62 (22.8)	31 (11.4)	Adjuvant therapies not specified
22.	Forrest et al 2014 (264)	Retrospective	Colorectal cancer	UK	134	mGPS (0/1/2)	54 (40)	_	80 (60)	32 (24)	22 (16)	Adjuvant therapies not specified
23.	Sun et al 2014 (265)	Retrospective	Colon cancer	China	255	mGPS (0/1/2)	_	_	163 (63.9)	71 (27.8)	21 (8.3)	Neoadjuvant or adjuvant not specified
24.	Nakagawa et al 2014 (266)	Retrospective	Colorectal liver metastases	Japan	343	mGPS (0/1/2)	_	_	295 (86.0)	33 (9.6)	15 (4.4)	20.1% patients received neoadjuvant chemotherapy and 63.0% received adjuvant chemotherapy
25.	Shibutani et al 2015 (267)	Retrospective	Colorectal cancer	Japan	254	GPS (0/1/2)	_	_	174 (68.5)	44 (17.3)	36 (14.2)	Adjuvant chemotherapy
26.	Ishizuka et al 2016 (126)	Retrospective	Colorectal cancer	Japan	627	GPS (2/0, 1)	_	_	346 (55.3)	177 (28.2)	104 (16.5)	Adjuvant therapies not specified

27.	Park et al 2016 (268)	Retrospective	Colorectal cancer	UK	228	GPS (0/1/2)	_	_	131 (58)	71 (31)	26 (11)	57.5% received adjuvant therapy
28.	Park et al 2016 (7)	Retrospective	Colorectal cancer	UK	1000	mGPS (0/1/2)	370 (37.0)	260 (26.0)	635 (63.5)	207 (20.7)	158 (15.8)	24.8% received adjuvant therapy and 9.8% received neoadjuvant therapy
29.	Chan et al 2016 (269)	Retrospective	Colorectal cancer	Australia	386	mGPS (0/1/2)	_	_	155 (40.2)	53 (13.7)	178 (46.1)	Patients with high-risk stage II and III colon cancer received adjuvant chemotherapy and those with stage II or III rectal cancers received neoadjuvant therapy
Colorectal Cancer Inoperable												
1.	Elahi et al 2004 (230)	Retrospective	Gastric and colorectal cancer	UK	99	GPS (0/1/2)	71 (71.7)	26 (26.3)	28 (28.3)	45 (45.5)	26 (26.2)	Palliative chemotherapy and best supportive care
2.	Read et al 2006 (270)	Prospective	Colorectal cancer	Australia	48	GPS (0/1/2)	48 (69)	14 (7)	15 (31)	26 (54)	7 (15)	Palliative chemo and radiotherapy as well as supportive care
3.	Leitch et al 2007 (247)	Retrospective	Colorectal liver metastasis	UK	84	GPS (0,1,2)	_	_	17 (20)	44 (52)	23 (28)	Palliative chemotherapy
4.	Ishizuka et al 2009 (271)	Retrospective	Colorectal cancer	Japan	112	mGPS: 1/2	40 (36)	79 (71)	72 (64)	4 (4)	36 (32)	FOLFIRI and FOLFOX chemotherapy
5.	Inoue et al 2013 (272)	Retrospective	Colorectal cancer	Japan	245	mGPS (1-2 vs. 0)	_	_	133 (54.3)	78 (31.8)	34 (13.9)	FOLFOX and FOLFIRI chemotherapy
6.	Dreanic et al 2015 (273)	Retrospective	Colorectal cancer	France	27	mGPS: 2 Inverse mGPS: 2	_	_	_	_	27 (100)	5-fluorouracil-based systemic chemotherapy and anti-VEGF

7.	Song et al 2015 (274)	Retrospective	Colorectal cancer	Korea	177	mGPS: (0 vs. 1 or 2)	63 (35.6)	13 (7.3)	114 (64.4)	52 (29.4)	11 (6.2)	Best supportive care
8.	Thomsen et al 2016 (162)	Prospective	Colorectal cancer	Norway and Denmark	374	mGPS (0/1/2)	_	_	165 (44.1)	166 (44.4)	43 (11.5)	Cetuximab and FLOX vs. Cetuximab and intermittent FLOX
Combined Total					**9998**				**6020 (60.2)**	**2503 (25.0)**	**1475 (14.8)**	
Head and Neck Operable												
1.	Farhan-Alanie et al 2015 (275)	Retrospective	Oral SCC	UK	178	GPS (0/1/2)	_	_	131 (74)	25 (14)	22 (12)	70 patients had adjuvant therapy
Head and Nick Inoperable												
1.	Li et al 2017 (276)	Prospective	Nasopharyngeal cancer	China	249	GPS (0/1/2)	-	-	209 (83.9)	33 (13.3)	7 (2.8)	5.2% received radiotherapy and 94.8% received chemoradiotherapy
2.	Chang et al 2017 (277)	Retrospective	Head and neck cancer	Taiwan	143	GPS (0/1/2)	-	-	39 (27.3)	72 (50.3)	32 (22.4)	Concurrent chemoradiotherapy
3.	Chang et al 2017 (278)	Retrospective	Head and neck cancer	Taiwan	139	GPS (0/1/2)	-	-	32 (23.0)	72 (51.8)	35 (25.2)	All patients treated with concurrent chemoradiotherapy
Combined Total					**709**				**411 (58.0)**	**202 (28.5)**	**96 (13.5)**	
Hepatopancreaticobiliary Cancer Operable												
1.	Jamieson et al 2011 (279)	Prospective	Pancreatic ductal cancer	UK	135	GPS (0/1/2)	_	_	74 (54.8)	31 (23.0)	30 (22.2)	54.8% patients received adjuvant therapy
2.	La Torre et al 2012 (280)	Retrospective	Pancreatic cancer	Italy	101	GPS (0/1/2)	_	_	32 (31.7)	35 (34.7)	34 (33.6)	25.7% of patients received adjuvant chemo and radiotherapy

3.	Jamieson et al 2012 (281)	Retrospective	Pancreatic ductal adenocarcinoma	UK	173	mGPS (0/1/2)	_	_	95 (26.3)	37 (13.7)	41 (10.3)	38.7% patients received adjuvant chemotherapy
4.	Stoz et al 2013 (282)	Retrospective	Pancreatic cancer	Austria	110	GPS (0/1/2)	_	_	73 (66.7)	21 (19)	16 (14.3)	80.0% received chemotherapy
5.	Wu et al 2014 (283)	Retrospective	Gallbladder cancer	China	85	GPS (0 vs 1/2)	>10: 43 (50.6)	<35: 14 (16.5)	38 (44.7)		GPS 1&2: 47 (55.3)	15.3% patients received adjuvant chemotherapy
6.	Shiba et al 2015 (284)	Retrospective	Gallbladder cancer	Japan	51	GPS (0/1/2)	_	_	38 (74.5)	8 (15.7)	5 (9.8)	Neoadjuvant and adjuvant therapy not specified
7.	Oshiro et al 2013 (285)	Retrospective	Cholangiocarcinoma	Japan	62	GPS (0/1/2)	_	_	32 (50)	20 (34)	10 (16)	Neoadjuvant and adjuvant therapy not specified
8.	Shiba et al 2013 (286)	Retrospective	Carcinoma of the ampulla of vater	Japan	30	GPS (0/1/2)	_	_	23 (76.7)	5 (16.7)	2 (6.6)	Neoadjuvant and adjuvant therapy not specified
9.	Ishizuka et al 2011 (146)	Retrospective	HCC	Japan	300	hGPS (0, 1/2) *CRP>0.3 mg/dl	>3: 63 (21.0)	150 (50.0)	237 (79.0)	22 (7.3)	41 (13.7)	Neoadjuvant and adjuvant therapy not specified
10.	Ishizuka et al 2012 (287)	Retrospective	HCC	Japan	398	GPS (0, 1/2)	263 (66.1)	238 (59.8)	156 (39.2)	214 (53.8)	28 (7.0)	Neoadjuvant and adjuvant therapy not specified
11.	Horino et al 2013 (288)	Retrospective	HCC	Japan	352	GPS (0/1/2)	26 (7.4)	61 (17.3)	280 (79.5)	57 (16.2)	15 (4.3)	Neoadjuvant and adjuvant therapy not specified
12.	Huang et al 2014 (289)	Prospective	HCC	China	349	GPS (0/1/2)	19 (5.4)	10 (2.9)	278 (79.7)	61 (17.4)	10 (2.9)	Neoadjuvant and adjuvant therapy not specified
13.	Ni et al 2015 (290)	Retrospective	HCC	China	367	GPS (0/1/2) mGPS (0/1/2)	_	_	GPS: 318 (86.6) mGPS: 331 (90.2)	GPS: 45 (12.3) mGPS: 32 (8.7)	GPS: 4 (1.1) mGPS: 4 (1.1)	Neoadjuvant and adjuvant therapy not specified
14.	Okamura et al 2015 (291)	Retrospective	HCC	Japan	256	GPS (0/1/2)	_	_	226 (88.3)	26 (10.2)	4 (1.5)	Neoadjuvant and adjuvant therapy not specified

15.	Abe et al 2016 (292)	Retrospective	HCC	Japan	46	GPS (0/ 1,2)	3 (6.5)	32 (69.6)	14 (30.4)	_	mGPS 1&2: 32 (69.6)	Neoadjuvant and adjuvant therapy not specified
16.	Fu et al 2016 (293)	Retrospective	HCC	China	Training: 772	GPS (0/1/2) mGPS (0/1/2)	_	_	GPS 0: 672 (87.0) mGPS 0: 696 (90.2)	GPS 1: 91 (11.8) mGPS 1: 68 (8.8)	GPS 2: 9 (1.2) mGPS 2: 8 (1.0)	Neoadjuvant and adjuvant therapy not specified
Hepatopancreaticobiliary Cancer Inoperable												
1.	Glen et al 2006 (294)	Retrospective	Pancreatic cancer	UK	187	GPS (0/1/2)	120 (64)	62 (33)	56 (30)	80 (43)	51 (27)	Palliative treatment with platinum based chemotherapy
4.	Martin et al 2014 (295)	Retrospective	Pancreatic cancer	Australia	124	mGPS: (0,1,2)	_	_	46 (37)	26 (21)	52 (42)	Chemotherapy for metastatic disease and radiotherapy for locally advanced disease
5.	Kasuga et al 2015 (296)	Retrospective	Pancreatic cancer	Japan	61	mGPS: 2	17 (27.9)	22 (36.1)	mGPS 0/1: 49 (80.3)	_	mGPS: 2 12 (19.7)	Gemcitabine and S-1 combination therapy (FGS) as salvage chemotherapy
6.	Mitsunaga et al 2016 (297)	Prospective	Pancreatic cancer	Japan	280 (Prospective: 141)	mGPS: 1 &2	>5: 46 (32.6)	_	79 (56.0)	39 (27.7)	23 (16.3)	GEM chemotherapy
7.	Moriwaki et al 2014 (298)	Retrospective	Biliary tract cancer	Japan	Total: 62	Continuous: GPS (0 vs. 1/2)	_	_	19 (30.6)	17 (27.4)	26 (42.0)	Chemotherapy with GEM and CDDP regimens
8.	Zhou et al 2015 (299)	Prospective	HCC	China	224	GPS (0/1/2) mGPS (0/1/2)	40 (18)	24 (11)	GPS: 99 (44.2) mGPS: 115 (51.3)	GPS: 101 (45.1) mGPS: 85 (38.0)	GPS: 24 (10.7) mGPS: 24 (10.7)	TRACE chemotherapy
9.	Hurwitz et al 2015 (153)	Prospective	Pancreatic cancer	USA	121	mGPS (0/1/2)	_	_	51 (42.2)	34 (28.1)	36 (29.7_	Capecitabine vs Capecitabine and ruxolitinib

Combined Total					**4507**				**2985 (66.2)**	**970 (21.5)**	**552 (12.3)**	
Pulmonary cancer operable												
1.	Pinato et al 2014 (300)	Retrospective	Lung cancer	UK	Total:220 mGPS: 199	GPS (0/1/2)	66 (31)	65 (32)	131 (65.8)	39 (19.6)	29 (14.6)	Adjuvant radio and chemotherapy
2.	Miyazaki et al 2015 (301)	Retrospective	NSCLC	Japan	94	GPS (0/1/2)	_	_	65 (67)	25 (25.8)	7 (7.2)	Neoadjuvant and adjuvant therapy not specified
3.	Kawashima et al 2015 (144)	Retrospective	Lung cancer	Japan	1043	GPS (0/1/2)	98 (9.4)	87 (8.3)	897 (86)	107 (10)	39 (4)	Neoadjuvant and adjuvant therapy not specified
4.	Fan et al 2016 (302)	Retrospective	NSCLC	China	1243	GPS (0/1/2) mGPS (0/1/2)	379 (30.5)	154 (12.4)	813 (65.4)	327 (26.3)	103 (8.3)	55.0% patients received chemotherapyand 17.7% patients received radiotherapy
Pulmonary cancer Inoperable												
1.	Forrest et al 2003 (303)	Retrospective	NSCLC	UK	161	GPS (0/1/2)	132 (82)	22 (22)	27 (16.8)	101 (62.7)	33 (20.5)	Chemotherapy mainly cisplatin and radical radio
2.	Leung et al 2012 (304)	Retrospective	Lung cancer	UK	261	mGPS (0/1/2)	149 (57)	41 (16)	59 (22.6)	163 (62.4)	39 (15.0)	Chemotherapy (mainly platinum based) and/or radical radiotherapy
3.	Gioulbasanis et al 2012 (305)	Retrospective	Lung cancer	Greece	96	GPS (1&2)	_	_	68 (70.8)	18 (18.8)	10 (10.4)	Platinum-based chemotherapy
4.	Simmons et al 2015 (306)	Prospective	Lung cancer	Greece	390	mGPS (0/1/2)	287 (73.6)	_	103 (26.4)	183 (46.9)	104 (26.7)	Best supportive care
5.	Zhou et al 2015 (307)	Retrospective	Lung cancer	China	359	mGPS 1&2	21 (33.7)	20 (5.6)	238 (66.3)	110 (30.6)	11 (3.1)	Radiotherapy and chemotherapy

												(Irinotecan, Etoposide)
6.	Jiang et al 2015 (308)	Prospective	Lung cancer	China	138	GPS: 1&2	_	_	95 (68.8)	32 (23.2)	11 (8.0)	Cisplatin based chemotherapy
7.	Rinehart et al 2013 (151)	Prospective	Lung cancer	USA	51	GPS (0/1/2)	_	_	9	32	10	Carboplatin and gemcitabine with or without dexamethasone
Combined Total					**4035**				**2502 (62.0)**	**1137 (28.2)**	**396 (9.8)**	
Multiple Cancers Operable												
Multiple Cancers Inoperable												
1.	Chua et al 2012 (163)	Prospective	Multiple cancers	Australia	68	mGPS (1&2)	43 (63.2)	17 (25.0	21 (31)	34 (50)	13 (19)	Single unit docetaxel treatment
2.	Partridge et al 2012 (309)	Retrospective	Multiple cancers	UK	102 (GPS 0/1/2)	mGPS (1&2)	_	_	16 (15.7)	20 (19.6)	66 (64.7)	Palliative best supportive care
3.	Laird et al 2013 (17)	Prospective	Multiple cancers	UK	Total: 2456 1825 (Test) 631 (Validation)	mGPS: 1&2	Test: >10: 1548 (63.0) Validation: >10: 345 (54.7)	Test: <35: 1281 (52.2) Validation: <35: 463 (73.4)	Total: 563 Test: 277 (15.2) Validation: 286 (45.3)	Total: 712 Test: 544 (29.8) Validation: 168 (26.6)	Total: 1181 Test: 1004 (55.0) Validation: 177 (28.1)	Chemotherapy, radiotherapy and BSC
4.	Anshushaug et al 2015 (310)	Retrospective	Multiple cancers	Norway	Total: 723 With mGPS: 521	GPS (1 & 2)	>10: 312 (59.9)		209 (40.1)	131 (25.1)	181 (34.8)	Palliative radio and chemotherapy
5.	Miura et al 2015 (311)	Prospective	Multiple cancers	Japan	1160	GPS 1&2	_	_	86 (7.4)	251 (21.6)	823 (70.9)	Palliative best supportive care

6.	De Paula Pantano et al 2016 (312)	Prospective	Multiple cancers	USA	459	mGPS 1&2	>10: 93 (20.3)	_	366 (79.7)	31 (6.8)	62 (13.5)	Palliative chemoptherapy and best supportive care
7.	Tan et al 2015 2015 (313)	Prospective	Multiple cancers	Australia	Total: 114 mGPS: 101	mGPS: 1/2	>10: 51 (50.5)	_	50 (49.5)	_	mGPS 1&2: 51 (50.5)	Chemotherapy
Combined Total					**4867**				**1311 (26.9)**	**1179 (24.2)**	**2377 (48.8)**	

Table 6.2:Summary of studies using GPS/mGPS to stratify patients undergoing operative and non-operative treatment for cancer.

	Patients (n)	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2
Breast cancer	181	100 (55.2)	61 (33.7)	20 (11.1)
Bladder cancer	2200	1443 (65.6)	613 (27.9)	144 (6.5)
Gynaecological cancer	1594	999 (62.7)	394 (24.7)	201 (12.6)
Prostate cancer	223	158 (70.9)	43 (19.3)	22 (9.9)
Gastro-oesophageal cancer	9590	6941 (72.4)	1670 (17.4)	979 (10.2)
Haematological cancer	430	90 (20.9)	165 (38.4)	175 (40.7)
Renal cancer	2559	1741 (68.0)	529 (20.7)	289 (11.3)
Colorectal cancer	9998	6020 (60.2)	2503 (25.0)	1475 (14.8)
Head and Neck cancer	709	411 (58.0)	202 (28.5)	96 (13.5)
Hepatopancreaticobiliary cancer	4507	2985 (66.2)	970 (21.5)	552 (12.3)
Pulmonary cancer	4035	2502 (62.0)	1137 (28.2)	396 (9.8)
Multiple cancers	4867	1311 (26.9)	1179 (24.2)	2377 (48.8)

Table 6.3: Summary of studies using mGPS to stratify patients undergoing operative and non-operative treatment for cancer.

	Patients (n)	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2
Breast Cancer				
Operative	–	–	–	–
Non-operative	181	100 (55.2)	61 (33.7)	20 (11.1)
Bladder Cancer				
Operative	2133	1410 (66.1)	596 (27.9)	127 (6.0)
Non-operative	67	33 (49.3)	17 (25.4)	17 (25.4)
Gynaecological cancer				
Operative	724	538 (74.3)	144 (19.9)	42 (5.8)
Non-operative	870	461 (53.0)	250 (28.7)	159 (18.3)
Prostate Cancer				
Operative	–	–	–	–
Non-operative	223	158 (70.8)	43 (19.3)	22 (9.9)
Gastro-oesophageal cancer				
Operative	7693	6076 (79.0)	1068 (13.9)	549 (7.1)
Non-operative	1897	865 (45.6)	602 (31.7)	430 (22.7)
Haematological cancer				
Operative	–	–	–	–
Non-operative	430	90 (20.9)	165 (38.4)	175 (40.7)
Renal cancer				
Operative	2417	1700 (70.3)	451 (18.7)	266 (11.0)
Non-operative	142	41 (28.9)	78 (54.9)	23 (16.2)
Colorectal cancer				

Operative	8832	5476 (62.0)	2088 (23.6)	1268 (14.4)
Non-operative	1166	544 (46.7)	415 (35.6)	207 (17.7)
Head and neck cancer				
Operative	178	131 (74)	25 (14)	22 (12)
Non-operative	531	280 (52.7)	177 (33.3)	74 (14.0)
Hepatopancreaticobiliary cancer				
Operative	3587	2586 (72.1)	673 (18.8)	328 (9.1)
Non-operative	920	399 (43.4)	297 (32.3)	224 (24.3)
Pulmonary cancer				
Operative	2579	1903 (73.8)	498 (19.3)	178 (6.9)
Non-operative	1456	599 (41.1)	639 (43.9)	218 (15.0)
Multiple cancers				
Operative	–	–	–	–
Non-operative	4867	1311 (26.9)	1179 (24.2)	2377 (48.8)
Total Operative	28,143			
Total Non-operative	12,750			
Combined Total	40,893			

7. THE PROGNOSTIC VALUE OF SYSTEMIC INFLAMMATION IN PATIENTS UNDERGOING SURGERY FOR COLON CANCER: COMPARISON OF COMPOSITE RATIOS AND CUMULATIVE SCORES

7.1 Introduction

Colorectal cancer is the fourth most common cancer in the UK and the second most common cause of cancer death (314). Despite death rates from colorectal cancer falling by approximately 14% over the last decade, approximately 40% of those diagnosed will die from their colorectal cancer (314). Surgery remains the primary modality of cure in these patients and therefore, there is a continuing interest in factors that will effectively identify patients at high risk of dying from their disease following potentially curative surgery.

As discussed in sections 1.2-1.4 over the last decade or so it has become clear that markers of the systemic inflammatory response are clinically useful to identify patients at high risk of tumour progression in a variety of common solid tumours, in particular lung and gastrointestinal cancer (37, 38). These markers of the systemic inflammatory response are usually based around composite ratios or cumulative scores of different circulating white blood cells or acute phase proteins representing the systemic responses of two different organs, lymphoid/myeloid tissue and liver respectively (Table 7.1). There have been two main approaches to the formation of these prognostic scores. One approach is to take the ratio of different white blood cells and then apply a prognostic threshold to the ratio such that outcome is effectively stratified. The most repeatedly validated example of this approach is the NLR based on the ratio of circulating neutrophil and lymphocyte counts (Table 7.1) (37, 38). Other validated examples are the PLR based on the ratio of circulating platelet and lymphocyte counts (Table 7.1) and the LMR based on the ratio of circulating lymphocyte and monocyte counts (Table 7.1) (37, 38). Also, recently a similar approach has been applied to the acute phase proteins, CRP and albumin to produce the CAR (Table 7.1) (37, 38). Although it is clear that the above ratios have prognostic value a disadvantage of

the ratio approach is that, depending on the threshold used, an abnormal ratio may be defined with one or both markers having a normal reference value.

A simpler approach is the cumulative prognostic score, where markers of the systemic inflammatory response are defined as normal or as abnormal based on their laboratory reference ranges such that two markers with normal values score lowest and have the best outcomes and two markers with abnormal values score highest and have the poorest outcomes poorest. The most widely validated example of this approach is the GPS based on the acute phase proteins CRP and albumin (Table 7.1) (37, 38). Also, recently the Neutrophil Platelet Score (NPS) using neutrophils and platelets has been reported (39). Clearly, the cumulative score approach can also be applied to the ratios described above (Table 7.1) such as NLR (termed NLS), PLR (termed PLS) and LMR (termed LMS).

Therefore, the aim of this Chapter was to compare the prognostic value of systemic inflammatory markers, in particular that of composite ratios and cumulative scores, in patients undergoing surgery for colon cancer.

7.2 Patients and Methods

Patients were identified from a prospectively collected and maintained database of colon cancer resections undertaken in a single surgical unit at Glasgow Royal Infirmary. Consecutive patients who met the following criteria were included: firstly, those who had preoperative measurement of serum CRP, albumin and differential blood cell counts within 30 days before surgery; secondly, those who on the basis of preoperative abdominal computed tomography and laparotomy findings were considered to have undergone potentially curative resection for colonic cancer between January 1997 and June 2014. Patients with inflammatory bowel disease-related cancer, who underwent resection with palliative intent or local resection only, or had not had preoperative measurement of CRP or albumin, were excluded (7). Tumours were staged using the fifth edition of the TNM classification which was standard practice in Glasgow Royal Infirmary until January 2018, with additional data taken from pathological reports issued after resection (315). After surgery, all patients were discussed at a multidisciplinary meeting involving surgeons, oncologists, radiologists, and pathologists with special interest in colorectal cancer; patients with stage III or high-risk stage II disease and no significant comorbidities precluding chemotherapy use were offered primarily 5-fluorouracil-based adjuvant chemotherapy on the basis of current guidelines at the time.

Preoperative serum CRP, albumin and differential blood cell counts were recorded prospectively. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR) and C-reactive protein/ albumin ratio (CAR) were all calculated by directly dividing the former by the latter (Table 7.1). The neutrophil lymphocyte score (NLS), platelet lymphocyte score (PLS), lymphocyte monocyte score (LMS), neutrophil platelet score (NPS) and mGPS were all constructed using normal reference ranges (Table 7.1).

Patients were routinely followed up for 5 years after surgery. Date and cause of death were crosschecked with the cancer registration system and the Registrar General (Scotland). Death records were complete until June 30th, 2017, which acted as the censor date. Cancer-specific survival (CSS) was measured from date of surgery until date of death from recurrent or metastatic colonic cancer. Overall survival (OS) was measured until the date of death from any cause. The West of Scotland Research Ethics Committee approved the study.

Statistical Analysis

The cut off values for individual ratios were examined using receiver operating characteristic (ROC) curve analyses. The threshold values of such characteristics were based on the most prominent point on the ROC curve for ‘‘sensitivity’’ and ‘‘1-specificity,’’ respectively. The optimal threshold values were defined using the Youden index (maximum (sensitivity + specificity - 1)) and these were compared with published validated values to determine the value used in the subsequent analysis (126, 316). The area under the ROC (AUROC) curve also was calculated. The relationship between NLR, PLR, LMR, CAR, NLS, PLS, LMS and mGPS and both cancer specific and overall survival was assessed using Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs). The relationship between NLR, PLR, LMR, CAR, NLS, PLS, LMS and mGPS and patient clinicopathological characteristics was assessed using Pearson Chi-Square tests. In order to adjust for multiple comparisons during the correlation of composite ratios and cumulative scores and clinicopathological characteristics a p-value of <0.01 was considered significant. All analyses were performed using SPSS version 22.0 (IBM Corp, Armonk, NY).

7.3 Results

From the prospectively maintained database 801 patients undergoing potentially curative resection for colon cancer were examined (Table 7.2). The majority of patients were over 65 years of age (69%), were male (54%), were overweight or obese (57%) and were ASA grade 2 or greater (83%). The majority of patients presented electively (86%), had an open resection (85%) and did not receive adjuvant therapy (75%). The majority of patients had either TNM stage II or III disease (86%) with moderate/well differentiated tumours (n=703, 89%) and venous invasion (52%). The majority of patients had no margin involvement (95%), peritoneal involvement (72%) or tumour perforation (97%) at time of resection. On follow up there were 237 (28%) cancer related deaths and 437 (52%) deaths overall.

The relationship between the composite ratios and cumulative scores and the clinicopathological characteristics of patients undergoing elective surgery for colon cancer is shown in Table 7.3 (n=689). There was statistically significant correlation between the majority of the composite ratios and cumulative scores and age ($p<0.01$), BMI ($p<0.01$), T-stage ($p<0.01$), venous invasion ($p<0.01$) and peritoneal involvement ($p<0.01$).

The relationship between composite ratios and cumulative scores and their component values in patients undergoing surgery for colon cancer is shown in Table 7.4 (n=801). The majority were not assigned as systemically inflamed prior to surgery according to either ratios or scores (NLR>5 19%, NLS>0 47%, PLR>150 65%, PLS>0 48%, NPS>0 28%, CAR>0.22 49%, mGPS>0 41%).

The median values for the components of the ratios and scores are shown in Table 7.4. An NLR 3-5 was associated with a median neutrophil count of 5.5 $x10^9$/l and a median lymphocyte count of 1.5 $x10^9$/l, both within the normal reference range. In contrast, an NLR >5 was associated with a median neutrophil count of 8.5 $x10^9$/l and a median lymphocyte count of 1.1 $x10^9$/l, both outside the normal reference range. A PLR>150 was associated

with a median platelet count of $325x10^9$/l and a median lymphocyte count of $1.4x10^9$/l, the platelet count being within the normal reference range. An LMR<2.4 was associated with a median lymphocyte count of $1.3x10^9$/l and a median monocyte count of $0.8x10^9$/l, monocyte count being within the normal reference range. A CAR>0.22 was associated with a median CRP concentration of 24mg/l and a median albumin concentration of 36g/l, albumin being within the normal reference range.

The relationship between validated ratios, scores and 5 year cancer specific survival in patients undergoing surgery for colon cancer is shown in Table 7.5 and Figures 7.1-7.4. On ROC analysis using standard thresholds and cancer specific survival as an end-point the AUC for TNM stage was 0.649, NLR was 0.577, NLS was 0.566, PLR was 0.538, PLS was 0.607, LMR was 0.613, LMS was 0.605, NPS was 0.580, CAR was 0.582 and mGPS was 0.591. When adjusted for TNM stage, NLR>5 ($p<0.001$), NLS 1 and 2 (both $p\leq0.01$), PLS 2 ($p<0.001$), LMR<2.4 ($p<0.001$), LMS 2 ($p<0.001$), NPS 2 ($p\leq0.001$), CAR> 0.22 ($p<0.001$), mGPS 2 ($p<0.001$) were significantly associated with cancer specific survival.

On ROC analysis using standard thresholds and 5 year overall survival as an end-point the following AUC for TNM stage was 0.569, NLR was 0.594, NLS was 0.586, PLR was 0.555, PLS was 0.620, LMR was 0.590, LMS was 0.585, NPS was 0.576, CAR was 0.603 and mGPS was 0.623. When adjusted for TNM stage, NLR>5 ($p<0.001$), NLS 1 and 2 (both $p\leq0.01$), PLS 2 ($p<0.001$), LMR<2.4 ($p<0.001$), LMS 2 ($p<0.001$), NPS 2 ($p\leq0.01$), CAR> 0.22 ($p<0.001$), mGPS 2 ($p<0.001$) were all significantly associated with overall survival (Table 7.5 and Figures 7.1-7.4).

The complementary prognostic value of the cumulative scores NPS and mGPS, markers of innate immune activation from two different organs, were examined in the context of TNM staging (Table 7.6). Within TNM stage II disease the 5 year cancer specific survival rate was 82% and the 5 year cancer specific survival rate varied between 86% and 73% according

to the NPS and between 86% and 79% according to the mGPS. The 5 year overall survival rate was 57% and the 5 year overall survival rate varied between 61% and 47% according to the NPS and between 65% and 48% according to the mGPS.

Within TNM stage III disease the 5 year cancer specific survival rate was 65% and the 5 year cancer specific survival rate varied between 67% and 60% according to the NPS and between 69% and 59% according to the mGPS. The 5 year overall survival rate was 47% and the 5 year overall survival varied between 51% and 37% according to the NPS and between 53% and 38% according to the mGPS (Table 7.6).

7.4 Discussion

The results of the present study directly compare, for the first time, the prognostic value of composite ratios and cumulative scores of the systemic inflammatory response. These ratios and scores, whether composed of white cells from lymphoid/ myeloid tissue or from acute phase proteins from the liver, had prognostic value, independent of TNM stage, in patients with colon cancer. Moreover, systemic inflammation scores from different organs had similar prognostic value. Taken together, the systemic inflammatory response represents an important prognostic domain to be monitored in patients with colon cancer.

In the present study it was of interest that the ratio thresholds did not always differentiate normal from abnormal values of the composite values. The discrepancy between the ratio threshold and the abnormal single component is shown in Figure 7.5. In Figure 7.5, using the line of best fit, an NLR>5 was associated with a median neutrophil count of approximately 7.5, at the top of the normal reference range. In contrast, an NLR>3 was associated with a neutrophil count of approximately 4.5, within in the normal reference range. With reference to PLR>150 it was associated with a platelet count of approximately 200, within the normal range (Figure 7.5). With reference to LMR<2.4 it was associated with a lymphocyte count of 1.5, at the bottom of the normal range (Figure 7.5). Finally, with reference to CAR>0.22 was associated with a CRP of 10 well above the normal range (Figure 7.5). Therefore, it is clear that a number of ratios (e.g. NLR>3 and PLR >150) do not describe components with abnormal values. Moreover, the ratios, compared with scores, consistently assigned a higher proportion of patients to be systemically inflamed. Given that scores based on abnormal value are simpler to construct and have similar and overlapping prognostic value, independent of TNM stage, compared with composite ratios (Table 7.5) the rationale for the continued use of such ratios is problematic. Indeed, recent clinical calculators for survival in patients with metastatic colorectal cancer, based on data of more than 20,000 patients from randomised controlled trials (ARCAD database), has incorporated

the white cell count, neutrophil count, platelet count and albumin level as scores rather than derived ratios (168, 173). Furthermore Dupré and Malik have argued that the variability of reported prognostic thresholds of NLR, PLR and LMR questions their reliability for routine clinical practice (166).

Although it is presumed that composite ratios of lymphoid/ myeloid cells and acute phase proteins reflect similar aspects of the systemic inflammatory response, it is clear from the plot of NLR and CAR (Figure 2.5) that these ratios do not simply mirror one another. In contrast, when cumulative scores such as NPS and mGPS, based on normal reference ranges, were compared there was better agreement in terms of systemic inflammatory response status and prognostic value (Table 7.6). However it should be noted that although CRP and albumin are similar proteins components of a differential WCC such as neutrophil count are composed of a number of cell types (164). Irrespective the cumulative score approach, based on normal reference ranges, improves our understanding of aspects of the activation of the innate systemic inflammatory response. The simplicity and consistency of this approach has much to commend it.

The innate systemic inflammatory response in patients with cancer, as well as incorporating responses from lymphoid/ myeloid tissue and the liver, incorporates responses from other organs and tissues. In particular, the response from the sympathetic nervous system is of interest since similar to that of NPS and mGPS it is intimately connected with immune responses (317). Having established, in patients with cancer, the prognostic value of simple and objective markers of activation of lymphoid/ myeloid and liver tissue activation, it would be of considerable interest to examine the prognostic value of objective markers of activation of the sympathetic nervous system.

In the present study there was a clear correlation between higher composite ratios and cumulative scores and increased age, BMI, advanced T-stage and the presence of both

venous and peritoneal invasion. These clinicopathological characterises are also directly associated with a poorer prognosis adding further weight to the prognostic ability of both composite ratios and cumulative score in patients with colonic cancer.

Recently Park and co-workers reported that the mGPS provides complimentary prognostic information to current TNM-based staging (7). When TNM staging and mGPS were combined 5-year OS ranged from 92% (TNM 0, mGPS=0) to 26% (stage III, mGPS=2) and 10-year OS ranged from 92% (TNM 0, mGPS=0) to 17% (TNM III, mGPS=2) ($P<0.001$) (7). This further highlights the prognostic ability of the mGPS which is complementary to the gold standard of TNM staging with both being routinely available worldwide (7).

The present study has a number of possible limitations. Although a relatively large prospective cohort there were small numbers of observations in some sub-group analysis. Furthermore, data relating to other factors that may have affected markers of the systemic inflammatory response such drugs taken prior to sampling were not available. Although the present study used the 5th rather than the 7th edition of the TNM staging system, this was recommended in the 2014 Colorectal Cancer Care Guidelines of the Royal College of Pathologists and as such is the basis for all current UK wide practice (6). Furthermore migration from the 5th to 7th edition would be expected to account for an upstaging from node negative to node positive disease in less than 3% of cases, with little subsequent effect on prognosis (6, 318, 319).

A maximum of a 30-day interval between laboratory testing and surgery maybe considered to be too long. However this timescale has been widely reported in the literature and consistent with the chronic nature of the systemic inflammatory response in patients with cancer (37). Also, patients with inflammatory bowel disease related cancers were not included in the analysis. As such the patient confounding factors of active systemic inflammatory disease and acute changes in the inflammatory state have been minimised.

In summary, present study directly compares, for the first time, the prognostic value of composite ratios and cumulative scores of the systemic inflammatory response. These ratios and scores, whether composed of white cells from lymphoid/ myeloid tissue or from acute phase proteins from the liver, had prognostic value, independent of TNM stage, in patients with colon cancer. However, cumulative scores, based on normal reference ranges, are simpler and more consistent for clinical use.

7.5 Tables and Footnotes

Table 7.1: Systemic inflammation based prognostic ratios and scores

Ratio/ Score	Ratio/Score
Neutrophil Lymphocyte Ratio (NLR):	
Neutrophil count: lymphocyte count	≤3
Neutrophil count: lymphocyte count	3-5
Neutrophil count: lymphocyte count	>5
Neutrophil Lymphocyte Score (NLS):	
Neutrophil Count ≤ 7.5 x 10^9/l and lymphocyte count ≥1.5 x 10^9/l	0
Neutrophil Count > 7.5 x 10^9/l and lymphocyte count ≥1.5 x 10^9/l	1
Neutrophil Count ≤ 7.5 x 10^9/l and lymphocyte count <1.5 x 10^9/l	1
Neutrophil Count > 7.5 x 10^9/l and lymphocyte count <1.5 x 10^9/l	2
Platelet Lymphocyte Ratio (PLR):	
Platelet count: lymphocyte count	≤150
Platelet count: lymphocyte count	>150
Platelet Lymphocyte Score (PLS):	
Platelet Count ≤ 400 x 10^9/l and lymphocyte count ≥1.5 x 10^9/l	0
Platelet Count > 400 x 10^9/l and lymphocyte count ≥1.5 x 10^9/l	1
Platelet Count ≤ 400 x 10^9/l and lymphocyte count <1.5 x 10^9/l	1
Platelet Count > 400 x 10^9/l and lymphocyte count <1.5 x 10^9/l	2
Lymphocyte Monocyte Ratio (LMR):	
Lymphocyte count: monocyte count	≥2.40
Lymphocyte count: monocyte count	<2.40
Lymphocyte Monocyte Score (LMS):	
Lymphocyte count ≥1.5 x 10^9/l and monocyte count ≤ 0.80 x 10^9/l	0
Lymphocyte count <1.5 x 10^9/l and monocyte count ≤ 0.80 x 10^9/l	1
Lymphocyte count ≥1.5 x 10^9/l and monocyte count > 0.80 x 10^9/l	1
Lymphocyte count <1.5 x 10^9/l and monocyte count > 0.80 x 10^9/l	2
Neutrophil Platelet Score (NPS):	
Neutrophil Count ≤ 7.5 x 10^9/l and platelet count ≤ 400 x 10^9/l	0
Neutrophil Count > 7.5 x 10^9/l and platelet count ≤ 400 x 10^9/l	1
Neutrophil Count ≤ 7.5 x 10^9/l and platelet count > 400 x 10^9/l	1
Neutrophil Count > 7.5 x 10^9/l and platelet count > 400 x 10^9/l	2
C-reactive protein Albumin Ratio (CAR):	
C-reactive protein: Albumin	≤0.22
C-reactive protein: Albumin	>0.22
modified Glasgow Prognostic Score (mGPS):	
C-reactive protein ≤ 10mg/l and Albumin ≥35 g/l	0
C-reactive protein > 10mg/l and Albumin ≥35 g/l	1
C-reactive protein > 10mg/l and Albumin <35 g/l	2

Table 7.2: The clinicopathological characteristics of patients undergoing surgery for colon cancer (n=801).

	Variables	n=801 (%)
Age (years)	<65	248 (31)
	65-74	270 (34)
	>75	283 (35)
Sex	Female	371 (46)
	Male	430 (54)
BMI[a]	Underweight	72 (12)
	Normal	190 (31)
	Overweight	192 (32)
	Obese	153 (25)
ASA Grade[b]	1	97 (17)
	2	243 (42)
	3	208 (36)
	4	29 (5)
Presentation	Elective	689 (86)
	Emergency	112 (14)
Type of Surgery	Open	679 (85)
	Laparoscopic	122 (15)
Neoadjuvant therapy[c]	No	782 (99)
	Yes	8 (1)
Adjuvant therapy[d]	No	574 (75)
	Yes	194 (25)
T stage	1	52 (6)
	2	76 (10)
	3	418 (52)
	4	255 (32)
N stage	0	507 (63)
	1	207 (26)
	2	87 (11)
TNM stage	1	116 (14)
	2	391 (49)
	3	294 (37)
Differentiation[e]	Mod/well	709 (89)
	Poor	86 (11)
Venous invasion[f]	No	383 (48)
	Yes	416 (52)
Margin involvement[f]	No	757 (95)
	Yes	42 (5)
Peritoneal involvement[f]	No	578 (72)
	Yes	221 (28)
Tumour Perforation[f]	No	772 (97)
	Yes	27 (3)

a

n=607, b n=575, c n=790, d n=778, e n=795, f n=799

Table 7.3: The correlation between composite ratios and cumulative scores and clinicopathological characteristics of patients undergoing elective surgery for colon cancer (n=689).

	Age	Sex	BMI	ASA Grade	T-stage	N-stage	Differentiation	Venous Invasion	Margin Involvement	Peritoneal Involvement	Tumour Perforation	Adjuvant Therapy
NLR	0.009	0.398	<0.001	0.156	0.069	0.287	0.018	0.002	0.219	0.195	<0.001	0.063
NLS	0.002	0.746	0.003	0.880	0.039	0.504	0.073	0.078	0.069	0.062	0.004	0.301
PLR	<0.001	0.391	<0.001	0.294	0.001	0.395	0.087	0.214	0.095	0.002	0.803	0.758
PLS	0.008	0.827	<0.001	0.337	0.001	0.449	0.029	0.002	0.012	0.005	0.043	0.907
LMR	<0.001	0.004	0.030	0.705	0.063	0.948	0.557	0.133	0.750	0.085	0.041	0.067
LMS	<0.001	0.872	0.165	0.841	0.001	0.412	0.044	0.158	0.033	<0.001	0.184	0.097
NPS	0.649	0.990	0.016	0.753	0.004	0.017	0.005	0.013	0.015	0.277	0.375	0.341
CAR	0.008	0.618	0.027	0.009	<0.001	0.071	0.001	0.011	0.037	0.007	0.004	0.341
mGPS	0.180	0.913	<0.001	0.294	<0.001	0.616	<0.001	0.006	0.005	0.003	0.001	0.422

*p<0.01 considered significant

Table 7.4: The relationship between composite ratios and cumulative scores and their component values in patients undergoing surgery for colon cancer (n=801).

			Median (range)	Median (range)
		n (%)	**Neutrophil**	**Lymphocyte**
NLR	≤3	388 (48.4)	4.2 (0.4-9.0)	2.0 (0.7-14.1)
	3-5	260 (32.5)	5.5 (2.1-17.5)	1.5 (0.5-4.7)
	>5	153 (19.1)	8.5 (2.2-21.3)	1.1 (0.3-2.5)
NLS	0	421 (52.6)	4.8 (1.7-7.5)	2.0 (1.5-14.1)
	1	325 (40.6)	5.1 (0.4-20.6)	1.3 (0.3-4.70)
	2	55 (6.9)	9.9 (7.6-21.3)	1.1 (0.5-1.4)
			Platelet	Lymphocyte
PLR[a]	≤150	237 (34.8)	248 (93-653)	2.1 (1.0-14.1)
	>150	445 (65.2)	325 (119-814)	1.40 (0.30-4.70)
PLS[a]	0	351 (51.5)	282 (94-396)	2.0 (1.5-14.1)
	1	283 (41.5)	292 (93-814)	1.3 (0.3-11.0)
	2	48 (7.0)	478 (406-698)	1.1 (0.6-1.4)
			Lymphocyte	Monocyte
LMR[b]	≥2.4	252 (61.0)	1.9 (0.6 -14.1)	0.6 (0.1-1.3)
	<2.4	161 (39.0)	1.3 (0.3-3.0)	0.8 (0.3-2.0)
LMS[b]	0	214 (51.8)	2.0 (1.5-14.1)	0.6 (0.1-0.8)
	1	169 (40.9)	1.3 (0.3-4.6)	0.7 (0.1-2.0)
	2	30 (7.3)	1.2 (0.6-1.4)	1.0 (0.9-1.9)
			Neutrophil	Platelet
NPS[a]	0	491 (72.0)	4.5 (0.4-7.50)	268 (93-400)
	1	140 (20.5)	6.7 (2.3-18.8)	415 (96-811)
	2	51 (7.5)	9.8 (7.6-20.60)	474 (406-814)
			CRP	Albumin
CAR	≤0.22	412 (51.4)	5 (0.1-9)	38 (21-49)
	>0.22	389 (48.6)	22 (6-339)	35 (15-47)
mGPS	0	474 (59.2)	5 (0.1-10)	38 (21-49)
	1	173 (21.6)	22 (11-220)	38 (35-47)
	2	154 (19.2)	37 (11-339)	31 (15-34)

a n= 682, b n= 413

Table 7.5: The relationship between validated ratios, scores and survival in patients undergoing surgery for colon cancer (n=801)

		Univariate		Multivariate Adjusted for TNM stage			Univariate		Multivariate Adjusted for TNM stage	
TNM stage	**AUC (95%CI)**	**CSS HR (95%CI)**	**p-value**	**CSS HR (95%CI)**	**p-value**	**AUC (95%CI)**	**OS HR (95%CI)**	**p-value**	**OS HR (95%CI)**	**p-value**
I (n=116)	0.649 (0.559-0.740)					0.569 (0.477-0.661)				
II (n=391)		4.39 (1.78-10.85)	0.001				1.73 (1.16-2.57)	0.007		
III (n=294)		9.86 (4.02-24.17)	<0.001				2.54 (1.70-3.79)	<0.001		
NLR/ NLS										
NLR <3 (n=388)	0.577 (0.529-0.624)					0.594 (0.554-0.633)				
NLR 3-5 (n=260)		1.22 (0.87-1.72)	0.251	1.28 (0.91-1.80)	0.152		1.21 (0.95-1.53)	0.118	1.26 (0.99-1.59)	0.061
NLR >5 (n=153)		2.06 (1.46-2.92)	<0.001	2.11 (1.50-3.00)	<0.001		1.85 (1.44-2.37)	<0.001	1.88 (1.46-2.42)	<0.001
NLS 0 (n=421)	0.566 (0.519-0.613)					0.586 (0.546-0.626)				
NLS 1 (n=325)		1.49 (1.10-2.01)	0.010	1.57 (1.16-2.12)	0.003		1.45 (1.17-1.79)	0.001	1.49 (1.21-1.85)	<0.001
NLS 2 (n=55)		2.01 (1.22-3.30)	0.006	1.85 (1.12-3.05)	0.016		1.68 (1.15-2.46)	0.007	1.59 (1.09-2.33)	0.016
PLR/ PLS[a]										
PLR≤150 (n=237)	0.538 (0.486-0.589)					0.555 (0.512-0.598)				
PLR >150 (n=445)		1.31 (0.92-1.86)	0.141	1.20 (0.84-1.70)	0.326		1.26 (0.98-1.63)	0.073	1.20 (0.93-1.55)	0.166
PLS 0 (n=351)	0.578 (0.525-0.631)					0.586 (0.542-0.629)				
PLS 1 (n=283)		1.39 (0.98-1.96)	0.061	1.33 (0.94-1.88)	0.106		1.34 (1.05-1.70)	0.020	1.29 (1.01-1.65)	0.040
PLS 2 (n=48)		2.77 (1.67-4.59)	<0.001	2.42 (1.46-4.01)	0.001		2.16 (1.46-3.18)	<0.001	1.94 (1.31-2.87)	0.001

LMR/ LMS[b]										
LMR ≥2.4 (n=161)	0.613 (0.539-0.688)					0.590 (0.528-0.652)				
LMR<2.4 (n=252)		2.62 (1.61-4.27)	<0.001	2.49 (1.53-4.06)	<0.001		2.08 (1.44-3.00)	<0.001	1.99 (1.38-2.87)	<0.001
LMS 0 (n=214)	0.605 (0.528-0.681)					0.585 (0.522-0.648)				
LMS 1 (n=169)		1.69 (0.99-2.86)	0.051	1.65 (0.97-2.81)	0.064		1.47 (0.99-2.17)	0.058	1.41 (0.95-2.10)	0.088
LMS 2 (n=30)		3.68 (1.81-7.49)	<0.001	3.67 (1.80-7.49)	<0.001		2.81 (1.59-4.95)	<0.001	2.76 (1.56-4.88)	<0.001
NPS[a]										
NPS 0 (n=491)	0.580 (0.526-0.634)					0.576 (0.532-0.619)				
NPS 1 (n=140)		1.76 (1.22-2.55)	0.003	1.47 (1.02-2.13)	0.042		1.64 (1.26-2.14)	<0.001	1.47 (1.12-1.92)	0.005
NPS 2 (n=51)		2.50 (1.52-4.10)	<0.001	2.14 (1.30-3.51)	0.003		1.83 (1.24-2.70)	0.002	1.65 (1.12-2.44)	0.011
CAR/ mGPS										
CAR≤0.22 (n=412)	0.582 (0.536-0.628)					0.603 (0.563-0.642)				
CAR >0.22 (n=389)		1.88 (1.40-2.51)	<0.001	1.76 (1.31-2.35)	<0.001		1.88 (1.53-2.31)	<0.001	1.84 (1.49-2.26)	<0.001
mGPS 0 (n=474)	0.591 (0.544-0.639)					0.623 (0.582-0.663)				
mGPS 1 (n=173)		1.35 (0.95-1.94)	0.099	1.22 (0.85-1.75)	0.282		1.49 (1.17-1.90)	0.001	1.44 (1.12-1.84)	0.004
mGPS 2 (n=154)		2.47 (1.77-3.46)	<0.001	2.31 (1.65-3.25)	<0.001		2.32 (1.81-2.99)	<0.001	2.28 (1.76-2.95)	<0.001

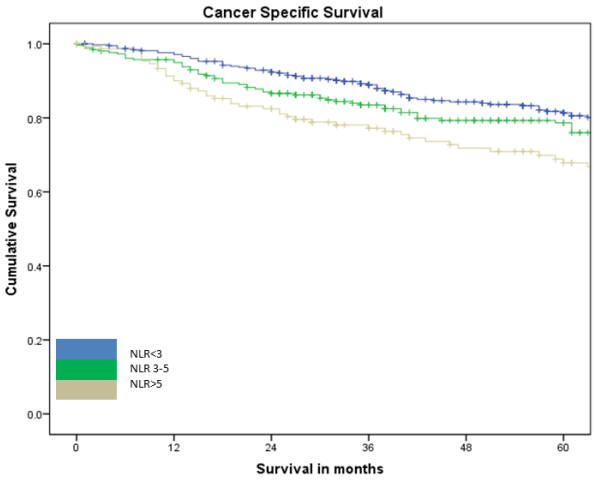
a n= 682, b n= 413

Table 7.6 The relationship between mGPS, NLS and 5 year cancer specific survival (CSS) and overall survival (OS) rates in patients undergoing potentially curative resection of TNM stage II (n=391) and III (n=294) colonic cancer.

	Stage II (n=322)							**Stage II (n=322)**					
	mGPS 0		**mGPS 1/2**			**mGPS 0-2**		**mGPS 0**		**mGPS 1/2**			**mGPS 0-2**
	n	**5 year CSS (%)**	**n**	**5 year CSS (%)**	**n**			**n**	**5 year OS (%)**	**n**	**5 year OS (%)**	**n**	
NPS 0	147 (85%)	88.4 (0.03)	78 (52%)	82.1 (0.04)	**225**	**86.2 (0.02)**		147 (85%)	66.7 (0.04)	78 (52%)	58.7 (0.06)	**225**	**61.3 (0.03)**
NPS 1/2	26 (15%)	69.2 (0.09)	71 (48%)	74.6 (0.05)	**97**	**73.2 (0.05)**		26 (15%)	57.7 (0.10)	71 (48%)	43.7 (0.06)	**97**	**47.4 (0.05)**
NPS 0-2	**173**	**85.5 (0.03)**	**149**	**78.5 (0.03)**	**322**	**82.3 (0.02)**		**173**	**65.3 (0.04)**	**149**	**47.7 (0.04)**	**322**	**57.1 (0.03)**
	Stage III (n=254)							**Stage III (n=254)**					
NPS 0	120 (82%)	70.0 (0.04)	50 (46%)	60.0 (0.07)	**170**	**67.1 (0.04)**		120 (82%)	54.2 (0.05)	50 (46%)	44.0 (0.07)	**170**	**51.2 (0.04)**
NPS 1/2	25 (18%)	64.0 (0.10)	59 (54%)	57.6 (0.07)	**84**	**59.5 (0.05)**		25 (18%)	48.0 (0.10)	59 (54%)	32.2 (0.06)	**84**	**36.9 (0.05)**
NPS 0-2	**145**	**69.0 (0.04)**	**109**	**58.7 (0.05)**	**254**	**64.6 (0.03)**		**145**	**53.1 (0.04)**	**109**	**37.6 (0.05)**	**254**	**46.5 (0.03)**

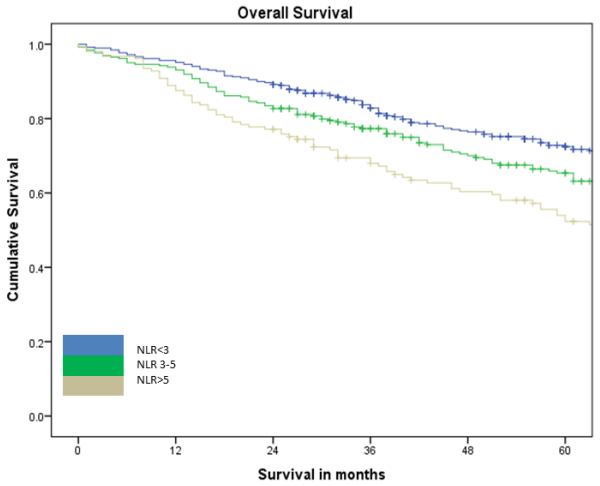
Values are expressed as % (standard error) survival not calculated if n<10.

7.6 Figures and Legends



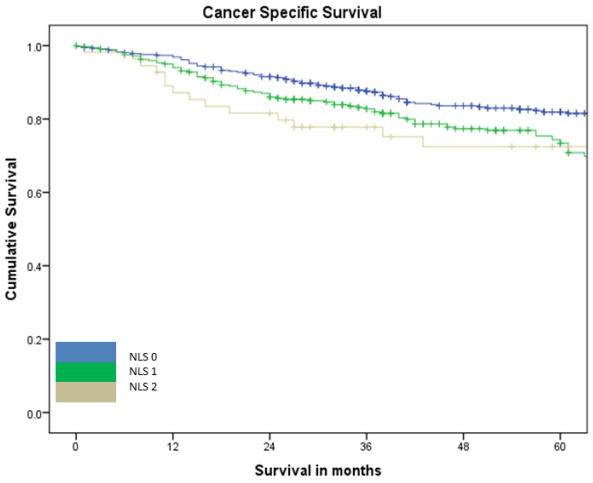
Number at risk	0	12	24	36	48	60
NLR<3	388	377	359	347	333	325
NLR 3-5	260	247	226	219	211	210
NLR>5	153	138	127	120	114	110

Figure 7.1a:



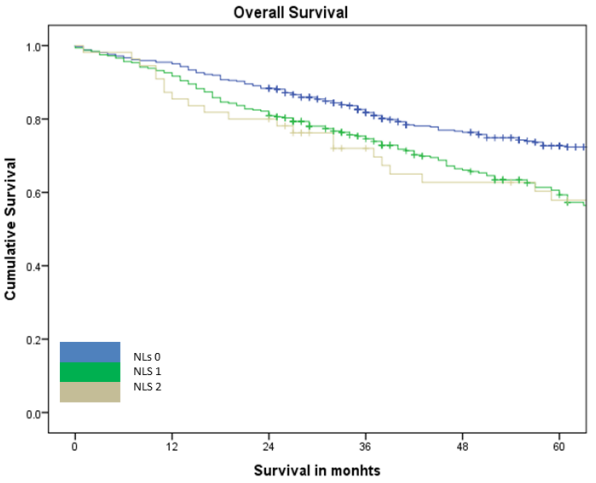
Number at risk	0	12	24	36	48	60
NLR<3	388	369	346	323	302	290
NLR 3-5	260	242	215	202	187	178
NLR>5	153	134	118	105	95	85

Figure 7.1b



Number at risk	0	12	24	36	48	60
NLS 0	421	408	386	371	358	353
NLS 1	325	306	281	272	259	251
NLS 2	55	48	45	43	41	41

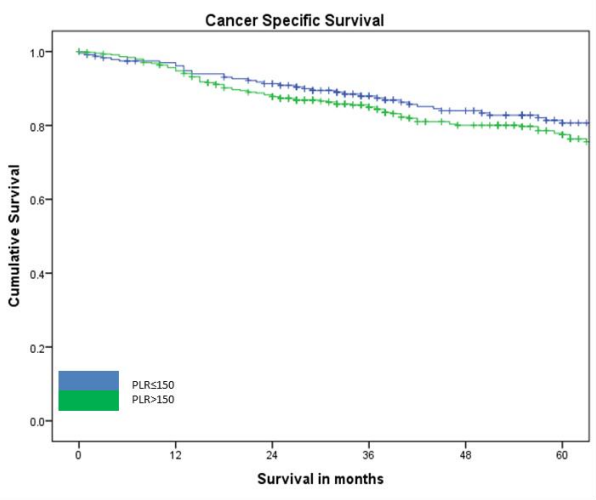
Figure 7.1c



Number at risk	0	12	24	36	48	60
NLS 0	388	367	339	313	294	282
NLS 1	260	233	198	179	156	139
NLS 2	153	145	142	138	134	132

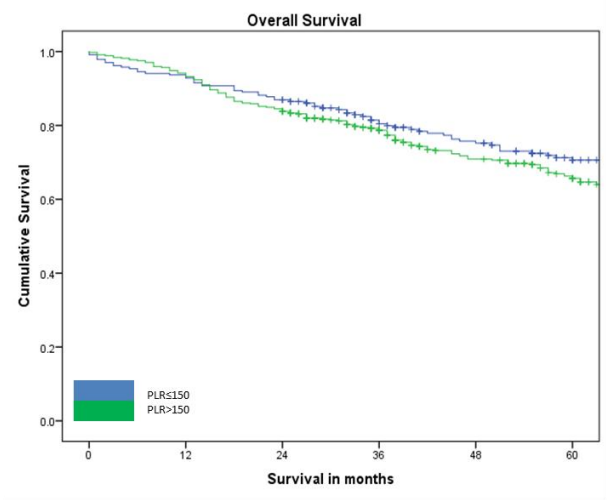
Figure 7.1d

Figure 7.1 a-d: The relationship between the NLR and NLS and both CSS and OS in patients undergoing surgery for colon cancer. NLR CSS (NLR<3-NLR3-5, p=0.216 and NLR3-5-NLR>5, p=0.005). NLR OS (NLR<3-NLR3-5, p=0.083 and NLR3-5-NLR>5, p=0.002). NLS CSS (NLS0-NLS1, p=0.007 and NLS1-NLS2, p=0.249). NLS OS (NLS0-NLS1, p<0.001 and NLS1-NLS2, p=0.474). Number at risk depicts the number of patients alive or not censored entering each time period.



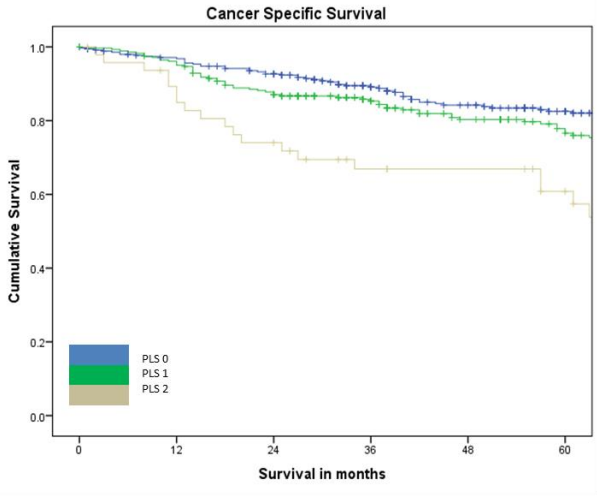
Number at risk	0	12	24	36	48	60
PLR≤150	237	228	217	210	203	198
PLR>150	445	422	392	381	365	358

Figure 7.2a



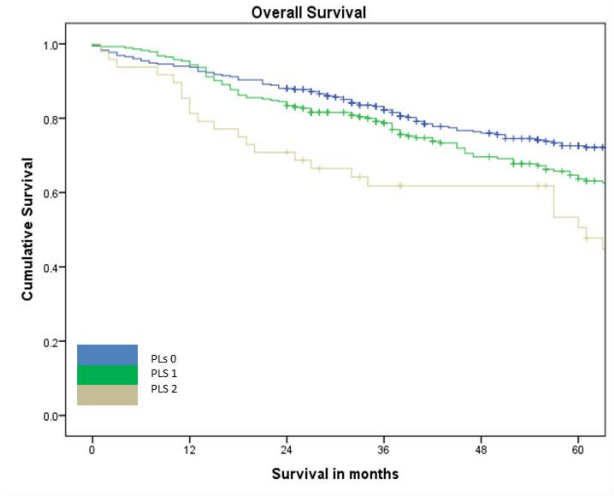
Number at risk	0	12	24	36	48	60
PLR≤150	237	220	206	192	182	174
PLR>150	445	415	373	352	324	307

Figure 7.2b



Number at risk	0	12	24	36	48	60
PLS 0	351	340	326	315	302	298
PLS 1	283	269	247	243	233	227
PLS 2	48	42	36	33	33	31

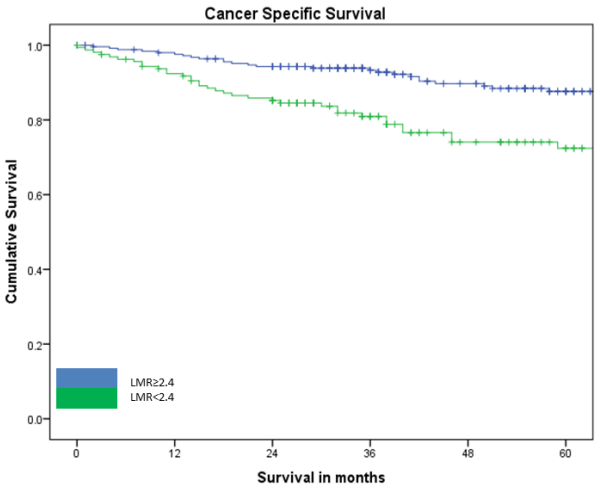
Figure 7.2c



Number at risk	0	12	24	36	48	60
PLS 0	351	329	309	290	272	263
PLS 1	283	267	236	224	204	192
PLS 2	48	39	34	30	30	26

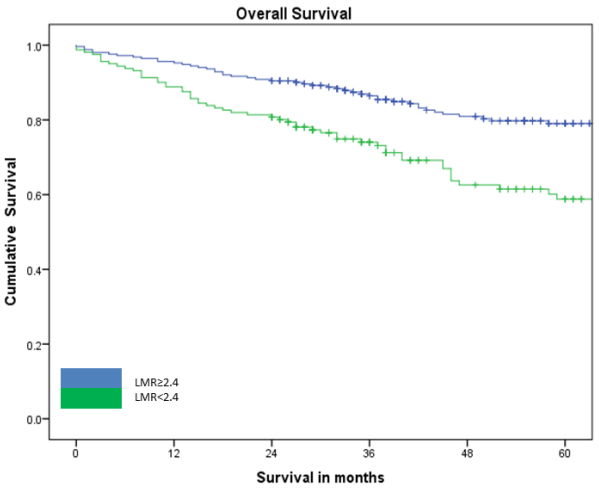
Figure 7.2d

Figure 7.2a-d: The relationship between the PLR and PLS and both CSS and OS in patients undergoing surgery for colon cancer. PLR CSS (PLR≤150-PLR>150, p=0.141). PLR OS (PLR≤150-PLR>150, p=0.061). PLS CSS (PLS0-PLS1, p=0.069 and PLS1-PLS2, p=0.006). PLS OS (PLS0-PLS1, p=0.016 and PLS1-PLS2, p=0.014). Number at risk depicts the number of patients alive or not censored entering each time period.



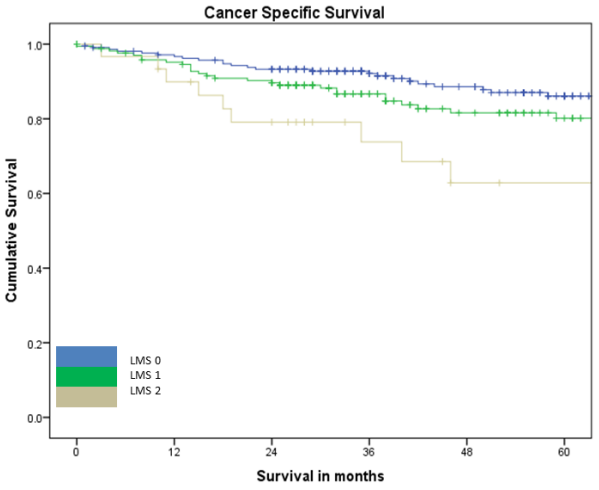
Number at risk	0	12	24	36	48	60
LMR≥2.4	252	246	238	236	235	227
LMR<2.4	161	149	138	133	127	126

Figure 7.3a



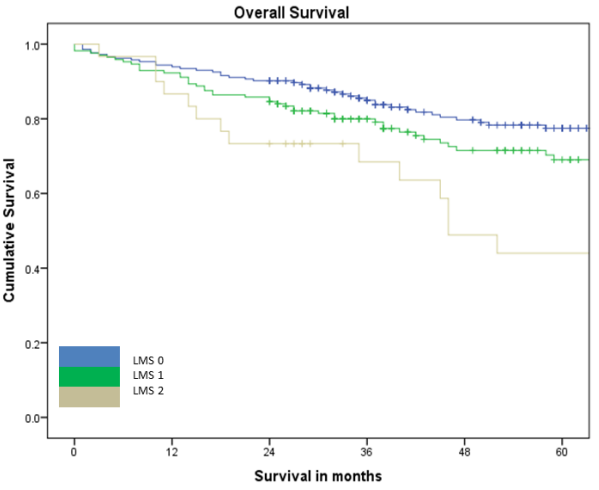
Number at risk	0	12	24	36	48	60
LMR≥2.4	252	240	228	219	209	206
LMR<2.4	161	143	130	121	110	107

Figure 7.3b



Number at risk	0	12	24	36	48	60
LMS 0	214	207	200	198	193	190
LMS 1	169	161	152	148	143	142
LMS 2	30	27	24	23	21	21

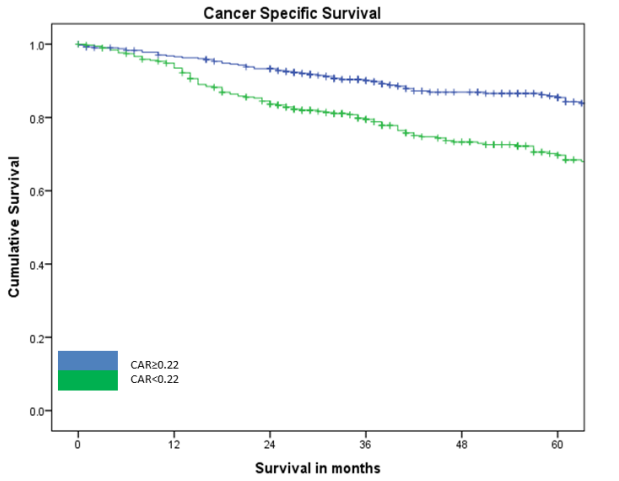
Figure 7.3c



Number at risk	0	12	24	36	48	60
LMS 0	214	201	193	183	175	172
LMS 1	169	156	143	136	127	125
LMS 2	30	26	22	21	17	16

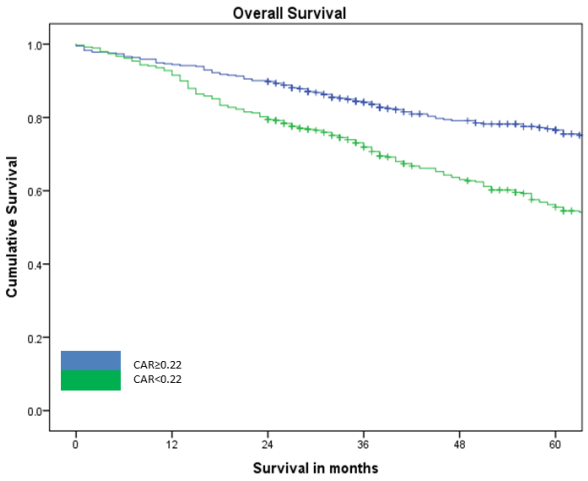
Figure 7.3d

Figure 7.3a-d: The relationship between the LMR and LMS and both CSS and OS in patients undergoing surgery for colon cancer. LMR CSS (LMR≥2.4-LMR<2.4, p<0.001). LMR OS (LMR≥2.4-LMR<2.4, p<0.001). LMS CSS (LMS0-LMS1, p=0.072 and LMS1-LMS2, p=0.023). LMS OS (LMS0-LMS1, p=0.067 and LMS1-LMS2, p=0.020). Number at risk depicts the number of patients alive or not censored entering each time period.



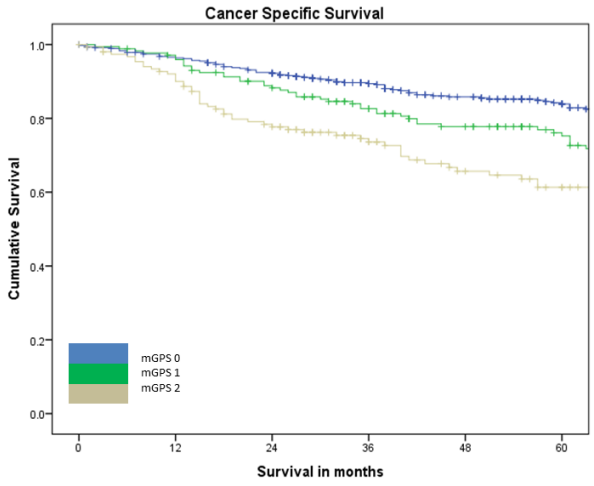
Number at risk	0	12	24	36	48	60
CAR≥0.22	412	398	385	373	363	359
CAR<0.22	389	364	327	313	295	286

Figure 7.4a



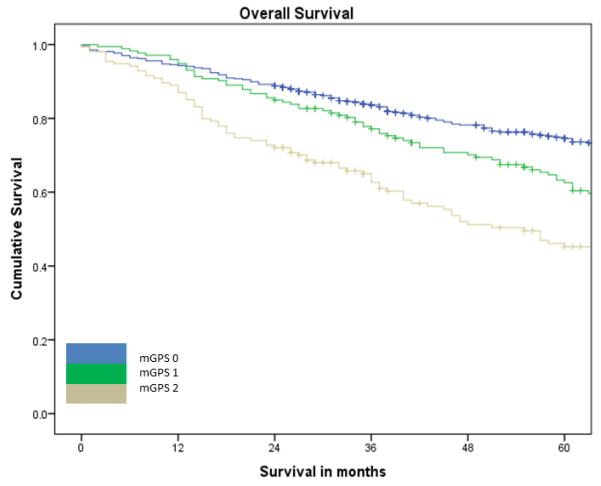
Number at risk	0	12	24	36	48	60
CAR≥0.22	412	400	370	348	331	323
CAR<0.22	389	356	309	282	254	230

Figure 7.4b



Number at risk	0	12	24	36	48	60
mGPS 0	474	457	438	426	413	407
mGPS 1	173	166	153	144	137	134
mGPS 2	154	139	121	116	108	104

Figure 7.4c



Number at risk	0	12	24	36	48	60
mGPS 0	474	447	421	398	377	364
mGPS 1	173	164	147	134	123	112
mGPS 2	154	134	121	68	84	77

Figure 7.4d

Figure 7.4a-d: The relationship between the CAR and mGPS and both CSS and OS in patients undergoing surgery for colon cancer. CAR CSS (CAR≥0.22-CAR<0.22, p<0.001). CAR OS (CAR≥0.22-CAR<0.22, p<0.001). mGPS CSS (mGPS0-mGPS1, p=0.113 and mGPS1-mGPS2, p=0.003). mGPS OS (mGPS0-mGPS1, p=0.002 and mGPS1-mGPS2, p=0.002). Number at risk depicts the number of patients alive or not censored entering each time period.

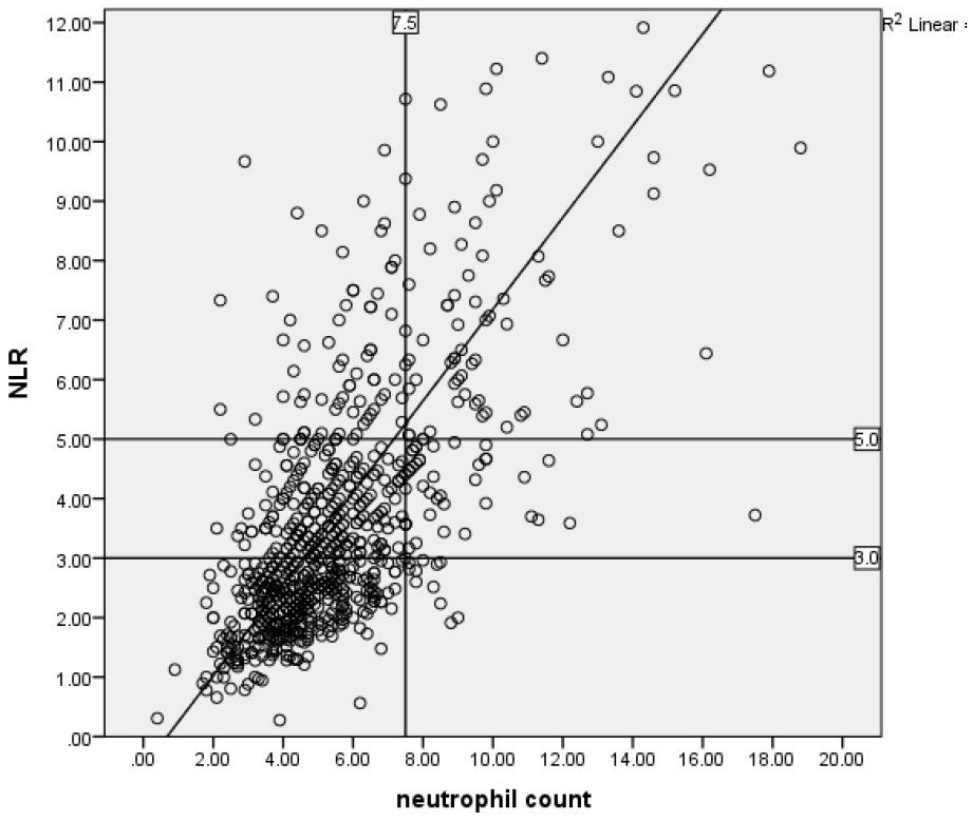


Figure 7.5a: rs=0.653, p<0.001

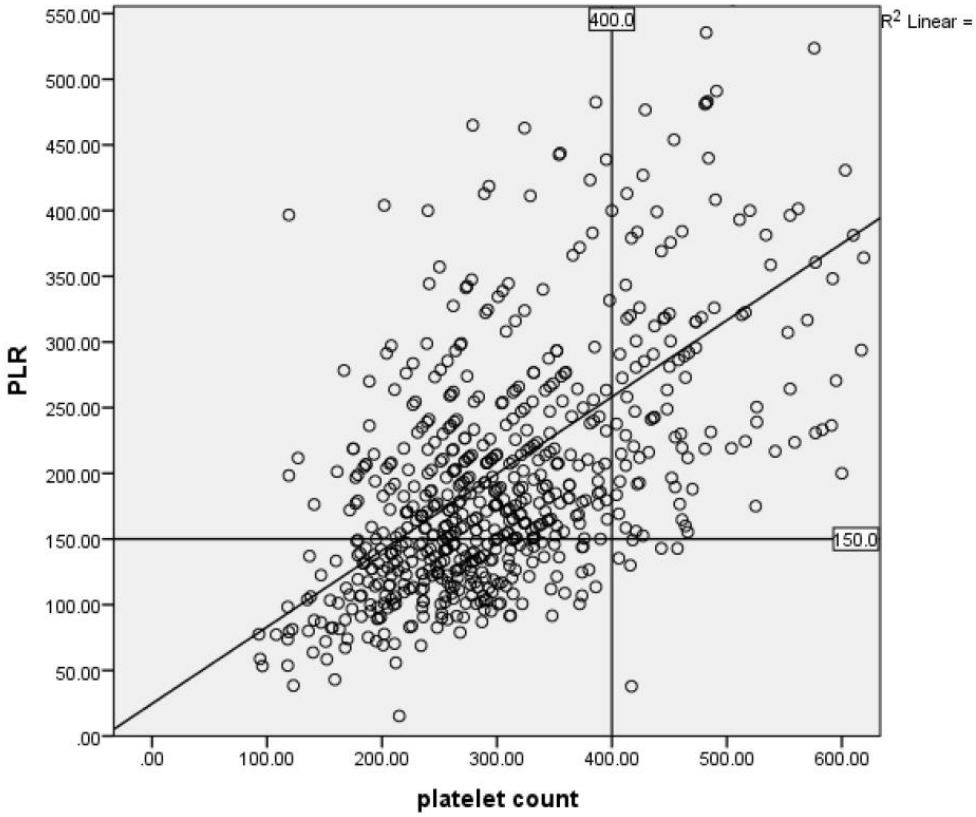


Figure 7.5b: rs=0.566, p<0.001

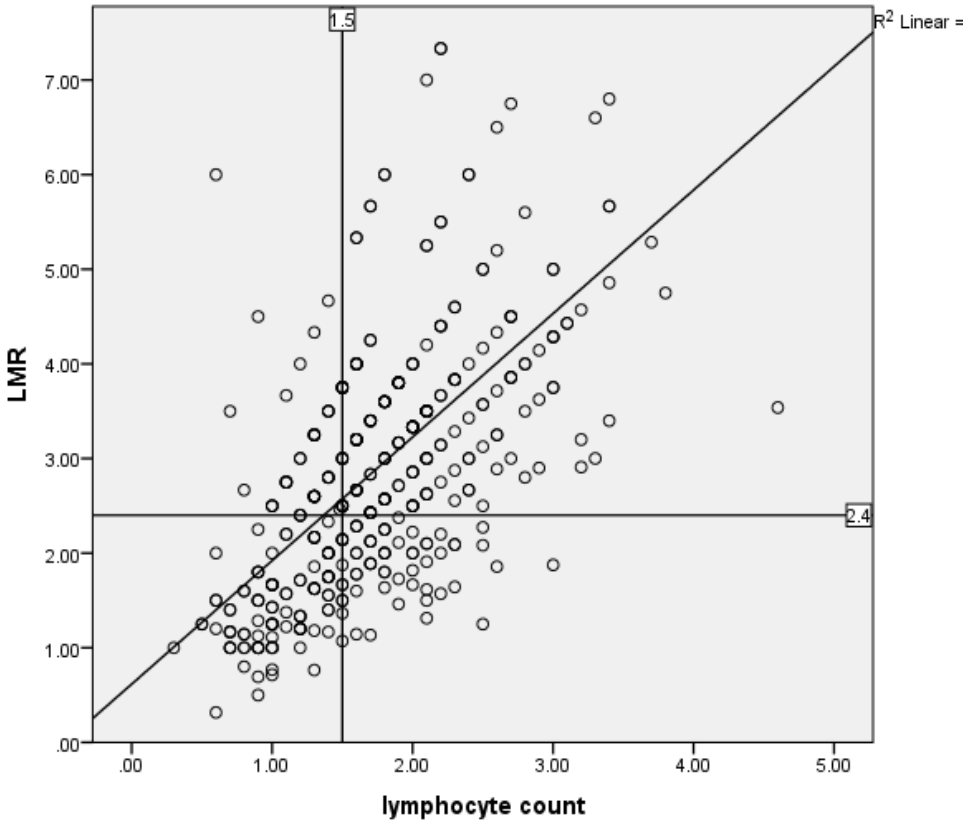


Figure 7.5c: rs=0.638, p<0.001

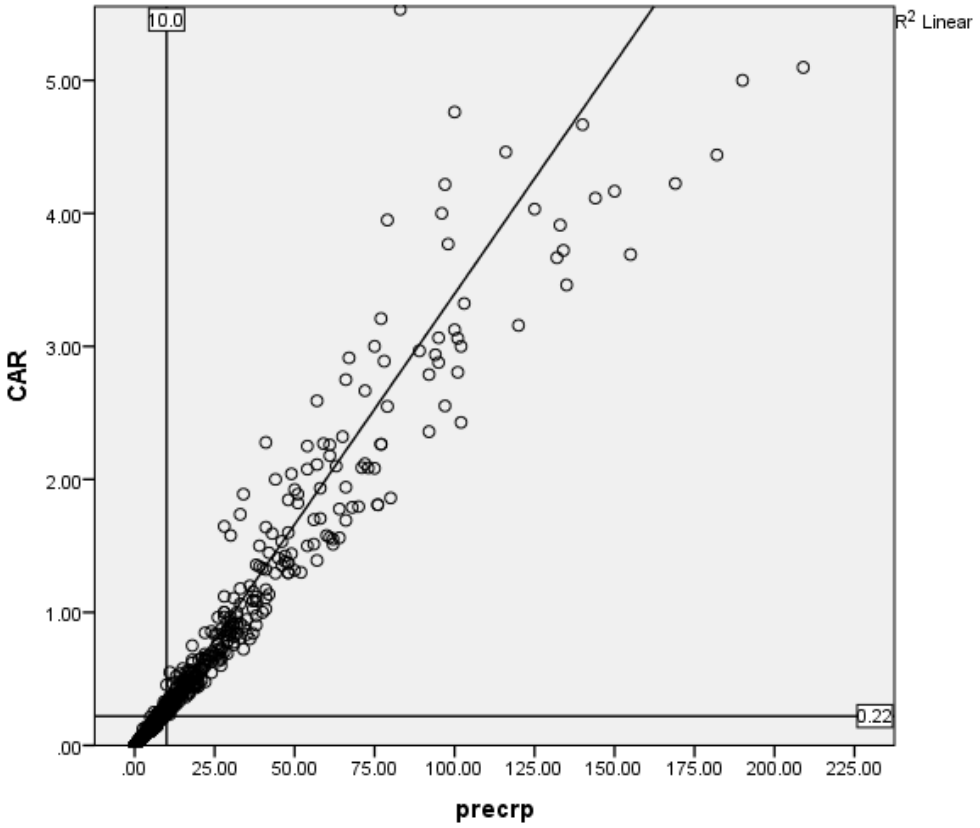


Figure 7.5d: rs=0.992, p<0.001

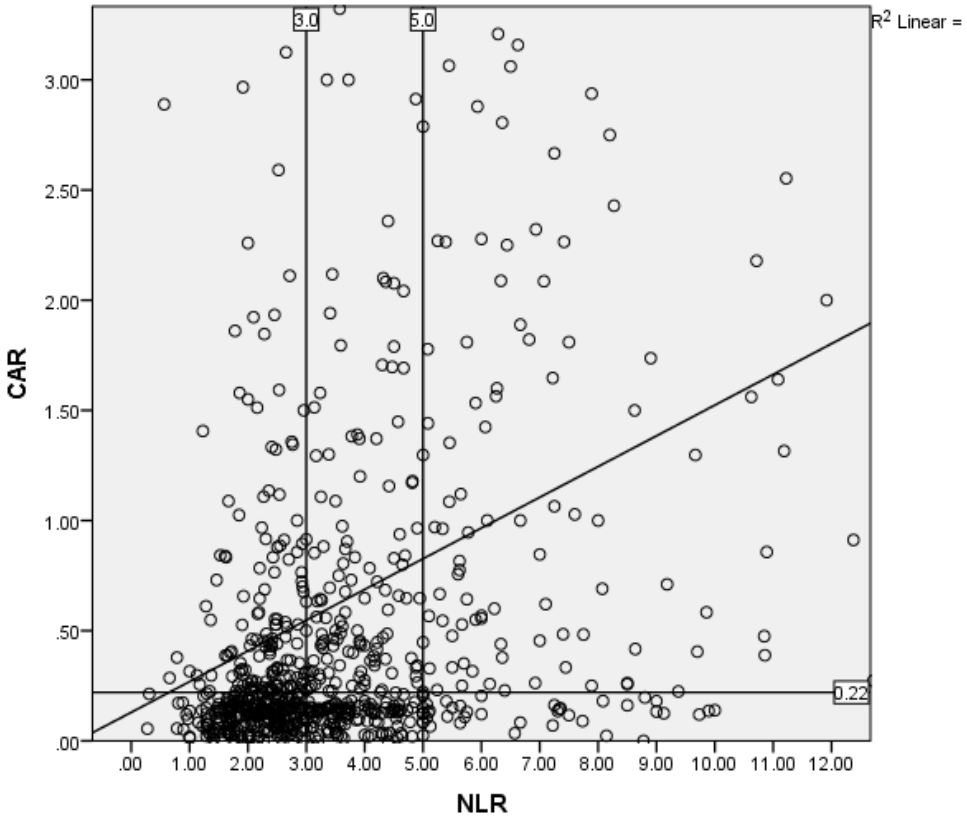


Figure 7.5e: rs=0.329, p<0.001

Figure 7.5a-e: Plot of preoperative neutrophil count and NLR, platelet count and PLR, lymphocyte count and LMR, CRP and CAR, NLR and CAR in all patients undergoing surgical resection for colon cancer

8. AN EXPLORATORY STUDY EXAMINING THE RELATIONSHIP BETWEEN PERFORMANCE STATUS, SYSTEMIC INFLAMMATION AND CYTOKINE PROFILES IN PATIENTS WITH ADVANCED CANCER

8.1 Introduction

As mentioned in Chapters 2 and 3 while a curative intent is the aim of any anti-cancer treatment, many patients go onto develop disseminated disease requiring systemic treatment with the aim of improving quality of life, while also improving survival (38). As a result, measures of Performance Status (PS) such as the Eastern Cooperative Oncology Group (ECOG) criteria gain increased clinical importance as they guide treatment as this has been consistently shown to predict survival.

Clinical biomarkers of the systemic inflammatory response (CRP, albumin, neutrophils and platelets) have also become established as having prognostic accuracy in advanced cancer. To illustrate, the modified Glasgow Prognostic Score (mGPS – combining CRP and Albumin) (37, 38) and the Neutrophil Platelet Score (NPS) (37, 38, 40) have been extensively validated as having prognostic value. Further, inflammation based prognostic scores have been combined with performance status in patients with advanced cancer to reliably stratify Quality of Life and survival (17, 25). These observations add to the firm role of systemic inflammation as the "seventh hallmark of cancer" and the "tip of the iceberg" in terms of cancer biology and treatment (117, 192, 193). Indeed, the activation of the systemic inflammatory response has been strongly implicated in tumorigenesis, aggressiveness of the disease and development of cachexia (7, 193, 194).

Beneath the "tip of the iceberg", cytokine activity plays an important part in the development of a systemic inflammatory response and symptoms of advanced disease (12). In patients with advanced cancer, pro-inflammatory cytokines become predominant leading to an up-

regulation of IL -1, TNF-α, IL-6, IL-8, IL-10, IL-18, TGF-β and Macrophage Migration Inhibitory Factor (MIF) (193, 320). However, these cytokines have not been routinely measured in patients with advanced cancer due to the lack of international standardisation of analysis and validation of prognostic value. In contrast, routine measures of the systemic inflammatory response, such as the acute phase proteins CRP and albumin, are well standardised internationally and, combined in the mGPS, have validated prognostic value (37, 38). Alternatively, neutrophils and platelets have been combined in the Neutrophil Platelet Score (NPS) to improve the prediction of survival (37, 38, 40). Nevertheless, these cytokines are of increasing interest due to the expanding armamentarium of immunomodulatory agents in the oncology setting.

Further, the relationship of these cytokines to established clinical factors (ECOG-PS) and mGPS is not understood. Understanding which cytokines are related to survival, performance status and clinical biomarkers of the inflammatory response may help inform potential treatment stratification in patients with advanced cancer (37, 38, 40). It is against this backdrop that a retrospective analysis of the results of a "Corticosteroids for Cancer Pain" trial was carried out (193, 321). Therefore, the primary aim of this Chapter was to examine the relationship between ECOG-PS, mGPS (and the validated prognostic framework ECOG-PS/ mGPS (17)), NPS and cytokine profiles in patients with advanced cancer.

8.2 Patients and Methods

This was a retrospective analysis of data already collected as part of a randomised double blind placebo control trial examining the analgesic effects of corticosteroids in patients with advanced cancer taking opioids (193). For the primary data collection, eligible patients met the following criteria: >18 years of age, a diagnosis of advanced cancer where curative treatment was not possible, taking opioids for moderate or severe cancer pain; pain level of 4 (on a 0±10 Numerical Rating Scale (NRS)) at inclusion; expected survival > 4 weeks. Exclusion criteria included diabetes mellitus, peptic ulcer disease, and concurrent use of NSAIDs (193). As part of this trial the following inflammatory biomarkers were collected at trial baseline: CRP, albumin, neutrophils, platelets, erythrocyte sedimentation rate (ESR), IL-1β, IL-1ra, TNF-α, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12(p70), IL-18, interferon-γ, TGF-β1, MIF, Macrophage Inflammatory Protein-1α (MIP-1α), Monocyte Chemoattractant Protein-1 (MCP-1) and soluble Tumour Necrosis Factor receptor-1 (sTNF-r1). sTNF-r1 was measured as it reflects TNF-α-activity, since TNF-α is among the most unstable cytokines (322, 323). The analytical methods are published previously (193). The cytokines were chosen on the basis of previous research on cancer related inflammation (110, 324, 325).

Overall survival (OS) was measured until the date of death from any cause. Ethical approval for the original study was given by the Regional Committee for Medical Research Ethics Central Norway (4.2007.846) and the Norwegian Directorate of Health, and this included further analysis of biobanked data; Clinical trial information NCT00676936, EudraCT No 2007-005617-19. Procedures were conducted in accordance with the Declaration of Helsinki, as revised in 1983.

Statistical Analysis:

Data are presented as medians, ranges, frequencies and percentages. The mGPS and the NPS were calculated according to methods previously described (39, 87). The relationship

between ECOG-PS, mGPS, NPS, and cytokine levels was examined using Independent Mann-Whitney U and Kruskal Wallis tests where appropriate. The IL-1ra and IL-6 concentrations below the LLOQ are given as ≤21.7 ng/L and ≤2.33 ng/L respectively. IL-1ra and IL-6 were analysed as continuous and dichotomized variables (IL-1ra: ≤170 ng/L (326) and IL-6: ≤10ng/L (327)). Given the explorative nature of this study, a significance level of <0.05 was considered significant. The time between the date of inclusion and the date of death of any cause was used to define overall survival (OS). Survival data were analysed using univariate Cox regression analysis. All statistical analysis was performed using SPSS version 22.0 (IBM Corp, Armonk, NY).

8.3 Results

The clinicopathological characteristics of patients are shown in Table 8.1. Of the forty-nine patients previously reported, (193) nine patients were removed due to incomplete data leaving 40 patients to be included in the present analysis. The majority of patients were less than 65 years of age (58%), normal or underweight (73%), had good ECOG-PS (53%), had non-hormone dependent disease (63%), and no ongoing oncological treatment (73%). Metastatic disease was present in 98% of patients with the most common sites being the liver and bone. The majority of patients had evidence of a systemic inflammatory response whether assessed by the mGPS (78%) or NPS (53%). All patients died on follow-up and the median survival was 91 days (4-933 days).

The relationship between ECOG-PS, mGPS, NPS and cytokine profiles are shown in Table 8.2. With increasing ECOG-PS (Table 8.2a - vis a vis deteriorating condition) there was a higher median value of IL-6 ($p=0.016$), ESR ($p=0.002$), CRP ($p<0.01$), albumin ($p<0.01$) and poorer survival ($p<0.001$). With increasing mGPS (Table 8.2b - vis a vis increasing inflammation) there was a higher median value of IL-6 ($p=0.016$), MIF ($p=0.010$), ESR ($p<0.01$) and poorer survival ($p<0.01$). With increasing NPS 2 (Table 8.2c - vis a vis increasing inflammation) there was a higher median value of TGF-β ($p<0.001$).

The relationship between ECOG-PS and mGPS framework and the cytokine profile is shown in Table 8.3. When those patients with an ECOG-PS 0/1 and mGPS0 were compared with those patients with an ECOG-PS 2 and mGPS2 there was a higher median value of IL-6 ($p=0.017$) and poorer survival ($p<0.001$). The majority of IL-1ra and IL-6 and concentrations were below the limit of detection. There was a clear increase in median IL-6 concentrations between mGPS 0/1 (2.33 ng/L) and mGPS 2 (21.1 ng/L). There was also a more progressive increase in IL-6 concentrations between NPS 1 (2.33 ng/L), NPS 2 (16.6 ng/L) and NPS 3 (33.6 ng/L). In addition, there was a clear increase in IL-6 concentrations between ECOG-PS 0/1 (2.33 ng/L) and ECPG_PS 2 (20.4 ng/L).

When IL-1ra, as a continuous variable, was compared with ECOG-PS there was no significant association between IL-1ra and ECOG-PS (p=0.076). When IL-1ra, as a continuous variable, was compared with mGPS there was no significant association between IL-1ra and mGPS (p=0.633). On univariate Cox regression analysis IL-1ra, as a continuous variable, was significantly associated with poorer overall survival (HR 1.00, 95%CI 1.00-1.01, p=0.007).

When IL-1ra (≤170/>170 pg/ml), as a dichotomized variable, was compared with ECOG-PS there was no significant association between IL-1ra and ECOG-PS (p=0.258). When IL-1ra, as a dichotomised variable, was compared with mGPS there was no significant association between IL-1ra and mGPS (p=0.756). On univariate Cox regression analysis IL-1ra, as a dichotomized variable, was not significantly associated with poorer overall survival (HR 1.68, 95%CI 0.73-3.86, p=0.253).

When IL-6, as a continuous variable, was compared with ECOG-PS there was a significant association between IL-6 and ECOG-PS (p=0.010). When IL-6, as a continuous variable, was compared with mGPS there was a significant association between IL-6 and mGPS (p=0.016). On univariate Cox regression analysis IL-6, as a continuous variable, was significantly associated with poorer overall survival (HR 1.03, 95%CI 1.01-1.04, p<0.001).

When IL-6 (≤10/>10 pg/ml), as a dichotomized variable, was compared with ECOG-PS there was a significant associations between IL-6 and ECOG-PS (p=0.034). When IL-6, as a dichotomised variable, was compared with mGPS there was a significant association between IL-6 and mGPS (p=0.022). On univariate Cox regression analysis IL-6, as a dichotomized variable, was significantly associated with poorer overall survival (HR 2.66, 95%CI 1.34-5.27, p=0.005).

8.4 Discussion

The results of the present study show that, on examination of cytokine profiles, only IL-6 was consistently associated with ECOG-PS and mGPS and their combination in patients with advanced cancer. Given the extensively validated prognostic value of the ECOG-PS/ mGPS framework, it is clear that of the cytokines measured, IL-6 may represent a potentially useful therapeutic target to improve patient status in the context of this framework.

Although the present study was carried out in a relatively small number of patients it does provide pilot data within the context of an established framework (ECOG-mGPS) that is known to effectively stratify quality of life (25, 206) and survival (17, 328) in patients with advanced cancer. The mGPS enables ready comparison between studies of different tumour types and stages of disease. Indeed, Kantola and colleagues in primary operable colorectal cancer (n=148) reported that the mGPS was associated with IL1-ra and IL-6 thus confirming the validity of the present results (329, 330).

Furthermore, in addition to ECOG performance status the utility of the mGPS in the randomised clinical trial setting is now recognised (54). For example, in a recent RCT of an anti-inflammatory agent targeting the IL-6 JAK STAT pathway the mGPS was shown to effectively stratify survival (153).

It has long been recognised that interleukin-6 is associated with pain, (331) weight loss, (332) and inflammatory responses in patients with cancer (333, 334). However, it is only in recent years that the systemic inflammatory response, in particular as measured by the mGPS, has become central to the symptoms associated with advanced cancer (25) and the repertoire of agents targeting IL-6 has been extensive enough to test this clinically in a robust manner (335).

There is good evidence that pain may be associated with increased levels of inflammatory parameters (25). The patients recruited to this study had cancer related pain requiring strong

analgesia for relief. Therefore, it may be that the systemic inflammatory response was higher than that in an unselected cohort of patients with advanced cancer. In the present study 78% of patients had an elevated mGPS compared with 68% of patients in a large unselected cohort (25). This suggests that the systemic inflammatory response was indeed higher in patients within this study and associated with increased pain requirements.

IL-6 is produced in a variety of cells including fibroblasts, endothelial cells, keratinocytes, macrophages, T-cells and mast cells. While it is true that cancer cells produce IL-6, the high circulating concentrations of IL-6 levels cannot be explained by tumour production alone. Indeed, recent studies have shown that monocytes produce significantly higher levels of IL-6 in cachectic cancer patients than in healthy controls and in patients with advanced pancreatic cancer. In addition neutrophil activity has also been implicated in potentiating tumour growth through the activation of specific inflammatory cytokines particularly IL-1 and IL-6 and via amino acid depletion (336) and promotes angiogenesis and the metastatic potential of cancer (336).

In a recent systematic review by Lippitz and co-workers including 11,583 patients serum IL-6 levels were found to correlate with survival in 82/101 studies comprising 85.6% of patients in 23 types of cancer (327). This percentage increased to 94.5% of reported patients when only dichotomized studies were included (327). Importantly, there was a significant correlation between higher serum IL-6 and tumour stage as described in 39/44 studies and 91% of reported patients where clinical parameters had been specified (327). The average IL-6 threshold was approximately 10pg/ml (327). In the present study when this threshold was applied IL-6 was significantly associated with ECOG-PS, mGPS and survival. Therefore, the results of the present study are consistent with the literature which defines IL-6 as a cancer-type-independent parameter for the progressive functional decline (ECOG-PS), the systemic inflammatory response (mGPS) and survival in patients with advanced cancer (327).

There is now the possibility to target IL-6 upstream and downstream. In terms of downstream signalling IL-6 is now recognised to be produced by multiple cell types in the tumour microenvironment including tumour cells, stromal cells and immune cells. Moreover, within these cell types IL-6 will activate the JAK/ STAT3 pathway and therefore has the potential not only to stimulate tumour cell growth but also reduce the efficacy of the immune cells to kill tumour cells (335). Therefore, although there are agents that can target IL-6 upstream and downstream, such complexity, and that most studies carried out have been pre-clinical, makes it difficult to predict the likely benefits of any particular agent in patients with advanced cancer. In this context, the results of the present study would suggest that such agents are target at patients with poor performance status and elevated systemic inflammatory response i.e. ECOG-PS 2 and mGPS 2 for moderation of symptoms.

To date the examination of agents targeting pro-inflammatory cytokines in the cancer setting has been limited. Infliximab and Etanercept (anti-TNF-α) have been studied and showed no benefit in muscle mass (a constitutional component of cancer cachexia) (337, 338). Clazakizumab, which targets IL-6, has also been examined in phase II trials and showed attenuation of muscle loss and improvements in anaemia, however no phase III trials are underway (339). It is of interest, however, that agents which target IL-1α, which is upstream of IL-6, have had beneficial effects on muscle mass and quality of life (340). The present work provides supporting evidence that agents targeting these cytokines are worthy of further exploration, however stratification using the ECOG-PS/mGPS framework should be incorporated into trial designs, to enable the effect of these agents to be optimised. Such an approach has been advocated recently (341) and demonstrated as being efficacious in similar settings (153).

In terms of upstream signalling, it was of interest that of the cytokines measured only IL-1ra was significantly associated with IL-6 (rs 0.537, $p<0.001$), CRP (rs 0.716, $p<0.001$) and neutrophil count (rs 0.606, $p<0.001$) (results not tabulated). There are also a number of

approaches to down regulate IL-1 signalling that look promising in patients with advanced cancer and worthy of clinical investigation (342).

Although assays have been available for the measurement of IL-6 in the plasma for approximately 30 years there remain a number of obstacles to be overcome before IL-6 will become a routinely available clinical test in patients with cancer. Until such time the ECOG-PS/mGPS framework will continue to offer reliable risk stratification for patients with advanced cancer.

While it should be noted that intractable pain and the associated physiological stress that this incurs has also been shown to lead to disease progression, long term opioid use is not without risk (343). Indeed, opioid administration, particularly long term administration has been shown to affect immune system function, angiogenesis, apoptosis, and invasion in a potentially deleterious manner (343, 344). Furthermore opioid administration can lead to suppression of the hypothalamic-pituitary-gonadal axis in both male and female patients leading to hypogonadism(343, 345). This suppresses anabolic activity and could potentiate secondary hypogonadism characteristics such as the loss of skeletal muscle mass which has a deleterious effect on both quality of life and outcomes in patients with cancer.

The present study had some limitations. In particular, there were relatively small numbers of patient observations in some of the subgroup analysis. Given the exploratory nature of this study, no correction for multiple testing was performed. Also, the present results are a retrospective analysis of data obtained from a study examining the relationship between cytokine concentrations and symptoms in patients with advanced cancer taking opioids(193). Prospective confirmation of the results obtained, and measurement of key cytokines would be important in future studies.

Given the previously validated prognostic value of the ECOG-PS/ mGPS framework (25), it is clear that of the cytokines measured, IL-6 may represent a potentially useful therapeutic target to improve patient status in the context of this framework.

In summary, the results of the present study show that IL-6 was consistently associated with ECOG-PS and mGPS and their combination in patients with advanced cancer. Moderation of circulating IL-6 concentrations should continue to be explored as a useful therapeutic treatment in these patients.

8.5 Tables and Footnotes

Table 8.1: Clinicopathological characteristics of patients within the "Corticosteroids and Cancer Pain" trial analysed as part of this study

	Variables	n=40 (%)
Age (years)	<65	23 (57.5)
	≥65	17 (42.5)
Sex	Female	18 (45.9)
	Male	22 (55.0)
BMI*	≤25	29 (76.4)
	>25	9 (23.6)
ECOG-PS	0/1	21 (52.5)
	2/3	19 (47.5)
mGPS	0: CRP ⩽ 10 mg/l and albumin ⩾35 g/l	9 (22.5)
	1: CRP >10 mg/l and albumin ⩾35 g/l	13 (32.5)
	2: CRP >10 mg/l and albumin <35 g/l	18 (45.0)
NPS	0: Neutrophils ≤ 7.5 $x10^9$/L and Platelets ≤400 $x10^9$/L	19 (47.5)
	1: Neutrophils >7.5 $x10^9$/L or Platelets >400 $x10^9$/L	14 (35.0)
	2: Neutrophils >7.5 $x10^9$/L and Platelets >400 $x10^9$/L	7 (17.5)
Cancer Type	Hormone Dependent	15 (37.5)
	Non-Hormone Dependent	25 (62.5)
Ongoing Oncological Treatment	Yes	11 (27.5)
	No	29 (72.5)
Survival	Alive	0 (0)
	Dead	40 (100.0)
Survival (Days)	Median (Range)	91 (4-933)

Table 8.2a-c: The relationship between ECOG-PS (3.2a), mGPS (7.2b), and NPS (7.2c) and the cytokine profile

Table 8.2a		**ECOG-PS Median (range)**			
Cytokines	**Normal Reference Range:**	**0/1 n=21**	**≥2 n=19**		**p-value**
IL-1 ra	<21.7 ng/L	21.7 (21.7-1641)	21.7 (21.7-4360)		0.357
IL-6	<2.33 ng/L	2.33 (2.33-58.7)	20.4 (2.33-97.3)		0.016
IL-18	<1.1 ng/L	99.5 (50.1-257)	107 (26.5-4588)		0.466
MCP-1	<1.5 ng/L	61.4 (30.4-188)	81.0 (19.6-1235)		0.654
MIF	<4.8 ng/L	142 (45.1-722)	135 (40.9-745)		0.520
sTNF-r1	<27.1 ng/L	10665 (813-24174)	12058 (3266-25934)		0.143
TGF-β	<1.2 ng/L	45124 (21856-66224)	50784 (26249-103280)		0.330
ESR	M: 0-22 mm/h F: 0.29mm/h	37 (3-136)	67 (18-109)		0.030
CRP	<3 mg/dl	20 (0.5-138)	64 (33-305)		0.002
Albumin	35-50 g/L	39 (28-48)	31 (17-44)		0.001
Neutrophil	2-7.5x10^9/L	3.7 (1.2-11)	6.4 (1-17.3)		0.040
Platelet	150-400x10^9/L	316 (80-592)	422 (115-689)		0.209
Survival (days)		200 (28-933)	50 (4-189)		<0.001
Table 8.2b		**mGPS Median (range)**			
Cytokines	**Normal Reference Ranges:**	**0 n=9**	**1 n=13**	**2 n=18**	**p-value**
IL-1 ra	<21.7 ng/L	21.7 (21.7-179)	21.7 (21.7-1641)	21.7 (21.7-4360)	0.633
IL-6	<2.33 ng/L	2.33 (2.33-39.9)	2.33 (2.33-58.7)	21.1 (2.33-118)	0.016
IL-18	<1.1 ng/L	84.6 (57.5-257)	107 (52.4-226)	103 (26.5-4588)	0.523
MCP-1	<1.5 ng/L	63.1 (43.7-164)	90.0 (30.4-188)	61.2 (19.6-1235)	0.254
MIF	<4.8 ng/L	85.4 (45.1-186)	329 (79.5-745)	127 (40.9-1348)	0.010
TGF-β	<27.1 ng/L	43279 (27144-57458)	47923 (21856-66224)	48293 (23402-103280)	0.430
sTNF-r1	<1.2 ng/L	8459 (813-15257)	11734 (3723-24174)	10953 (3266-33794)	0.359
ESR	M: 0-22 mm/h F: 0.29mm/h	16 (3-87)	40 (11-95)	72 (18-136)	0.002
Neutrophil	2-7.5x10^9/L	3.5 (1.2-9.5)	5.7 (2.2-11)	6.45 (1-17.4)	0.060
Platelet	150-400x10^9/L	316 (156-353)	400 (80-592)	406 (72-728)	0.516
Survival (days)		511 (21-933)	117 (28-406)	51 (4-474)	0.003
Table 8.2c		**NPS Median (range)**			
Cytokines	**Normal Reference Ranges:**	**0 n=19**	**1 n=14**	**2 n=7**	**p-value**
IL-1 ra	<21.7 ng/L	21.7 (21.7-1640)	21.7 (21.7-519)	21.7 (21.7-4360)	0.483
IL-6	<2.33 ng/L	2.33 (2.33-58.7)	16.6 (2.33-105)	33.6 (2.33-118)	0.052
IL-18	<1.1 ng/L	95.0 (52.4-257)	107 (26.5-191)	153 (74.2-4588)	0.247
MCP-1	<1.5 ng/L	59.3 (19.6-164)	70.1 (36.5-188)	81 (36.4-1235)	0.863
MIF	<4.8 ng/L	126 (40.9-722)	126 (73.6-745)	338 (128-1348)	0.088
TGF-β	<27.1 ng/L	37694 (21856-50694)	51113 (23402-103280)	61194 (40449-66224)	<0.001
sTNF-r1	<1.2 ng/L	9267 (813-25934)	11286 (3723-33794)	15257 (8459-22060)	0.170
ESR	M: 0-22 mm/h F: 0.29mm/h	37 (3-102)	53.5 (6-136)	72 (15-109)	0.161
CRP	<3 mg/dl	33 (0.5-138)	47 (3.8-167)	138 (1.9-305)	0.020
Albumin	35-50 g/L	36 (25-45)	33 (24-48)	31 (14-40)	0.173
Survival (days)		132 (14-933)	77 (38-406)	37 (4-474)	0.154

Table 8.3: The relationship between combined ECOG-PS 0/1 and mGPS 0 and combined ECOG-PS 2 and mGPS 2 and cytokine levels

n=19	LLOQ:	ECOG-PS 0/1 & mGPS 0 (n=7) Median (range)	ECOG-PS 2 & mGPS 2 (n=12) Median (range)	p-value
IL-1 ra	<21.7 ng/L	21.7 (21.7-179)	21.7 (21.7-4360)	0.711
IL-6	<2.33 ng/L	2.33 (2.33-2.33)	15.9 (2.33-97.3)	0.017
IL-18	<1.1 ng/L	84.6 (57.5-257)	100 (26.5-4588)	0.711
MCP-1	<1.5 ng/L	59.3 (43.7-164)	67.6 (19.6-1235)	0.902
MIF	<4.8 ng/L	85.4 (45.1-186)	107 (40.9-635)	0.432
sTNF-r1	<27.1 ng/L	7618 (813-14901)	11064 (3266-25934)	0.167
TGF-β	<1.2 ng/L	37226 (27144-49734)	48293 (26249-103280)	0.068
Survival (days)		638 (92-933)	60 (14-189)	<0.001

9. THE RELATIONSHIP BETWEEN CT-DERIVED BODY COMPOSITION, THE SYSTEMIC INFLAMMATORY RESPONSE AND SURVIVAL IN PATIENTS UNDERGOING SURGERY FOR COLORECTAL CANCER

9.1 Introduction

As mentioned above in section 1.4.2 in the past weight loss and BMI have been used as an indicator of nutritional decline and poor prognosis in patients with cancer (41, 346). However, due to the increased number of patients presenting in an overweight or obese state in the developed world the use of simple weight loss and BMI as a prognostic indicator has been questioned (66, 70, 347, 348). The ability to use routine CT scans to measure body composition, in particular skeletal muscle, has resulted in a marked increase in interest in using skeletal muscle index and skeletal muscle density to predict outcomes in patients with cancer, particularly in colorectal cancer (349).

There is evidence supporting a disproportionate loss of skeletal muscle tissue to be an independent prognostic factor for both cancer-specific and overall survival in patients with colorectal cancer (350). Specifically muscle loss has been associated with poor treatment tolerance and efficacy (351), worse quality of life and increased morbidity (352). For example, in a large study Caan and co-workers reported that in patients with colorectal cancer there was a significant association between lower skeletal muscle index (SMI) and worse overall survival (353). Also, Malietzis and co-workers reported that in patients with colorectal cancer there was a significant association between lower skeletal muscle density and worse overall survival (354).

The importance of the systemic inflammatory response as a unifying mechanism for weight loss and loss of lean tissue in patients with cancer is increasingly recognised (81, 346, 355). Therefore, it is of interest that SMI and SMD have been repeatedly reported to be inversely associated with measures of the systemic inflammatory response such as the NLR and mGPS

(45, 71, 356-360), that are recognised to have prognostic value in their own right (38, 54). However, this relationship is not clear. It is possible that some patients with sarcopenia may have systemic inflammation and some patients with myosteatosis might similarly have systemic inflammation, but the coexistence of those three features is poorly understood. If the above association was due to the erosion of the SMI and SMD by an ongoing systemic inflammatory response it might be anticipated that the prognostic value of SMI and SMD was largely dependent on the presence of a systemic inflammatory response. It might also be anticipated that low SMI and SMD would influence the relationship between the systemic inflammatory response and survival.

To our knowledge, no study has comprehensively examined the relationship between CT derived body composition, systemic inflammatory response, as measured by the mGPS, and survival in patients with primary operable colorectal cancer. Therefore, the aim of this Chapter was to examine the above relationships in a prospectively maintained database of patients with colorectal cancer undergoing potentially curative resection.

9.2 Patients and Methods

Consecutive patients who underwent elective, potentially curative resection for colorectal cancer between March 2008 and June 2017 at a single centre were identified from a prospectively maintained database. Those patients with a preoperative CT scan and a recorded height and weight were included.

Patients were classified according to Body Mass Index (BMI) as underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9) and obese (BMI ≥30) was recorded. All tumours were staged according to TNM 5th edition. Preoperative haematological and biochemical markers were recorded.

The cause and date of death were confirmed with the Registrar General (Scotland) until 1st June 2017 that served as the censor date. Informed consent was obtained from patients prior to surgery. Those with metastatic colorectal cancer and those who underwent emergency surgery or palliative surgery were excluded from the study. Ethical approval was granted by the West of Scotland Research Ethics Committee, Glasgow.

Methods:

CT derived body composition analysis at the level of the third lumbar vertebra was carried out using NIH Image J version 1.47, http://rsbweb.nih.gov/ij/ as described in Chapter 2. A summary of all thresholds used can be found in (Table 9.1).

Measurements were performed by two individuals and inter-rater reliability was assessed in a sample of 30 patient images using inter-class correlation coefficients (ICCC) (TFA ICCC = 1.000, SFA ICCC = 1.000, VFA ICCC = 1.000, SMA ICCC = 0.998, SMD ICCC = 0.972). Investigators were blind to patient's demographic and clinico-pathological status.

An autoanalyzer was used to measure serum CRP (mg/L) and albumin (g/L) concentrations (Architect; Abbot Diagnostics, Maidenhead, UK). The mGPS, NLR and NPS were derived as previously described (99).

Statistical Analysis:

Body composition measurements were presented as median and range and compared using Mann-Whitney or Kruskal-Wallis tests. Categorical variables were analysed using χ^2 test for linear-by-linear association, or χ^2 test for 2 by 2 tables.

Mortality within 30 days of the index procedure or during the index admission were excluded from subsequent survival analysis. The time between the date of surgery and the date of death of any cause was used to define overall survival (OS). Survival data were analysed using univariate and multivariate Cox regression. Those variables associated to a degree of $p<0.1$ were entered into a backward conditional multivariate model.

Missing data were excluded from analysis on a variable by variable basis. Two tailed p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 21.0. SPSS Inc., Chicago, IL, USA).

9.3 Results

In total, 832 patients were identified as having undergone potentially curative surgery for colorectal cancer of these, 182 were excluded due to missing eligible CT scans, clinicopathological data or blood test results. A further five patients were excluded as they died in the immediate postoperative period. A total of 650 patients (354 males, 296 females) were included in final analyses.

There have been a number of definitions of SMI using CT-scans. Nevertheless, it is clear that muscle mass varies in male and female patients and with BMI. SMI has been defined differently in male and female patients and according to BMI which are summarised Table 9.1. In the present study SMI (Dolan) thresholds were derived using ROC curve analysis to determine thresholds associated with overall survival in this population. This was also conducted using validated online biomarker cutoff optimization software (361). In male patients, the clinically significant cutoff for SMI with a BMI<25 was 45cm^2/m^2 and for male patients with a BMI≥25 was 53cm^2/m^2. The clinically significant cutoff for SMI in female patients with a BMI<25 was 39cm^2/m^2 and for female patients with a BMI≥25 was 41cm^2/m^2. Given that these SMI threshold values (Dolan BMI>25) were similar to those of Martin (Table 9.1) and to facilitate comparison of studies the threshold values of Martin were used in the analysis. In addition, the association between sarcopenia (Martin) and sarcopenia (Dolan BMI>25) was strong ($p<0.001$). For example, when Martin and co-workers thresholds were used 43.5% of patients had sarcopenia and when Dolan and co-workers thresholds were used 42.9% of patients had sarcopenia (Table 9.1).

In the present study in male patients, the clinically significant cutoff for SMI with a BMI<30 was 45.6cm^2/m^2 and for male patients with a BMI≥30 was 56.8cm^2/m^2. The clinically significant cutoff for SMI in female patients with a BMI<25 was 39.1cm^2/m^2 and for female patients with a BMI≥30 was 44.6cm^2/m^2. Given that these SMI threshold values (Dolan

BMI>30) were not similar to those of Caan (Table 9.1) the threshold values of Caan were not used in the subsequent analysis.

With reference to SMD Martin and colleagues in 1,473 patients with multistage lung and GI cancers defined SMD (myosteatosis) as an SMD <41HU in patients with BMI <25kg/m^2 and <33HU in patients with BMI ≥25kg/m (66). In contrast, Xiao and co-workers in 3,051 non-metastatic stage I-III colorectal cancer defined myosteatosis according to sex as <35.5HU in males and <32.5HU in females (362). In the present study SMD (Dolan) thresholds were derived using ROC curve analysis to determine thresholds associated with overall survival in this population. This was also conducted using validated online biomarker cutoff optimization software (361). The clinically significant cutoff for SMD in patients in the present cohort with a BMI<25 was 34 HU and for patients with a BMI≥25 was 32 HU. Given that these SMD threshold values (Dolan BMI>25) were not similar to Martin and were not used in the subsequent analysis.

In the present study the clinically significant cutoff for SMD in male patients was 34.1 HU and in female patients was 34.4 HU. Given that these SMD threshold values (Dolan Male/Female) were similar to Xiao and to facilitate comparison of studies the threshold vales of Xiao were used in the analysis. In addition, the association between SMD (Xiao) and SMD (Dolan Male/Female) was strong ($p<0.001$). For example, when Xiao and coworkers thresholds were used 47.5% of patients had myosteatosis and when Dolan and coworkers thresholds were used 46.8% of patients had myosteatosis.

The relationship between clinicopathological characteristics, body composition and overall survival is shown in Table 9.2. The majority of patients were over 65 years of age (64%), overweight or obese (68%), with some comorbidities (88%) and node negative disease (67%). The majority of tumours were located in the right colon (38%) and rectum (37%) and an open surgical approach was applied in 62% of cases. A total of 528 patients were alive

at the censor date with a median survival was 44 months (range 1-110 months). Deaths by any cause occurred in 122 patients (18%); 71 (11%) of which were cancer specific. On univariate survival analysis, age, ASA, TNM stage and the mGPS were significantly associated with overall survival (all p<0.001). Of the body composition parameters BMI, SFI, VO, SMI (Martin, Dolan and Caan) and SMD (Martin, Dolan and Xiao) were significantly associated with overall survival (all p<0.05). SMI and SMD were weakly associated (Figure 9.1). On comparison of SMI (Martin) and SMD (Xiao), both SMI (HR 1.68, 95%CI 1.17-2.41, p=0.005) and SMD (HR 1.47, 95%CI 1.02-2.11, p=0.040) were independently associated with overall survival.

The relationship between SMI (Martin), SMD (Xiao) and mGPS and the clinicopathological characteristics are shown in Table 9.3, Table 9.4, and Table 9.5 respectively. A low SMI (Martin) was significantly associated with older age, higher mGPS, lower BMI and lower SMD (Martin, Dolan and Xiao) (all p<0.001). A low SMD (Xiao) was significantly associated with older age, female sex, higher ASA a right sided tumour, mGPS, lower BMI, SFI, VO and lower SMI (Martin, Dolan and Xiao) (all p<0.05). An elevated mGPS was significantly associated with a high ASA, TNM stage, tumour location, NLR, NPS, BMI>25, SMI (Martin, Dolan and Caan) and SMD (Martin and Dolan) (all p<0.05).

The relationship between SMI (Martin) high/low groups, SMD (Xiao) high/low groups and mGPS high/low groups and overall survival are shown in Figure 9.2, Figure 9.3, Figure 9.4. On comparison of SMI (Martin), SMD (Xiao) and mGPS, SMI (Martin) (HR 1.50, 95%CI 1.04-2.18, p=0.031), SMD (Xiao) (HR 1.42, 95%CI 0.98-2.05, p=0.061) and mGPS (HR 1.44, 95%CI 1.15-1.79, p=0.001) were independently associated with overall survival (Table 9.6).

In patients with a mGPS of 0, SMI (Martin) (HR 1.48, 95%CI 0.97-2.28, p=0.071 and SMD (Xiao) (HR 1.50, 95%CI 0.97-2.33, p=0.068) were weakly associated with overall survival

(Table 9.6). In patients with a mGPS of 1/2, SMI (Martin) (HR 2.02, 95%CI 0.98-4.18, p=0.058) was weakly associated with overall survival (Table 9.6).

Low SMI (Martin) was present in 40% of patients with an mGPS of 0. In contrast, low SMI (Martin) was present in 66% of patients with an mGPS of 2. Low SMD (Xiao) was present in 52% of patients with an mGPS of 0. In contrast, SMD (Xiao) was present in 64% of patients with an mGPS of 2. A combination of Low SMI (Martin) and Low SMD (Xiao) was present with a mGPS 0 in 23.4% of patients. In contrast, a combination of Low SMI (Martin) and Low SMD (Martin) was present with a mGPS 2 in 45.5% of patients.

9.4 Discussion

The results of the present comprehensive study, in patients with colorectal cancer who were largely overweight, and using CT derived body composition analysis showed that sarcopenia (SMI) and myosteatosis (SMD) were significantly associated with survival. Moreover, SMI and SMD were associated with the presence of a systemic inflammatory (in particular the mGPS) and had independent prognostic value. Therefore, the present results support the routine measurement of the SMI, SMD and mGPS as part of the clinical and nutritional assessment in patients with cancer (52, 346, 363).

Colorectal cancer has been extensively examined with reference to CT derived body composition and most studies have reported that either SMI or SMD are associated with survival. In contrast, few studies have included a measurement of the systemic inflammatory response in their analysis. In those studies that included a white cell measure of the systemic inflammatory response such as NLR, SMI and SMD were reported to be independently associated with survival (45, 360). Irrespective, the systemic inflammatory response (however measured) is associated with lower SMI and SMD. These observations may have profound implications for the treatment of sarcopenia and myosteatosis in patients with colorectal cancer and, potentially, other common solid tumours.

Such cross sectional data cannot determine whether a low SMI or SMD results in the presence of systemic inflammation or whether the presence of systemic inflammation results in low SMI or SMD. From the present results, it is clear that a low SMI, SMD or both can occur in the absence of systemic inflammation. However, the proportions of patients with a low SMI, SMD or both is substantially greater in the presence of systemic inflammation. It may be that in those patients that simply improving dietary intake and activity will improve SMI and SMD. In contrast, in those patients with a mGPS 1/2 it may be that moderation of the systemic inflammatory response is required in addition to improve SMI and SMD (355).

In order to better understand the nature of this relationship it will be important to carry out longitudinal and intervention studies.

With reference to longitudinal studies Wallengren and colleagues reported that, in 471 patients with advanced cancer, a CRP>10mg/L had less muscle mass (using dual energy X-ray absorptiometry) on study entry and lost muscle at an accelerated rate during follow-up (43). Mallietzis and co-workers reported that, in 856 patients with operable colorectal cancer, an NLR>3 was associated with lower muscle mass (CT scan) over time (44). Both studies concluded that systemic inflammation was a risk factor for muscle loss and may be a useful marker of catabolic drive. However, the loss of muscle quality has yet to be examined in this relationship. Therefore, further longitudinal studies are required if the relationship between skeletal muscle mass and quality, the systemic inflammatory response and survival is to be further elucidated. To our knowledge the above relationship has not been examined in interventional studies.

It was of interest that, in the present study, approximately 50% of patients had a low SMI or SMD. Compared with other cohorts of patients with early stage colorectal cancer treated with surgical resection these figures appear high and similar to that reported in the terminal stage of the disease. Given that these percentages were similar using various thresholds of (Dolan, Martin, Caan and Xiao) for patients in this cohort, this may suggest that there is a baseline level of poor muscle quantity and quality within this population. This is perhaps not surprising given the deprivation levels of patients referred to Glasgow Royal Infirmary. Indeed, in Glasgow 190,000 or just under 32% of the city's population resides in the 10% of the most deprived areas of the UK (so called "Glasgow effect") (364). This is associated with a poor diet and physical fitness and high levels of alcohol consumption and smoking which would have a direct effect on both muscle quantity and quality. Indeed, when direct comparisons are made with functional testing such as the ASA scoring in the present and other reported studies. For example, in the present study 33% of patients had an ASA score

of ≥3 (severe systemic disease) compared to a recent combined study of 2,100 UK and Canadian patients undergoing elective surgery for colorectal cancers where 20% had an ASA score of ≥3 (365). In addition, when the 763 UK based patients of this study were examined in isolation 11% had an ASA score of ≥3 (45). Therefore, it is clear that the present patient cohort had higher levels of comorbid disease and lower levels of physical function and this may account for, in part, the high percentage of patients with a low SMI and SMD.

Indeed, it was of interest that in the present study ASA was significantly associated with SMD and not SMI. A similar relationship has recently been reported between SMD but not SMI and the Charleston comorbidity index (362). This confirms the clinical utility of SMD as there is increasing recognition that an increase in muscle mass is not necessarily associated with an increased in function (340, 366). It may be that an improvement in muscle quality rather than mass will result in an improvement in physical function.

Limitations of the present study include its retrospective nature and that only patients with an electronically available CT scan were included. However, the study population was relatively large, well-documented in terms of clinicopathological characteristics and measures of the systemic inflammatory response and relatively mature follow-up. Furthermore, different validated threshold values were applied to the CT body composition parameters.

In summary, the present study provides comprehensive evidence that both low skeletal muscle mass and quality has a significant relationship to the systemic inflammatory response and to survival in patients with operable colorectal cancer. This supports the incorporation of the SMI, SMD and mGPS as part of the clinical and nutritional assessment in patients with cancer. This relationship also suggests potential therapeutic interventions.

9.5 Tables and Footnotes

Table 9.1: CT derived body composition measures and thresholds used

Body Composition Measurement	Frequency n (%)
High SFI (69):	
Males>50.0 cm^2m^2 and Females>42.0 cm^2m^2	No: 116 (17.8%) Yes: 534 (82.2%)
Visceral obesity (66, 70):	
VFA: Males >160 cm^2 and Females >80 cm^2	No: 177 (27.2%) Yes: 473 (72.8%)
Sarcopenia	
SMI (Martin) (66):	
Males: BMI<25kg/m^2 and SMI<43 cm^2m^2 or BMI≥25kg/m^2 and SMI<53 cm^2m^2 Females: BMI<5kg/m^2 and SMI<41 cm^2m^2 or BMI≥25kg/m^2 and SMI<41 cm^2m^2	No: 367 (56.5%) Yes: 283 (43.5%)
SMI (Dolan BMI>25): Males: BMI<25kg/m^2 and SMI<45 cm^2m^2 or BMI≥25kg/m^2 and SMI<53 cm^2m^2 Females: BMI<25kg/m^2 and SMI<39 cm^2m^2 or BMI≥25kg/m^2 and SMI<41 cm^2m^2	No: 371 (57.1%) Yes: 279 (42.9%)
SMI (Caan) (353):	
Males: BMI<30kg/m^2 and SMI<52.3 cm^2m^2 or BMI≥30kg/m^2 and SMI<54.3 cm^2m^2 Females: BMI<30kg/m^2 and SMI<38.6 cm^2m^2 or BMI≥30kg/m^2 and SMI<46.6 cm^2m^2	No: 313 (48.2%) Yes: 337 (51.8%)
SMI (Dolan BMI>30)	
Males: BMI<30kg/m^2 and SMI<45.6cm^2m^2 or BMI≥30kg/m^2 and SMI<56.8 cm^2m^2 Females: BMI<30kg/m^2 and SMI<39.1 cm^2m^2 or BMI≥30kg/m^2 and SMI<44.6 cm^2m^2	No: 386 (59.4%) Yes: 264 (40.6%)
Myosteatosis	
SMD (Martin) (66):	
BMI<25kg/m^2 and SMD<41 HU or BMI≥25kg/m^2 and SMD<33HU	No: 258 (39.7%) Yes: 392 (60.3%)
SMD (Dolan BMI>25)	
BMI<25kg/m^2 and SMD<34 HU or BMI≥25kg/m^2 and SMD<32HU	No: 343 (52.8%) Yes: 307 (47.2%)
SMD (Xiao) (362):	
Males<35.5HU and Females<32.5HU	No: 309 (47.5%) Yes: 341 (52.5%)
SMD (Dolan Male/Female)	
Males<34.1 HU and Females<HU 34.4 HU	No: 304 (46.8%) Yes: 346 (53.2%)

Table 9.2: The relationship between clinicopathological characteristics, CT derived body composition and survival in patients undergoing elective surgery for colorectal cancer (n=650): univariate survival analysis

Characteristic		n= 650 (%)	Overall Survival HR (95% CI)	P-value
	Clinico-pathological			
Age	≤65	234 (36.0)	1.64 (1.29-2.08)	<0.001
	65 - 74	251 (38.6)		
	>74	165 (25.4)		
Sex	Female	296 (45.5)	1.19 (0.83-1.70)	0.351
	Male	354 (54.5)		
ASA score	1	141 (21.7)	1.56 (1.23-1.97)	<0.001
	2	297 (45.7)		
	3	193 (29.7)		
	4	19 (2.9)		
Laparoscopic Surgery	No	407 (62.6)	0.68 (0.45-1.03)	0.072
	Yes	243 (37.4)		
TNM	0	14 (2.2)	1.67 (1.31-2.14)	<0.001
	I	155 (23.8)		
	II	263 (40.5)		
	III	218 (33.5)		
Venous Invasion	No	266 (40.9)	1.26 (0.87-1.82)	0.217
	Yes	384 (59.1)		
Tumour Location	Right and Transverse	247 (38.0)	0.84 (0.58-1.23)	0.373
	Left	145 (22.3)		
	Rectum	237 (36.5)		
	Total and Subtotal	21 (3.2)		
Adjuvant Chemotherapy	No	463 (71.2)	0.70 (0.45-1.08)	0.102
	Yes	187 (28.8)		
	Systemic inflammation			
mGPS	0	499 (76.8)	1.55 (1.25-1.91)	<0.001
	1	63 (9.7)		
	2	88 (13.5)		
NLR	≤3	369 (56.8)	1.40 (0.98-1.99)	0.066
	>3	281 (43.2)		
NPS	0	568 (87.4)	1.66 (1.16-2.36)	0.005
	1	67 (10.3)		
	2	15 (2.3)		
	Body composition			
BMI (kg/m^2)	<25	219 (33.7)	0.60 (0.39-0.91)	0.015
	≥25	431 (66.3)		
High SFI	No	116 (17.8)	0.60 (0.40-0.89)	0.011
	Yes	534 (82.2)		
Visceral obesity	No	177 (27.2)	0.68 (0.47-0.98)	0.040
	Yes	473 (72.8)		
Low SMI (Sarcopenia)				
SMI (Martin)	No	367 (56.5)	1.74 (1.21-2.49)	0.003
	Yes	283 (43.5)		
SMI (Dolan BMI>25)	No	371 (57.1)	1.77 (1.24-1.54)	0.002
	Yes	279 (42.9)		
SMI (Caan)	No	313 (48.2)	1.58 (1.09-2.28)	0.016
	Yes	337 (51.8)		
SMI (Dolan BMI>30)	No	386 (59.4)	1.60 (1.12-2.28)	0.010
	Yes	264 (40.6)		
Low SMD (Myosteatosis)				
SMD (Martin)	No	258 (39.7)	1.84 (1.25-2.72)	0.002
	Yes	392 (60.3)		
SMD (Dolan BMI>25)	No	343 (52.8)	1.57 (1.10-2.25)	0.013
	Yes	307 (47.2)		
SMD (Xiao)	No	309 (47.5)	1.54 (1.07-2.22)	0.020
	Yes	341 (52.5)		
SMD (Dolan Male/Female)	No	304 (46.8)	1.58 (1.10-2.27)	0.014
	Yes	346 (53.2)		

Table 9.3: The relationship between Sarcopenia (Martin), clinicopathological characteristics, and systemic inflammation in patients undergoing elective surgery for colorectal cancer (n=650)

Characteristic		High SMI (No Sarcopenia n=367)	Low SMI (Sarcopenia n=283)	P-value
	Clinico-pathological			
Age	≤65	160 (43.6)	74 (26.1)	<0.001
	65 - 74	133 (36.2)	118 (41.7)	
	>74	74 (20.2)	91 (32.2)	
Sex	Female	163 (44.4)	133 (47.0)	0.513
	Male	204 (55.6)	150 (53.0)	
ASA score	1	81 (22.1)	60 (21.2)	0.159
	2	167 (45.5)	130 (45.9)	
	3	113 (30.8)	80 (28.3)	
	4	6 (1.6)	13 (4.6)	
Laparoscopic Surgery	No	220 (59.9)	187 (66.1)	0.109
	Yes	147 (40.1)	96 (33.9)	
TNM	0	9 (2.5)	5 (1.8)	0.032
	I	101 (27.5)	54 (19.1)	
	II	133 (36.2)	130 (45.9)	
	III	124 (33.8)	94 (33.2)	
Venous Invasion	No	154 (42.0)	112 (39.6)	0.540
	Yes	213 (58.0)	171 (60.4)	
Tumour Location	Right and Transverse	138 (37.6)	109 (38.5)	0.293
	Left	77 (21.0)	68 (24.0)	
	Rectum	143 (39.0)	94 (33.2)	
	Total and Subtotal	9 (2.5)	12 (4.2)	
Adjuvant Chemotherapy	No	208 (56.7)	177 (62.5)	0.091
	Yes	159 (43.3)	106 (37.5)	
	Systemic inflammation			
mGPS	0	298 (81.2)	201 (71.0)	<0.001
	1	39 (10.6)	24 (8.5)	
	2	30 (8.2)	58 (20.5)	
NLR	≤3	220 (59.9)	149 (52.7)	0.063
	>3	147 (40.1)	134 (47.3)	
NPS	0	328 (89.4)	240 (84.8)	0.220
	1	32 (8.7)	35 (12.4)	
	2	7 (1.9)	8 (2.8)	
	Body composition			
BMI (kg/m^2)	<25	103 (28.1	116 (41)	0.001
	≥25	264 (71.9)	167 (59)	
High SFI	No	67 (18.3)	49 (17.3)	0.756
	Yes	300 (81.7)	234 (82.7)	
Visceral obesity	No	98 (26.7)	79 (27.9)	0.731
	Yes	269 (73.3)	204 (72.1)	
Low SMI (Sarcopenia)				
SMI (Dolan BMI>25)	No	356 (97.0)	15 (5.3)	<0.001
	Yes	11 (3.0)	268 (94.7)	
SMI (Caan)	No	275 (74.9)	38 (13.4)	<0.001
	Yes	92 (25.1)	245 (86.6)	
SMI (Dolan BMI>30)	No	315 (85.8)	71 (25.1)	<0.001
	Yes	52 (14.2)	212 (74.9)	
Low SMD (Myosteatosis)				
SMD (Martin)	No	177 (48.2)	81 (28.6)	<0.001
	Yes	190 (51.8)	202 (71.4)	
SMD (Dolan BMI>25)	No	224 (61.0)	119 (42.0)	<0.001
	Yes	143 (39.0)	164 (58.0)	
SMD (Xiao)	No	196 (53.4)	113 (39.9)	0.001
	Yes	171 (46.6)	170 (60.1)	
SMD (Dolan BMI Male/Female)	No	197 (53.7)	107 (37.8)	<0.001
	Yes	170 (46.3)	176 (62.2)	

Table 9.4: The relationship between SMD (Xiao), clinicopathological characteristics and systemic inflammation in patients undergoing surgery for colorectal cancer (n=650)

Characteristic		Low SMD (Xiao)		
	Clinico-pathological	No (n=309)	Yes (n=341)	p-value
Age	≤65	149 (48.2)	85 (24.9)	<0.001
	65 - 74	108 (35.0)	143 (41.9)	
	>75	52 (16.8)	113 (33.1)	
Sex	Female	167 (54.0)	129 (37.8)	<0.001
	Male	142 (46.0)	212 (62.2)	
ASA score	1	91 (29.4)	50 (14.7)	<0.001
	2	140 (45.3)	157 (46.0)	
	3	72 (23.3)	121 (35.5)	
	4	6 (1.9)	13 (3.8)	
Laparoscopic Surgery	No	195 (63.1)	212 (62.2)	0.805
	Yes	114 (36.9)	129 (37.8)	
TNM	0	7 (2.3)	7 (2.1)	0.934
	I	77 (24.9)	78 (22.9)	
	II	123 (39.8)	140 (41.1)	
	III	102 (33.0)	116 (34.0)	
T stage	0	7 (2.3)	7 (2.1)	0.327
	1	34 (11.0)	45 (13.2)	
	2	59 (19.1)	45 (13.2)	
	3	160 (51.8)	184 (54.0)	
	4	49 (15.9)	60 (17.6)	
N stage	0	208 (67.3)	226 (66.3)	0.898
	1	76 (24.6)	84 (24.6)	
	2	25 (8.1)	31 (9.1)	
Venous Invasion	No	133 (43.0)	133 (39.0)	0.296
	Yes	176 (57.0)	208 (61.0)	
Tumour Location	Right and Transverse	108 (35.0)	139 (40.8)	0.041
	Left	64 (20.7)	81 (23.8)	
	Rectum	127 (41.1)	110 (32.3)	
	Total and Subtotal	10 (3.2)	11 (3.2)	
Adjuvant Chemotherapy	No	103 (33.3)	84 (24.6)	0.027
	Yes	206 (66.7)	257 (75.4)	
	Systemic inflammation			
mGPS	0	242 (78.3)	257 (75.4)	0.045
	1	35 (11.3)	28 (8.2)	
	2	32 (10.4)	56 (16.4)	
NLR	≤3	183 (59.2)	186 (54.5)	0.229
	>3	126 (40.8)	155 (45.5)	
NPS	0	273 (88.3)	295 (86.5)	0.738
	1	30 (9.7)	37 (10.9)	
	2	6 (1.9)	9 (2.6)	
	Body composition			
BMI (kg/m2)	<25	136 (44.0)	83 (24.3)	<0.001
	≥25	173 (56.0)	258 (75.7)	
High SFI	No	76 (24.6)	40 (11.7)	<0.001
	Yes	233 (75.4)	301 (88.3)	
Visceral obesity	No	126 (40.8)	51 (15.0)	<0.001
	Yes	183 (59.2)	290 (85.0)	
Sarcopenia				
Low SMI (Martin)	No	196 (63.4)	171 (50.1)	<0.001
	Yes	113 (36.6)	170 (49.9)	
Low SM (Dolan BMI>25)	No	204 (66.0)	167 (49.0)	<0.001
	Yes	105 (34.0)	174 (51.0)	
Low SMI (Caan)	No	179 (57.9)	134 (39.3)	<0.001
	Yes	130 (42.1)	207 (60.7)	
Low SM (Dolan BMI>30)	No	211 (68.3)	175 (51.3)	<0.001
	Yes	98 (31.7)	166 (48.7)	
Myosteatosis				
Low SMD (Martin)	No	233 (75.4)	25 (7.3)	<0.001
	Yes	76 (24.6)	316 (92.7)	
Low SMD (Dolan BMI>25)	No	303 (98.1)	40 (11.7)	<0.001
	Yes	6 (1.9)	301 (88.3)	
Low SMD (Dolan Male/Female)	No	284 (91.8)	20 (5.9)	<0.001
	Yes	25 (8.1)	321 (94.1)	

Table 9.5: The relationship between mGPS, clinicopathological characteristic and systemic inflammation in patients undergoing elective surgery for colorectal cancer (n=650)

Characteristic		mGPS 0	mGPS 1&2 (n=151)	P-value
	Clinico-pathological			
Age	≤65	185 (37.1)	49 (32.5)	0.410
	65 - 74	193 (38.7)	58 (38.4)	
	>74	121 (24.2)	44 (29.1)	
Sex	Female	228 (45.7)	68 (45.0)	0.887
	Male	271 (54.3)	83 (55.0)	
ASA score	1	120 (24.0)	21 (13.9)	0.036
	2	221 (44.3)	76 (50.3)	
	3	146 (29.3)	47 (31.1)	
	4	12 (2.4)	7 (4.6)	
Laparoscopic Surgery	No	303 (60.7)	104 (68.9)	0.070
	Yes	196 (39.3)	47 (31.1)	
TNM	0	13 (2.6)	1 (0.7)	<0.001
	I	135 (27.1)	20 (13.2)	
	II	173 (34.7)	90 (59.6)	
	III	178 (35.7)	40 (26.5)	
Venous Invasion	No	199 (39.9)	67 (44.4)	0.325
	Yes	300 (60.1)	84 (55.6)	
Tumour Location	Right and Transverse	175 (35.1)	72 (47.7)	0.014
	Left	112 (22.4)	33 (21.9)	
	Rectum	197 (39.5)	40 (26.5)	
	Total and Subtotal	15 (3.0)	6 (4.0)	
Adjuvant Chemotherapy	No	293 (66.9)	92 (68.7)	0.704
	Yes	206 (33.1)	59 (31.3)	
	Systemic inflammation			
NLR	≤3	308 (61.7)	61 (40.4)	<0.001
	>3	191 (38.3)	90 (59.6)	
NPS	0	459 (92.0)	109 (72.2)	<0.001
	1	38 (7.6)	29 (19.2)	
	2	2 (0.4)	13 (8.6)	
	Body composition			
BMI (kg/m^2)	<25	156 (31.3)	63 (41.7)	0.017
	≥25	343 (68.7)	88 (58.3)	
High SFI	No	84 (16.8)	32 (21.2)	0.220
	Yes	415 (83.2)	119 (78.8)	
Visceral obesity	No	129 (25.9)	48 (31.8)	0.151
	Yes	370 (74.1)	103 (68.2)	
Low SMI (Sarcopenia)				
SMI (Martin)	No	298 (59.7)	69 (45.7)	0.002
	Yes	201 (40.3)	82 (54.3)	
SMI (Dolan BMI>25)	No	299 (59.9)	72 (47.7)	0.008
	Yes	200 (40.1)	79 (52.3)	
SMI (Caan)	No	254 (50.9)	59 (39.1)	0.011
	Yes	245 (49.1)	92 (60.9)	
SMI (Dolan BMI>30)	No	309 (61.9)	77 (51.0)	0.017
	Yes	190 (38.1)	74 (49.0)	
Low SMD (Myosteatosis)				
SMD (Martin)	No	214 (42.9)	44 (29.1)	0.002
	Yes	285(57.1)	107 (70.9)	
SMD (Dolan BMI>25)	No	274 (54.9)	69 (45.7)	0.047
	Yes	225 (45.1)	82 (54.3)	
SMD (Xiao)	No	242 (48.5)	67 (44.4)	0.374
	Yes	257 (51.5)	84 (55.6)	
SMD (Dolan Male/Female)	No	241 (48.3)	63 (41.7)	0.156
	Yes	258 (51.7)	88 (58.3)	

Table 9.6: The relationship between SMI, SMD, mGPS, Sarcopenia and overall survival in patients undergoing elective surgery for colorectal cancer (n=650)

Independent, Mutually Adjusted Association	HR (95% CI)	p-value
All Patients n=650		
mGPS	1.44 (1.15-1.79)	0.001
Low SMI (Martin)	1.50 (1.04-2.18)	0.031
Low SMD (Xiao)	1.42 (0.98-2.05)	0.061
mGPS 0 n=499		
Low SMI (Martin)	1.48 (0.97-2.28)	0.071
Low SMD (Xiao)	1.50 (0.97-2.33)	0.068
mGPS 1/2 n=151		
Low SMI (Martin)	2.02 (0.98-4.18)	0.058
Low SMD (Xiao)	1.30 (0.67-2.54)	0.438

9.6 Figures and Legends

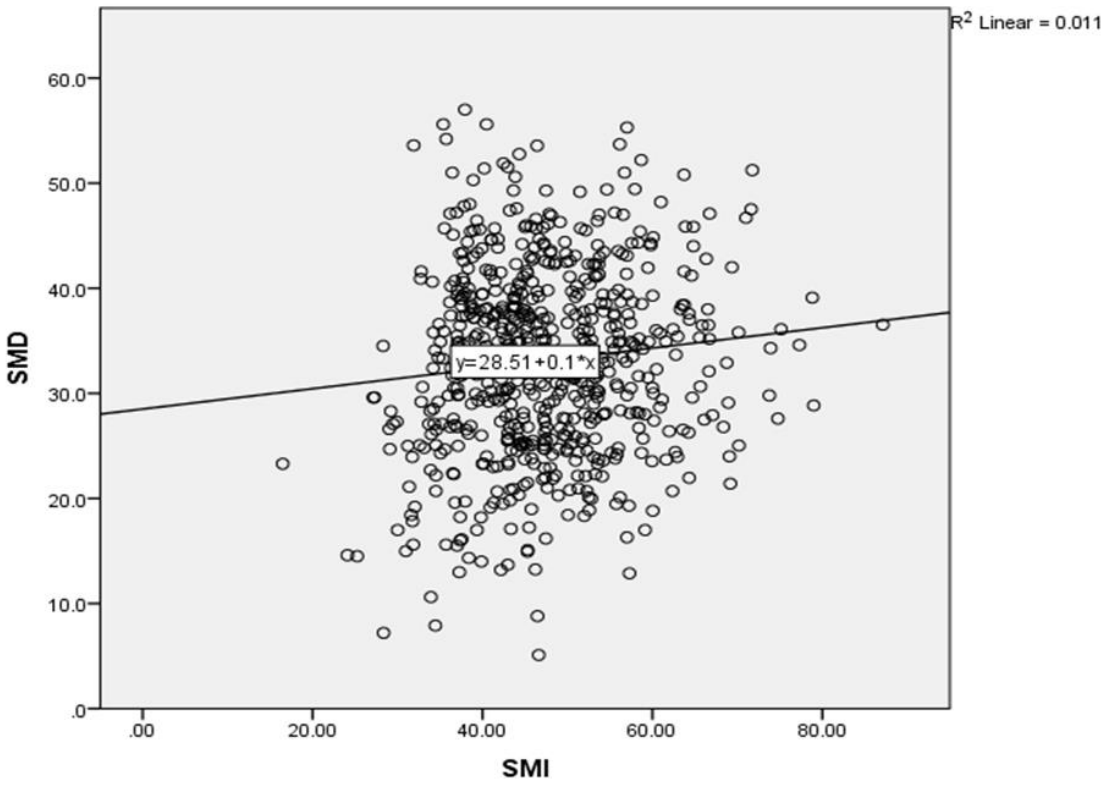
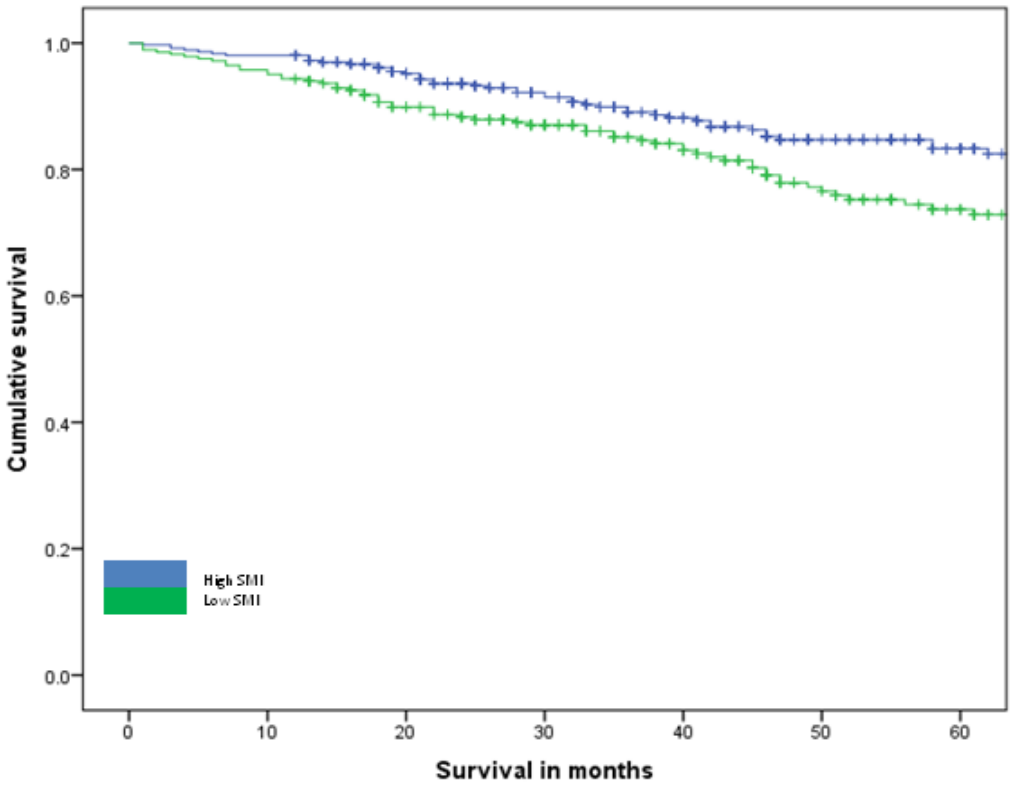
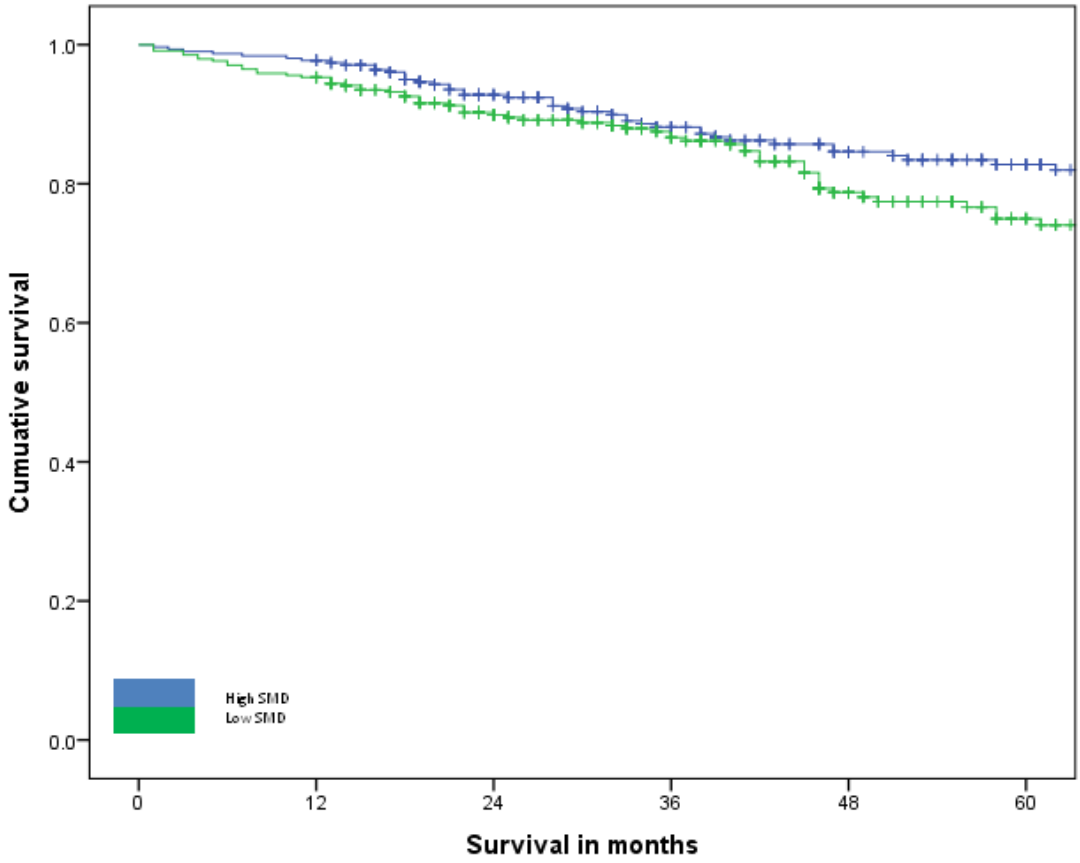


Figure 9.1: The relationship between SMI and SMD in patients undergoing elective surgery for colorectal cancer (n=650)



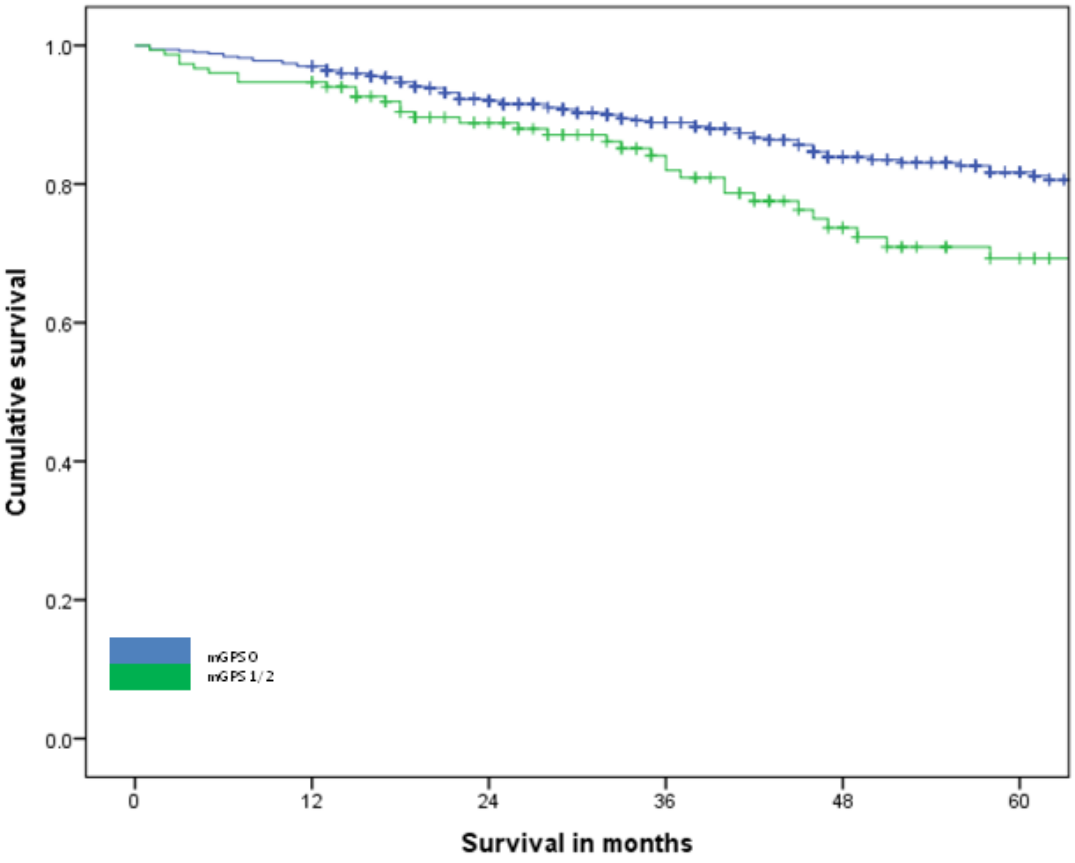
Number at risk	0	12	24	36	48	60
High SMI	367	360	345	333	324	322
Low SMI	283	267	261	249	240	238

Figure 9.2: The relationship between SMI (Martin) and overall survival (n=650, p=0.002)



Number at risk	0	12	24	36	48	60
High SMD	309	302	288	277	270	267
Low SMD	241	229	208	200	185	180

Figure 9.3: The relationship between SMD (Xiao) and overall survival (n=650, p=0.019)



Number at risk	0	12	24	36	48	60
mGPS 0	499	484	465	449	343	429
mGPS= 1/2	151	143	135	128	121	118

Figure 9.4: The relationship between mGPS and overall survival (n=650, p=0.010)

10. COMPARISON OF THE PROGNOSTIC VALUE OF ECOG-PS, mGPS AND BMI/WL IN PATIENTS WITH ADVANCED CANCER: IMPLICATIONS FOR A CLINICALLY IMPORTANT FRAMEWORK FOR ASSESSMENT AND TREATMENT OF CANCER

10.1 Introduction

The recognition of the poor prognosis associated with the syndrome of cachexia dates back to ancient Greece. These observations remain valid today as in patients with advanced cancer, progressive involuntary loss of body weight and lean tissue, anorexia, weakness and fatigue (cancer cachexia) are associated with poor survival (43). Despite the clinical recognition of the syndrome of cancer cachexia, performance status remains the most useful clinical measure on which to base likely patient outcome to treatment and prognosis (25).

There is now good evidence that the presence of a systemic inflammatory response, as evidenced by the mGPS is associated with the loss of lean tissue, anorexia, weakness and fatigue and poor survival in patients with advanced cancer (38, 367). Moreover, in combination with ECOG-PS has been shown to effectively stratify the above measures of cachexia (17, 25).

In contrast, Martin and colleagues (2015), in a large cohort study of more than 11,000 patients with advanced cancer proposed that cachexia should be graded according to the concurrent Body Mass Index (BMI) and the degree of weight loss (WL) (368). They showed that both had independent prognostic value and effectively stratified survival. However degree of WL may be limited due to its inaccurate and/or subjective reporting whilst BMI may be less useful as many patients with advanced cancer are overweight (368).

Therefore, while ECOG-PS, mGPS and BMI/WL grade are all valid prognostic scores, and are related to cancer cachexia, to date, there has been no direct comparison of their prognostic value in patients with advanced cancer. Such a comparison may inform clinical

practice as to which factors are associated with reduced survival and in turn inform the assessment and treatment of cancer cachexia. Therefore, the aim of this Chapter was to carry out such a comparison in a prospective cohort of patients with advanced cancer.

10.2 Patients and Methods

Patients:

An international database of patients with advanced cancer was analysed. All data were collected prospectively across 18 sites in the UK and Ireland (cancer centres, hospitals, and specialist palliative care units) over a five-year period (2011-2016). Eligible patients met the following criteria: ≥18 years of age; advanced cancer (defined as metastatic cancer [histological, cytological or radiological evidence], locally advanced or receiving anti-cancer therapy with palliative intent); able to complete study questionnaires; provide a venous blood sample and with a recorded ECOG-PS. Patients were excluded if they had breast or prostate carcinoma with only bone metastases as their survival times could be many years and therefore an argument could be made that they did not in fact have advanced cancer. Patients who were undergoing active anti-cancer therapy or not, on both an inpatient and outpatient basis were included. The study had ethics committee approval in both the UK and Ireland and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The study adhered to the STROBE guidelines for cohort studies.

Individual centres were opened at staggered time points. Within each centre, patients who fulfilled the eligibility criteria were invited to participate and consented on a sequential basis therefore reducing selection bias. All assessments, including blood sampling, were performed on the day of consent.

Prognostic markers

Autobiographical and clinical data including the patient's age, sex, ECOG-PS, mGPS, BMI/WL grade, underlying primary disease, and the presence of metastasis were recorded (6, 25, 369).

Bio-markers: CRP and albumin combined in the mGPS. An autoanalyzer was used to measure serum CRP (mg/L) and albumin (g/L) concentrations (Architect; Abbot Diagnostics, Maidenhead, UK). The mGPS and BMI/WL grade was derived as previously described (99, 369).

Statistical Analysis:

Categorical variables were analysed using χ^2 test for linear-by-linear association, or χ^2 test for 2 by 2 tables. The time between the date of study entry and the date of death of any cause was used to define overall survival (OS). A survival time of 3 months or greater was used to define 3-month survival rate. Survival data were analysed using univariate and multivariate Cox regression. In addition to significant variables of interest on univariate analysis the predefined variables age, sex and cancer location were entered into a backward conditional multivariate model. Cox Regression analysis was carried out for ECOG-PS, mGPS and BMI/WL grade to establish proportional Hazard Ratios.

Two tailed p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 21.0. SPSS Inc., Chicago, IL, USA).

10.3 Results

A total of 730 patients (390 males, 340 females) met the eligibility criteria. The clinicopathological characteristics of the study population is shown in Table 10.1. The majority of patients were over 65 years of age (55.8%), had an ECOG-PS>0/1 (56.0%), mGPS>0 (55.5%), BMI≥25 (50.7%), <2.5% weight loss (56.8%) and had metastatic disease (85.8%). The majority of tumours were gastrointestinal (42.9%) and lung (28.2%) cancers. The median overall survival (OS) for the entire cohort was 7.3 months (95% CI: 1.0-73.63 months). At the time of censoring, 182 patients (39.5%) were still alive. Median follow up time for these patients was 6.6 months (95% CI: 5.8-7.1 months).

The relationship between ECOG-PS, mGPS and BMI/WL grade and overall survival in patients with advanced cancer is shown in Table 10.2a and Figures 10.1-10.3. On multivariate cox regression analysis ECOG-PS (HR 1.61 95%CI 1.42-1.83, p<0.001), mGPS (HR 1.53, 95%CI 1.39-1.69, p<0.001) and BMI/WL grade (HR 1.41, 95%CI 1.25-1.60, p<0.001) remained independently associated with overall survival.

In patients with an ECOG-PS 0/1 the relationship between mGPS and BMI/WL grade and overall survival in patients with advanced cancer is shown in Table 10.2b. On multivariate cox regression analysis mGPS (HR 1.50, 95%CI 1.32-1.72, p<0.001) and BMI/WL Grade (HR 1.29, 95%CI 1.06-1.56, p=0.009) remained independently associated with overall survival.

In patients with an ECOG-PS 2 the relationship between mGPS and BMI/WL grade and overall survival in patients with advanced cancer is shown in Table 10.2c. On multivariate cox regression analysis mGPS (HR 1.56, 95%CI 1.32-1.86, p<0.001) and BMI/WL Grade (HR 1.46, 95%CI 1.19-1.80, p<0.001) remained independently associated with overall survival.

In patients with an ECOG-PS 3/4 the relationship between mGPS and BMI/WL grade and overall survival in patients with advanced cancer is shown in Table 10.2d. On multivariate cox regression analysis mGPS (HR 1.55, 95%CI 1.12-2.15, p=0.009) and BMI/WL grade (HR 1.53, 95%CI 1.11-2.12, p=0.010) remained independently associated with overall survival.

The relationship between ECOG-PS, mGPS and 3-month survival is shown in Table 10.3. In patients with an ECOG-PS of 0/1 there was a significant association between mGPS and 3-months survival (p<0.001). In patients with an ECOG-PS of 2 there was a significant association between mGPS and 3-months survival (p<0.001). In patients with an ECOG-PS of 3/4 there was a non-significant association between mGPS and 3-months survival (p=0.102). In patients with an ECOG-PS of 0-4 there was a significant association between mGPS and 3-months survival (p<0.001).

In patients with an mGPS of 0 there was a significant association between ECOG-PS and 3-months survival (p<0.001). In patients with an mGPS of 1 there was a significant association between ECOG-PS and 3-months survival (p=0.021). In patients with an mGPS of 2 there was a significant association between ECOG-PS and 3-months survival (p<0.001). In patients with an mGPS of 0-2 there was a significant association between ECOG-PS and 3-months survival (p<0.001).

The relationship between ECOG-PS, mGPS and 3-month survival in patients with a BMI/WL grade 0/1 is shown in Table 10.4. In patients with an ECOG-PS of 0/1 there was a significant association between mGPS and 3-months survival (p=0.001). In patients with an ECOG-PS of 2 there was a trend to a significant association between mGPS and 3-months survival (p=0.085). In patients with an ECOG-PS of 3/4 there was a non-significant association between mGPS and 3-months survival (p=0.741). In patients with an ECOG-PS of 0-4 there was a significant association between mGPS and 3-months survival (p<0.001).

In patients with an mGPS of 0 there was a significant association between ECOG-PS and 3-months survival (p=0.001). In patients with an mGPS of 1 there was a non-significant association between ECOG-PS and 3-months survival (p=0.343). In patients with an mGPS of 2 there was a significant association between ECOG-PS and 3-months survival (p=0.003). In patients with an mGPS of 0-2 there was a significant association between ECOG-PS and 3-months survival (p<0.001).

10.4 Discussion

The results of the present study show that in a prospective cohort of patients with advanced cancer and a median survival of 7 months, the majority of patients had a good performance status and a low BMI/WL grade (minimal weight loss, normal BMI). In contrast, the majority of patients had evidence of a systemic inflammatory response. Although ECOG-PS, mGPS and BMI/WL grade all effectively stratified overall survival when adjusted for age, sex and tumour type, both ECOG-PS and mGPS also stratified patient survival in those patients with a low BMI/WL grade. Therefore, the combination of ECOG-PS and mGPS reliably stratifies survival in patients with advanced cancer (17, 25, 331).

The results of the present study are consistent with the work of Martin and colleagues who examined the relationship between weight loss grade, performance status and the GPS in more than 2,500 patients with advanced cancer and a median survival of 7.6 months (370). Unfortunately, to date this data has only been published in abstract form. Nevertheless, the tabulated data in abstract is consistent with the present analysis and their conclusions that "a combination of BMI/ WL grades, PS and GPS consistently stratifies advanced cancer patients in to very different survival groups, and could be considered as diagnostic criteria for cachexia" have been confirmed and extended in the present study (370).

The results of the present study indicate the importance of the systemic inflammatory response not only as a prognostic factor but also to inform the nutritional and functional decline associated with advanced cancer. Indeed, in those patients who had both a good performance status and good BMI/WL grade (no obvious functional decline or weight loss), the mGPS effectively stratified median survival between 11.4 months and 7.5 months. Furthermore, in those patients 42%, had an elevated mGPS. One interpretation of the findings is that obvious weight loss in patients with advanced cancer is a later event than functional decline, and that functional decline is a later event than the development of a

systemic inflammatory response (349). Therefore, it may be that the mGPS should form the basis of stratification of likely survival in patients with advanced cancer. Irrespective, greater prominence should be given to the assessment of the systemic inflammatory response (as evidenced by the mGPS) in patients with advanced cancer (38). Moreover, the systemic inflammatory response, as evidenced by the mGPS, may be considered a cardinal feature of the syndrome of cancer cachexia (194, 355). If this proves to be the case then the systemic inflammatory response will become an important therapeutic target for cancer cachexia in the coming years (82). Indeed, targeting the inflammatory response to treat cancer cachexia has been proposed as a therapy with clinical trials now underway (371, 372). Trials have looked at this in the past but importantly patients were not entered into these trials on the basis of their inflammatory response.

The present results support recent observations in the literature. For example, with reference to cachexia Morley (2019) commented that although the cachexia score (CASCO) has been identified "as the best screening test available for cachexia, a quicker screen that may be equally effective is the Glasgow Prognostic Score" (373). Indeed, this has been previously proposed by Douglas and McMillan (2014) (355) and the importance of the systemic inflammatory response as a stratification factor randomised trials is now recognised (54). Therefore, it will be important that a direct comparison of the CASCO and ECOG-PS/mGPS tools is carried out in terms of body composition, quality of life and survival in patients with advanced cancer (374). Moreover, such work is the basis of the rationalisation of the multiple tools developed to identify clinically important cachexia, sarcopenia and malnutrition.

The present study had a number of limitations. The majority of patients were undergoing palliative care. As a result, it could be assumed that there had a high symptom burden which has been shown to be associated with worse outcomes. Furthermore, despite recruitment occurring across 18 sites, the patient cohort may not be completely representative of patients

with advanced cancer. However, they were well defined in terms of the components of know and validated prognostic scores which will allow for direct comparison with other populations in future studies. Finally, the method of patient recruitment/sampling strategy was opportunistic. However, the heterogeneity of the primary cancer types suggests that the recruitment process while being opportunistic was robust.

In summary, while ECOG-PS, mGPS and BMI/WL grade are all valid prognostic scores the ECOG/mGPS framework is more robust and may form the basis of risk stratification of survival in patients with advanced cancer.

10.5 Tables and Footnotes

Table 10.1: Clinicopathological characteristics of patients with advanced cancer (n=730)

Characteristic		n=730 (%)
	Clinico-pathological	
Age	<65	323 (44.2)
	65 - 74	225 (30.8)
	>74	182 (24.9)
Sex	Male	390 (53.4)
	Female	340 (46.6)
Cancer Location	Lung	206 (28.2)
	GI	313 (42.9)
	Other	211 (28.9)
Metastatic Disease	No	104 (14.2)
	Yes	626 (85.8)
	Previous Ant-Cancer Therapy	
Chemotherapy	No	148 (20.3)
	Yes	582 (79.7)
Radiotherapy	No	572 (78.4)
	Yes	158 (21.6)
Hormones	No	678 (92.9)
	Yes	52 (7.1)
	Performance status	
ECOG-PS	0/1	409 (56.0)
	2	240 (32.9)
	3/4	81 (11.1)
	Systemic Inflammation	
mGPS	0	325 (44.5)
	1	111 (15.2)
	2	294 (40.3)
	Body composition	
BMI	≤20.0 kg/m^2	99 (13.6)
	20-21.9 kg/m^2	92 (12.6)
	22-24.9 kg/m^2	174 (23.4)
	25-27.9 kg/m^2	156 (21.4)
	≥28.0 kg/m^2	209 (28.6)
% Weight Loss	<2.5	415 (56.8)
	≥2.5	315 (43.2)
BMI/WL grade	0/1	404 (55.3)
	2/3	241 (33.0)
	4	85 (11.6)

Table 10.2: The relationship between ECOG, mGPS and BMI/WL grade and overall survival in patients with advanced cancer.

Characteristics	Univariate	p-value	Multivariate	p-value	Multivariate Adjusted for Age, Sex and Cancer Location	p-value
Table 10.2a ECOG-PS 0/1-4 (n=730)						
ECOG-PS	1.85 (1.63-2.09)	<0.001	1.61 (1.42-1.83)	<0.001	1.64 (1.44-1.86)	<0.001
mGPS	1.63 (1.48-1.80)	<0.001	1.53 (1.39-1.69)	<0.001	1.49 (1.35-1.64)	<0.001
BMI/WL grade	1.48 (1.30-1.67)	<0.001	1.41 (1.25-1.60)	<0.001	1.39 (1.23-1.58)	<0.001
Table 10.2b ECOG-PS 0/1 (n=409)						
mGPS	1.51 (1.32-1.72)	<0.001	1.50 (1.32-1.72)	<0.001	1.44 (1.26-1.65)	<0.001
BMI/WL grade	1.29 (1.07-1.56)	0.007	1.29 (1.06-1.56)	0.009	1.25 (1.03-1.51)	0.024
Table 10.2b ECOG-PS 2 (n=240)						
mGPS	1.59 (1.34-1.89)	<0.001	1.56 (1.32-1.86)	<0.001	1.53 (1.28-1.82)	<0.001
BMI/WL grade	1.50 (1.22-1.84)	<0.001	1.46 (1.19-1.80)	<0.001	1.43 (1.16-1.76)	0.001
Table 10.2c ECOG-PS 3/4 (n=81)						
mGPS	1.42 (1.04-1.95)	0.029	1.55 (1.12-2.15)	0.009	1.54 (1.11-2.14)	0.009
BMI/WL grade	1.37 (1.02-1.84)	0.039	1.53 (1.11-2.12)	0.010	1.58 (1.15-2.19)	0.005

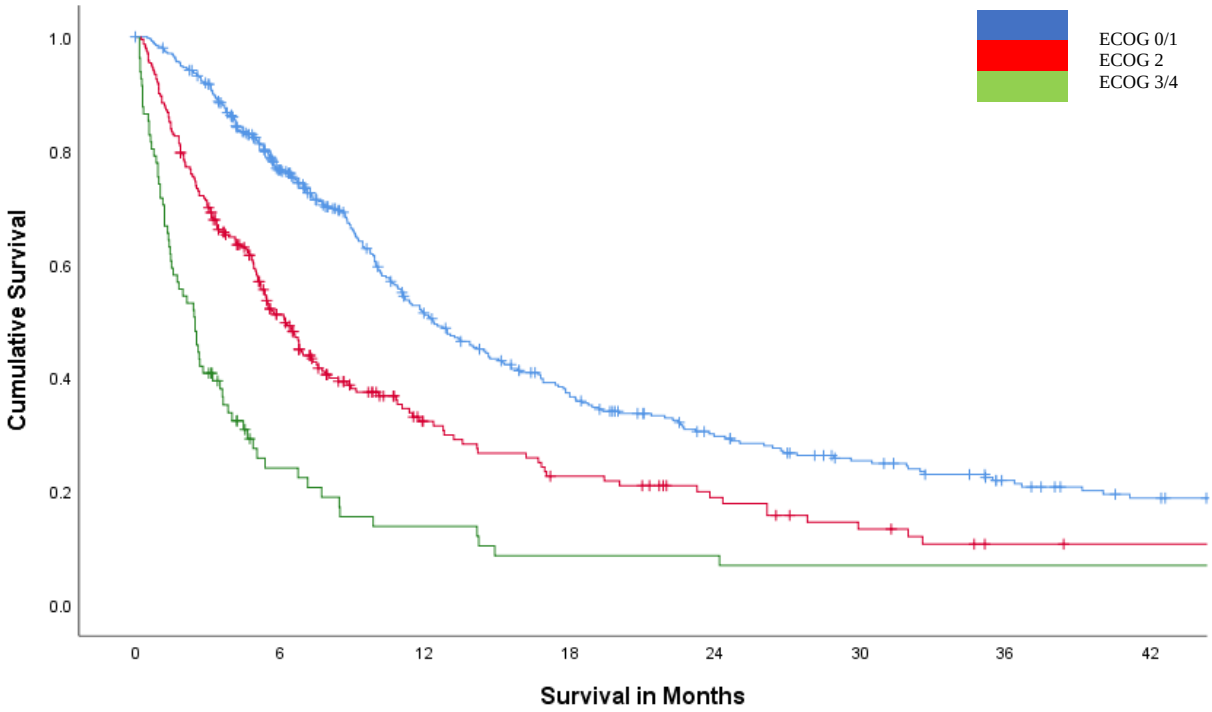
Table 10.3: The relationship between the ECOG-PS, mGPS and 3 month survival rate in patients with advanced cancer (n=730)

ECOG-PS		mGPS=0	mGPS=1	mGPS=2	mGPS 0-2	
		n (%)	n (%)	n (%)	n (%)	P-value
0-1	N	226	56	127	409	
	Survival Rate at 3 months	218 (96.5%)	46 (82.1%)	105 (82.7%)	369 (90.26%)	<0.001
	Median Survival	10.9	7.0	7.0	9.1	
	95% CI	9.2-12.3	5.3-10.2	5.7-8.9	8.0-10.0	
2	N	87	42	111	240	
	Survival Rate at 3 months	76 (87.4%)	28 (66.7%)	62 (55.9%)	166 (69.2%)	<0.001
	Median Survival	7.3	5.0	3.5	5.2	
	95% CI	6.1-9.8	3.1-6.6	2.6-4.8	4.6-5.7	
3-4	N	12	13	56	81	
	Survival Rate at 3 months	8 (66.7%)	6 (46.2%)	19 (33.9%)	33 (40.7%)	0.102
	Median Survival	5.9	2.6	1.9	2.5	
	95% CI	2.5-14.2	0.6-4.5	1.2-2.7	1.5-3.1	
ECOG-PS 0/1-4	N	325	111	294	730	
	Survival Rate at 3 months	302 (92.9%)	80 (72.1%)	186 (63.3%)	568 (77.8%)	<0.001
	Median Survival	9.6	5.3	4.2	6.6	
	95% CI	8.4-10.8	4.2-6.6	3.6-5.1	5.8-7.1	
P-value		<0.001	0.021	<0.001	<0.001	

Table 10.4: The relationship between the ECOG-PS, mGPS and 3 month survival rate in patients with a BMI/WL grade 0/1 and advanced cancer (n=404)

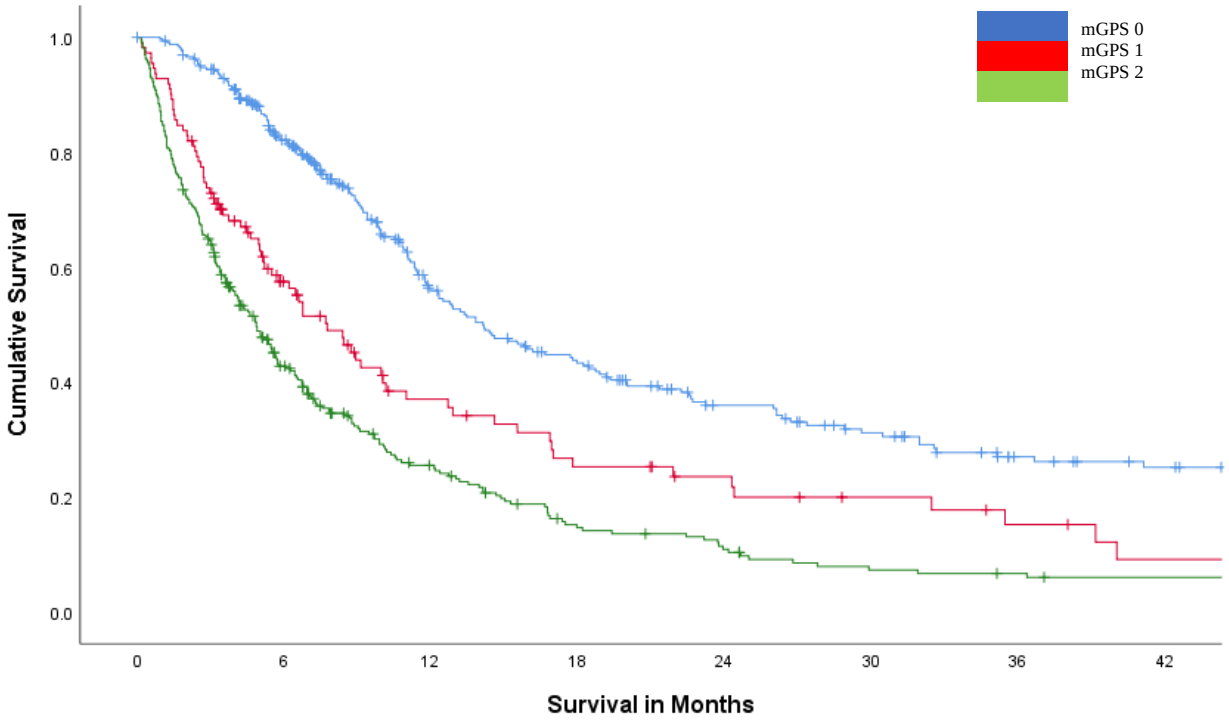
ECOG-PS		mGPS=0	mGPS=1	mGPS=2	mGPS 0-2	
		n (%)	n (%)	n (%)	n (%)	P-value
0-1	N	148	32	73	253	
	Survival Rate at 3 months	144 (97.3%)	26 (81.3%)	62 (84.9%)	232 (91.7%)	0.001
	Median Survival	11.4	9.4	7.5	9.9	
	95% CI	9.2-14.4	4.0-17.8	6.1-9.9	8.7-11.4	
2	N	49	24	45	118	
	Survival Rate at 3 months	44 (89.8%)	21 (87.5%)	33 (73.3%)	98 (83.1%)	0.085
	Median Survival	7.9	6.6	4.9	6.7	
	95% CI	6.8-10.7	5.0-8.9	3.7-6.6	5.2-7.6	
3-4	N	6	5	22	33	
	Survival Rate at 3 months	4 (66.7%)	3 (60%)	11 (50.0%)	18 (54.5%)	0.741
	Median Survival	7.2	3.4	2.9	3.2	
	95% CI	1.0-73.2	0.6-8.4	1.2-5.0	1.8-5.0	
ECOG-PS 0/1-4	N	203	61	140	404	
	Survival Rate at 3 months	192 (94.6%)	50 (82.0%)	106 (75.7%)	348 (86.1%)	<0.001
	Median Survival	10.0	7.5	5.7	7.9	
	95% CI	8.9-11.7	5.8-8.9	4.8-7.1	7.3-8.9	
P-value		0.001	0.343	0.003	<0.001	

10.6 Figures and Legends



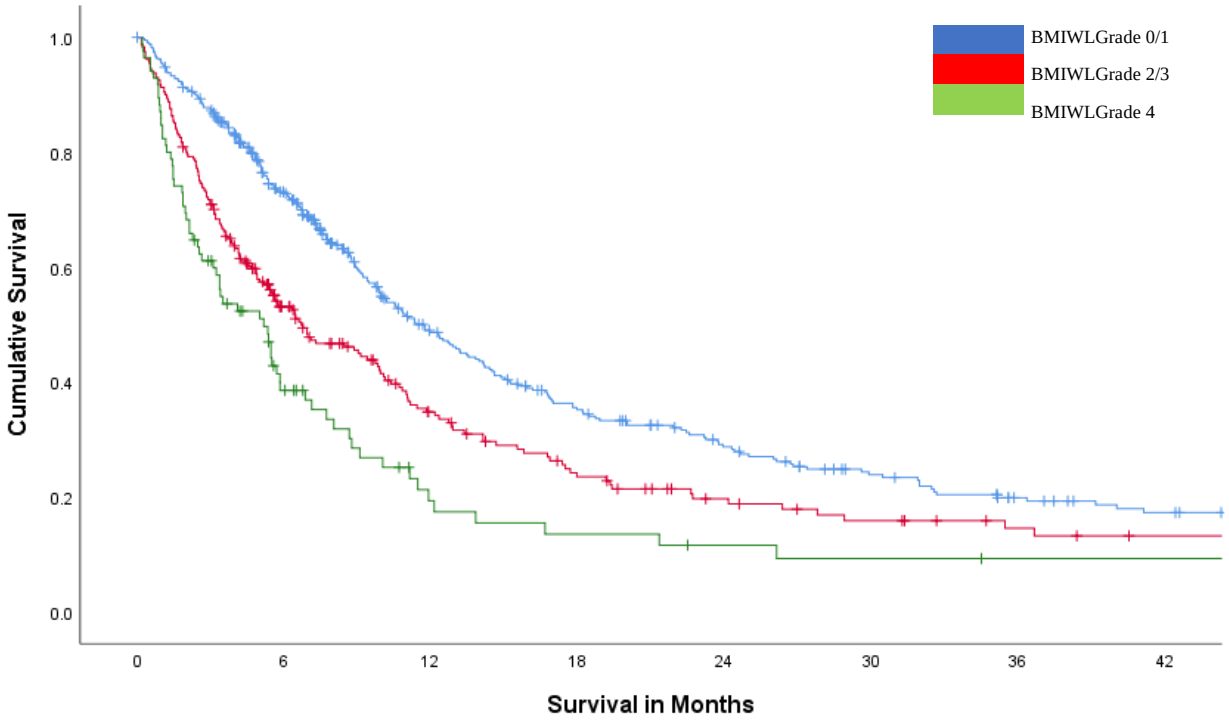
Number at risk	0	6	12	18	24	30	36	42
ECOG 0/1	409	317	236	194	176	166	159	154
ECOG 2	240	127	95	83	79	74	72	72
ECOG 3/4	81	22	16	13	12	12	12	12

Figure 10.1: The relationship between the ECOG-PS and OS in patients with advanced cancer (n=730, Log rank test: ECOG-PS 0/1-2: p<0.001, ECOG-PS 2-3/ 4:p<0.001, ECOG-PS 0/1-3/4: p<0.001). Number at risk depicts the number of patients alive or not censored entering each time period.



Number at risk	0	6	12	18	24	30	36	42
mGPS 0	325	270	207	180	166	158	152	150
mGPS 1	111	66	50	42	41	39	37	35
mGPS 2	294	130	90	68	61	55	64	53

Figure 10.2: The relationship between the mGPS and OS in patients with advanced cancer (n=730, Log rank test: mGPS 0-1: p<0.001, mGPS1-2: 0.006, mGPS 0-2: p<0.001). Number at risk depicts the number of patients alive or not censored entering each time period.



Number at risk	0	6	12	18	24	30	36	42
BMIWLGrade 0/1	404	300	224	187	171	160	152	148
BMIWLGrade 2/3	241	131	99	82	77	73	72	71
BMIWLGrade 4	85	35	24	21	20	19	19	19

Figure 10.3: The relationship between the BMIWL grade and OS in patients with advanced cancer (n=730, Log rank test: BMIWL grade 0/1-2/3: p<0.001, BMIWL grade 2/3-4: p<0.001, ECOG-PS 0/1-4: p=0.010). Number at risk depicts the number of patients alive or not censored entering each time period.

11. THE RELATIONSHIP BETWEEN THE ECOG-PS/mGPS FRAMEWORK, CT-DERIVED BODY COMPOSITION, PHYSICAL FUNCTION TESTS AND SURVIVAL IN PATIENTS WITH ADVANCED CANCER

11.1 Introduction

As mentioned in Chapters 3 and 5 there is now good evidence that measures of the systemic inflammatory response predict survival in patients with advanced cancer both in the observational (38) and randomised clinical trial setting (54). In particular, the mGPS is a simple, objective clinically useful measure of the systemic inflammatory response since it has been extensively validated and its thresholds are well defined compared with other measures of the systemic inflammatory such as the NLR (166, 375). In patients with advanced cancer it has been proposed that the mGPS is used with ECOG performance status (ECOG-PS), the so called ECOG-PS/ mGPS framework (17, 54, 206, 376). This framework has more recently been shown to be associated with quality of life (25) and externally validated [12, 13, 14]. Therefore, with the increasing integration of oncology and palliative care, the ECOG-PS/ mGPS framework is a solid basis on which to examine the prognostic value of other measures (377).

The use of the ECOG-PS has been criticised as being subjective, inaccurate and overly optimistic (378). As a result there has been an increased interest in the use of more objective measures of performance status in patients with advanced cancer. In patients with advanced cancer there is evidence supporting a disproportionate loss of skeletal muscle tissue, measured from a CT scan, to be an independent prognostic factor for both cancer-specific and overall survival (350). Specifically muscle loss has been associated with poor treatment tolerance and efficacy (351), poorer quality of life and increased morbidity (352). Alternatively, objective performance tests such as hand grip strength (HGS), the 2min walk test (2MWT) and the timed get up and go tests (TUG) may be useful replacements for ECOG-PS. However, it is not clear how this ECOG-PS/ mGPS framework is associated

with body composition and physical function tests. Therefore, the aim of this Chapter was to examine the relationship between ECOG-PS/ mGPS framework, CT-derived body composition, physical function tests and survival in patients with advanced cancer.

11.2 Patients and Methods

Patients:

A biobank of data from patients with advanced cancer was analysed. All data were collected prospectively across 9 sites in the UK and Ireland (cancer centres, hospitals, and specialist palliative care units) over a five-year period (2011-2016). Eligible patients provided written informed consent, were adults, had advanced cancer (defined as metastatic cancer [histological, cytological or radiological evidence], locally advanced or receiving anti-cancer therapy with palliative intent), had the ability to comply with study procedures including provision of a venous blood sample (taken on the day of consent). Patients were either inpatients or outpatients, undergoing anti-cancer therapy or not. The primary data collection studies had ethics appropriate ethics approval and were conducted in accordance with the Declaration of Helsinki. The study adhered to the STROBE guidelines for cohort studies.

Prognostic markers

Patient's age, sex, and demographics were recorded, as were details of underlying disease including metastases. Validated prognostic tools/factors highlighted from a recent systematic review by Simmons and co-workers were included in the analysis (379).

Bio-markers: CRP and albumin combined in the mGPS. An autoanalyzer was used to measure serum CRP (mg/L) and albumin (g/L) concentrations (Architect; Abbot Diagnostics, Maidenhead, UK). The mGPS was derived as previously described (99).

Body composition: CT images were obtained at the level of the third lumbar vertebra as previously described in Chapter 2. Patients whose scans were taken 3 months or more prior to study entry were excluded from the study. Scans with significant movement artefact or missing region of interest were not considered for inclusion. CT images were analysed as described in Chapter 2 using NIH Image J (version 1.47) or OsiriX software (version 4.1.1).

Both imaging software packages have been shown to provide excellent agreement for body composition measures (380). Thresholds were calculated as described in Chapter 2 and a summary of all thresholds used can be found in Table 11.1.

Measurements were performed by two individuals and inter-rater reliability was assessed in a sample of 20 patient images using inter-class correlation coefficients (ICCC) (SMA ICCC = 0.986, SMD ICCC = 0.964). Investigators were blind to patient's demographic and clinico-pathological status.

Physical function: ECOG-PS, 2MWT and TUG tests (measured in 186 patients in UK) and HGS (measured in 103 patients in Ireland) and the presence of metastases and weight loss at study entry were assessed by either the treating clinician or clinical research staff. TUG and 2MWT test completion were recorded contemporaneously with completion being recorded as a test pass. A failure of TUG was classed as an inability to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down. A failure of 2MWT was classed as an inability of an individual to walk without assistance for 2 minutes in total. A weak HGS was defined as <26 kg in men and <16kg in women (381). Patients who achieved HGS results below the above thresholds were deemed to have failed the HGS test. All objective measurements were then combined in the combined objective performance test (COPT) to give a pass/fail reading.

Statistical Analysis:

Body composition measurements were presented as median and range and compared using Mann-Whitney or Kruskal-Wallis tests. Categorical variables were analysed using χ^2 test for linear-by-linear association, or χ^2 test for 2 by 2 tables.

The time between the date of study entry and the date of death of any cause was used to define OS. Survival data were analysed using univariate and multivariate Cox regression analysis. In addition to significant variables of interest on univariate analysis the predefined

variables age, sex and cancer location were entered into a backward conditional multivariate model. Kaplan Meier analysis was carried out for ECOG-PS and mGPS to establish proportional Hazard Ratios.

Missing data were excluded from analysis on a variable by variable basis. Two tailed p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 21.0. SPSS Inc., Chicago, IL, USA).

11.3 Results

A total of 289 patients (141 males, 148 females) met the eligibility criteria. The relationship between clinicopathological characteristics, body composition, physical function and overall survival is shown in Table 11.2. All objective functional tests were combined in the COPT in 289 patients in the UK and Ireland. The majority of patients were under 65 years of age (50.2%), BMI≤25 (50.9%) and had metastatic disease (86.9%). The majority of tumours were GI (33.6%) and lung (32.2%) cancers. The median overall survival (OS) for the entire cohort was 6.7 months (95% CI: 8.9-11.0 months). At the time of censoring, 104 patients (36%) were still alive. Median follow up time for these patients was 11.7 months (95% CI: 13.3-17.4 months). Correlation analysis showed a non-significant positive association between low SMI and TUG (rs: 0.091, p=0.215), 2MWT (rs: 0.096, p=0.191), HGS (rs: 0.032, p=0.751) and COPT (rs: 0.067, p=0.258). In contrast correlation analysis showed a significant positive association between low SMD and TUG (rs: 0.167, p=0.023), 2MWT (rs: 0.184, p=0.012), HGS (rs: 0.223, p=0.024) and COPT (rs: 0.185, p=0.002). On univariate survival analysis tumour location, previous chemotherapy, mGPS (Figure 11.2), ECOG-PS (Figure 11.1), SMI, SMD, TUG failure, 2MWT failure, HGS failure and COPT failure were associated with survival (all<0.05).

The relationship between ECOG-PS and mGPS scoring and SMI in patients with advanced cancer is shown in Table 11.3a. There was a significant association between low SMI and ECOG-PS (p<0.05). There was no significant association between low SMI and mGPS. There was an increase in the percentage of patients having a low SMI from 43.4% in patients with an ECOG-PS≤1 and a mGPS=0 and to 58.8% in patients with an ECOG-PS=2 and a mGPS=2 (p=0.029).

The relationship between ECOG-PS and mGPS scoring and SMD in patients with advanced cancer is shown in Table 11.3b. There was a significant association between a low SMD and ECOG-PS (p<0.001). There was a significant association between a low SMD and mGPS

($p<0.05$). There was an increase in the percentage of patients classified as having myosteatosis with a low SMD from 48.2% in patients with an ECOG-PS≤1 and a mGPS=0 to 68.6% in patients with an ECOG-PS=2 and a mGPS=2 ($p=0.011$).

The relationship between ECOG-PS and mGPS scoring and TUG test failure in patients with advanced cancer is shown in Table 11.3c. There was a significant association between TUG test failure and ECOG-PS ($p<0.001$). There was no significant association between TUG test failure and mGPS. There was an increase in the percentage of patients classified as having failed to complete TUG testing from 24.4% in patients with an ECOG-PS≤1 and a mGPS=0 to 36.8% in patients with an ECOG-PS=2 and mGPS=2 ($p=0.329$).

The relationship between ECOG-PS and mGPS scoring and 2MWT failure in patients with advanced cancer is shown in Table 11.3d. There was a significant association between 2min walk failure and ECOG-PS ($p<0.001$). There was no significant association between 2MWT failure and mGPS. There was an increase in the percentage of patients classified as having failed to complete 2min walk testing from 26.7% in patients with an ECOG-PS≤1 and a mGPS=0 to 36.8% in patients with an ECOG-PS=2 and a mGPS=2 ($p=0.307$).

The relationship between ECOG-PS and mGPS scoring and HGS test failure in patients with advanced cancer is shown in Table 11.3e. There was no significant association between HGS failure and ECOG-PS. There was a significant association between HGS test failure and mGPS ($p<0.01$). There was an increase in the percentage of patients classified as having failed to complete HGS testing from 23.7% in patients with an ECOG-PS≤1 and a mGPS=0 to 61.5% in patients with an ECOG-PS=2 and a mGPS=2 ($p=0.362$).

The relationship between ECOG-PS and mGPS scoring and COPT failure in patients with advanced cancer is shown in Table 11.3f. There was a significant association between COPT failure and ECOG-PS ($p<0.001$). There was a significant association between COPT failure and mGPS ($p<0.01$). There was an increase in the percentage of patients classified as having

failed to complete COPT testing from 24.1% in patients with an ECOG-PS≤1 and a mGPS=0 to 43.1% in patients with an ECOG-PS=2 and a mGPS=2 (p=0.183).

The relationship between ECOG-PS, mGPS and SMI and overall survival in patients with advanced cancer is shown in Table 11.4a. On multivariate cox regression analysis ECOG-PS (HR 1.90, 95%CI 1.51-2.39, p<0.001), mGPS (HR 1.71, 95%CI 1.45-2.02, p<0.001) and low SMI (HR 1.39, 95%CI 1.04-1.86, p=0.027) remained independently associated with overall survival.

The relationship between ECOG-PS, mGPS and low SMD and overall survival in patients with advanced cancer is shown in Table 11.4b. On multivariate cox regression analysis ECOG-PS (HR 1.91, 95%CI 1.52-2.39, p<0.001) and mGPS (HR 1.70, 95%CI 1.44-2.00, p<0.001) remained independently associated with overall survival.

The relationship between ECOG-PS, mGPS and TUG test failure and overall survival in patients with advanced cancer is shown in Table 11.4c. On multivariate cox regression analysis ECOG-PS (HR 2.18, 95%CI 1.61-2.94, p<0.001), mGPS (HR 1.89, 95%CI 1.51-2.37, p<0.001) and TUG test failure (HR 1.82, 95%CI 1.22-2.72, p=0.003) remained independently associated with overall survival.

The relationship between ECOG-PS, mGPS and 2MWT failure and overall survival in patients with advanced cancer is shown in Table 11.4d. On multivariate cox regression analysis ECOG-PS (HR 2.22, 95%CI 1.65-2.98, p<0.001), mGPS (HR 1.89, 95%CI 1.51-2.37, p<0.001) and 2MWT failure (HR 1.83, 95%CI 1.24-2.73, p=0.003) remained independently associated with overall survival.

The relationship between ECOG-PS, mGPS and HGS test failure and overall survival in patients with advanced cancer is shown in Table 11.4e. On multivariate cox regression analysis mGPS (HR 1.55, 95%CI 1.20-2.01, p=0.001) and HGS test failure (HR 1.63, 95%CI 1.03-2.59, p=0.039) remained independently associated with overall survival.

The relationship between ECOG-PS, mGPS and COPT failure and overall survival in patients with advanced cancer is shown in Table 11.4f. On multivariate cox regression analysis ECOG-PS (HR 1.83, 95%CI 1.45-2.30, p<0.001), mGPS (HR 1.65, 95%CI 1.39-1.95, p<0.001) and COPT failure (HR 1.63, 95%CI 1.21-2.19, p=0.001) remained independently associated with overall survival.

11.4 Discussion

The results of the present study show that ECOG-PS/ mGPS framework was associated with body composition parameters and physical function tests and these all had prognostic value. In particular, ECOG-PS was consistently associated with physical function tests. However, with the exception of handgrip strength, no body composition measure or physical function test displaced the prognostic value of ECOG-PS within the ECOG-PS/ mGPS framework. These results confirm the clinical reliability and prognostic importance of the ECOG-PS/ mGPS framework and suggest that physical function tests may further improve the objective nature of this framework in patients with advanced cancer.

In the randomised clinical oncology trial setting performance status has become, through routine clinical use, an important established predictor of outcome and as a result an entry criteria for many trials. Similarly, in this setting, it is becoming clear that markers of the systemic inflammatory response have prognostic value. In particular, the mGPS through its established objective thresholds has recently been reported to predict response to treatment in a number of randomised trials (54). Therefore, it may be that the systemic inflammatory, as evidenced by the mGPS, will also become an important entry criteria for patients in randomised clinical trials. On this basis the ECOG-PS/ mGPS framework has considerable potential to better select patients with advanced cancer for active oncological treatment.

In the present study the quantity and quality of skeletal muscle and physical function tests were shown to have prognostic value. These measures were also shown to be consistently associated with ECOG-PS. Given the subjective nature of ECOG-PS it was of interest to examine whether any of these measures could replace ECOG-PS in the framework. With survival as an endpoint, HGS appeared to be superior to SMI and SMD and was the only physical function test to displace ECOG-PS in the framework. However, HGS results were available in only 103 patients compared with 267 that had ECOG-PS data. In Table 11.2 the confidence intervals for HGS were wider than for ECOG-PS, despite broadly similar hazard

ratios. Therefore, while the results for HGS look more impressive they would seem to be less reliable in this model. HGS seems to offer a similar level of discrimination to ECOG-PS however practically in an oncology outpatient context, ECOG-PS is far easier to measure. Therefore, the results of this study suggest that the ECOG-PS/mGPS framework should be the method of assessment of choice in patients with advanced cancer.

In the present study it was of interest that SMD was significantly associated with both the ECOG-PS and mGPS. Furthermore, there was a significant positive association between SMD and TUG, 2MWT, HGS and COPT. One interpretation of the present cross-sectional results would be that the quality of skeletal muscle determines the strength and the performance status of the patient with advanced cancer patient. This interpretation would be consistent with the results of a recent study by Williams and co-workers who reported that SMD was related to physical function impairments including activities of daily living (ADL), climbing stairs, walking and TUG (382). Furthermore, that the presence of systemic inflammatory response degrades the quality of the skeletal muscle. If this were to be the case then it might be anticipated that down regulation of the systemic inflammatory response, compared with placebo, would result in better preservation of muscle density, muscle strength and performance status. This hypothesis is the subject of a number of ongoing randomised clinical trials. For example, there is a randomised placebo controlled phase III trial underway of a multimodal intervention (Exercise, nutrition, anti-inflammatory medication) in patients with advanced lung or pancreatic cancer undergoing anti-cancer therapy with palliative intent (NCT02330926) (371). The aim of this trial is to prevent or attenuate loss of weight, muscle and physical function using a multimodal intervention which is anti-inflammatory. The findings from the associated phase II trial provide grounds for optimism for the ongoing phase III trial (383).

It was of interest that a BMI>25, high SFI and the presence of visceral obesity was associated with better overall survival. There is evidence in the literature that high level of subcutaneous

and visceral fat were both associated with an increased risk of developing cancer, more post operative complications and worse outcomes (384). However there is also evidence in the literature that obesity can have a protective effect in patients with cancer, particularly those with advanced disease, termed the obesity paradox (385, 386).

Lennon and co-workers in a recent review examined the obesity paradox in cancer (385). There are both host and tumour factors which could explain this phenomenon including detection bias (385). Obese patients are at an increased risk of both diabetes and cardiovascular disease which are often diagnosed later in life (387). During their initial workup for these new diagnoses incidental, non-symptomatic early stage cancers can be picked up (385). Another potential explanation could be reverse causality which refers to the observation that some patients with a normal BMI at diagnosis were previously obese (388). These patients have more advanced disease which is driving their weight loss and leading to poorer outcomes (385). There is also evidence that some tumours in obese patients have less aggressive characteristics and are more susceptible to systemic treatment such as neoadjuvant chemotherapy (389-391). Finally, it may be that excess adipose tissue serves as a nutrient reserve and confers a survival advantage in times of stress, such as anti-cancer treatment (385, 392)."

Limitations of the present study include that identical physical function test data was not available in all patients. In addition, 86.9% of patients had metastatic disease requiring regular opioid administration. Long term opioid use in particular has been shown to lead to hypogonadism in both men and women (343). This gonadal suppression can lead to reduced anabolic activity with decreased skeletal muscle mass and an associated reduction in quality of life and outcomes (343, 344). However, the study population was relatively large, well-documented in terms of clinicopathological characteristics and measures of the systemic inflammatory response and had relatively mature follow-up.

In summary, the ECOG-PS/ mGPS framework was associated with body composition parameters and physical function tests and these all had prognostic value. These results confirm the clinical reliability and prognostic importance of the ECOG-PS/ mGPS framework in patients with advanced cancer.

11.5 Tables and Footnotes

Table 11.1: CT derived body composition measures and thresholds used

Body Composition Measurement
Sarcopenia
Low SMI (Martin) (66):
Males: BMI<25kg/m^2 and SMI<43 cm^2m^2 or BMI≥25kg/m^2 and SMI<53 cm^2m^2 Females: BMI<25kg/m^2 and SMI<41 cm^2m^2 or BMI≥25kg/m^2 and SMI<41 cm^2m^2
Myosteatosis
Low SMD (Martin) (66):
BMI<25kg/m^2 and SMD<41 HU or BMI≥25kg/m^2 and SMD<33HU

Table 11.2: The relationship between clinicopathological characteristics, CT derived body composition, physical function and overall survival in patients with advanced cancer (n=289)

Characteristic			Univariate		Multivariate Adjusted for Age, Sex and Cancer Location	
		n=289 (%)	Overall Survival HR (95% CI)	P-value	Overall Survival HR (95% CI)	P-value
	Clinico-pathological					
Age	<65	144 (49.8)	0.76 (0.97-1.17)	0.763	1.00 (0.83-1.20)	0.974
	65 - 74	88 (30.4)				
	>74	57 (19.7)				
Sex	Male	141 (48.8)	1.05 (0.78-1.40)	0.759	1.08 (0.81-1.44)	0.616
	Female	148 (51.2)				
Cancer Location	Lung	93 (32.2)	1.29 (1.08-1.55)	0.006	1.29 (1.08-1.55)	0.006
	GI	97 (33.6)				
	Other	99 (34.3)				
Metastatic Disease	No	38 (13.1)	0.99 (0.62-1.58)	0.980	1.03 (0.64-1.63)	0.917
	Yes	251 (86.9)				
	Previous Anti-Cancer Therapy					
Chemotherapy[1]	No	36 (14.8)	0.49 (0.32-0.75)	0.001	0.50 (0.33-0.76)	0.001
	Yes	207 (85.2)				
Radiotherapy[1]	No	167 (68.7)	1.13 (0.85-1.50)	0.411	1.16 (0.87-1.55)	0.319
	Yes	76 (31.3)				
Hormones[1]	No	208 (87.4)	1.01 (0.73-1.40)	0.937	1.13 (0.82-1.56)	0.471
	Yes	30 (12.6)				
	Body composition					
Sarcopenia						
Low SMI (Martin)	No	153 (52.9)	1.38 (1.03-1.84)	0.031	1.36 (1.02-1.82)	0.037
	Yes	136 (47.1)				
Myosteatosis						
Low SMD (Martin)	No	118 (40.8)	1.54 (1.14-2.07)	0.005	1.54 (1.14-2.09)	0.005
	Yes	171 (59.2)				
	Systemic inflammation					
mGPS	0	124 (42.9)	1.79 (1.52-2.10)	<0.001	1.79 (1.52-2.10)	<0.001
	1	43 (14.9)				
	2	122 (42.2)				
	Functional Testing					
ECOG-PS	0/1	162 (56.1)	2.17 (1.72-2.73)	<0.001	2.31 (1.82-2.92)	<0.001
	2	105 (36.3)				
	3	22 (7.6)				
TUG Test Failure[4]	No	118 (63.4)	2.31 (1.57-3.40)	<0.001	2.43 (1.64-3.59)	<0.001
	Yes	68 (36.6)				
2MWT Failure[4]	No	113 (60.8)	2.28 (1.54-3.36)	<0.001	2.41 (1.63-3.57)	<0.001
	Yes	73 (39.2)				
HGS Test Failure[4]	No	64 (62.1)	1.89 (1.20-2.98)	0.006	1.96 (1.24-3.09)	0.004
	Yes	39 (37.9)				
COPT Failure	No	182 (63.0)	2.06 (1.54-2.76)	<0.001	2.14 (1.60-2.87)	<0.001
	Yes	107 (37.0)				

[1]: 46 patients missing [2]: 51 patients missing [3]: 4 patients missing [4]: 103 patients missing [5]: 186 Patients missing

Table 11.3: The relationship between ECOG, mGPS and measures of body composition and objective performance status measurements in patients with advanced cancer (n=289)

Table 11.3a									
ECOG-PS	mGPS=0		mGPS=1		mGPS=2		All		P
n=289	**n**	**Low SMI (Martin) n (%)**	**n**	**Low SMI (Martin) n (%)**	**n**	**Low SMI (Martin) n (%)**	**n**	**Low SMI (Martin) n (%)**	
0-1	83	36 (43.4)	23	5 (21.7)	56	24 (42.9)	162	65 (40.1)	0.151
2	39	21 (53.8)	15	6 (40.0)	51	30 (58.8)	105	57 (54.8)	0.436
3	2	1 (50.0)	5	4 (80.0)	15	9 (60.0)	22	14 (63.6)	0.166
All	124	58 (46.8)	43	15 (34.9)	122	63 (51.6)	289	136 (47.1)	0.285
P		0.555		0.041		0.202		0.021	
Table 11.3b									
ECOG-PS	mGPS=0		mGPS=1		mGPS=2		All		P
n=289	**n**	**Low SMD (Martin) n (%)**	**n**	**Low SMD (Martin) n (%)**	**n**	**Low SMD (Martin) n (%)**	**n**	**Low SMD (Martin) n (%)**	
0-1	83	40 (48.2)	23	11 (47.8)	56	34 (60.7)	162	85 (52.5)	0.311
2	39	19 (48.7)	15	11 (73.3)	51	35 (68.6)	105	65 (61.9)	0.096
3	2	2 (100.0)	5	5 (100.0)	15	14 (93.3)	22	21 (95.5)	0.783
All	124	61 (49.2)	43	27 (62.8)	122	83 (68.0)	289	171 (59.2)	0.010
P		0.350		0.053		0.055		<0.001	
Table 11.3c									
ECOG-PS	mGPS=0		mGPS=1		mGPS=2		All		P
n=186	**n**	**TUG test failure n (%)ǂ**	**n**	**TUG test failure n (%)ǂ**	**n**	**TUG test failure n (%)ǂ**	**n**	**TUG test failure n (%)ǂ**	
0-1	45	11 (24.4)	13	3 (23.1)	33	8 (24.2)	91	22 (24.2)	0.995
2	28	9 (32.1)	10	7 (70.0)	38	14 (36.8)	76	30 (39.5)	0.098
3	2	2 (100.0)	5	5 (100.0)	12	9 (75.0)	19	16 (84.2)	0.354
All	75	22 (29.3)	28	15 (53.6)	83	31 (37.3)	186	68 (36.6)	0.074
P		0.066		0.006		0.008		<0.001	
Table 11.3d									
ECOG-PS	mGPS=0		mGPS=1		mGPS=2		All		P
n=186	**n**	**2MWT failure n (%)ǂ**	**n**	**2MWT failure n (%)ǂ**	**n**	**2MWT failure n (%)ǂ**	**n**	**2MWT failure n (%)ǂ ǂ**	
0-1	45	12 (26.7)	13	3 (23.1)	33	11 (33.3)	91	26 (28.6)	0.727
2	28	10 (35.7)	10	7 (70.0)	38	14 (36.8)	76	31 (40.8)	0.130
3	2	2 (100.0)	5	5 (100.0)	12	9 (75.0)	19	16 (84.2)	0.354
All	75	24 (32.0)	28	15 (53.6)	83	34 (41.0)	186	73 (39.2)	0.125
P		0.081		0.006		0.033		<0.001	
Table 11.3e									
ECOG-PS	mGPS=0		mGPS=1		mGPS=2		All		P
n=103	**n**	**HGS test failure n (%)ɻ**	**n**	**HGS test failure n (%)ɻ**	**n**	**HGS test failure n (%)ɻ**	**n**	**HGS test failure n (%)ɻ**	
0-1	38	9 (23.7)	10	3 (30.0)	23	11 (47.8)	71	23 (32.4)	0.146
2	11	2 (18.2)	5	4 (80.0)	13	8 (61.5)	29	14 (48.3)	0.031
3	0	0 (100.0)	0	0 (0)	3	2 (66.7)	3	2 (66.7)	NA
All	49	11 (22.4)	15	7 (46.7)	39	21 (53.8)	103	39 (37.9)	0.008
P		0.700		0.067		0.656		0.192	
Table 11.3f									
ECOG-PS	mGPS=0		mGPS=1		mGPS=2		All		P
n-289	**n**	**COPT failure n (%)**	**n**	**COPT failure n (%)**	**N**	**COPT failure n (%)**	**n**	**COPT failure n (%)**	
0-1	83	20 (24.1)	23	6 (26.1)	56	19 (33.9)	162	45 (27.8)	0.438
2	39	11 (28.2)	15	11 (73.3)	51	22 (43.1)	105	44 (41.9)	0.010
3	2	2 (100.0)	5	5 (100.0)	15	11 (73.3)	22	18 (81.8)	0.320
All	124	33 (26.6)	43	22 (51.2)	122	52 (42.6)	289	107 (37.0)	0.004
P		0.054		0.001		0.023		<0.001	

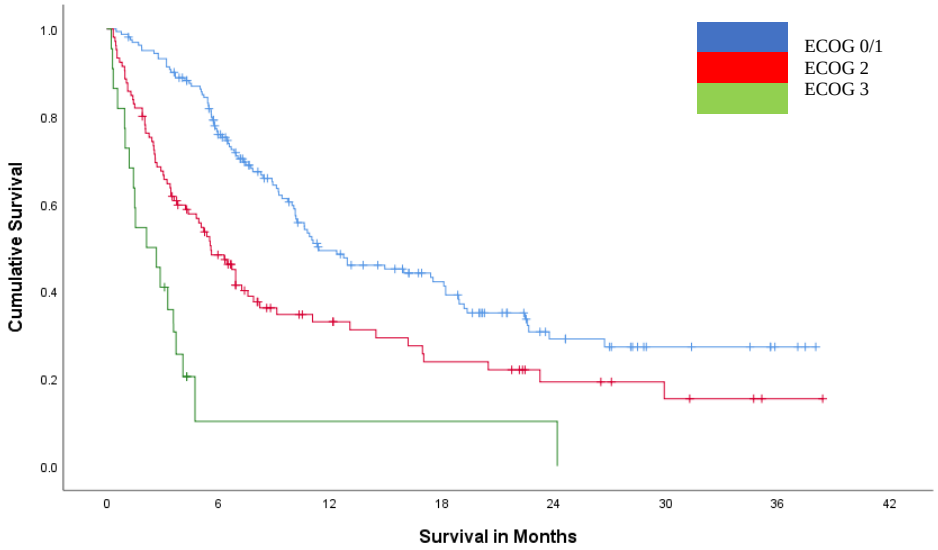
ɿ: 46 patients missing ɬ: 51 patients missing ǂ: 4 patients missing ɻ: 103 patients missing ɹ: 186 Patients missing

Table 11.4: The relationship between ECOG-PS, mGPS, SMI, SMD and physical function and overall survival in patients with advanced cancer (n=289)

Table 11 4a						
Characteristics	**Univariate**	**p-value**	**Multivariate**	**p-value**	**Multivariate Adjusted for Age, Sex and Cancer Location**	**p-value**
ECOG-PS	2.17 (1.72-2.73)	<0.001	1.90 (1.51-2.39)	<0.001	2.03 (1.60-2.57)	<0.001
mGPS	1.79 (1.52-2.10)	<0.001	1.71 (1.45-2.02)	<0.001	1.65 (1.39-1.95)	<0.001
Low SMI (Martin)	1.38 (1.03-1.84)	0.032	1.39 (1.04-1.86)	0.027	1.36 (1.02-1.83)	0.037
Table 11.4b						
Characteristics	**Univariate**	**p-value**	**Multivariate**	**p-value**	**Multivariate Adjusted for Age, Sex and Cancer Location**	**p-value**
ECOG-PS	2.17 (1.72-2.73)	<0.001	1.91 (1.52-2.39)	<0.001	2.04 (1.62-2.58)	<0.001
mGPS	1.79 (1.52-2.10)	<0.001	1.70 (1.44-2.00)	<0.001	1.63 (1.38-1.93)	<0.001
Low SMD (Martin)	1.54 (1.13-2.07)	0.005	—	0.363	—	0.185
Table 11.4c						
Characteristics	**Univariate**	**p-value**	**Multivariate**	**p-value**	**Multivariate Adjusted for Age, Sex and Cancer Location**	**p-value**
ECOG-PS	2.17 (1.72-2.73)	<0.001	2.18 (1.61-2.94)	<0.001	2.18 (1.61-2.94)	<0.001
mGPS	1.79 (1.52-2.10)	<0.001	1.89 (1.51-2.37)	<0.001	1.89 (1.51-2.37)	<0.001
TUG Test Failure┤	2.31 (1.57-3.40)	<0.001	1.82 (1.22-2.72)	0.003	1.82 (1.22-2.72)	0.003
Table 11.4d						
Characteristics	**Univariate**	**p-value**	**Multivariate**	**p-value**	**Multivariate Adjusted for Age, Sex and Cancer Location**	**p-value**
ECOG-PS	2.17 (1.72-2.73)	<0.001	2.22 (1.65-2.98)	<0.001	2.22 (1.65-2.98)	<0.001
mGPS	1.79 (1.52-2.10)	<0.001	1.89 (1.51-2.37)	<0.001	1.89 (1.51-2.37)	<0.001
2MWT Failure┤	2.28 (1.54-3.36)	<0.001	1.83 (1.24-2.73)	0.003	1.83 (1.24-2.73)	0.003
Table 11.4e						
Characteristics	**Univariate**	**p-value**	**Multivariate**	**p-value**	**Multivariate Adjusted for Age, Sex and Cancer Location**	**p-value**
ECOG-PS	2.17 (1.72-2.73)	<0.001	—	0.304	—	0.146
mGPS	1.79 (1.52-2.10)	<0.001	1.55 (1.20-2.01)	0.001	1.53 (1.18-1.98)	0.001
HGS Test Failure┘	1.89 (1.20-2.98)	0.006	1.63 (1.03-2.59)	0.039	1.68 (1.06-2.68)	0.029
Table 11.4f	**Univariate**	**p-value**	**Multivariate**	**p-value**	**Multivariate Adjusted for Age, Sex and Cancer Location**	**p-value**
ECOG-PS	2.17 (1.72-2.73)	<0.001	1.83 (1.45-2.30)	<0.001	1.93 (1.52-2.45)	<0.001
mGPS	1.79 (1.52-2.10)	<0.001	1.65 (1.39-1.95)	<0.001	1.59 (1.34-1.88)	<0.001
COPT Failure	2.06 (1.54-2.76)	<0.001	1.63 (1.21-2.19)	0.001	1.68 (1.25-2.27)	0.001

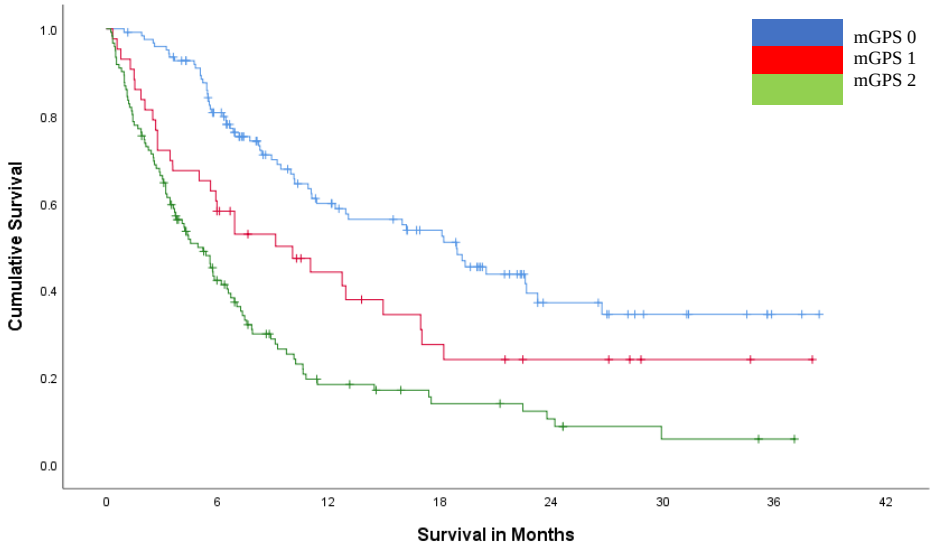
┐: 46 patients missing ┤: 51 patients missing ┼: 4 patients missing ┘: 103 patients missing ┴: 186 Patients missing

11.6 Figures and Legends



Number at risk	0	6	12	18	24	30	36	42
ECOG 0/1	162	112	60	41	17	8	3	0
ECOG 2	105	45	19	13	7	4	1	0
ECOG 3/4	22	1	0	0	0	0	0	0

Figure 11.1: The relationship between the ECOG-PS and OS in patients with advanced cancer. (Median Survival in months: ECOG-PS 0/1: 11.37, ECOG-PS 2: 5.58 ECOG-PS 3: 2.13). Number at risk depicts the number of patients alive or not censored entering each time period.



Number at risk	0	6	12	18	24	30	36	42
mGPS 0	124	92	51	39	15	8	2	0
mGPS 1	43	24	12	8	5	2	1	0
mGPS 2	122	43	15	9	6	2	1	0

Figure 11.2: The relationship between the mGPS and OS in patients with advanced cancer. (Median Survival in months: mGPS 0: 18.86, mGPS 1: 10.03, mGPS 2: 4.94). Number at risk depicts the number of patients alive or not censored entering each time period.

12. THE RELATIONSHIP BETWEEN LONGITUDINAL CHANGES IN CT DERIVED BODY COMPOSITION AND OUTCOMES IN PATIENTS PREVIOUSLY TREATED WITH SURGERY FOR COLORECTAL CANCER

12.1 Introduction

As mentioned in Chapter 9 patients with colorectal cancer in a similar pattern to other solid organ tumours disease progression is associated with a progressive nutritional and functional decline resulting in poor response to treatment and poor survival (41, 346).

The relationship between weight loss and poor outcomes in patients with cancer has long been established. More recently, it has become clear that, through CT derived body composition analysis, this is in the main due to the loss of skeletal muscle mass (41, 346). This may be due poor treatment tolerance and efficacy (48, 351), worse quality of life and increased morbidity (352). The basis of the relationship between a disproportionate loss of skeletal muscle mass and poor outcomes in patients with cancer is not clear. There is evidence that there is a direct association between the magnitude of the systemic inflammatory response, as evidenced by systemic inflammation based scores such as the mGPS and NLR, and low SMI and low SMD in patients with colorectal cancer (44, 52, 356, 360). However, whether this relationship is causal or merely associative is not known since few longitudinal and interventional studies have been published date.

McMillan and coworkers reported that, in a longitudinal study of 18 male patients with advanced cancer, those patients with an elevated CRP concentration lost body cell mass (using a total body potassium counter) at a higher rate (20). Wallengren and colleagues reported that, in a longitudinal study of 471 patients with advanced cancer, those patients with an elevated CRP concentration had less muscle mass (using dual energy X-ray absorptiometry) on study entry and lost muscle mass at an accelerated rate during follow-up, particularly in males (43). In addition, Malietzis and co-workers reported that, in 856

patients with operable colorectal cancer, those patients with an NLR>3 had lower muscle mass (using CT) on study entry and regained muscle mass at a lower rate following surgery (44). These longitudinal studies suggest that systemic inflammation is a risk factor for muscle loss and that this may vary according to sex. Moreover, given the differential relationship between muscle mass and physical function further longitudinal studies are required to examine these relationships.

Therefore, the aim of this Chapter was to delineate the relationship between longitudinal changes in CT derived body composition, clinicopathological characteristics and the systemic inflammatory response in patients with colorectal cancer.

12.1 Patients and Methods:

Patients:

Consecutive patients who underwent elective, potentially curative resection for colorectal cancer between March 2008 and June 2016 at a single centre were identified from a prospectively maintained database. Those patients with a preoperative and follow-up CT scan and a recorded height and weight were included in the study.

Patients were classified according to Body Mass Index (BMI) as underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9) and obese (BMI >30). All tumours were staged according to TNM 5th edition. Preoperative haematological and biochemical markers were recorded.

The cause and date of death were confirmed with the Registrar General (Scotland) until 1st June 2018 which served as the censor date. Informed consent was obtained from patients prior to surgery. Those with metastatic colorectal cancer and those who underwent emergency surgery or palliative surgery were excluded from the study. Ethical approval was granted by the West of Scotland Research Ethics Committee, Glasgow.

Methods:

Pre-operative and initial follow-up CT images were obtained at the level of the third lumbar vertebra as previously described (356) as part of their routine clinical follow up. The median time from pre-operative scan to follow up scan was 12 months (6-18 months). Scans with significant movement artefact or missing region of interest were excluded from study. Each image was analysed using a free-ware program (NIH Image J version 1.47, http://rsbweb.nih.gov/ij/) as described in Chapter 2. Thresholds were calculated as described in Chapter 2.

High High SMI (Dolan Male/Female) was defined as patients with a high SMI in both the pre-op and follow up CT scans. High Low SMI (Dolan Male/Female) was defined as patients

with a high SMI in the pre-op and a low SMI in the follow up CT scans. Low High SMI (Dolan Male/Female) was defined as patients with a low SMI in the pre-op and a high SMI in the follow up CT scans. Low Low SMI (Dolan Male/Female) was defined as patients with a low SMI in both the pre-op and follow up CT scans.

High High SMD (Dolan Male/Female) was defined as patients with a high SMD in both the pre-op and follow up CT scans. High Low SMD (Dolan Male/Female) was defined as patients with a high SMD in the pre-op and a low SMD in the follow up CT scans. Low High SMD (Dolan Male/Female) was defined as patients with a low SMD in the pre-op and a high SMD in the follow up CT scans. Low Low SMD (Dolan Male/Female) was defined as patients with a low SMI in both the pre-op and follow up CT scans.

Measurements were performed by two individuals and inter-rater reliability was assessed in a sample of 30 patient images using inter-class correlation coefficients (ICCC) (TFA ICCC = 1.000, SFA ICCC = 1.000, VFA ICCC = 1.000, SMA ICCC = 0.998, SMD ICCC = 0.972). Investigators were blind to patient's demographic and clinico-pathological status.

An autoanalyzer was used to measure serum CRP (mg/L) and albumin (g/L) concentrations (Architect; Abbot Diagnostics, Maidenhead, UK). The mGPS and NLR were derived as previously described (99). BMI measurements and bloods were not routinely carried out on follow up.

Statistical Analysis:

Body composition measurements were presented as median and ranges and compared using paired Wilcoxon tests. Categorical variables were analysed using paired McNemar tests. Binary logistic regression was used to compare significant variables.

Mortality within 30 days of the index procedure or during the index admission were excluded from subsequent survival analysis. The time between the date of surgery and the date of death of any cause was used to define overall survival (OS). Survival data were analysed

using univariate and multivariate Cox regression. Those variables associated to a degree of $p<0.1$ were entered into a backward conditional multivariate model.

Missing data were excluded from analysis on a variable by variable basis. Two tailed p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 21.0. SPSS Inc., Chicago, IL, USA).

12.2 Results

In total, 704 patients were identified as having undergone potentially curative surgery for colorectal cancer with initial scans being available. Of these, 229 were excluded due to missing follow-up CT scans, clinicopathological data or blood test results. A further five patients were excluded as they died in the immediate postoperative period. A total of 470 patients (258 males, 212 females) were included in final analyses.

The majority of patients were over 65 years of age (62%), overweight or obese (67%), with some comorbidities (77%) and node negative disease (67%). The majority of tumours were located in the right colon (38%) and rectum (36%) and an open surgical approach was applied in 61% of cases. A total of 373 patients were alive at the censor date and a median survival was 55 months (range 1-122 months). Deaths by any cause occurred in 97 patients (21%); 62 (13%) of which were cancer specific.

Temporal changes in body composition are shown in Figures 12.1 and 12.2. The majority of patients did not change the SMI (81%) or SMD (72%) status on follow-up. In male patients at the time of surgery 50.8% of patients had a high SMI (no sarcopenia) and 49.2% of patients had a low SMI (sarcopenia). On post-operative follow up scanning at a median of 12 months 90.1% of those patients with an initial high SMI remained high. On post-operative follow up scanning at a median of 12 months 73.2% of those patients with an initial low SMI remained low.

In female patients at the time of surgery 55.7% of patients had a high SMI (no sarcopenia) and 44.3% of patients had a low SMI (sarcopenia). On post-operative follow up scanning at a median of 12 months 90.7% of those patients with an initial high SMI remained high. On post-operative follow up scanning at a median of 12 months 64.9% of those patients with an initial low SMI remained low (Figure 12.1).

In male patients at the time of surgery 47.7% of patients had a high SMD (no myosteatosis) while 52.3% of patients had a low SMI (myosteatosis). On post-operative follow up scanning at a median of 12 months 66.7% of those patients with an initial high SMD remained high. On post-operative follow up scanning at a median of 12 months 73.3% of those patients with an initial low SMD remained low (Figure 12.2).

In female patients at the time of surgery 52.0% of patients had a high SMD (no myosteatosis) while 48.0% of patients had a low SMI (myosteatosis). On post-operative follow up scanning at a median of 12 months 62.7% of those patients with an initial high SMD remained high. On post-operative follow up scanning at a median of 12 months 86.3% of those patients with an initial low SMD remained low.

The relationship between High High vs Low Low SMI (Dolan) and clinicopathological characteristics and survival in male patients is shown in Table 12.1. Compared with the High High SMI group, the Low Low SMI group were older ($p<0.001$), received less adjuvant chemotherapy ($p<0.05$), had a higher mGPS and NLR (both $p<0.05$) and had lower BMI≥25, pre-op SFI, follow up SFI, pre-op visceral obesity and follow up visceral obesity (all $p<0.01$). The Low Low SMI group also had a lower 3-year overall survival rate ($p<0.01$)

The relationship between High High vs Low Low SMI (Dolan) and clinicopathological characteristics and survival in female patients is shown in Table 12.2. Compared with the High High SMI group, the Low Low SMI group were older ($p<0.01$), had more open surgery ($p<0.05$), had a higher mGPS ($p<0.05$) and had lower BMI≥25, follow up SFI, pre-op visceral obesity and follow up visceral obesity (all $p<0.01$). The Low Low SMI group also had a lower 3-year overall survival rate ($p<0.01$)

The relationship between High High vs Low Low SMD (Dolan) and clinicopathological characteristics and survival in male patients is shown in Table 12.3. Compared with the High High SMD group, the Low Low SMD group were older ($p<0.001$), and had higher BMI≥25,

pre-op SFI, follow up SFI, pre-op visceral obesity and follow up visceral obesity (all $p<0.01$).

The relationship between High High vs Low Low SMD (Dolan) and clinicopathological characteristics and survival in female patients is shown in Table 12.4. Compared with the High High SMD group, the Low Low SMD group were older ($p<0.01$), had a higher ASA ($p<0.001$), had a higher mGPS ($p<0.10$) and had higher BMI≥25, pre-op SFI, follow up SFI, pre-op visceral obesity and follow up visceral obesity (all $p<0.001$). The Low Low SMI group also had a lower 3-year overall survival rate ($p<0.05$)

The relationship between longitudinal measurements in SMI (Dolan) and SMD (Dolan) in males and females combined are shown in Table 12.5. On Cox-regression analysis, compared with the High High SMI group, the Low Low SMI group had poorer overall survival (HR 2.09, 95%CI 1.33-3.30, $p\leq0.001$). Only 5% and 14% of patients were in the High Low SMI and the Low High SMI groups respectively. When this analysis was adjusted for pre-operative age, sex, TNM stage and mGPS (Table 12.5), age (HR 1.59, 95%CI 1.21-2.09, $p\leq0.001$), TNM (HR 1.70, 95%CI 1.27-2.29, $p<0.001$) and mGPS (HR 1.40, 95%CI 1.10-1.79, $p<0.01$) remained independently associated with survival.

On Cox-regression analysis, compared with the High High SMD group, the Low Low SMD group had poorer overall survival (HR 1.91, 95%CI 1.16-3.14, $p<0.05$). Only 17% and 11% of patients were in the High Low SMD and the Low High SMD groups respectively. When this analysis was adjusted for pre-operative age, sex, TNM stage and mGPS (Table 12.5), age (HR 1.59, 95%CI 1.21-2.09, $p\leq0.001$), TNM (HR 1.70, 95%CI 1.27-2.29, $p<0.001$) and mGPS (HR 1.40, 95%CI 1.10-1.79, $p<0.01$) remained independently associated with survival.

12.3 Discussion

The results of the present longitudinal study show clearly that the majority of male and female patients did not change their SMI status (overall ~90% High High and ~65% Low Low) over the period of approximately 12 months following surgery for colorectal cancer. Furthermore, compared with High High SMI status, the Low Low SMI status was associated with greater prevalence of a pre-operative systemic inflammatory response (mGPS 17% and 26% respectively) and poorer overall survival, but not TNM stage. Taken together the results of the present longitudinal study would indicate that low muscle mass is established early in the disease process, resistant to removal of the primary tumour and is associated with the presence of a systemic inflammatory response.

The present observations are consistent with the few longitudinal studies in primary operable colorectal cancer. Mallietz and coworkers (2016) using linear regression modelling compared longitudinal measurements at different time points in >800 patients and although it is not possible to derive the percentage of patients who had stable SMI it is clear that this was the majority of patients (44). Furthermore, Brown and coworkers (2018) reported in a longitudinal study of 1924 patients that, over a period of approximately 14 months, the majority of patients had stable SMI and SMD (both ~60%) (393).

There is now good evidence that both muscle mass and muscle quality predict overall survival in colorectal cancer and other common solid tumours. In the present longitudinal study, there was a consistent association between skeletal muscle index and the systemic inflammatory response. If these were causally linked, then it might be expected that changes in SMI status would be associated with changes in systemic inflammatory status. However, it is clear that few patients changed their SMI status. Moreover, in the present study longitudinal measurements of the systemic inflammatory response were not taken as part of patient follow-up. It was of interest that more patients (almost three times as many) changed from Low SMI to High SMI than from High SMI to Low SMI. This former group is of

particular interest since there appears to have been an improvement in their nutritional status and this subgroup warrants further investigation.

These observations have a number of implications. Firstly, they would suggest that, since SMI is relatively stable over at least 12 months, the die is cast at an early stage and it is likely that most of the prognostic value of SMI can be derived from the initial measurements in primary operable colorectal cancer. Secondly, the consistent association in both cross sectional and now in a longitudinal study between a low SMI and the presence of a systemic inflammatory response may suggest that these are causally linked. Indeed, when adjusted for age, sex, TNM and mGPS changes in both SMI and SMD lost their significance. Although there is abundant evidence that the systemic inflammatory response is associated with profound catabolism of skeletal muscle and may also block anabolism, few studies have attempted to target directly the systemic inflammatory response and monitor skeletal muscle mass in patients with either primary operable cancer or in advanced inoperable cancer. Furthermore, there is evidence that prehabilitation can improve outcomes in patients with cancer. Indeed, in a recent study combining three prehabilitation trials Trépanier and co-workers showed that prehabilitation was associated with improved 5-year disease free survival in patients with stage III colorectal cancer (394). However, the effect of such prehabilitation on the modulation of the inflammatory response is not clear. It may be that such prehabilitation programs are better targeted at patients with less of a systemic inflammatory response.

Future prospective longitudinal studies would be required to investigate this. However, the management of patient expectations will continue to be essential as the early onset of skeletal muscle loss found in the Chapter is unlikely to be reversed. As such it may be that the future aim of any prehabilitation regime is that it be multimodal targeting multiple aspects of the disease.

Limitations of the present study include its retrospective nature and that only patients with an electronically available CT scan were included in the analysis. However, the study population was relatively large, well-documented in terms of clinicopathological characteristics and measures of the systemic inflammatory response and relatively mature follow-up.

In summary, the present longitudinal study provides new evidence that low skeletal muscle mass is established early in the disease course, maintained following resection of the primary tumour and associated with the presence of a systemic inflammatory response in patients with colorectal cancer. Intervention studies are required to establish whether the relationship between low skeletal muscle mass and the systemic inflammatory response is causal in nature.

12.4 Tables and Footnotes

Table 12.1: Relationship between changes in SMI and clinicopathological characteristics in male patients undergoing surgery for colorectal cancer (n= 211).

Characteristic		High SMI n=118 (%)	Low SMI n=93 (%)	p-value
	Clinico-pathological			
Age	**≤65**	59 (50.0)	23 (24.7)	<0.001
	65 - 74	49 (41.5)	37 (39.8)	
	>74	10 (8.5)	33 (35.5)	
ASA score	**1**	28 (23.7)	21 (22.6)	0.584
	2	58 (49.2)	40 (43.0)	
	3	29 (24.6)	27 (29.0)	
	4	3 (2.5)	5 (5.4)	
Laparoscopic Surgery	**No**	70 (59.3)	56 (60.2)	0.896
	Yes	48 (40.7)	37 (39.8)	
TNM	**0**	2 (1.7)	2 (2.2)	0.279
	I	37 (31.4)	22 (23.7)	
	II	36 (30.5)	40 (43.0)	
	III	43 (36.4)	29 (31.2)	
Venous Invasion	**No**	53 (44.9)	34 (36.6)	0.221
	Yes	65 (55.1)	59 (63.4)	
Tumour Location	**Right and Transverse**	44 (37.3)	28 (30.1)	0.406
	Left	24 (20.3)	25 (26.9)	
	Rectum	47 (39.8)	35 (37.6)	
	Total and Subtotal	3 (2.5)	5 (5.4)	
Adjuvant Chemotherapy	**No**	65 (55.1)	63 (67.7)	0.026
	Yes	53 (44.9)	30 (32.3)	
	Systemic inflammation			
mGPS	**0**	98 (83.1)	69 (74.2)	0.028
	1	14 (11.9)	9 (9.7)	
	2	6 (5.1)	15 (16.1)	
NLR	**<3**	70 (59.3)	44 (47.3)	0.016
	3-5	37 (31.4)	27 (29.0)	
	>5	11 (9.3)	22 (23.7)	
	Body composition			
BMI (kg/m^2)	**<25**	12 (10.2)	57 (61.3)	<0.001
	≥25	106 (89.8)	36 (38.7)	
Pre-op High SFI	**No**	18 (15.3)	37 (39.8)	<0.001
	Yes	100 (84.7)	56 (60.2)	
Follow up High SFI	**No**	17 (14.4)	30 (32.3)	0.002
	Yes	101 (85.6)	63 (67.7)	
Pre-op Visceral Obesity	**No**	20 (16.9)	40 (43.0)	<0.001
	Yes	98 (83.1)	53 (57.0)	
Follow up Visceral Obesity	**No**	16 (13.6)	38 (40.9)	<0.001
	Yes	102 (86.4)	55 (59.1)	
Low SMD (Myosteatosis)				
Pre-op SMD (Dolan Male/Female)	**No**	65 (55.1)	44 (47.3)	0.262
	Yes	53 (44.9)	49 (52.7)	
Follow up SMD (Dolan Male/Female)	**No**	58 (49.2)	38 (40.9)	0.230
	Yes	60 (50.8)	55 (59.1)	
Overall 3-year survival rate (%)		101 (85.6)	66 (71.0)	0.009

Table 12.2: Relationship between changes in SMI and clinicopathological characteristics in female patients undergoing surgery for colorectal cancer (n= 168)

Characteristic		High High SMI n= 107 (%)	Low Low SMI n= 61 (%)	p-value
	Clinico-pathological			
Age	**≤65**	47 (43.9)	14 (23.0)	0.018
	65 - 74	35 (32.7)	31 (50.8)	
	>74	25 (23.4)	16 (26.2)	
ASA score	**1**	16 (15.0)	16 (26.2)	0.179
	2	57 (53.3)	29 (47.5)	
	3	33 (30.8)	14 (23.0)	
	4	1 (0.9)	2 (3.3)	
Laparoscopic Surgery	**No**	58 (54.2)	45 (73.8)	0.012
	Yes	49 (45.8)	16 (26.2)	
TNM	**0**	2 (1.9)	0 (0)	0.173
	I	27 (25.2)	9 (14.8)	
	II	49 (45.8)	28 (45.9)	
	III	29 (27.1)	24 (39.3)	
Venous Invasion	**No**	43 (40.2)	23 (37.7)	0.751
	Yes	64 (59.8)	38 (62.3)	
Tumour Location	**Right and Transverse**	46 (43.0)	29 (47.5)	0.090
	Left	31 (29.0)	10 (16.4)	
	Rectum	30 (28.0)	20 (32.8)	
	Total and Subtotal	0 (0)	2 (3.3)	
Adjuvant Chemotherapy	**No**	58 (54.2)	38 (71.7)	0.147
	Yes	49 (45.8)	23 (28.3)	
	Systemic inflammation			
mGPS	**0**	89 (83.2)	46 (75.4)	0.034
	1	9 (8.4)	3 (3.3)	
	2	9 (8.4)	13 (21.3)	
NLR	**<3**	60 (56.1)	37 (60.7)	0.845
	3-5	35 (32.7)	18 (29.5)	
	>5	12 (11.2)	6 (9.8)	
	Body composition			
BMI (kg/m^2)	**<25**	15 (14.0)	35 (57.4)	<0.001
	≥25	92 (86.0)	26 (42.6)	
Pre-op High SFI	**No**	6 (5.6)	7 (11.5)	0.171
	Yes	101 (94.4)	54 (88.5)	
Follow up High SFI	**No**	3 (2.8)	10 (16.4)	0.002
	Yes	104 (97.2)	51 (83.6)	
Pre-op Visceral Obesity	**No**	16 (15.0)	23 (37.7)	0.001
	Yes	91 (85.0)	38 (62.3)	
Follow up Visceral Obesity	**No**	17 (15.9)	20 (32.8)	0.011
	Yes	90 (84.1)	41 (67.2)	
Low SMD (Myosteatosis)				
Pre-op SMD (Dolan Male/Female)	**No**	56 (52.3)	33 (54.1)	0.826
	Yes	51 (47.7)	28 (45.9)	
Follow up SMD (Dolan Male/Female)	**No**	42 (39.3)	24 (39.3)	0.991
	Yes	65 (60.7)	37 (60.7)	
Overall 3-year survival rate (%)		93 (86.9)	42 (68.9)	0.005

Table 12.3: Relationship between changes in SMD and clinicopathological characteristics in male patients undergoing surgery for colorectal cancer (n= 181)

Characteristic		High High SMD n= 82 (%)	Low Low SMD n=99 (%)	p-value
	Clinico-pathological			
Age	**≤65**	50 (61.0)	19 (19.2)	<0.001
	65 – 74	24 (29.3)	45 (45.5)	
	>74	8 (9.8)	35 (35.4)	
ASA score	**1**	26 (31.7)	18 (18.2)	0.059
	2	28 (34.1)	51 (51.5)	
	3	23 (28.0)	27 (27.3)	
	4	5 (6.1)	3 (3.0)	
Laparoscopic Surgery	**No**	54 (65.9)	57 (57.6)	0.255
	Yes	28 (34.1)	42 (42.4)	
TNM	**0**	2 (2.4)	2 (2.0)	0.486
	I	23 (28.0)	26 (26.3)	
	II	26 (31.7)	42 (42.4)	
	III	31 (37.8)	29 (29.3)	
Venous Invasion	**No**	35 (42.7)	37 (37.4)	0.468
	Yes	47 (57.3)	62 (62.6)	
Tumour Location	**Right and Transverse**	25 (30.5)	40 (40.4)	0.267
	Left	18 (22.0)	24 (24.2)	
	Rectum	37 (45.1)	31 (31.3)	
	Total and Subtotal	2 (2.4)	4 (4.0)	
Adjuvant Chemotherapy	**No**	46 (56.1)	65 (65.7)	0.084
	Yes	36 (43.9)	34 (34.3)	
	Systemic inflammation			
mGPS	**0**	67 (81.7)	75 (75.8)	0.208
	1	10 (12.2)	10 (10.1)	
	2	5 (6.1)	14 (14.1)	
NLR	**<3**	46 (56.1)	55 (55.6)	0.666
	3-5	24 (29.3)	25 (25.3)	
	>5	12 (14.6)	19 (19.2)	
	Body composition			
BMI (kg/m^2)	**<25**	37 (45.1)	21 (21.2)	0.001
	≥25	45 (54.9)	78 (78.8)	
Pre-op High SFI	**No**	35 (42.7)	12 (12.1)	<0.001
	Yes	47 (57.3)	87 (87.9)	
Follow up High SFI	**No**	28 (34.1)	10 (10.1)	<0.001
	Yes	54 (65.9)	89 (89.9)	
Pre-op Visceral Obesity	**No**	38 (46.3)	13 (13.1)	<0.001
	Yes	44 (53.7)	86 (86.9)	
Follow up Visceral Obesity	**No**	36 (43.9)	11 (11.1)	<0.001
	Yes	46 (56.1)	88 (88.9)	
Low SMI (Sarcopenia)				
Pre-op SMI (Dolan Male/Female)	**No**	48 (58.5)	43 (43.43)	0.043
	Yes	34 (41.4)	56 (56.57)	
Follow up SMI (Dolan Male/Female)	**No**	46 (56.1)	52 (52.52)	0.631
	Yes	36 (43.9)	47 (47.48)	
Overall 3-year survival rate (%)		65 (79.3)	78 (78.8)	0.937

Table 12.4: Relationship between changes in SMD and clinicopathological characteristics in female patients undergoing surgery for colorectal cancer (n= 157)

Characteristic		High SMD n= 69 (%)	Low SMD n=88 (%)	p-value
	Clinico-pathological			
Age	**≤65**	31 (44.9)	23 (26.1)	0.002
	65 – 74	31 (44.9)	42 (42.0)	
	>74	7 (10.1)	28 (31.8)	
ASA score	**1**	28 (40.6)	6 (6.8)	<0.001
	2	30 (43.5)	49 (55.7)	
	3	11 (15.9)	29 (33.0)	
	4	0 (0)	4 (4.5)	
Laparoscopic Surgery	**No**	42 (60.9)	59 (67.0)	0.423
	Yes	27 (39.1)	29 (33.0)	
TNM	**0**	1 (1.4)	1 (1.1)	0.953
	I	14 (20.3)	15 (17.0)	
	II	33 (47.8)	45 (51.1)	
	III	21 (30.4)	27 (30.7)	
Venous Invasion	**No**	26 (37.7)	33 (37.5)	0.981
	Yes	43 (62.3)	55 (62.5)	
Tumour Location	**Right and Transverse**	19 (27.5)	44 (50.0)	0.034
	Left	20 (29.0)	18 (20.5)	
	Rectum	29 (42.0)	24 (27.3)	
	Total and Subtotal	1 (1.4)	2 (2.3)	
Adjuvant Chemotherapy	**No**	36 (52.2)	53 (60.2)	0.124
	Yes	33 (47.8)	35 (39.8)	
	Systemic inflammation			
mGPS	**0**	56 (81.2)	66 (75.0)	0.054
	1	8 (11.6)	5 (5.7)	
	2	5 (7.2)	17 (19.3)	
NLR	**<3**	44 (63.8)	45 (51.1)	0.280
	3-5	18 (26.1)	30 (34.1)	
	>5	7 (10.1)	13 (14.8)	
	Body composition			
BMI (kg/m^2)	**<25**	38 (55.1)	20 (22.7)	<0.001
	≥25	31 (44.9)	68 (77.3)	
Pre-op High SFI	**No**	13 (18.8)	2 (2.3)	<0.001
	Yes	56 (81.2)	86 (97.7)	
Follow up High SFI	**No**	14 (20.3)	0 (0)	<0.001
	Yes	55 (79.7)	88 (100.0)	
Pre-op Visceral Obesity	**No**	36 (52.2)	4 (4.5)	<0.001
	Yes	33 (47.8)	84 (95.5)	
Follow up Visceral Obesity	**No**	36 (52.2)	3 (3.4)	<0.001
	Yes	33 (47.8)	85 (93.6)	
Low SMI (Sarcopenia)				
Pre-op SMI (Dolan Male/Female)	**No**	35 (50.7)	49 (55.7)	0.537
	Yes	34 (49.3)	39 (44.3)	
Follow up SMI (Dolan Male/Female)	**No**	45 (65.2)	55 (62.5)	0.725
	Yes	24 (34.8)	33 (37.5)	
Overall 3-year survival rate (%)		61 (88.4)	65 (73.9)	0.023

Table 12.5: The relationship between changes in SMI and SMD and overall survival in patients undergoing surgery for colorectal cancer & the relationship between changes in SMI and SMD and overall survival adjusted for age, sex, TNM and mGPS in patients undergoing surgery for colorectal cancer

Characteristic		Follow-Up		
		n= 470 (%)	Overall Survival HR	p-value
All patients (n=470)				
Sarcopenia				
Low SMI (Dolan Male/Female)	High High SMI (Dolan Male/Female)	225 (47.9)	Ref	
	High Low SMI (Dolan Male/Female)	24 (5.1)	1.93 (0.75-4.98)	0.172
	Low High SMI (Dolan Male/Female)	67 (14.3)	1.62 (0.87-3.00)	0.126
	Low Low SMI (Dolan Male/Female)	154 (32.8)	2.09 (1.33-3.30)	0.001
Myosteatosis				
Low SMD (Dolan Male/Female)	High High SMD (Dolan Male/Female)	151 (32.1)	Ref	
	High Low SMD (Dolan Male/Female)	82 (17.4)	1.40 (0.76-2.60)	0.283
	Low High SMD (Dolan Male/Female)	50 (10.6)	1.41` (0.70-2.88)	0.338
	Low Low SMD (Dolan Male/Female)	187 (39.8)	1.91 (1.16-3.14)	0.011
Characteristic			Follow-Up	
		n= 470 (%)	Overall Survival HR adjusted for age, sex, TNM and mGPS	p-value
All patients (n=470)				
Sarcopenia				
Low SMI (Dolan Male/Female)	High High SMI (Dolan Male/Female)	225 (47.9)	Ref	
	High Low SMI (Dolan Male/Female)	24 (5.1)	2.18 (0.84-5.62)	0.108
	Low High SMI (Dolan Male/Female)	67 (14.3)	1.15 (0.61-2.18)	0.673
	Low Low SMI (Dolan Male/Female)	154 (32.8)	1.57 (0.98-2.52)	0.062
Myosteatosis				
Low SMD (Dolan Male/Female)	High High SMD (Dolan Male/Female)	151 (32.1)	Ref	
	High Low SMD (Dolan Male/Female)	82 (17.4)	1.32 (0.71-2-46)	0.381
	Low High SMD (Dolan Male/Female)	50 (10.6)	1.01 (0.49-2.09)	0.977
	Low Low SMD (Dolan Male/Female)	187 (39.8)	1.36 (0.79-2.33)	0.262

12.5 Figures and Legends

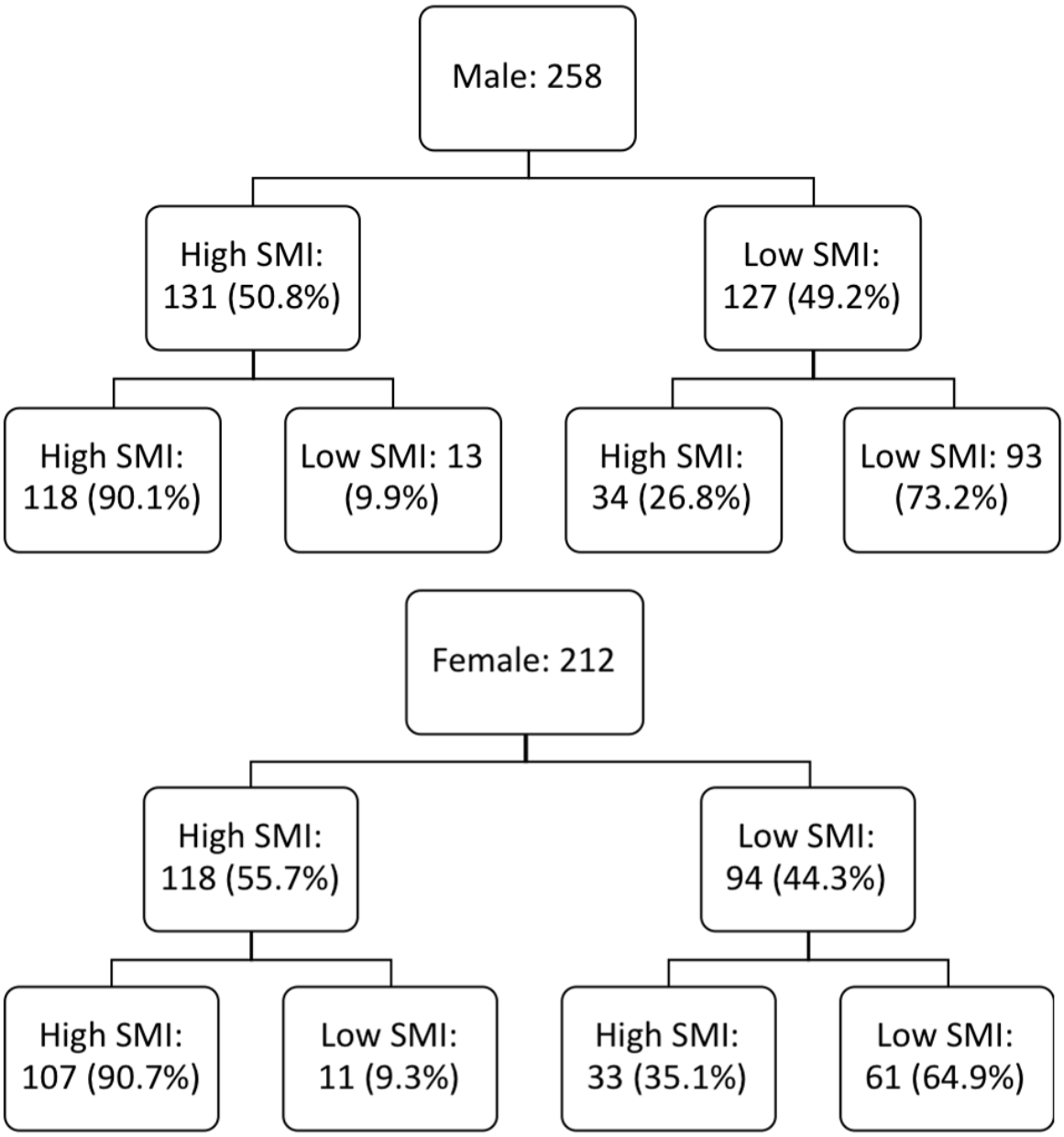


Figure 12.1: Prisma diagram of changes SMI (Dolan) between initial staging and 12 month follow up CT scans in male (n=258) and female (n=212) patients undergoing surgery for colorectal cancer.

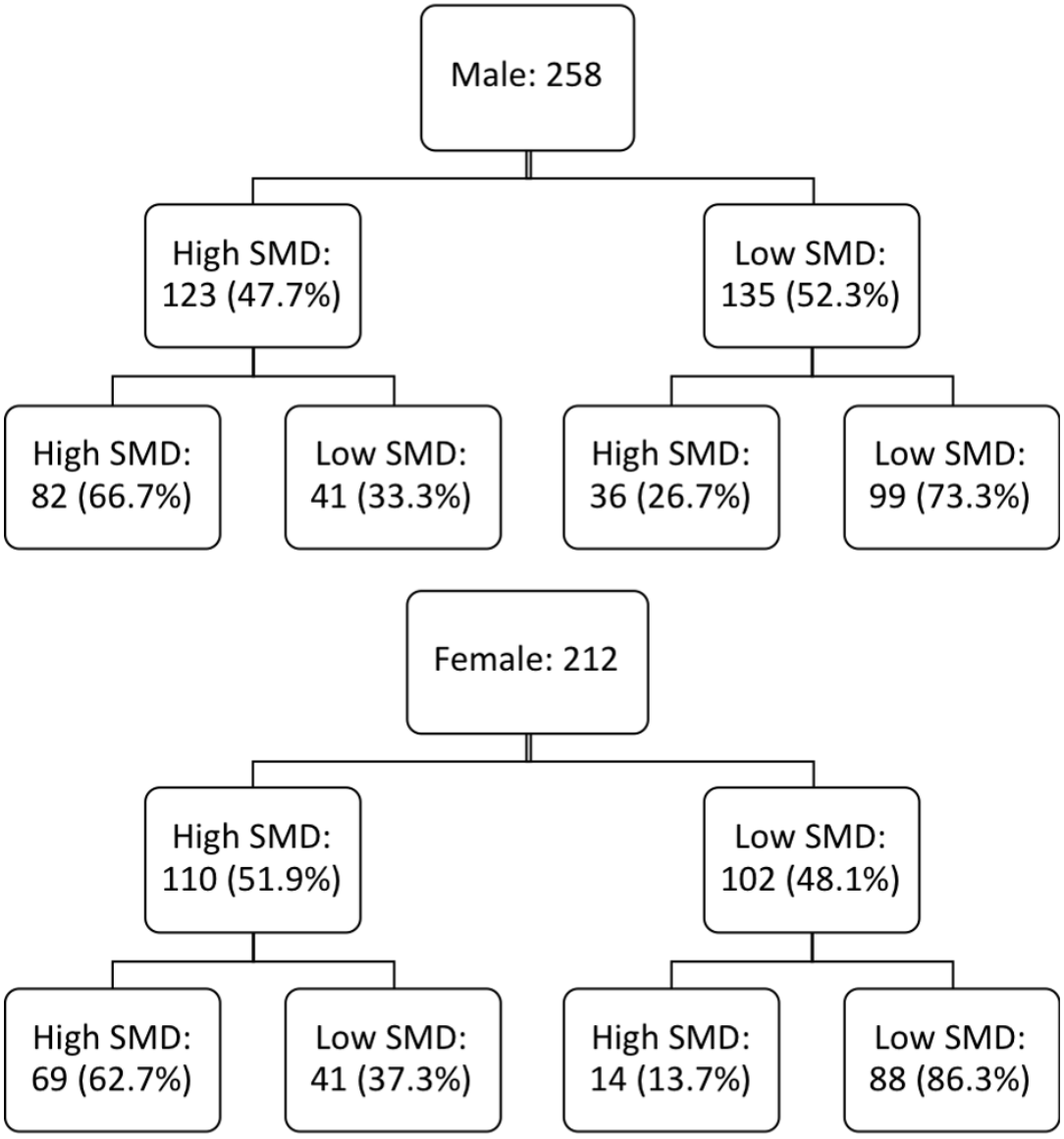


Figure 12.2: Prisma diagram of changes SMD (Dolan) between initial staging and 12 month follow up CT scans in male (n= 258) and female (n=212) patients undergoing surgery for colorectal cancer.

13. THE RELATIONSHIP BETWEEN GLUCOSE METABOLISM AND HOST SYSTEMIC INFLAMMATORY RESPONSE IN PATIENTS WITH CANCER: A SYSTEMATIC REVIEW

13.1 Introduction

As mentioned in Chapters 3-5 four cancers- lung, colorectal, breast and prostate account for approximately half of all new cases and deaths (114). At a cellular level there are several traits of cancer that define its malignancy. These include genome instability, limitless replicative potential, self-sufficiency in growth signals, insensitivity to anti-growth signals, the ability to evade apoptosis, sustained angiogenesis, tissue invasion and metastasis, abnormal metabolic pathways, inflammation and evasion of the immune system (395, 396). All these hallmarks create what is known as the tumour microenvironment (TME, (268, 395, 396)). The TME is composed of heterogeneous cell populations including tumour cells, immune cells, fibroblasts, adipocytes, blood vessels and the extracellular matrix. Therefore, there are interactions between malignant and non-transformed cells via a host of signalling molecules) (397). The tumour and its environment are constantly interacting, and this is an integral part of the tumour physiology, structure and function. The relationship between the tumour and its environment is essential to promote tumour cell growth and the development of metastasis (192).

An important and long recognised characteristic of tumour cells is the dysregulated cellular energetics that results in the increased uptake of glucose (398). Warburg observed that tumour cells predominately produced adenosine 5′-triphosphate (ATP) via a high rate of glycolysis and consumption of glucose via the conversion of glucose to lactic acid. He recognised that this was inefficient for the tumour cell to produce ATP when compared to normal oxidative phosphorylation (398, 399). Moreover, due to this anaerobic glycolysis and lactic acid formation the TME would become acidic allowing for the de-differentiation

of normal and malignant cells (400). Warburg hypothesised that this metabolic defect was the basis of tumour formation. In recent years it has been concluded that this metabolic defect is the result of genetic damage. Nevertheless, the impact of such dysregulated energetics of the tumour cell remains of considerable interest.

The TME is likely to have a direct impact on the innate immune response and activation of the systemic inflammatory response. This can be evidenced by increases in the circulating acute phase proteins such as CRP and albumin and innate immune cells such as neutrophils and monocytes (7). These immune cells are also metabolically active requiring large amounts of glucose.

The prognostic value of the CRP, albumin and neutrophil counts in cancer has been well established in observational studies (85, 87). In the last 15 years there has been a movement towards the use of combined prognostic scores such as the GPS/mGPS (CRP and albumin) and ratios such as the NLR (neutrophils and lymphocytes) to standardise and maximise prognostic value (37, 38).

Therefore, it is of interest that imaging studies of the tumour have become an important element in the evaluation of detecting, staging and management of patients with cancer (401). Positron Emission Tomography (PET) is an established nuclear imaging technique based on the uptake of glucose that can examine the metabolism of tumours. However, PET provides relatively poor anatomical information whereas CT is commonly used in the initial diagnosis and staging of cancers.

The recent routine clinical combination of PET and CT gives anatomic information with associated assessment of tumour physiological activity (49). This provides better identification of metabolically active lesions improving the diagnostic accuracy and localisation of both the primary and metastatic lesions. In the oncological setting the tracer ^{18}F-2-fluoro-2-deoxy-D-glucose (18FDG) is commonly used due to its longer half-life which

aids in transportation and clinical application (76). However, a disadvantage of this tracer is that it is not tumour cell specific and can accumulate where there are metabolically active cells such as immune cells. For example, it is recognised to accumulate in bone marrow, presumably due to formation of metabolically active immune cells. This additional variability that can occur with uptake parameters such as the standardized uptake value (SUV, which depends on appropriate calibration and reconstruction methods with inter-site variability, and dependence on lesion or organ segmentation) has resulted in normalising uptake to other metabolically active tissues. Interestingly, an elevated bone marrow to liver ratio has been reported to have prognostic value in a variety of common solid tumours and an increased cytokine load due to malignancy (402).

Based on the above, it is hypothesised that glucose metabolism in both tumour and host inflammatory responses are related. This present review is timely given the rapidly expanding role of immune therapies (e.g. immune checkpoint inhibition and adoptive T-cell therapy) to treat patients with metastatic cancers. Therefore, the aim of this Chapter was to carry out a systematic review of the relationship between tumour and host inflammatory glucose metabolism using PETCT. A better understanding of these processes would be useful to inform therapeutic strategies for patients with cancer.

13.2 Patients and Methods

This systematic review of published literature was undertaken as outlined in Chapter 2. The primary outcome of interest of this systematic review was the relationship between tumour and host inflammatory glucose metabolism specifically using PETCT imaging in patients with cancer. The secondary outcome of interest of this systematic review was the association between tumour and host inflammatory glucose metabolism as measured by PETCT imaging and survival in patients with cancer. Studies were identified via a literature search between 1984 and 2018 using the following keywords: cancer, malignancy, metastasis, inflammation, glucose, positron, CT and PETCT (last search update on 31st March 2018).

To be eligible for inclusion, studies had to meet the following criteria. (a) Patients with cancer (b) PETCT analysis the imaging modality used (c) Tumour (T), bone marrow (BM) and/or node (N) activity measured by either SUVmax, SUVmean, SUVpeak, bone marrow to liver ratio (BLR: mean BMSUV to mean Liver SUV ratio), metabolic tumour volume (MTV) and/or total lesion glycolysis (TLG: SUVmean × MTV). (d) markers of the systemic inflammatory response in the form of acute phase proteins (CRP and albumin) or components of the differential blood cell counts (neutrophils, leukocytes, monocytes and platelets) and their composite scores such as the mGPS, PLR and NLR. Exclusion criteria included (a) studies not carried out in patients with cancer (b) studies not using PETCT as the main imaging modality (c) studies not assessing tumour and bone marrow activity and (d) studies not including measurement of the systemic inflammatory response. Due to the small number of studies and the heterogeneity of tumour type and tumour/bone marrow activity assessment, meta-analysis was not carried out.

13.3 Results

Study Selection Process

The study selection process is summarised in Figure 13.1. Initial search strategy identified 207 articles whose titles and abstracts were reviewed. Articles were excluded if they had not been carried out in humans (n=64), no full texts were available (n=12), those that were a systematic review/meta-analysis (n=32) and those not published in English (n=6). This led to a review of the full text of 93 articles. A further 83 articles were excluded as there was no direct comparison between the systemic inflammatory response and PET-CT output. The remaining 10 articles had their bibliographies reviewed in a systematic manner. This identified a further 2 articles to be included in the final analysis leading to final figure of 12 articles considered in the present systematic review (402-413).

Overall Analysis

The twelve included studies contained a total of 2,468 patients with the number of patients included in individual studies varying from 32 to 1,034 (Table 13.1). There was a wide variety in cancer anatomical locations including lung (n=4), oral (n=3), colorectal (n=2), gastric (n=1), head and neck (n=1) and multiple anatomical locations (n=1). Geographically studies were from Korea (n=5), China (n=2), Belgium (n=1), Taiwan (n=1), Canada (n-1), Japan (n=1) and the UK (n=1).

The majority of studies showed a direct relationship between the host systemic inflammatory response and the indices of FDG accumulation as measured by BLR (n=5), BMSUVmax (n=4), TSUVmax (n=4), BMSUVmean (n=2), NSUVmax (n=2), SUVpeak (n=1), MTV (n=1) and TLG (n=1). In addition, the majority of studies showed a direct relationship between survival and indices of FDG accumulation BLR (n=3), TSUVmax (n=2), BMSUVmean (n=2), BMSUVmax (n=1), NSUVmax (n=1) and TLG (n=1).

All studies used the radioisotope 18F-FDG. There was some variation in the type of scanners used with the most common scanners being Siemens (n=5) and General Electric (n=4). In all studies patients were required to fast for minimum of 4-6 hours prior to the PET-CT study protocol being initiated and fasting blood glucose levels were measured prior to the administration of 18F-FDG. The majority of studies had a blood glucose threshold level of < 150.0 mg/dL for the injection of the radioisotope. There was some variation in the activity of 18F-FDG administered, however all studies used weight based protocols with administered activities ranging between 230-555 MBq. PET acquisition in the majority of studies was from base of skull to proximal thigh, using 6 – 8 bed positions, acquired 60 minutes post FDG administration. All reconstructions involved CT attenuation correction and iterative reconstruction algorithms specific to the camera manufacturer's software. Regions of interest (ROI) were either drawn freehand, using a minimum SUV cut off or by using isocontour software. The SUV parameters measured varied slightly although in general the maximum and mean SUV values were measured for the primary tumour (TSUVmax, TSUVmean), nodal disease (NSUVmax, NSUVmean) and bone marrow (BMSUVmax, BMSUVmean). The bone marrow to liver ratio (BLR) was defined using SUVmean measurements in the bone marrow, obtained mainly from vertebral bodies, and SUVmean from an ROI in the right lobe of liver.

The majority of studies focused on patients with stage I-III disease who were treated with surgical resection with or without adjuvant chemoradiotherapy (n=8). In those studies where surgery was not the mainstay of treatment only one study had a majority of metastatic disease (79.2%) (406). Two studies were in Ear Nose and Throat (ENT) cancers with the treatment of choice being concurrent chemoradiotherapy and definitive radiotherapy (406, 408). One study was in patients with advanced Non-Small Cell Lung Cancer (NSCLC) not amenable to surgical resection and one study was in multiple cancer types again not amenable to surgical resection (402, 410).

The majority of studies use singular markers of the systemic inflammatory response including the WCC (n=9), CRP (n=7), haemoglobin (n=4), albumin (n=3), neutrophils (n=2), platelets (n=2), lymphocytes (n=1) and monocytes (n=1). In addition, composite ratios and scores were used in several studies including the NLR (n=7), PLR (n=5) and mGPS (n=1). Multiple markers of the systemic inflammatory response were used however there was considerable heterogeneity in the specific markers used.

Therefore, a meta-analysis could not be meaningfully carried out due to the heterogeneity of tumour stage, tumour type and markers of the systemic inflammatory response.

Relationship Between Tumour Glucose Metabolism using TSUVmax/mean, BMSUVmax/mean and BLR and Host Inflammatory Responses

As can be seen in Table 13.1 the majority of studies would appear to be significantly association between activation of the systemic inflammatory response and increased tumour, bone marrow and nodal uptake in PET-CT. In particular, the largest study (n=1034) included in this review reported such a relationship (407).

Jeong and coworkers compared the prognostic values of circulating blood cell-based parameters and tumour FDG uptake in patients with stage I NSCLC (407). In total 1034 patients were included in this study. They were all newly diagnosed with NSCLC and underwent PET-CT scanning as part of their preoperative workup prior to undergoing surgical resection (407). Biochemical and haematological measurements in the form of WCC, neutrophil, lymphocyte and platelet counts were taken (407). These were then used to calculate the composite ratios NLR and PLR. PET-CT scan analysis focused on tumour FDG uptake (407).

The median age of the included patients was 61.6 years and 58.9% were male with 50.6% having never smoked (407). The majority of patients had adenocarcinomas (76.7%) and

were treated by lobectomy (87.1%) (407). There were 144 recurrences and the median follow up was 29.5 months (407). Patients with a high TSUVmax had significantly higher WCC ($p<0.001$), neutrophil ($p<0.001$) and lymphocyte counts ($p=0.002$), and a greater NLR ($p=0.016$) (407). On univariate Cox regression analysis, WCC ($p=0.028$), TSUVmax ($p<0.001$), age ($p<0.001$), gender ($p=0.003$), smoking ($p=0.002$), cell type ($p=0.001$), and TNM stage ($p<0.001$) were significantly associated with disease specific survival (407). On multivariate analysis, TSUVmax (HR: 2.22 95% CI, 1.52–3.25; $p<0.001$), tumour stage (HR: 2.11 95% CI, 1.47–3.01; $p<0.001$), and old age (HR:1.03 95% CI, 1.01–1.05; $p=0.002$) remained independently prognostic in terms of disease specific survival (407).

13.4 Discussion

The results of the present systematic review showed that, in the majority of studies, there was a direct relationship between the tumour and bone marrow glucose uptake and host systemic inflammatory responses in patients with common solid tumours.

Both tumour and nodal glucose uptake and bone marrow glucose uptake were associated with poor outcome in these patients. Although bone marrow FDG accumulation may mainly reflect inflammatory responses, tumour and nodal FDG accumulation reflect the malignant grade of the tumour cells in addition to the inflammatory responses. Therefore, it may be that the nature of their associations with survival will be different.

Taken together the present review provides new insight into the interaction between tumour and host. This may suggest new approaches to more optimal therapeutic targeting and monitoring strategies for patients with cancer.

The basis of the relationship between tumour glucose uptake and markers of the systemic inflammatory response is not clear. The importance of the tumour microenvironment is increasingly appreciated. In addition to the tumour cells themselves stromal cells and inflammatory cells are now recognised to play a role in growth and progression of cancer. The predominant cells in the tumour stroma are the cancer-associated fibroblasts that have been shown to promote tumour progression and invasion through the production of growth factors, cytokines and metabolites and stimulate blood vessel formation (414). Such stromal cell activity is intimately linked to inflammatory cell activity and macrophages contribute to tumour progression and spread by the promotion of genetic instability, protection and nurturing of cancer stem cells, promotion of metastatic spread and the downregulation of the protective T-cell driven adaptive immune response (117, 415, 416). In turn, such macrophage activity appears to be dependent on the tumour stage, tissue involvement and microbiota (415). The macrophage influence on tumour activity can be pro-inflammatory

and tumour growth promoting via the classical M1 pathway commonly upregulated by the inflammatory cytokines TNF-α and IL-6 (417). As well as anti-inflammatory and tumour growth reducing via the alternative M2 pathway commonly upregulated by the anti-inflammatory cytokines IL-4 and IL-10 (417).

The importance of neutrophil activity and infiltrate in cancer progression and metastasis has become an increasingly recognised prognostic domain. Neutrophil activity has been shown to increase tumour progression by facilitating and encouraging angiogenesis (336). Neutrophil activity has also been implicated in potentiating tumour growth through the activation of specific inflammatory cytokines particularly IL-1 and IL-6 and via amino acid depletion (336) and promotes angiogenesis and the metastatic potential of cancer (336). Neutrophils have also been shown to direct cancer cell growth towards endothelial cells which can lead to increased haematological spread promoting distant metastasis (336). Indeed in the pre-metastatic state in patients with advanced cancer neutrophil clusters or localised build-ups in distant organs has been shown to be predictive of eventual metastatic spread (336).

Finally, it has also been postulated that cytokines produced by the tumour/stroma complex can lead to marrow mesenchymal cell recruitment as a thus providing a potential explanation for increased marrow activation seen in the present review (416).

However, there is recognised uptake of 18FDG by both tumour and inflammatory cells and that the TME consists of both tumour and inflammatory cells (418). Therefore, part of the glucose uptake into the tumour may be due to the infiltration of inflammatory cells. Indeed, Rosenberg and colleagues proposed caution when analysing PETCT scans as the marrow hypermetabolism shown may be due to inflammation and not necessarily where the tumour cells are located (419).

While bone marrow mesenchymal stem cells, monocyte or platelet progenitor cells are unregulated during the response to active malignancy an elevation of neutrophils which is quantitatively the most important cell type has been consistently seen in patients with active cancer as shown by the prognostic strength of neutrophils singularly and NLR (38, 40)."

However, confirmation of this hypothesis will require careful histological examination of the areas of both tumour and bone marrow increased signal uptake." Irrespective, it is clear that both tumour and inflammatory cells display signs of the "Warburg effect" and it may be that both contribute to the increased lactate dehydrogenase and its prognostic value observed in patients with cancer (420, 421).

In the present review it was confirmed that there was a relationship between tumour and bone marrow glucose uptake and poor outcome in patients with cancer confirming its clinical utility. Given that two recent meta-analysis have established the prognostic strength of both singular and combined markers of the systemic inflammatory response in both operable and inoperable disease across multiple cancer types (37, 38) it remains to be determined whether the prognostic value of tumour and bone marrow glucose uptake is determined by the systemic inflammatory response or vice versa.

While the majority of the above studies used singular markers of the systemic inflammatory response these have now been surpassed by the use of composite ratios and cumulative scores (37, 38). Furthermore in a recent study in operable colon cancer Dolan and co-workers showed that both composite ratios and cumulative scores had prognostic value, independent of TNM stage (40). However, cumulative scores, based on normal reference ranges, are simpler and more consistent for clinical use and should be used in future research to investigate the association between FDG-PET imaging and host inflammatory responses"

The importance of the relationship between tumour and bone marrow glucose uptake and the systemic inflammatory response is of more than academic interest particularly in the era

of immunomodulatory therapy for patients with advanced cancer. In particular, modulation of the innate and adaptive immune responses will shed new light on the nature of this relationship (422). Furthermore, while there was some heterogeneity in the results, there was a relationship between tumour and bone marrow glucose uptake and poor outcomes in five studies including 1,525 patients.

To our knowledge this is the first systematic review to examine the relationship between tumour glucose metabolism using PETCT imaging and host inflammatory responses. From the review there appeared to be a direct relationship between the tumour and bone marrow glucose uptake and host systemic inflammatory responses in patients with common solid tumours. Furthermore, there was a relationship between tumour and bone marrow glucose uptake and poor outcome in these patients.

13.1 Tables and Footnotes

Table 13.1: Studies showing the relationship between tumour, bone marrow and nodal glucose metabolism and host systemic inflammatory responses in patients with cancer

Author	Date	Country	(n)	Type of Cancer	Tracer	Measurements	Readings	Correlation	Survival
Prevost et al (403)	2006	Canada	120	Lung	18-FDG	TSUVmean TSUVmax BMSUVmax BLR WCC, Hb, Platelets	TSUVmean: 6.2 (1.4-23) BMSUVmax:1.5 (0.6-3.2) BLR: 1 (0.6-2.4)	Spearman correlation TSUVmax BMSUVmax: (r=0.20 p<0.05) BLR: NS WCC (NS) Hb (NS) Platelets (NS) BMSUVmax BLR: (r=0.76 p<0.05) TSUVmax: (r=0.20 p<0.05) WCC (r=0.38 p<0.05) Hb (r=-0.30 p<0.05) Platelets (r=0.24 p<0.05) BLR BMSUVmax: 0.76 p<0.05) TSUVmax: NS WCC (r=0.49 p<0.05) Hb (NS) Platelets (r=0.30 p<0.05)	Kaplan-Meir OS: Median survival (95%CI) TSUVmax (weight adjusted) ≥10: 227 (122-690) p=0.003 BMSUVmax≥1.7: 151 (83-690) p=0.00006 BLR<1.5: 724 (553-1,094) p=0.00004 Multivariate Cox Regression OS: BMSUVmax: RR: 1.6 95%CI 1.1-2.3 p=0.008
Cicone et al (404)	2008	Belgium	35	SCC of head and neck	18-FDG	TSUVmax TSUVmean BMSUVmax, BMSUVmean, Tumour size, Hb, WCC, Platelet, RBC	TSUVmax: 10.4 (3.2-29.9) TSUVmean: 7.8 (2.6-24.6) BMSUVmean: 1.4 (0.7-2.4)	Pearson's Correlation TSUVmax: No correlation with any blood parameters TSUVmean: WCC (r=0.44; p=0.011) BMSUVmean: No correlation with any blood parameters	CSS: Multivariate Cox Regression BMSUVmean: p=0.04 (No HR or CI given) OS: Multivariate Cox Regression BMSUVmean: p=0.03 (No HR or CI given)

Inoue et al (402)	2009	Japan	32	Multiple	18-FDG	BMSUVmean, LiverSUVmean, BLR, WCC, RBC, Platelet, CRP	BMSUV mean: 1.4±0.3 Liver SUV mean: 1.8±0.3 BLR: 0.75±0.16	Pearson's Correlation BMSUVmean: WCC: (r=0.28 p=NS) RBC (r=0.42. p<0.05) Platelet (r=-0.06 p=NS) CRP (r=0.25 p=NS) BLR: WBC (r=0.35 p<0.05) RBC (r=0.12 p=NS) Platelet (r=0.06 p=NS) CRP (r=0.50 p<0.005)	Not carried out for PET-CT markers
Chang et al (405)	2013	Taiwan	151	Oral cavity squamous cell carcinoma	18-FDG	SUVmax, CRP	TSUVmax≥19.3	Spearman Correlation TSUVmax: CRP (r=Not given p<0.001)	Not carried out for PET-CT markers
Chen at al.(406)	2013	China	106	Pharyngo-laryngeal	18-FDG	TSUVmax, NSUVmax, CRP	TSUVmax≥8.6mg/L NSUVmax≥5.7ng/ml	Chi-squared test TSUVmax CRP (p=0.472) NSUVmax CRP (p=0.014)	Not carried out for PET-CT markers
Jeong et al (407)	2016	South Korea	1034	Lung	18- FDG	TSUVmax WBC, Neutrophil, Lymphocyte, NLE	TSUV max>7.83	Linear Correlation: TSUVmax: WCC (r=0.208 p<0.001) Neutrophil (r=0.175 p<0.001) Lymphocyte (r=0.101 p=0.001) NLR (r=0.004 p=0.004)	Multivariate Cox Regression: OS: TSUVmax>7.83: HR: 2.222 95%CI 1.518-3.254 p<0.001
Zhong et al (408)	2017	China	121	Naso-pharyngeal carcinoma	18- FDG	TSUVmax, NSUVmax, Neutrophils, Monocytes, Leukocytes	TSUVmax: >12.35 NSUVmax >10.15	Spearman's Correlation TSUVmax: Leukocytes (r=0.203 p=0.025), neutrophils (r=0.238 p=0.009) monocytes (r=0.185 p=0.043) NSUVmax: Leukocytes (r=0.068 p=0.46), neutrophils (r=0.023 p=0.802) monocytes (p=0.024 p=0.024)	Kaplan Meier PFS: TSUVmax>12.35: p=0.204 NSUVmax>10.15 p=0.004 DMFS: TSUVmax>12.35: Not conducted NSUVmax>10.15 p=0.003 Multivariate Cox Regression:

									PFS: NSUVmax>10.15: HR:2.572 95%CI 1.121-5.898 p=0.026 Multivariate Cox Regression: DMFS: NSUVmax>10.15: HR:3.065 95%CI 1.145-8.201 p=0.026
Lee et al (409)	2017	South Korea	110	Lung	18- FDG	TSUVmax, MBSUVmax BLR Albumin, CRP NLR, PLR, WCC, Hb	TSUVmax: 7.65 (0.80-19.00) MBSUVmax: 1.47 (0.94-2.63) BLR: 0.72 (0.46-1.40)	Spearman Correlation BMSUVmax: Albumin (r=-0.062 p=0.50) CRP (r=0.279 p=0.003) NLR (r=0.236 p=0.01) PLR (r=0.137 p=0.20) WCC (r=-0.210 p=0.03) Hb (r=-0.038 p=0.70) BLR: Albumin (r=-0.227 p=0.02) CRP (r=0.437 p=0.001) NLR (r=0.305 p=0.001) PLR (r=0.318 p<0.01) WCC (r=0.278 p=0.03) Hb (r=-0.069 p=0.50)	Multivariate Cox Regression: PFS: TSUVmax>6.5: HR:3.169 95%CI 1.43-6.99 p=0.005 BLR>0.8: HR: 2.49 95%CI 1.25-4.94 p=0.01 OS: TSUVmax>6.5: HR:4.49 95%CI 1.05-19.92 p=0.04 BLR>0.8: HR: 2.15 95%CI 0.69-7.87 p=0.20
Lee et al (410)	2017	South Korea	106	Lung	18- FDG	TSUVmax, MTV TLG BMSUVmax BLR WCC, Hb, NLR, PLR, Albumin, CRP	TSUVmax: 10.48 (1.40-32.19) MTV: 20.97 (1.10-650.75) TLG: 138.47 (2.80-3715.78) MBSUVmax: 1.57 (0.94-2.22) BLR: 0.79 (0.45-1.50)	Spearman Correlation BMSUVmax: WCC (r=0.294 p=0.002) Hb (r=-0.015 p=0.8) NLR (r=0.034 p=0.7) PLR (r=0.070 p=0.4) Albumin (r=-0.190 p=0.05) CRP (r=0.296 p=0.002) BLR: WCC (r=0.396 p<0.001) Hb (r=-0.114 p=0.2) NLR (r=0.281 p=0.06) PLR (r=0.070 p=0.5) Albumin (r=-0.349 p<0.001) CRP (r=0.428 p<0.001)	Univariate Cox Regression: PFS: MTV: 1.00 (1.00-1.01) p=0.40 TLG: 1.00 (0.99-1.01) p=0.50 Multivariate Cox Regression PFS: TSUVmax: HR:0.99 95%CI 0.92-1.04 p=0.5 BMSUVmax: HR:0.73 95%CI 0.18-3.05 p=0.73

									BLR: HR: 14.44 95%CI 2.60-80.28 p=0.002 Univariatee Cox Regression OS: BMSUVmax: HR: 2.01 95%CI 0.53-7.65 p=0.30 Multivariate Cox Regression OS: TSUVmax: HR:1.00 95%CI 0.99-1.01 p=0.9 MTV: HR: 1.00 95%CI 0.99-1.02 p=0.7 TLG: HR: 1.08 (0.94-1.22) p=0.07 BLR: HR: 1.24 95%CI 0.60-24.61 p=0.90
Lee et al (411)	2017	South Korea	309	Gastric	18- FDG	BMSUVmax BLR CRP, Albumin, Hb, NLR, PLR	TSUVmax: 4.71 (2.62-37.80) BMSUVmax: 1.45 (0.55-2.66) BLR: 0.70 (0.28-1.35)	Spearman correlation BMSUVmax TSUVmax: (r=0.093 p=0.104) WCC: (r=0.039 p=0.600) Hb (r=-0.117 p=0.039) NLR (r=0.121 p=0.033) PLR (r=0.158 p=0.005) Albumin (r=-0.041 p=0.474) CRP (r=0.100 p=0.079) BLR TSUVmax: (r=0.212 p=0.002) WCC: (r=0.003 p=0.563) Hb: (r=-0.172 p=0.002) NLR: (r=0.224 p=0.001) PLR: (r=0.250 p<0.001) Albumin (r=-0.168 p=0.003) CRP (r=0.094 p=0.100)	Multivariate Cox Regression RFS: TSUVmax: HR: 1.33 95%CI 0.70-2.39 p=0.215 BMSUVmax: HR: 0.94 95%CI 0.38-2.33 p=0.945 BLR : HR : 6.42 95%CI 2.07-19.84 p=0.001 OS : TSUVmax : HR : 2.89 95%CI 0.96-8.72 p=0.059 BLR: HR: 10.39 95%CI 1.34-80.33 p=0.025
McSorley et al (412)	2017	United Kingdom	103	Colorectal	18- FDG	TSUVmax TSUVpeak	TSUVmax: 11 (0-35) TSUVpeak: 8 (0-29)	Categorical data: Chi squared test	Univariate Cox Regression

						MTV TLG mGPS, NLR	MTV: 4 (0-311) TLG: 28 (0-3124)	Continuous data: Mann-Whitney U test Pre-Op Scans (n=33): No association between TSUVmax, TSUVpeak, MTV, TLG, mGPS and NLR Post-Op Scans (n=70) NLR≥5: TSUVmax (20 vs 7 p=0.002) SUVpeak (14 vs 4 p<0.001) MTV (29mL vs 2mL p=0.001) TLG (338g vs 9g p<0.001) mGPS 1/2: TSUVmax (11 vs 6 p=0.048) SUVpeak (8 vs 4 p=0.046) MTV (13mL vs 2mL p=0.005) TLG (146g vs 10g p=0.004)	Post op cohort (n=70) CSS: TSUVmax: HR: 2.02 95%CI 0.82-4.98 p=0.128 MTV : HR : 1.68 95%CI 0.66-4.22 p=0.275 Multivariate Cox Regression Post op cohortes (n=70) CSS: TSUVpeak: HR: 2.39 95%CI 0.95-5.99 p=0.064 TLG : HR :2.51 95%CI 1.00-6.28 p=0.720
Lee et al (413)	2017	South Korea	226	Colorectal	18-FDG	TSUVmax Tumour size BMSUVmean, WCC, CRP, NLR, PLR	TSUVmax: 10.85 (2.54-48.80) BMSUVmean: 1.67 (0.63-3.12)	Spearman's correlation: BMSUVmean: TSUVmax: (r=0.266 p<0.001) Tumour size: (r=0.159 p<0.017) WCC (r=0.160 p=0.016) CRP (r=0.252 p<0.001) NLR (r=0.223 p<0.001) PLR (r=-0.109 p=0.131)	Univariate Cox Regression RFS : TSUVmax>10.50 : HR : 0.59 95%CI 0.29-1.20 p=0.145 BMSUVmean>1.90 : HR : 2.94 95%CI 1.30-6.63 p=0.009

13.2 Figures and Legends

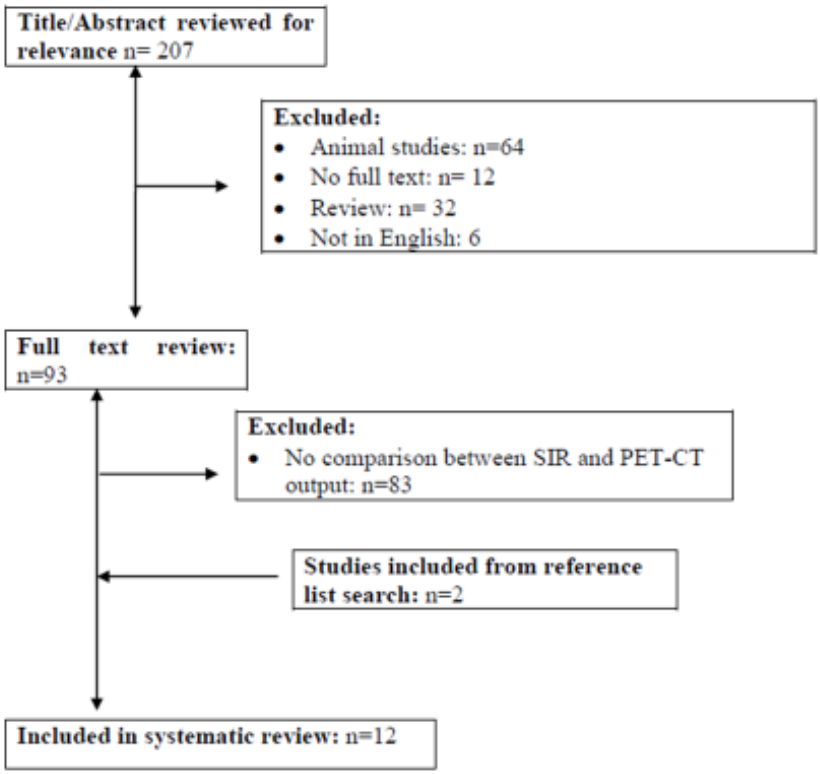


Figure1. A PRISMA Flowchart demonstrating study selection process.

Figure 13.1: A PRISMA Flowchart demonstrating study selection process

.

14. THE USE OF CT AND PET-CT IMAGING TO MEASURE BODY COMPOSITION AND TUMOUR ACTIVITY IN PATIENTS WITH ADVANCED LUNG CANCER TREATED WITH RADIOTHERAPY

14.1 Introduction

Globally, lung cancer is the most common cancer type and is responsible for 1.69 million deaths per year (79). In the UK lung cancer is the 3rd most common cancer accounting for 13% of all new cancer cases (423). In Scotland lung cancer accounts for 16% of all new cancers with a 5 year survival below the UK average at 9.8%.

The relationship between CT defined body composition and outcomes in patients with lung cancer has been widely reported (59). Differences in skeletal muscle quantity as measured by skeletal muscle index and quality as measured by skeletal muscle density have both been shown to directly relate to patient morbidity, response to treatment and survival (354, 360, 424, 425).

In two recent reviews, monitoring of the systemic inflammatory response was shown to be prognostic in both operable and advanced lung cancer (37, 38). In addition, the importance of the systemic inflammatory response as a unifying mechanism for weight loss, loss of lean tissue and poor outcomes in patients with cancer is increasingly recognized (81, 346, 355). Indeed, it has been reported that SMI and SMD are inversely associated with measures of the systemic inflammatory response such as the NLR and mGPS (45, 52, 356-360, 426). However, the role of tumour glucose uptake in the above relationship is not clear.

Positron Emission Tomography (PET) is an established nuclear imaging technique based on the uptake of glucose that reflects the metabolic activity of tumours and combined with CT scanning gives both anatomic and metabolic assessment of the tumour and metastases (49), commonly using the tracer ^{18}F-2-fluoro-2-deoxy-D-glucose (18FDG) (76). It is of interest therefore that in a systematic review there was a direct relationship between both tumor and

bone marrow 18FDG uptake and the systemic inflammatory response on PET-CT (53). In addition, the majority of the studies also showed a direct relationship between tumour glucose uptake and poor outcomes (53). This suggests a potential mechanism of action for the multi-systemic effects of the systemic inflammatory response in patients with cancer (402).

It may be hypothesised that high tumour glucose uptake causes loss of skeletal muscle directly and that this is related to patient outcomes. Therefore, the aim of the present Chapter was to examine the relationship between imaging derived tumour glucose uptake, body composition, the systemic inflammatory response and mortality in patients with lung cancer.

14.2 Patients and Methods

Patients:

All patients with clinically confirmed non metastatic lung cancer treated with radical radiotherapy in North Glasgow between June 2008 and December 2012, who also underwent staging CT and 18F FDG-PETCT imaging prior to their treatment at the Beatson Oncology Centre, Glasgow were included in the study. Patients had routine blood sampling including a full blood count, serum CRP and albumin concentration at the time of their staging scan. Patients were followed up for 5 years or until death.

Methods:

Data were collected prospectively in a database, anonymised and subsequently analyzed including patient demographics, clinicopathological, oncological and radiological data. Body composition CT scan analysis and 18F FDG-PETCT scan analysis were performed retrospectively by clinicians blinded to clinical outcomes and markers of systemic inflammatory response as outlined in Chapter 2.

An autoanalyzer was used to measure serum CRP (mg/L) and albumin (g/L) concentrations (Architect; Abbot Diagnostics, Maidenhead, UK). The mGPS and NLR were derived as previously described (99).

Body Composition CT Analysis:

CT images were obtained, and analysis was carried out at the level of the third lumbar vertebra as previously described in Chapter 2. Patients whose scans were taken 3 months or more prior to commencing radiotherapy were excluded from the study. Scans with significant movement artefact or missing region of interest were not considered for inclusion. Each image was analysed using Image J (NIH version 1.47, http://rsbweb.nih.gov/ij/) shown to provide reliable measurements (356).

Measurements were performed by two individuals and inter-rater reliability was assessed in a sample of 30 patient images using inter-class correlation coefficients (ICCC) (TFA ICCC = 1.000, SFA ICCC = 1.000, VFA ICCC = 1.000, SMA ICCC = 0.986, SMD ICCC = 0.974). Investigators were blind to patient's demographic and clinico-pathological status.

18F FDG-PETCT:

18F FDG-PETCT scanning was performed as outlined in Chapter 2.

Statistical Analysis:

ROC curve analysis determined the optimum thresholds for SUVmax, SUVmean, MTV and TLG. Body composition and PET-CT measurements were presented as median and range and compared using Mann-Whitney or Kruskal-Wallis tests. Categorical variables were analysed using $\chi 2$ test for linear-by-linear association, or $\chi 2$ test for 2 by 2 tables.

Univariate and multivariate survival data were analysed using Cox's proportional hazards model. Variables associated with overall survival at a significance level of $p < 0.1$ on univariate analysis were included in multivariate modelling using backward conditional regression where a two-sided p value <0.05 was considered statistically significant. Overall survival was defined as time from date of 18F FDG-PETCT to date of death due to any cause. P values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 21.0. SPSS Inc., Chicago, IL, USA).

14.3 Results

In total, 251 patients were identified as having undergone potentially curative radiotherapy for lung cancer. Of these, 61 were excluded due to scanning taking place more than 3 months before commencing radiotherapy. A further 71 patients were excluded due to absent markers of the systemic inflammatory response, CT derived body composition measurements and a histological diagnosis of small cell lung cancer (SCLC). A total of 119 patients (57 males, 62 females) were included in final analyses. The relationship between clinicopathological characteristics, tumour activity, body composition, markers of the systemic inflammatory response and overall survival are shown in Table 14.1. The majority of patients were over 65 years of age (86%), overweight (53%), with an ECOG-PS 0 or 1 (57%), node negative disease (54%) and an mGPS 1/2 (51%). All patients were treated with radiotherapy, six patients received additional chemotherapy and two received concurrent chemoradiotherapy. The majority of patients had an elevated TLG (61%) as determined by ROC curve analysis.

On follow-up, 107 patients died, and the median survival was 22 months (range 3-91 months). On univariate survival analysis, lung cancer stage ($p<0.01$), mGPS ($p<0.05$), NLR ($p<0.01$), Low SMD ($p<0.05$) and TLG ($p<0.001$) were associated with overall survival.

The relationship between the TLG ($\leq$68.89/>68.89) and clinicopathological characteristics in patients lung cancer are shown in Table 14.2. TLG (>68.89) was significantly associated with sex ($p<0.05$), TNM stage ($p<0.001$), mGPS ($p<0.01$) and SUVmax ($p<0.001$).

The relationship between clinicopathological characteristics, tumour activity, body composition, markers of the systemic inflammatory response and overall survival in patients with lung cancer is shown in Table 14.3. On multivariate survival analysis only TLG>68.89 (HR:2.03, 95%CI 1.35-3.07, *$p<0.001$*) was independently associated with overall survival.

14.4 Discussion

The results of the present study show that, in a cohort of patients with lung cancer undergoing radical radiotherapy, there was a significant association between TLG (metabolic activity) and the mGPS (systemic inflammatory response). These results are consistent with a recent systematic review which reported a relationship between markers of the systemic inflammatory response and PET-CT parameters (53). However, there was not a significant association between TLG and SMI (skeletal muscle mass). This relationship has not, to our knowledge, been previously examined in cancer patients but it has long been thought that the metabolic activity of the tumour was insufficient, with perhaps the exception of a large metastatic burden, to account for the catabolic changes seen in patients with cancer (427). Therefore, given that only TLG was independently associated with survival the present results would suggest that tumour metabolic activity is indirectly associated with the loss of muscle mass in patients with lung cancer.

The mechanism by which a metabolically active tumour evokes a systemic inflammatory response is not clear. However, there are a number of plausible mechanisms. Tumour hypoxia and necrosis and the production of lactate result in the local activation of innate immune cells and production of pro-inflammatory cytokines, including interleukin-6 (IL-6), stimulating production of CRP (428, 429). Circulating IL-6 levels are linked to tumour necrosis and both local and systemic inflammatory responses in patients undergoing resection for colorectal cancer (428). An alternative hypothesis is that circulating tumour cells activate myeloid cells in the bone marrow to produce such pro-inflammatory cytokines, in particular IL-6 (429). Indeed, there is some evidence from PET-CT studies there is increased uptake of glucose from the bone marrow and that the SUVmax from the bone marrow is also associated with markers of the systemic inflammatory response (53). In the present study, glucose uptake was only examined in the tumour. Irrespective, both of these

mechanisms would, in turn, result in a progressive catabolic state with subsequent breakdown of skeletal muscle resulting in a cachectic state.

The results of the present study are also consistent with the proposal of McAllister and Weinberg that the systemic inflammatory response is the tip of the cancer iceberg reflecting cytokine activity, disordered metabolism and the development of cancer associated symptoms such as loss of appetite, fatigue and poor physical function (25, 192, 430). Given the present results and the increasing importance of the inflammatory responses in the assessment and treatment of lung cancer, it will be of considerable interest to better define the relationship between tumour metabolic activity and the components of the tumour microenvironment including tumour inflammatory cell infiltrate (9, 431), the tumour stroma (432, 433) and tumour mutational burden measured with circulating tumour DNA .

The present study had a number of limitations including that the data was retrospectively analysed from a prospective audit of clinical practice, the majority of patients were treated with radiotherapy in isolation (97%). Also, that histological tumour type was not determined in 21% of cases due to concurrent comorbidities and therefore the present cohort may be a relatively heterogeneous group. However, the present study also has a number of strengths. To our knowledge, this is the first study to comprehensively examine the nature of the relationship between tumour metabolic activity, body composition, the systemic inflammatory response and survival in patients with cancer. The measurements were carried out within one month of each other and the sample size compares favourably to previous studies in the field (53). Indeed, given the routine clinical measurements used in the present study these results are readily validated and give a new insight into these relationships in patients with cancer.

In summary, in patients treated with radical radiotherapy, tumour glucose uptake was associated with activation of systemic inflammatory response and mortality but not lower

skeletal muscle mass. These results provide new insight into the nature of skeletal muscle loss in patients with cancer and suggest that the loss of lean tissue is secondary and not to the direct metabolic activity of the tumour.

14.5 Tables and Footnotes

Table 14.1: The relationship between clinicopathological characteristics, tumour activity, body composition, markers of the systemic inflammatory response and overall survival in patients with lung cancer.

Characteristics	n=119 (%)	*Univariate Cox Regression Analysis OS*	*p-value*
Sex			
Male	57 (47.9)	1.34 (0.91-1.97)	*0.141*
Female	62 (52.1)		
Age			
<65	17 (14.3)	1.04 (0.79-1.37)	*0.768*
65-74	54 (45.4)		
>75	48 (40.3)		
TNM			
I	42 (35.3)	1.40 (1.12-1.74)	*0.003*
II	22 (18.5)		
III	55 (46.2)		
ECOG – PS			
0/1	68 (57.1)	0.74 (0.50-1.09)	*0.126*
≥2	51 (42.9)		
Inflammatory Response			
mGPS			
0	58 (48.7)	1.30 (1.06-1.61)	*0.014*
1	20 (16.8)		
2	41 (34.5)		
NLR			
<3	53 (44.5)	1.38 (1.09-1.76)	*0.009*
3-5	35 (29.4)		
>5	31 (26.1)		
Body Composition:			
BMI kg/m^2			
≤25	56 (47.1)	0.77 (0.54-1.13)	*0.182*
>25	63 (52.9)		
Visceral Obesity			
VFA	134.23 (14.35-577.08)	1.00 (0.99-1.01)	*0.780*
Visceral Obesity			
No	45 (37.8)	0.81 (0.55-1.20)	*0.292*
Yes	74 (62.2)		
Sarcopenia			
SMI	44.23 (29.40-74.36)	1.00 (0.98-1.02)	*0.899*
Low SMI			
No	61 (51.3)	0.98 (0.67-1.44)	*0.930*
Yes	58 (48.7)		
Myosteatosis			
SMD	34.53 (9.58-51.24)	1.03 (1.00-1.05)	*0.043*
Low SMD			
No	45 (37.8)	0.66 (0.44-0.97)	*0.035*
Yes	74 (62.2)		
PET-CT Analysis			
TLG	102.66 (3.47-2070.90)	1.01 (1.00-1.02)	*<0.001*
TLG > 68.89			
No	47 (29.5)	2.18 (1.46-3.26)	*<0.001*
Yes	72 (60.5)		

Table 14.2: The relationship between TLG and clinicopathological characteristics in patients with lung cancer

Characteristics	Low TLG (n=47)	High TLG (n=72)	*p-value*
Sex			
Male	29 (61.7)	28 (38.9)	*0.015*
Female	18 (38.3)	44 (61.1)	
Age			
<65	5 (10.60	12 (16.7)	*0.578*
65-74	21 (44.7)	33 (45.8)	
>75	21 (44.7)	27 (37.5)	
TNM			
I	27 (57.4)	15 (20.8)	*<0.001*
II	8 (17.0)	14 (19.4)	
III	12 (25.5)	43 (59.7)	
ECOG – PS			
0/1	28 (59.6)	40 (55.6)	*0.665*
≥2	19 (40.4)	32 (44.4)	
Inflammatory Response			
mGPS			
0	31 (66.0)	27 (37.5)	*0.006*
1	7 (14.9)	13 (18.1)	
2	9 (19.1)	32 (44.4)	
NLR			
<3	26 (55.3)	27 (37.5)	*0.146*
3-5	12 (25.5)	23 (31.9)	
>5	9 (19.1)	22 (30.6)	
Body Composition:			
BMI kg/m^2			
≤25	19 (40.4)	37 (51.4)	*0.241*
>25	28 (59.6)	35 (48.6)	
Visceral Obesity			
VFA	128.94 (15.33-577.08	140.19 (14.35-549.90)	*0.683*
Visceral Obesity			
No	17 (36.2)	28 (38.9)	*0.765*
Yes	30 (63.8)	44 (61.1)	
Sarcopenia			
SMI	43.34 (29.43-66.36)	45.35 (29.40-74.36)	*0.350*
Low SMI			
No	24 (51.1)	37 (51.4)	*0.972*
Yes	23 (48.9)	35 (48.6)	
Myosteatosis			
SMD	31.80 (9.58-48.04)	35.31 (13.98-51.24)	*0.098*
Low SMD			
No	15 (31.9)	30 (41.7)	*0.284*
Yes	32 (68.1)	42 (58.3)	
PET-CT Analysis			
SUV max	10.20 (3.1-23.7)	17.55 (4.00-36.90)	*<0.001*
SUVmax > 11.40			
No	28 (59.6)	16 (22.2)	*<0.001*
Yes	19 (40.4)	56 (77.8)	
Survival			
Survival rate (1 year)			
No	5 (10.6)	26 (36.1)	*0.002*
Yes	42 (89.4)	46 (63.9)	

Table 14.3: The relationship between clinicopathological characteristics, tumour activity, body composition, markers of the systemic inflammatory response and overall survival in patients with lung cancer: Univariate and multivariate analysis.

Characteristics	n=119 (%)	*Univariate Cox Regression Analysis OS*	*p-value*	*Multivariate Cox Regression Analysis OS*	*p-value*
Sex					
Male	57 (47.9)	1.34 (0.91-1.97)	*0.141*	–	–
Female	62 (52.1)				
Age					
<65	17 (14.3)	1.04 (0.79-1.37)	*0.768*	–	–
65-74	54 (45.4)				
>75	48 (40.3)				
TNM					
I	42 (35.3)	1.40 (1.12-1.74)	*0.003*	–	0.112
II	22 (18.5)				
III	55 (46.2)				
ECOG – PS					
0/1	68 (57.1)	0.74 (0.50-1.09)	*0.126*	–	–
≥2	51 (42.9)				
Inflammatory Response					
mGPS					
0	58 (48.7)	1.30 (1.06-1.61)	*0.014*	–	0.097
1	20 (16.8)				
2	41 (34.5)				
Body Composition:					
BMI kg/m^2					
≤25	56 (47.1)	0.77 (0.54-1.13)	*0.182*	–	–
>25	63 (52.9)				
Visceral obesity					
No	45 (37.8)	0.81 (0.55-1.20)	*0.292*	–	–
Yes	74 (62.2)				
Sarcopenia					
Low SMI					
No	61 (51.3)	0.98 (0.67-1.44)	*0.930*	–	–
Yes	58 (48.7)				
Myosteatosis					
Low SMD					
No	45 (37.8)	0.66 (0.44-0.97)	*0.035*	–	0.181
Yes	74 (62.2)				
PET-CT Analysis					
TLG > 68.89					
No	47 (29.5)	2.18 (1.46-3.26)	*<0.001*	2.03 (1.35-3.07)	0.001
Yes	72 (60.5)				

15. CONCLUSIONS

15.1 Overview of thesis

It has been widely reported that patient outcomes are due to a complex and symbiotic relationship between tumour and host factors including the systemic inflammatory response (7). Body composition is increasingly recognised as an important prognostic domain in patients with cancer. There is evidence supporting a disproportionate loss of skeletal muscle tissue is associated with poor treatment tolerance and efficacy (351), worse quality of life, increased morbidity (352) and poorer survival in patients with cancer (350). Tumour metabolic activity has long been proposed as a driving force behind host factors including the systemic inflammatory response in patients with cancer. Recently the combination of PET and CT scanning has allowed for quantification of tumour metabolic activity as well as the identification of other metabolically active tissue in patients with cancer suggesting new mechanism connecting tumour activity, the systemic inflammatory response and body composition. Therefore, the aim of this thesis was to examine the relationship between the systemic inflammatory response, CT-derived body composition, tumour metabolic activity and outcomes in patients with cancer.

The results of two large systematic reviews and meta-analysis of the relationship between the systemic inflammatory response and outcomes in patients with operable and inoperable cancer can be found in Chapter 3 and 4 respectively (37, 38). In these studies which contained 442 articles in total, a clear relationship between the systemic inflammatory response and both cancer specific and overall survival is demonstrated. These studies were mostly retrospective observational studies however in Chapter 5 a further systematic review containing 36 prospective randomised control trials adds to the weight of evidence behind the use of the systemic inflammatory response in patients with cancer (54). Indeed, in Chapter 6, the systemic inflammatory response, as evidenced by the GPS/mGPS, was shown to be common in both primary operable and advanced inoperable cancers particularly in lung

and gastrointestinal cancers with 73.1% of patients being inflamed (Figure 15.1). Therefore, the systemic inflammation "iceberg" is in plain sight and should be factored into future treatment plans of patients with cancer. These results will have profound implications for the future design of randomised control trials with monitoring of the systemic inflammatory response being incorporated into future trials in pancreatic cancer and potentially being used to aid with inclusion and exclusion criteria (167).

The most common methods of assessing the systemic inflammatory response is with the use of composite ratios and cumulative scores constructed with different acute phase proteins or components of the differential white cell count (40). The two most commonly used composite ratios and cumulative scores would be NLR and the GPS/mGPS respectively (40). The results of Chapter 7 directly compare the prognostic value of composite ratios and cumulative scores in patients with colon cancer (Figure 15.1). Both ratios and scores, whether composed of white cells from lymphoid/ myeloid tissue or from acute phase proteins from the liver, had prognostic value, independent of TNM stage. However, cumulative scores, based on normal reference ranges, are simpler and more consistent for clinical use. This will have significant impact on future clinical practice particularly with the incorporation of monitoring of the systemic inflammatory response into clinical trial protocols. It also suggests that monitoring of the systemic inflammatory response should be incorporated into routine clinical practice to a greater extent to aid in clinical decision making and discharge planning (434).

On a local level, monitoring of the systemic inflammatory response in the form of the mGPS has been incorporated into standard clinical practice at the multidisciplinary team level in patients with lung cancer where it aids in clinical decision making. In a surgical setting monitoring of the post operative inflammatory response also forms an important part of clinical decision making and helps guide post operative imaging and discharge planning.

The results of Chapter 8 suggest a relationship between the inflammatory cytokine IL-6 and the systemic inflammatory response as measured by mGPS and performance as measured by ECOG-PS and their combination in patients with advanced cancer. This suggests another potential therapeutic target aimed at moderation of circulating IL-6 concentrations in patients with cancer. With the introduction of immunotherapies such as infliximab and clazakizumab which have been shown to be effective at modulating the inflammatory response in patients with cancer (337, 339) this modulation has become more effective and could be expanded to the majority of solid organ cancers (Figure 15.1).

The use of CT-derived body composition analysis is an expanding area of clinical interest and has been shown to directly relate to both the inflammatory response and outcomes in patients with cancer particularly colorectal cancer (52, 354). The two most commonly used software packages for image analysis are ImageJ and Slice-O-Matic. The results of Chapter 2 show that when directly compared ImageJ consistently gave higher values of different body composition parameters when compared to Slice-O-Matic (Figure 15.1). This led to more patients being diagnosed as viscerally obese and less being classified as sarcopenic. With the drive towards the incorporation of CT derived body composition analysis to standard clinical practice there must be a concurrent drive towards standardisation irrespective of the software package used (Figure 15.1). As a direct result of this a decision was made to calculate new thresholds for both sarcopenia and myosteatosis to be included in the remaining Chapters of this thesis (Figure 15.1).

Skeletal muscle is a highly physiologically active tissue and both the mass and quality of skeletal muscle has been shown to effect the level of physiological reserve and outcomes in patients with cancer (48, 66, 369, 370). The results of Chapter 9 suggest a significant relationship between low skeletal muscle mass, skeletal muscle quality and survival in patients with operable colorectal cancer (Figure 15.1). This would support the incorporation

of the measurement of skeletal muscle mass and density as well as the systemic inflammatory response into the clinical and nutritional assessment of patients with operable cancers. It also suggests that moves should be made to modulate the inflammatory response prior to surgery either with systemic anti-inflammatories or with steroid administration at induction (435).

The relationship between weight loss and outcomes has led to a number of studies using BMI/WLGrades to predict outcomes in patients with cancer particularly advanced disease. However, in Chapter 10 the use of the combined ECOG-PS/mGPS framework was shown to be more robust (Figure 15.1). As a result, it is suggested that the ECOG/mGPS framework form the basis for risk stratification of survival in patients with advanced cancer. The results of Chapter 11 show that both skeletal muscle mass and quality were associated with the systemic inflammatory response and measurements of physical function in patients with advanced cancer (Figure 15.1). Therefore, in the future CT-derived body composition analysis could add further weight to the widely used ECOG-PS/mGPS framework in patients with advanced cancer.

Longitudinal changes in body composition have been shown to have significant impact on outcomes in patients with cancer (44). Indeed, a considerable amount of clinical research including several randomised control trials has looked at ways to reverse the changes in body composition associated with cancer. This can be through the use of targeted pharmacological treatments or both organised pre and post treatment exercise programs (383, 436). However, the results of Chapter 12 which suggest that changes in body composition occur early in the disease process and are maintained even after the resection of the primary tumour suggests that the die is already cast and that the effectiveness of interventions at altering body composition may be met with minimal results (Figure 15.1). This highlights the importance of screening programs which identify patients at an early stage before they become

symptomatic (437). In the future patient expectations will also need to be managed with the realisation that even after curative surgical or oncological treatment a return to pre-diagnosis physical performance is unlikely and that the aim of any systemic treatment should be to arrest any further decline in muscle quality and quality.

There is evidence in the literature that chemotherapy can have a deleterious effect on outcomes particularly in inpatients with advanced cancers (438). Indeed Temel and co-workers in a recent RCT suggested that patients treated with early best supportive care could have better outcomes when compared to those undergoing active systemic oncological treatments including chemotherapy (29, 438). The pathophysiology of this remains to be fully elicited however there is some evidence that chemotherapy induced loss of skeletal muscle may lead to reduced physiological reserves and poorer outcomes in patients with cancer (439, 440). This is particularly true in metastatic colorectal cancer as can be seen by the results of two recent studies by Huemer and Köstek where chemotherapy was associated with a deterioration of skeletal muscle and poorer outcomes (439, 441). However, this reported association is not universal. Indeed, in a recent study in patients receiving palliative chemotherapy for advanced lung cancer Stene and co-workers found that approximately 50% of patients maintained or increased their skeletal muscle mass (442).

It would be of considerable interest to assess the effect of chemotherapy on body composition in patients with both operative and inoperative cancers. In this thesis this was not possible as CT scans often pre-dated the administration of chemotherapy in both operative and advanced cancers. However, future work particularly prospective work in pancreatic cancer with both pre and post chemotherapy scans being available will allow for this relationship to be better delineated.

The results of Chapter 13 examine the relationship between tumour physiology as measured but glucose metabolism and the host systemic inflammatory response (Figure 15.1). This systematic review suggests a direct relationship between the tumour and bone marrow glucose uptake and host systemic inflammatory responses in patients with common solid tumours. These results are confirmed in Chapter 14 which suggests that tumour metabolic activity as measured by tumour glucose uptake was associated with the systemic inflammatory response and mortality but not changes in body composition in patients with lung cancer (Figure 15.1). This suggests that the systemic effects of cancer including changes in body composition with their associated reduction in physical function and survival is mediated by the systemic inflammatory response activated through the bone marrow and not by the direct action of the tumour. This would provide further evidence that the early targeting of the systemic inflammatory response could provide a fruitful treatment strategy aimed at maintaining skeletal muscle mass and function while also improving quality of life and outcomes in patients with cancer.

Finally, the systemic inflammatory response has a direct relationship with changes in body composition and outcomes in patients with cancer. Interestingly this association would seem to be independent of tumour metabolic activity and potentially tumour stage. Cancer related changes in body composition and their associated effect on performance status seem to be established early in the disease process and maintained despite treatments targeting the tumour specifically. The work presented in this thesis would suggest that new and novel treatment strategies utilising stratification and targeting of the systemic inflammatory response would be of benefit. Such strategies could form part of an integrated treatment plan including prehabilitation in order to arrest any skeletal muscle loss and to improve outcomes in patients with cancer.

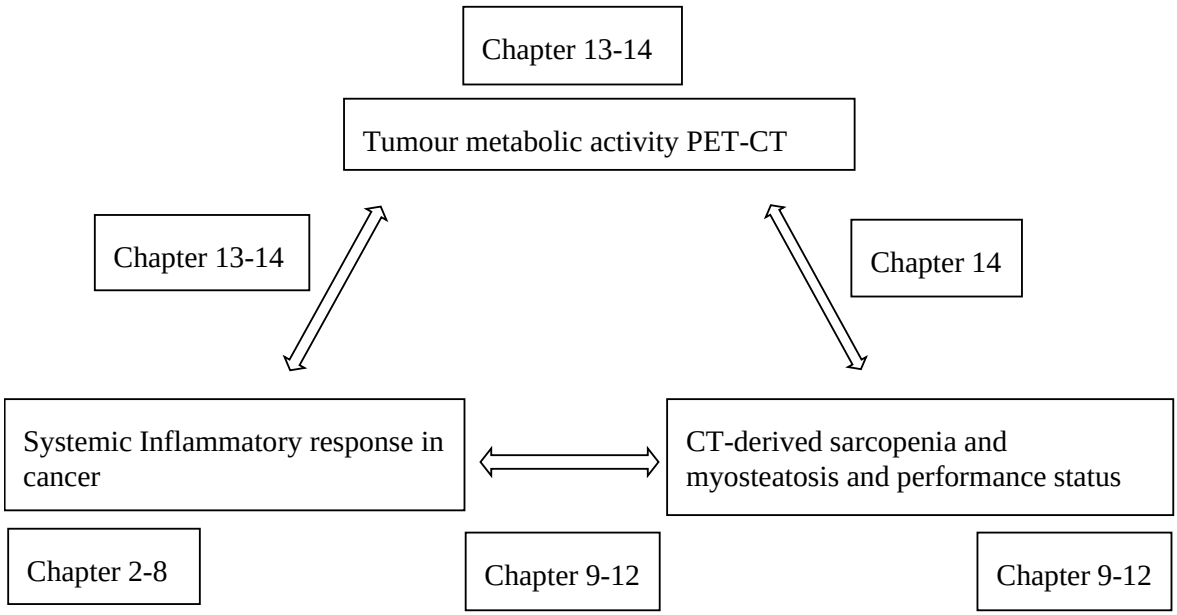


Figure 15.1: Schematic representation of relationships investigated in this theses and chapters relating to each

15.2 Future work

15.2.1 The relationship between the systemic inflammatory response, body composition, phenotypic subtyping and survival in patients with operable colorectal cancer

Further investigation of the tumour metabolic activity, systemic inflammation and body composition trinity will be the focus of future work leading on from this thesis. To this end we are currently conducting a study examining the relationship between the systemic inflammatory response, body composition, histological tumour subtypes and survival in patients with operable colorectal cancer. This study will be directly relating the body composition and systemic inflammation data collected as part of this thesis to phenotypic tumour subtyping. This will be carried out on formalin fixed paraffin embedded tissue samples collected at the time of surgical resection. Three phenotypic characteristics will be examined; Ki67 proliferation index, Klintrup-Makinen (KM) grade for inflammatory infiltrate and stromal invasion using tumour stroma percentage (TSP).

Immunohistochemical analysis for Ki67 will be performed using established protocols from the Institute of Cancer Sciences with appropriate positive and negative controls. KM grade will be assessed by examining immune cell density at the invasive margin on hematoxylin and eosin (H&E) stained full sections of the tumour taken at the deepest point of invasion. Tumours will be graded as low if absent or patchy immune cell infiltrate and graded as high if immune cell infiltrate forms a thin band or florid cup. TSP will be carried out using H&E-stained full sections taken at the deepest point of invasion. TSP will be calculated across the full section and graded as low if ≤50% stromal infiltration and high if >50% stromal infiltration. Patients will then be grouped into one of four phenotypic subtypes as shown in Table 15.1 below.

This study will aid in identifying the driving force behind systemic inflammation. It may be that active tumour metabolism stimulates inflammation and this causes weight loss and loss

of function which leads to poor survival. Alternatively, it may be that cachectic muscle drives up the inflammatory response leading to reduced survival.

A better understanding of this complex interaction will therefore allow us to better plan treatment interventions such as the use of non-steroidal anti-inflammatories or systemic steroids. Also, the ability to more accurately predict prognoses is of vital importance for patients with cancer. This could help with better counselling post-diagnosis improving the patient journey. This will help us achieve the aim of realistic medicine to support patient centred care, improve shared decision making and reduce unwarranted variation. It will allow patients to make more informed decisions about the type of treatment they would like to embark on and the realistic likelihood of success.

Table 15.1: Summary of phenotypic subtypes of patients undergoing surgical resection for colorectal cancer

	Immune	Proliferative	Latent	Stromal
KM grade	High	Low	Low	Low
Ki67	Any	High	Low	Any
TSP	Any	Low	Low	High

15.2.2 Investigating the relationship between molecular subtype, clinical outcomes and body composition in patients undergoing neoadjuvant therapy for Pancreatic Cancer.

In addition to the above work in colorectal cancer additional future work will focus on relating body composition analysis to precision medicine in pancreatic cancer. Numerous studies have demonstrated the significant benefit of neoadjuvant treatment in both resectable and borderline resectable pancreatic cancers (443-445). However, recent studies have shown that only around 75% of patients complete the full neoadjuvant chemotherapy regime (445). Reasons for failure to complete neoadjuvant therapy include disease progression and deterioration in performance status. It has previously been reported in approximately 1200 patients with resected pancreatic cancer that those with aggressive tumour biology particularly the aggressive squamous subtype are less likely to complete adjuvant chemotherapy and this is associated with poor performance status (446). This suggests that the differences in metabolic profiles of the particularly aggressive squamous subtype may predispose patients to cancer cachexia through metabolic effects in the cancer epithelial compartment.

PRECISION-Panc is a therapeutic development platform that aims to integrate pre-clinical discovery with clinical trials in order to facilitate precision oncology in pancreatic cancer. Under the clinical development umbrella of PRECISION-Panc is PRIMUS (Pancreatic Cancer Individualised Multi-arm Umbrella Study), a clinical trial platform that is aimed at finding the right trial for the patient. By providing a portfolio of clinical trials, targeting different molecular sub-groups in different disease stages, will allow multiple novel therapeutic opportunities for patients. This will allow clinical testing in individually small, yet cumulatively large patient groups which is aimed both at early stage drug development and larger scale Phase II / III studies.

PRIMUS-002 is a Phase II study examining two neoadjuvant regimes, FOLFOX-A (Folinic Acid, Fluorouracil, Oxaliplatin and nab-Paclitaxel) and Gemcitabine-Abraxane (Gemcitabine with nab-Paclitaxel) focusing on biomarker and liquid biopsy development (Figure 15.2). The aims of this study will be to investigate the impact of body composition on clinical outcomes in patients undergoing neoadjuvant therapy for pancreatic cancer in the PRIMUS-002 trial, to investigate the relationship between CT-derived body composition measurements, molecular subtypes and the systemic inflammatory response in patients with pancreatic cancer. Finally, to correlate molecular subtype and molecular pathways with sarcopenia and myosteatosis to identify pre-treatment biomarkers predicting deteriorating performance status whilst identifying novel therapeutic targets using a systems biology approach.

Data will be prospectively collected through the PRECISION-Panc platform. All patients identified through PRECISION-Panc will enrol in the PRECISION-Panc master protocol (Figure 15.3) and undergo molecular profiling from endoscopic guided fine-needle core biopsy. Molecular assays performed will include the Glasgow Precision Oncology (GPOL) Clinical Cancer Genome, and transcriptomic analysis using gene expression arrays or RNA sequencing. Patients recruited to PRIMUS-002 will be allocated to either FOLFOX-A or Gemcitabine-Abraxane arm based on performance status and age and will have extensive clinical annotation as per clinical trial standards. Patients will undergo CT scans at diagnosis, after chemotherapy, and after radiotherapy (in selected cases) prior to surgery. Enabling a timeline of body composition analysis during the neoadjuvant treatment journey. Blood tests to determine mGPS will be taken prior to treatment start and at set intervals according to the trial protocol. Response to therapy will be determined by pathological regression score and radiology RECIST criteria. Body composition analysis will be carried out as outline in Chapter 2 using Slice-O-Matic.

Analysis into body composition will potentially enable clinicians to identify patients who may not tolerate treatment (resection or chemotherapy) due to poor nutritional status. Such patients may benefit from home nutritional support and/or a dedicated 'prehabilitation' programme (447) with the aim of optimising or at least arresting further physiological decline prior to intervention. Furthermore, patients predicted not to be able to tolerate systemic chemotherapy regimens can enter clinical trials with targeted therapies with less toxicity as they open in the PRECISION-Panc clinical trial portfolio. This study will for the first time combine CT-derived body composition with in depth genomic and transcriptomic analyses, and objective evidence of the systemic inflammatory response in patients with pancreatic cancer. Furthermore, as part of the PRECISION-Panc umbrella, prospectively collected clinico-pathological and patient follow-up/outcome data will be available allowing objective assessment of longitudinal changes in body composition to be assessed.

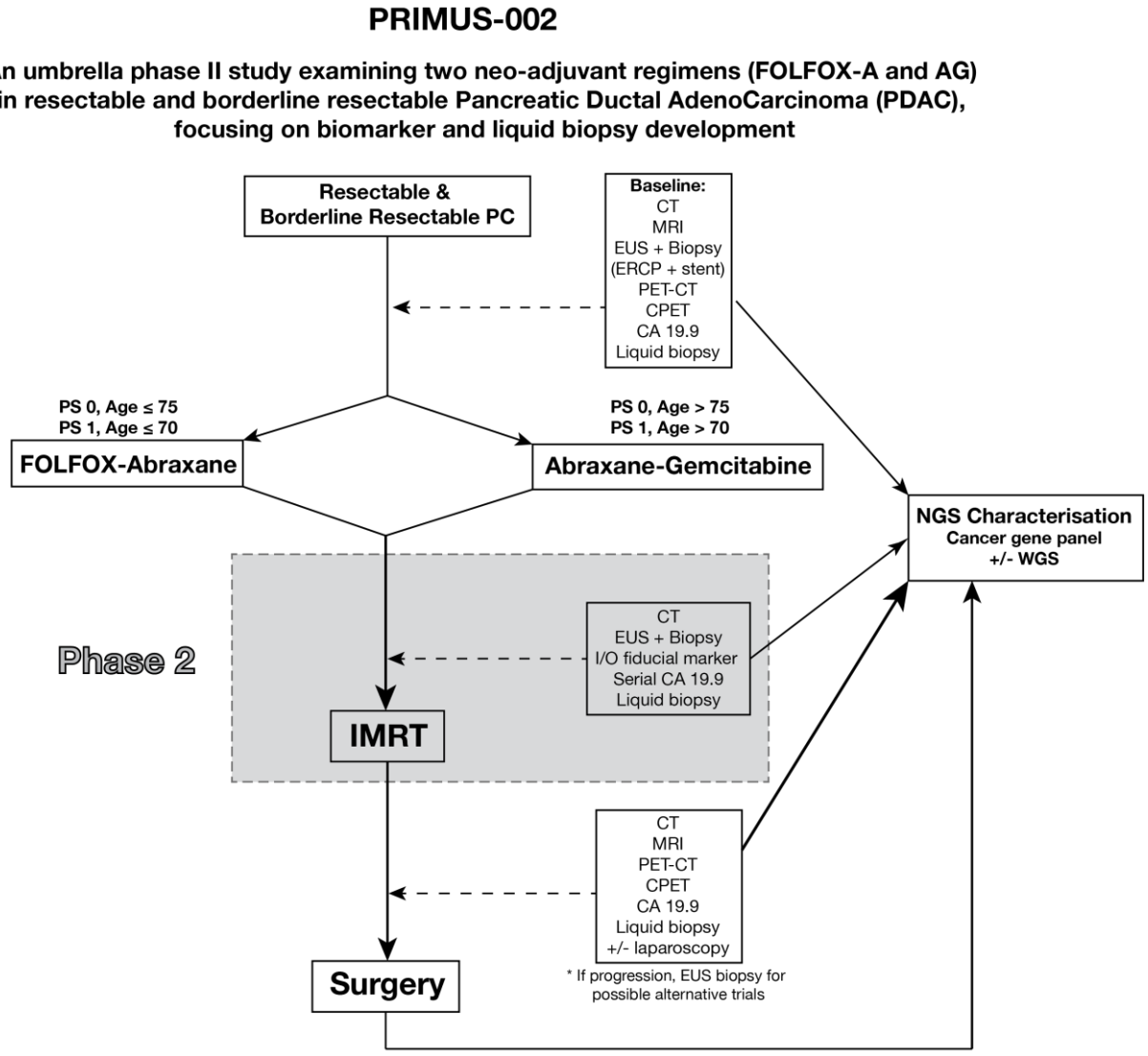


Figure 15.2: PRIMUS-002 patient flow. Patients are allocated to either FOLFOX-A or AG arm based on performance status. Pre-treatment investigations included next generation sequencing (genome and transcriptome) of tumour biopsy, CT and PET-CT. This is repeated after chemo prior to surgery or radiotherapy (Phase 2 introduced after initial safety period).

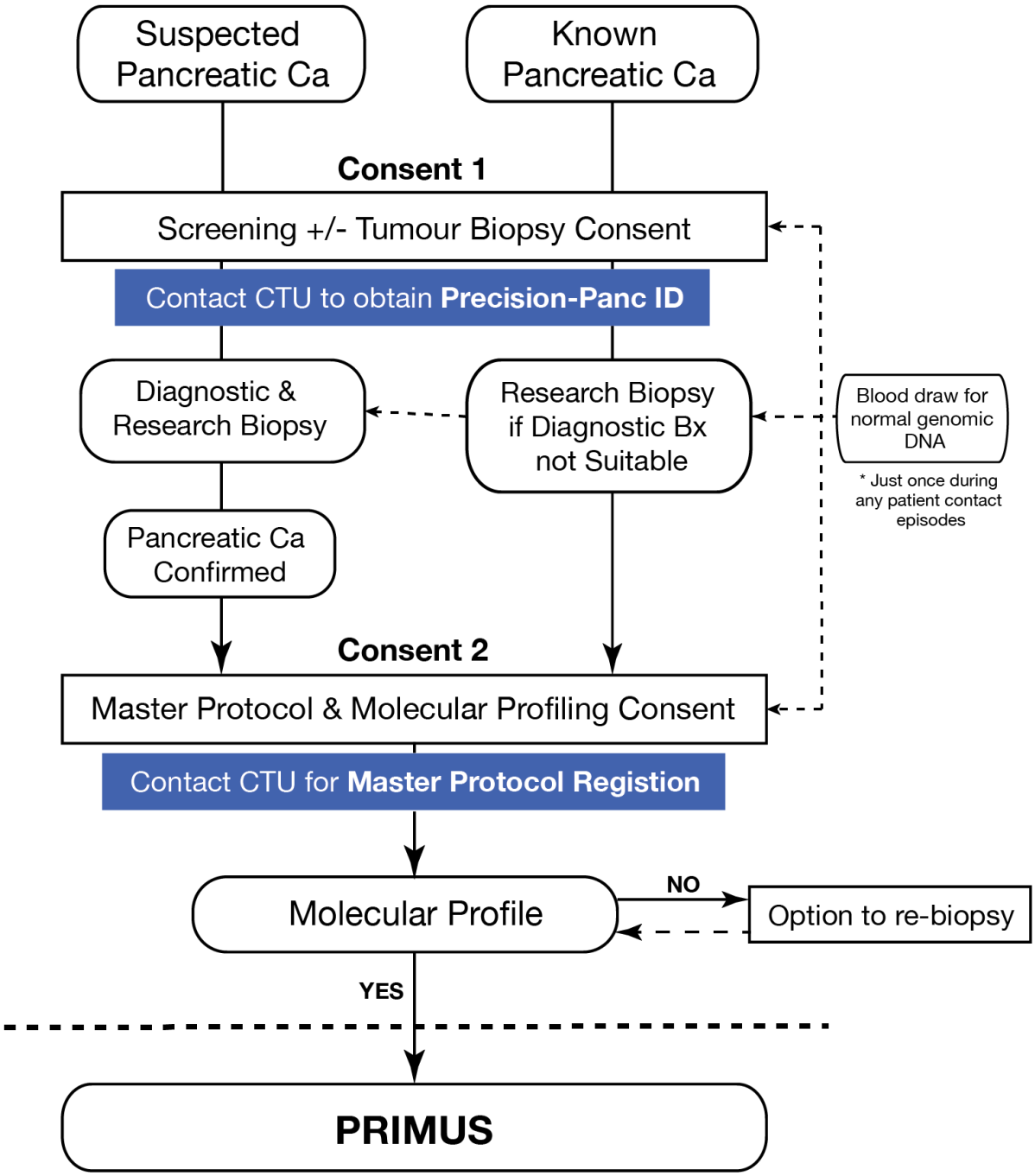


Figure 15.3: The *PRECISION-Panc* Master Protocol. Patients are screened at time of diagnostic biopsy to allow additional samples for molecular profiling. This ensures rapid turn around from biopsy to recruitment.

16. List of References

1. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3(11):991-8.

2. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity. 2004;21(2):137-48.

3. Janeway CA, Jr. How the immune system protects the host from infection. Microbes Infect. 2001;3(13):1167-71.

4. Janeway CA, Jr., Medzhitov R. Innate immune recognition. Annu Rev Immunol. 2002;20:197-216.

5. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell. 2010;141(1):39-51.

6. Park JH, Ishizuka M, McSorley ST, Kubota K, Roxburgh CSD, Nagata H, et al. Staging the tumor and staging the host: A two centre, two country comparison of systemic inflammatory responses of patients undergoing resection of primary operable colorectal cancer. American journal of surgery. 2017.

7. Park JH, Watt DG, Roxburgh CS, Horgan PG, McMillan DC. Colorectal Cancer, Systemic Inflammation, and Outcome: Staging the Tumor and Staging the Host. Annals of surgery. 2016;263(2):326-36.

8. House AK, Watt AG. Survival and the immune response in patients with carcinoma of the colorectum. Gut. 1979;20(10):868-74.

9. Park JH, van Wyk H, Roxburgh CSD, Horgan PG, Edwards J, McMillan DC. Tumour invasiveness, the local and systemic environment and the basis of staging systems in colorectal cancer. Br J Cancer. 2017;116(11):1444-50.

10. Kim J, Bae JS. Tumor-Associated Macrophages and Neutrophils in Tumor Microenvironment. Mediators of inflammation. 2016;2016:6058147.

11. Morley JJ, Kushner I. Serum C-reactive protein levels in disease. Ann N Y Acad Sci. 1982;389:406-18.

12. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. The New England journal of medicine. 1999;340(6):448-54.

13. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. Biochem J. 1990;265(3):621-36.

14. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860-7.

15. Vakkila J, Lotze MT. Inflammation and necrosis promote tumour growth. Nat Rev Immunol. 2004;4(8):641-8.

16. DeNardo DG, Johansson M, Coussens LM. Immune cells as mediators of solid tumor metastasis. Cancer Metastasis Rev. 2008;27(1):11-8.

17. Laird BJ, Kaasa S, McMillan DC, Fallon MT, Hjermstad MJ, Fayers P, et al. Prognostic factors in patients with advanced cancer: a comparison of clinicopathological factors and the development of an inflammation-based prognostic system. Clinical cancer research : an official journal of the American Association for Cancer Research. 2013;19(19):5456-64.

18. McMillan DC, Preston T, Watson WS, Simpson JM, Fearon KC, Shenkin A, et al. Relationship between weight loss, reduction of body cell mass and inflammatory response in patients with cancer. The British journal of surgery. 1994;81(7):1011-4.

19. Falconer JS, Fearon KC, Ross JA, Elton R, Wigmore SJ, Garden OJ, et al. Acute-phase protein response and survival duration of patients with pancreatic cancer. Cancer. 1995;75(8):2077-82.

20. McMillan DC, Scott HR, Watson WS, Preston T, Milroy R, McArdle CS. Longitudinal study of body cell mass depletion and the inflammatory response in cancer patients. Nutrition and cancer. 1998;31(2):101-5.

21. O'Gorman P, McMillan DC, McArdle CS. Longitudinal study of weight, appetite, performance status, and inflammation in advanced gastrointestinal cancer. Nutrition and cancer. 1999;35(2):127-9.

22. Barber MD, Ross JA, Fearon KC. Changes in nutritional, functional, and inflammatory markers in advanced pancreatic cancer. Nutrition and cancer. 1999;35(2):106-10.

23. McMillan DC, Wigmore SJ, Fearon KC, O'Gorman P, Wright CE, McArdle CS. A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. Br J Cancer. 1999;79(3-4):495-500.

24. Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. Am J Clin Nutr. 2006;83(4):735-43.

25. Laird BJ, Fallon M, Hjermstad MJ, Tuck S, Kaasa S, Klepstad P, et al. Quality of Life in Patients With Advanced Cancer: Differential Association With Performance Status and Systemic Inflammatory Response. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34(23):2769-75.

26. Mayor S. UK audit shows need for greater caution with chemotherapy in very sick patients. Bmj. 2008;337:a2498.

27. Prigerson HG, Bao Y, Shah MA, Paulk ME, LeBlanc TW, Schneider BJ, et al. Chemotherapy Use, Performance Status, and Quality of Life at the End of Life. JAMA Oncol. 2015;1(6):778-84.

28. Garrido MM, Prigerson HG, Bao Y, Maciejewski PK. Chemotherapy Use in the Months Before Death and Estimated Costs of Care in the Last Week of Life. Journal of pain and symptom management. 2016;51(5):875-81.e2.

29. Temel JS, Greer JA, El-Jawahri A, Pirl WF, Park ER, Jackson VA, et al. Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer: A Randomized Clinical Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(8):834-41.

30. Cho IR, Park JC, Park CH, Jo JH, Lee HJ, Kim S, et al. Pre-treatment neutrophil to lymphocyte ratio as a prognostic marker to predict chemotherapeutic response and survival outcomes in metastatic advanced gastric cancer. Gastric Cancer. 2014;17(4):703-10.

31. Ramsey S, Lamb GW, Aitchison M, Graham J, McMillan DC. Evaluation of an inflammation-based prognostic score in patients with metastatic renal cancer. Cancer. 2007;109(2):205-12.

32. Simmons CP, McMillan DC, McWilliams K, Sande TA, Fearon KC, Tuck S, et al. Prognostic Tools in Patients with Advanced Cancer: A Systematic Review. J Pain Symptom Manage. 2017.

33. Lawrence T, Willoughby DA, Gilroy DW. Anti-inflammatory lipid mediators and insights into the resolution of inflammation. Nat Rev Immunol. 2002;2(10):787-95.

34. Becker C, Fantini MC, Schramm C, Lehr HA, Wirtz S, Nikolaev A, et al. TGF-beta suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling. Immunity. 2004;21(4):491-501.

35. Berg DJ, Davidson N, Kuhn R, Muller W, Menon S, Holland G, et al. Enterocolitis and colon cancer in interleukin-10-deficient mice are associated with aberrant cytokine production and CD4(+) TH1-like responses. J Clin Invest. 1996;98(4):1010-20.

36. Harrison C, Kiladjian JJ, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. The New England journal of medicine. 2012;366(9):787-98.

37. Dolan RD, Lim J, McSorley ST, Horgan PG, McMillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with operable cancer: Systematic review and meta-analysis. Sci Rep. 2017;7(1):16717.

38. Dolan RD, McSorley ST, Horgan PG, Laird B, McMillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: Systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017;116:134-46.

39. Watt DG, Proctor MJ, Park JH, Horgan PG, McMillan DC. The Neutrophil-Platelet Score (NPS) Predicts Survival in Primary Operable Colorectal Cancer and a Variety of Common Cancers. PloS one. 2015;10(11):e0142159.

40. Dolan RD, McSorley ST, Park JH, Watt DG, Roxburgh CS, Horgan PG, et al. The prognostic value of systemic inflammation in patients undergoing surgery for colon cancer: comparison of composite ratios and cumulative scores. Br J Cancer. 2018;119(1):40-51.

41. Aapro M, Arends J, Bozzetti F, Fearon K, Grunberg SM, Herrstedt J, et al. Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. Annals of oncology : official journal of the European Society for Medical Oncology. 2014;25(8):1492-9.

42. Trajkovic-Vidakovic M, de Graeff A, Voest EE, Teunissen SC. Symptoms tell it all: a systematic review of the value of symptom assessment to predict survival in advanced cancer patients. Crit Rev Oncol Hematol. 2012;84(1):130-48.

43. Wallengren O, Iresjo BM, Lundholm K, Bosaeus I. Loss of muscle mass in the end of life in patients with advanced cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2015;23(1):79-86.

44. Malietzis G, Currie AC, Johns N, Fearon KC, Darzi A, Kennedy RH, et al. Skeletal Muscle Changes After Elective Colorectal Cancer Resection: A Longitudinal Study. Annals of surgical oncology. 2016;23(8):2539-47.

45. Malietzis G, Johns N, Al-Hassi HO, Knight SC, Kennedy RH, Fearon KC, et al. Low Muscularity and Myosteatosis Is Related to the Host Systemic Inflammatory Response in Patients Undergoing Surgery for Colorectal Cancer. Annals of surgery. 2016;263(2):320-5.

46. Lundholm K, Gelin J, Hyltander A, Lonnroth C, Sandstrom R, Svaninger G, et al. Anti-inflammatory treatment may prolong survival in undernourished patients with metastatic solid tumors. Cancer research. 1994;54(21):5602-6.

47. Madeddu C, Dessi M, Panzone F, Serpe R, Antoni G, Cau MC, et al. Randomized phase III clinical trial of a combined treatment with carnitine + celecoxib +/- megestrol

acetate for patients with cancer-related anorexia/cachexia syndrome. Clinical nutrition (Edinburgh, Scotland). 2012;31(2):176-82.

48. Malietzis G, Aziz O, Bagnall NM, Johns N, Fearon KC, Jenkins JT. The role of body composition evaluation by computerized tomography in determining colorectal cancer treatment outcomes: a systematic review. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2015;41(2):186-96.

49. Griffeth LK. Use of PET/CT scanning in cancer patients: technical and practical considerations. Proc (Bayl Univ Med Cent). 2005;18(4):321-30.

50. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010;363(8):733-42.

51. McSorley S, Dolan R, Roxburgh C, McMilllan D, Horgan P. How and why systemic inflammation worsens quality of life in patients with advanced cancer. Expert review of quality of life in cancer care. 2017;2:167-75.

52. Dolan RD, Almasaudi AS, Dieu LB, Horgan PG, McSorley ST, McMillan DC. The relationship between computed tomography-derived body composition, systemic inflammatory response, and survival in patients undergoing surgery for colorectal cancer. J Cachexia Sarcopenia Muscle. 2019;10(1):111-22.

53. Dolan RD, McLees NG, Irfan A, McSorley ST, Horgan PG, Colville D, et al. The relationship between tumour glucose metabolism and host systemic inflammatory responses in patients with cancer: A systematic review. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2018.

54. Dolan RD, Laird BJA, Horgan PG, McMillan DC. The prognostic value of the systemic inflammatory response in randomised clinical trials in cancer: A systematic review. Critical Reviews in Oncology / Hematology. 2018;132:130-7.

55. Dolan RD, McMillan DC. The prevalence of cancer associated systemic inflammation: Implications of prognostic studies using the Glasgow Prognostic Score. Crit Rev Oncol Hematol. 2020;150:102962.

56. Higgins JG, S. Cochrane Handbook for Systematic Reviews of Interventions. London John Wiley & Sons Ltd; 2011.

57. Janssen I, Ross R. Linking age-related changes in skeletal muscle mass and composition with metabolism and disease. J Nutr Health Aging. 2005;9(6):408-19.

58. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. The journals of gerontology Series A, Biological sciences and medical sciences. 2006;61(10):1059-64.

59. Daly LE, Prado CM, Ryan AM. A window beneath the skin: how computed tomography assessment of body composition can assist in the identification of hidden wasting conditions in oncology that profoundly impact outcomes. The Proceedings of the Nutrition Society. 2018;77(2):135-51.

60. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147(8):755-63.

61. Fearon KC, Voss AC, Hustead DS, Group CCS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr. 2006;83(6):1345-50.

62. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nature reviews Cancer. 2014;14(11):754-62.

63. Donohoe CL, Ryan AM, Reynolds JV. Cancer cachexia: mechanisms and clinical implications. Gastroenterol Res Pract. 2011;2011:601434.

64. Long DE, Villasante Tezanos AG, Wise JN, Kern PA, Bamman MM, Peterson CA, et al. A guide for using NIH Image J for single slice cross-sectional area and composition analysis of the thigh from computed tomography. PloS one. 2019;14(2):e0211629.

65. Roubenoff R. Sarcopenia: Effects on Body Composition and Function. The Journals of Gerontology: Series A. 2003;58(11):M1012-M7.

66. Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31(12):1539-47.

67. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. Acta Physiol (Oxf). 2014;210(3):489-97.

68. Skipworth RJE. A tale of two CT studies: the combined impact of multiple human body composition projects in cancer. J Cachexia Sarcopenia Muscle. 2019;10(1):6-8.

69. Ebadi M, Martin L, Ghosh S, Field CJ, Lehner R, Baracos VE, et al. Subcutaneous adiposity is an independent predictor of mortality in cancer patients. Br J Cancer. 2017;117(1):148-55.

70. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629-35.

71. McSorley ST, Black DH, Horgan PG, McMillan DC. The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer. Clinical nutrition (Edinburgh, Scotland). 2018;37(4):1279-85.

72. Irving BA, Weltman JY, Brock DW, Davis CK, Gaesser GA, Weltman A. NIH ImageJ and Slice-O-Matic computed tomography imaging software to quantify soft tissue. Obesity (Silver Spring). 2007;15(2):370-6.

73. TomoVision. sliceOmatic. 2 ed. 3280 Ch. Milletta, Magog, Qc: TomoVision 2020.

74. Teigen LM, Kuchnia AJ, Nagel E, Deuth C, Vock DM, Mulasi U, et al. Impact of Software Selection and ImageJ Tutorial Corrigendum on Skeletal Muscle Measures at the Third Lumbar Vertebra on Computed Tomography Scans in Clinical Populations. JPEN J Parenter Enteral Nutr. 2018;42(5):933-41.

75. Abbass T, Dolan RD, Laird BJ, McMillan DC. The Relationship between Imaging-Based Body Composition Analysis and the Systemic Inflammatory Response in Patients with Cancer: A Systematic Review. Cancers (Basel). 2019;11(9).

76. Miele E, Spinelli GP, Tomao F, Zullo A, De Marinis F, Pasciuti G, et al. Positron Emission Tomography (PET) radiotracers in oncology--utility of 18F-Fluoro-deoxy-glucose (FDG)-PET in the management of patients with non-small-cell lung cancer (NSCLC). J Exp Clin Cancer Res. 2008;27:52.

77. Lee P, Kupelian P, Czernin J, Ghosh P. Current concepts in F18 FDG PET/CT-based Radiation Therapy planning for Lung Cancer. Frontiers in Oncology. 2012;2(71).

78. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015;42(2):328-54.

79. WHO. World Health Organization Cancer Fact Sheet London World Health Organization 2017 [cited 2017 10/04]. Available from: http://www.who.int/mediacentre/factsheets/fs297/en/.

80. Garraway LA, Verweij J, Ballman KV. Precision oncology: an overview. J Clin Oncol. 2013;31(15):1803-5.

81. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Current opinion in clinical nutrition and metabolic care. 2009;12(3):223-6.

82. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol. 2014;15(11):e493-e503.

83. Johns N, Hatakeyama S, Stephens NA, Degen M, Degen S, Frieauff W, et al. Clinical classification of cancer cachexia: phenotypic correlates in human skeletal muscle. PLoS One. 2014;9(1):e83618.

84. Kerem M, Ferahkose Z, Yilmaz UT, Pasaoglu H, Ofluoglu E, Bedirli A, et al. Adipokines and ghrelin in gastric cancer cachexia. World J Gastroenterol. 2008;14(23):3633-41.

85. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88(1):218-30.

86. McMillan DC. An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. Proc Nutr Soc. 2008;67(3):257-62.

87. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer treatment reviews. 2013;39(5):534-40.

88. Zhou T, Zhan J, Hong S, Hu Z, Fang W, Qin T, et al. Ratio of C-Reactive Protein/Albumin is An Inflammatory Prognostic Score for Predicting Overall Survival of Patients with Small-cell Lung Cancer. Sci Rep. 2015;5:10481.

89. Yamashita S, Kohjimoto Y, Iguchi T, Koike H, Kusumoto H, Iba A, et al. Prognostic factors and risk stratification in patients with castration-resistant prostate cancer receiving docetaxel-based chemotherapy. BMC Urol. 2016;16:13.

90. Shibutani M, Maeda K, Nagahara H, Ohtani H, Iseki Y, Ikeya T, et al. The pretreatment albumin to globulin ratio predicts chemotherapeutic outcomes in patients with unresectable metastatic colorectal cancer. BMC Cancer. 2015;15:347.

91. Yao Y, Zhao M, Yuan D, Gu X, Liu H, Song Y. Elevated pretreatment serum globulin albumin ratio predicts poor prognosis for advanced non-small cell lung cancer patients. J Thorac Dis. 2014;6(9):1261-70.

92. Chan AW, Chan SL, Mo FK, Wong GL, Wong VW, Cheung YS, et al. Albumin-to-alkaline phosphatase ratio: a novel prognostic index for hepatocellular carcinoma. Dis Markers. 2015;2015:564057.

93. Marsik C, Kazemi-Shirazi L, Schickbauer T, Winkler S, Joukhadar C, Wagner OF, et al. C-reactive protein and all-cause mortality in a large hospital-based cohort. Clin Chem. 2008;54(2):343-9.

94. Proctor MJ, McMillan DC, Horgan PG, Fletcher CD, Talwar D, Morrison DS. Systemic inflammation predicts all-cause mortality: a glasgow inflammation outcome study. PLoS One. 2015;10(3):e0116206.

95. Watt DG, Roxburgh CS, White M, Chan JZ, Horgan PG, McMillan DC. A Survey of Attitudes towards the Clinical Application of Systemic Inflammation Based Prognostic Scores in Cancer. Mediators Inflamm. 2015;2015:842070.

96. Bain B, Seed M, Godsland I. Normal values for peripheral blood white cell counts in women of four different ethnic origins. Journal of clinical pathology. 1984;37(2):188-93.

97. Azab B, Camacho-Rivera M, Taioli E. Average values and racial differences of neutrophil lymphocyte ratio among a nationally representative sample of United States subjects. PloS one. 2014;9(11):e112361.

98. Bain BJ. Ethnic and sex differences in the total and differential white cell count and platelet count. Journal of clinical pathology. 1996;49(8):664-6.

99. McMillan DC. Cancer and systemic inflammation: stage the tumour and stage the host. Br J Cancer. 2013;109(3):529.

100. Crozier JE, McKee RF, McArdle CS, Angerson WJ, Anderson JH, Horgan PG, et al. The presence of a systemic inflammatory response predicts poorer survival in patients receiving adjuvant 5-FU chemotherapy following potentially curative resection for colorectal cancer. Br J Cancer. 2006;94(12):1833-6.

101. Dreyer SB, Powell AG, McSorley ST, Waterston A, Going JJ, Edwards J, et al. The Pretreatment Systemic Inflammatory Response is an Important Determinant of Poor Pathologic Response for Patients Undergoing Neoadjuvant Therapy for Rectal Cancer. Ann Surg Oncol. 2017;24(5):1295-303.

102. Carruthers R, Tho LM, Brown J, Kakumanu S, McCartney E, McDonald AC. Systemic inflammatory response is a predictor of outcome in patients undergoing preoperative chemoradiation for locally advanced rectal cancer. Colorectal Dis. 2012;14(10):e701-7.

103. Lee BN, Dantzer R, Langley KE, Bennett GJ, Dougherty PM, Dunn AJ, et al. A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. Neuroimmunomodulation. 2004;11(5):279-92.

104. De PM, Lewis CE. Macrophage regulation of tumor responses to anticancer therapies. Cancer Cell. 2013;23(3):277-86.

105. Wood LJ, Nail LM, Gilster A, Winters KA, Elsea CR. Cancer chemotherapy-related symptoms: evidence to suggest a role for proinflammatory cytokines. Oncol Nurs Forum. 2006;33(3):535-42.

106. Wood LJ, Nail LM, Perrin NA, Elsea CR, Fischer A, Druker BJ. The cancer chemotherapy drug etoposide (VP-16) induces proinflammatory cytokine production and sickness behavior-like symptoms in a mouse model of cancer chemotherapy-related symptoms. Biol Res Nurs. 2006;8(2):157-69.

107. Tsavaris N, Kosmas C, Vadiaka M, Kanelopoulos P, Boulamatsis D. Immune changes in patients with advanced breast cancer undergoing chemotherapy with taxanes. Br J Cancer. 2002;87(1):21-7.

108. Plate JM, Plate AE, Shott S, Bograd S, Harris JE. Effect of gemcitabine on immune cells in subjects with adenocarcinoma of the pancreas. Cancer Immunol Immunother. 2005;54(9):915-25.

109. Pusztai L, Mendoza TR, Reuben JM, Martinez MM, Willey JS, Lara J, et al. Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. Cytokine. 2004;25(3):94-102.

110. Wang XS, Shi Q, Williams LA, Mao L, Cleeland CS, Komaki RR, et al. Inflammatory cytokines are associated with the development of symptom burden in patients with NSCLC undergoing concurrent chemoradiation therapy. Brain Behav Immun. 2010;24(6):968-74.

111. Hoos A. Development of immuno-oncology drugs - from CTLA4 to PD1 to the next generations. Nat Rev Drug Discov. 2016;15(4):235-47.

112. Hoos A, Ibrahim R, Korman A, Abdallah K, Berman D, Shahabi V, et al. Development of ipilimumab: contribution to a new paradigm for cancer immunotherapy. Semin Oncol. 2010;37(5):533-46.

113. Ruxolitinib Benefits Some with Pancreatic Cancer. Cancer Discov. 2015;5(12):1231.

114. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010;6(1):149-63.

115. Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly DS, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. European journal of cancer (Oxford, England : 1990). 2011;47(17):2633-41.

116. Bosanquet N, Sikora K. The economics of cancer care in the UK. Lancet Oncol. 2004;5(9):568-74.

117. Mantovani A, Romero P, Palucka AK, Marincola FM. Tumour immunity: effector response to tumour and role of the microenvironment. Lancet (London, England). 2008;371(9614):771-83.

118. McMillan DC, Crozier JE, Canna K, Angerson WJ, McArdle CS. Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. International journal of colorectal disease. 2007;22(8):881-6.

119. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Combination of platelet count and neutrophil to lymphocyte ratio is a useful predictor of postoperative survival in patients with colorectal cancer. Br J Cancer. 2013;109(2):401-7.

120. Ishizuka M, Oyama Y, Abe A, Kubota K. Combination of platelet count and neutrophil to lymphocyte ratio is a useful predictor of postoperative survival in patients undergoing surgery for gastric cancer. Journal of surgical oncology. 2014;110(8):935-41.

121. Zhang H, Zhang L, Zhu K, Shi B, Yin Y, Zhu J, et al. Prognostic Significance of Combination of Preoperative Platelet Count and Neutrophil-Lymphocyte Ratio (COP-NLR) in Patients with Non-Small Cell Lung Cancer: Based on a Large Cohort Study. PloS one. 2015;10(5):e0126496.

122. Neal CP, Cairns V, Jones MJ, Masood MM, Nana GR, Mann CD, et al. Prognostic performance of inflammation-based prognostic indices in patients with resectable colorectal liver metastases. Medical oncology (Northwood, London, England). 2015;32(5):144.

123. Feng JF, Huang Y, Liu JS. Combination of neutrophil lymphocyte ratio and platelet lymphocyte ratio is a useful predictor of postoperative survival in patients with esophageal squamous cell carcinoma. OncoTargets and therapy. 2013;6:1605-12.

124. Cummings M, Merone L, Keeble C, Burland L, Grzelinski M, Sutton K, et al. Preoperative neutrophil:lymphocyte and platelet:lymphocyte ratios predict endometrial cancer survival. Br J Cancer. 2015;113(2):311-20.

125. Li C, Wen TF, Yan LN, Li B, Wang WT, Yang JY, et al. Postoperative neutrophil-to-lymphocyte ratio plus platelet-to-lymphocyte ratio predicts the outcomes of hepatocellular carcinoma. The Journal of surgical research. 2015;198(1):73-9.

126. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Shibuya N, Kubota K. Clinical Significance of the C-Reactive Protein to Albumin Ratio for Survival After Surgery for Colorectal Cancer. Annals of surgical oncology. 2016;23(3):900-7.

127. Xu XL, Yu HQ, Hu W, Song Q, Mao WM. A Novel Inflammation-Based Prognostic Score, the C-Reactive Protein/Albumin Ratio Predicts the Prognosis of Patients with Operable Esophageal Squamous Cell Carcinoma. PloS one. 2015;10(9):e0138657.

128. Miyata H, Yamasaki M, Kurokawa Y, Takiguchi S, Nakajima K, Fujiwara Y, et al. Prognostic value of an inflammation-based score in patients undergoing pre-operative chemotherapy followed by surgery for esophageal cancer. Exp Ther Med. 2011;2(5):879-85.

129. Ha HR, Oh DY, Kim TY, Lee K, Kim K, Lee KH, et al. Survival Outcomes According to Adjuvant Treatment and Prognostic Factors Including Host Immune Markers in Patients with Curatively Resected Ampulla of Vater Cancer. PloS one. 2016;11(3):e0151406.

130. Tomita M, Shimizu T, Ayabe T, Nakamura K, Onitsuka T. Elevated preoperative inflammatory markers based on neutrophil-to-lymphocyte ratio and C-reactive protein predict poor survival in resected non-small cell lung cancer. Anticancer Res. 2012;32(8):3535-8.

131. Chen XL, Xue L, Wang W, Chen HN, Zhang WH, Liu K, et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: a retrospective cohort study. Oncotarget. 2015;6(38):41370-82.

132. Sung HH, Jeon HG, Jeong BC, Seo SI, Jeon SS, Choi HY, et al. Clinical significance of prognosis using the neutrophil-lymphocyte ratio and erythrocyte sedimentation rate in patients undergoing radical nephroureterectomy for upper urinary tract urothelial carcinoma. BJU international. 2015;115(4):587-94.

133. East JM, Hogan J, Samaha G, Medani M, MacKerricher W, Polinkevych S, et al. Ratios derived from an array of standard haematological indices predict the oncological outcome in colon cancer. Colorectal Dis. 2014;16(6):442-9.

134. Shen SL, Fu SJ, Chen B, Kuang M, Li SQ, Hua YP, et al. Preoperative aspartate aminotransferase to platelet ratio is an independent prognostic factor for hepatitis B-induced hepatocellular carcinoma after hepatic resection. Annals of surgical oncology. 2014;21(12):3802-9.

135. Aurello P, Tierno SM, Berardi G, Tomassini F, Magistri P, D'Angelo F, et al. Value of preoperative inflammation-based prognostic scores in predicting overall survival and disease-free survival in patients with gastric cancer. Annals of surgical oncology. 2014;21(6):1998-2004.

136. Sun KY, Xu JB, Chen SL, Yuan YJ, Wu H, Peng JJ, et al. Novel immunological and nutritional-based prognostic index for gastric cancer. World journal of gastroenterology. 2015;21(19):5961-71.

137. Li Y, Jia H, Yu W, Xu Y, Li X, Li Q, et al. Nomograms for predicting prognostic value of inflammatory biomarkers in colorectal cancer patients after radical resection. International journal of cancer. 2016;139(1):220-31.

138. Christina EC, Cornelia C, Edgar S. Neoadjuvant radiotherapy plus radical surgery for locally advanced stage III/IV oral cancer: Analysis of prognostic factors affecting overall survival. Oral oncology. 2016;60:1-7.

139. Wang YQ, Jin C, Zheng HM, Zhou K, Shi BB, Zhang Q, et al. A novel prognostic inflammation score predicts outcomes in patients with ovarian cancer. Clinica chimica acta; international journal of clinical chemistry. 2016;456:163-9.

140. Toyokawa T, Kubo N, Tamura T, Sakurai K, Amano R, Tanaka H, et al. The pretreatment Controlling Nutritional Status (CONUT) score is an independent prognostic factor in patients with resectable thoracic esophageal squamous cell carcinoma: results from a retrospective study. BMC cancer. 2016;16:722.

141. Nakamura M, Iwahashi M, Nakamori M, Ojima T, Katsuda M, Iida T, et al. New prognostic score for the survival of patients with esophageal squamous cell carcinoma. Surgery today. 2014;44(5):875-83.

142. Arigami T, Okumura H, Matsumoto M, Uchikado Y, Uenosono Y, Kita Y, et al. Analysis of the Fibrinogen and Neutrophil-Lymphocyte Ratio in Esophageal Squamous Cell Carcinoma: A Promising Blood Marker of Tumor Progression and Prognosis. Medicine (Baltimore). 2015;94(42):e1702.

143. Hirashima K, Watanabe M, Shigaki H, Imamura Y, Ida S, Iwatsuki M, et al. Prognostic significance of the modified Glasgow prognostic score in elderly patients with gastric cancer. J Gastroenterol. 2014;49(6):1040-6.

144. Kawashima M, Murakawa T, Shinozaki T, Ichinose J, Hino H, Konoeda C, et al. Significance of the Glasgow Prognostic Score as a prognostic indicator for lung cancer surgery. Interact Cardiovasc Thorac Surg. 2015;21(5):637-43.

145. Takeno S, Hashimoto T, Shibata R, Maki K, Shiwaku H, Yamana I, et al. The high-sensitivity modified Glasgow prognostic score is superior to the modified Glasgow prognostic score as a prognostic predictor in patients with resectable gastric cancer. Oncology. 2014;87(4):205-14.

146. Ishizuka M, Kubota K, Kita J, Shimoda M, Kato M, Sawada T. Usefulness of a modified inflammation-based prognostic system for predicting postoperative mortality of patients undergoing surgery for primary hepatocellular carcinoma. Journal of surgical oncology. 2011;103(8):801-6.

147. Guthrie GJ, Roxburgh CS, Farhan-Alanie OM, Horgan PG, McMillan DC. Comparison of the prognostic value of longitudinal measurements of systemic inflammation in patients undergoing curative resection of colorectal cancer. Br J Cancer. 2013;109(1):24-8.

148. Wang DS, Luo HY, Qiu MZ, Wang ZQ, Zhang DS, Wang FH, et al. Comparison of the prognostic values of various inflammation based factors in patients with pancreatic cancer. Medical oncology (Northwood, London, England). 2012;29(5):3092-100.

149. Okuno M, Ebata T, Yokoyama Y, Igami T, Sugawara G, Mizuno T, et al. Evaluation of inflammation-based prognostic scores in patients undergoing hepatobiliary resection for perihilar cholangiocarcinoma. J Gastroenterol. 2016;51(2):153-61.

150. MacDonald N. Terminology in cancer cachexia: importance and status. Current opinion in clinical nutrition and metabolic care. 2012;15(3):220-5.

151. Rinehart J, Arnold S, Kloecker G, Lim A, Zaydan MA, Baeker T, et al. Phase II randomized trial of carboplatin and gemcitabine with or without dexamethasone pre-treatment in patients with Stage IV non-small cell lung cancer. Cancer Chemother Pharmacol. 2013;71(5):1375-83.

152. Okuno T, Wakabayashi M, Kato K, Shinoda M, Katayama H, Igaki H, et al. Esophageal stenosis and the Glasgow Prognostic Score as independent factors of poor prognosis for patients with locally advanced unresectable esophageal cancer treated with chemoradiotherapy (exploratory analysis of JCOG0303). Int J Clin Oncol. 2017;22(6):1042-9.

153. Hurwitz HI, Uppal N, Wagner SA, Bendell JC, Beck JT, Wade SM, 3rd, et al. Randomized, Double-Blind, Phase II Study of Ruxolitinib or Placebo in Combination With Capecitabine in Patients With Metastatic Pancreatic Cancer for Whom Therapy With Gemcitabine Has Failed. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(34):4039-47.

154. Linton A, Pond G, Clarke S, Vardy J, Galsky M, Sonpavde G. Glasgow prognostic score as a prognostic factor in metastatic castration-resistant prostate cancer treated with docetaxel-based chemotherapy. Clin Genitourin Cancer. 2013;11(4):423-30.

155. Honecker F, Harbeck N, Schnabel C, Wedding U, Waldenmaier D, Saupe S, et al. Geriatric assessment and biomarkers in patients with metastatic breast cancer receiving first-line mono-chemotherapy: Results from the randomized phase III PELICAN trial. J Geriatr Oncol. 2017.

156. Chua ML, Tan SH, Kusumawidjaja G, Shwe MT, Cheah SL, Fong KW, et al. Neutrophil-to-lymphocyte ratio as a prognostic marker in locally advanced nasopharyngeal carcinoma: A pooled analysis of two randomised controlled trials. European journal of cancer (Oxford, England : 1990). 2016;67:119-29.

157. Cox S, Hurt C, Grenader T, Mukherjee S, Bridgewater J, Crosby T. The prognostic value of derived neutrophil to lymphocyte ratio in oesophageal cancer treated with definitive chemoradiotherapy. Radiother Oncol. 2017;125(1):154-9.

158. Vivaldi C, Caparello C, Musettini G, Pasquini G, Catanese S, Fornaro L, et al. First-line treatment with FOLFOXIRI for advanced pancreatic cancer in clinical practice: Patients' outcome and analysis of prognostic factors. International journal of cancer. 2016;139(4):938-45.

159. Grenader T, Nash S, Plotkin Y, Furuse J, Mizuno N, Okusaka T, et al. Derived neutrophil lymphocyte ratio may predict benefit from cisplatin in the advanced biliary cancer: the ABC-02 and BT-22 studies. Annals of oncology : official journal of the European Society for Medical Oncology. 2015;26(9):1910-6.

160. van Soest RJ, Templeton AJ, Vera-Badillo FE, Mercier F, Sonpavde G, Amir E, et al. Neutrophil-to-lymphocyte ratio as a prognostic biomarker for men with metastatic castration-resistant prostate cancer receiving first-line chemotherapy: data from two randomized phase III trials. Annals of oncology : official journal of the European Society for Medical Oncology. 2015;26(4):743-9.

161. Kumar R, Geuna E, Michalarea V, Guardascione M, Naumann U, Lorente D, et al. The neutrophil-lymphocyte ratio and its utilisation for the management of cancer patients in early clinical trials. Br J Cancer. 2015;112(7):1157-65.

162. Thomsen M, Kersten C, Sorbye H, Skovlund E, Glimelius B, Pfeiffer P, et al. Interleukin-6 and C-reactive protein as prognostic biomarkers in metastatic colorectal cancer. Oncotarget. 2016;7(46):75013-22.

163. Chua W, Clarke SJ, Charles KA. Systemic inflammation and prediction of chemotherapy outcomes in patients receiving docetaxel for advanced cancer. Support Care Cancer. 2012;20(8):1869-74.

164. Rosales C. Neutrophil: A Cell with Many Roles in Inflammation or Several Cell Types? Frontiers in Physiology. 2018;9:113.

165. Roxburgh CS, McMillan D. Cancer, immunity and inflammation. In: Kerr DJ, Haller DG, van de Velde CJH, Baumann M, editors. Oxford Textbook of Oncology Oxford Textbook of Oncology 3ed. Oxford Oxford University Press; 2015. p. 109-39.

166. Dupre A, Malik HZ. Inflammation and cancer: What a surgical oncologist should know. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2018;44(5):566-70.

167. Ter Veer E, van Rijssen LB, Besselink MG, Mali RMA, Berlin JD, Boeck S, et al. Consensus statement on mandatory measurements in pancreatic cancer trials (COMM-PACT) for systemic treatment of unresectable disease. Lancet Oncol. 2018;19(3):e151-e60.

168. Sjoquist KM, Renfro LA, Simes RJ, Tebbutt NC, Clarke S, Seymour MT, et al. Personalizing Survival Predictions in Advanced Colorectal Cancer: The ARCAD Nomogram Project. Journal of the National Cancer Institute. 2017.

169. Lee Y, Kim SH, Han JY, Kim HT, Yun T, Lee JS. Early neutrophil-to-lymphocyte ratio reduction as a surrogate marker of prognosis in never smokers with advanced lung adenocarcinoma receiving gefitinib or standard chemotherapy as first-line therapy. J Cancer Res Clin Oncol. 2012;138(12):2009-16.

170. Grenader T, Waddell T, Peckitt C, Oates J, Starling N, Cunningham D, et al. Prognostic value of neutrophil-to-lymphocyte ratio in advanced oesophago-gastric cancer: exploratory analysis of the REAL-2 trial. Annals of oncology : official journal of the European Society for Medical Oncology. 2016;27(4):687-92.

171. Bruix J, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: Analysis of two phase III studies. J Hepatol. 2017;67(5):999-1008.

172. Goldstein D, El-Maraghi RH, Hammel P, Heinemann V, Kunzmann V, Sastre J, et al. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. Journal of the National Cancer Institute. 2015;107(2).

173. Renfro LA, Goldberg RM, Grothey A, Sobrero A, Adams R, Seymour MT, et al. Clinical Calculator for Early Mortality in Metastatic Colorectal Cancer: An Analysis of Patients From 28 Clinical Trials in the Aide et Recherche en Cancerologie Digestive Database. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(17):1929-37.

174. Wood G, Grenader T, Nash S, Adams R, Kaplan R, Fisher D, et al. Derived neutrophil to lymphocyte ratio as a prognostic factor in patients with advanced colorectal cancer according to RAS and BRAF status: a post-hoc analysis of the MRC COIN study. Anticancer Drugs. 2017;28(5):546-50.

175. Passardi A, Scarpi E, Cavanna L, Dall'Agata M, Tassinari D, Leo S, et al. Inflammatory indexes as predictors of prognosis and bevacizumab efficacy in patients with metastatic colorectal cancer. Oncotarget. 2016;7(22):33210-9.

176. Correale P, Botta C, Rotundo MS, Guglielmo A, Conca R, Licchetta A, et al. Gemcitabine, oxaliplatin, levofolinate, 5-fluorouracil, granulocyte-macrophage colony-stimulating factor, and interleukin-2 (GOLFIG) versus FOLFOX chemotherapy in metastatic colorectal cancer patients: the GOLFIG-2 multicentric open-label randomized phase III trial. J Immunother. 2014;37(1):26-35.

177. Hazama S, Nakamura Y, Tanaka H, Hirakawa K, Tahara K, Shimizu R, et al. A phase IotaI study of five peptides combination with oxaliplatin-based chemotherapy as a first-line therapy for advanced colorectal cancer (FXV study). Journal of translational medicine. 2014;12:108.

178. Lorente D, Mateo J, Templeton AJ, Zafeiriou Z, Bianchini D, Ferraldeschi R, et al. Baseline neutrophil-lymphocyte ratio (NLR) is associated with survival and response to treatment with second-line chemotherapy for advanced prostate cancer independent of baseline steroid use. Annals of oncology : official journal of the European Society for Medical Oncology. 2015;26(4):750-5.

179. Sonpavde G, Pond GR, Armstrong AJ, Clarke SJ, Vardy JL, Templeton AJ, et al. Prognostic impact of the neutrophil-to-lymphocyte ratio in men with metastatic castration-resistant prostate cancer. Clinical genitourinary cancer. 2014;12(5):317-24.

180. Fox P, Hudson M, Brown C, Lord S, Gebski V, De SP, et al. Markers of systemic inflammation predict survival in patients with advanced renal cell cancer. Br J Cancer. 2013;109(1):147-53.

181. Ojerholm E, Smith A, Hwang WT, Baumann BC, Tucker KN, Lerner SP, et al. Neutrophil-to-lymphocyte ratio as a bladder cancer biomarker: Assessing prognostic and predictive value in SWOG 8710. Cancer. 2017;123(5):794-801.

182. Romano A, Parrinello NL, Consoli ML, Marchionni L, Forte S, Conticello C, et al. Neutrophil to lymphocyte ratio (NLR) improves the risk assessment of ISS staging in newly diagnosed MM patients treated upfront with novel agents. Ann Hematol. 2015;94(11):1875-83.

183. Bigot F, Castanon E, Baldini C, Hollebecque A, Carmona A, Postel-Vinay S, et al. Prospective validation of a prognostic score for patients in immunotherapy phase I trials: The Gustave Roussy Immune Score (GRIm-Score). European journal of cancer (Oxford, England : 1990). 2017;84:212-8.

184. Diakos CI, Tu D, Gebski V, Yip S, Wilson K, Karapetis CS, et al. Is the derived neutrophil to lymphocyte ratio (dNLR) an independent prognostic marker in patients with metastatic colorectal cancer (mCRC)? Analysis of the CO.17 and CO.20 studies. Annals of Oncology. 2016;27(suppl_6):588P-P.

185. Diakos CI, Wilson K, Asher R, Gebski V, Yip S, van Hazel G, et al. Is baseline neutrophil to lymphocyte ratio (NLR) an independent prognostic biomarker for progression free survival (PFS) and overall survival (OS) in metastatic colorectal cancer (mCRC)? Analysis of the AGITG MAX study. Annals of Oncology. 2016;27(suppl_6):589P-P.

186. De Maio E, Touati N, Litière S, Sleijfer S, van der Graaf WTA, Le Cesne A, et al. 1502PEvolution in neutrophil-to-lymphocyte ratio (NLR) among advanced soft tissue sarcoma (STS) patients treated with pazopanib within EORTC 62043/62072 trials. Annals of Oncology. 2017;28(suppl_5):mdx387.028-mdx387.028.

187. Coleman N, Michalarea V, Alken S, Perez Lopez R, Tunariu N, Petruckevitch A, et al. 346PPrognostic Impact of neutrophil to lymphocyte ratio (NLR) in patients (pts) with recurrent primary malignant brain tumours (PMBT) in phase I (Ph1) trials: The Royal Marsden (RMH) Experience. Annals of Oncology. 2017;28(suppl_5):mdx366.020-mdx366.020.

188. Wang-Gillam A, Chen L-T, Li C-P, Bodoky G, Dean A, Lee K-H, et al. The prognostic value of baseline neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) for predicting clinical outcome in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan (nal-IRI; MM-398) + 5-fluorouracil and leucovorin (5-FU/LV) vs 5-FU/LV. Journal of Clinical Oncology. 2017;35(15_suppl):e15795-e.

189. Smyth EC, Kouvelakis K, Peckitt C, Waddell T, Watkins D, Rao S, et al. 204PRash, neutrophil-lymphocyte ratio (NLR) and survival in the REAL3 trial. Annals of Oncology. 2017;28(suppl_10):mdx660.011-mdx660.011.

190. Clarke SJ, Burge ME, Feeney K, Jones K, Gibbs P, Molloy MP, et al. The prognostic role of inflammatory markers in patients with metastatic colorectal cancer treated with bevacizumab. Journal of Clinical Oncology. 2018;36(4_suppl):719-.

191. Argiles G, Yoshino T, Ohtsu A, Mayer RJ, Winkler R, Amellal N, et al. Prognostic value of neutrophil-to-lymphocyte ratio (NLR) on overall survival (OS), progression free survival (PFS) and disease control rate (DCR) in patients with metastatic colorectal cancer (mCRC) from the RECOURSE study. Journal of Clinical Oncology. 2018;36(4_suppl):744-.

192. McAllister SS, Weinberg RA. The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis. Nat Cell Biol. 2014;16(8):717-27.

193. Paulsen O, Laird B, Aass N, Lea T, Fayers P, Kaasa S, et al. The relationship between pro-inflammatory cytokines and pain, appetite and fatigue in patients with advanced cancer. PloS one. 2017;12(5):e0177620.

194. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clinical nutrition (Edinburgh, Scotland). 2017;36(1):11-48.

195. Proctor MJ, Talwar D, Balmar SM, O'Reilly DS, Foulis AK, Horgan PG, et al. The relationship between the presence and site of cancer, an inflammation-based prognostic score and biochemical parameters. Initial results of the Glasgow Inflammation Outcome Study. Br J Cancer. 2010;103(6):870-6.

196. Coyle C, Cafferty FH, Rowley S, MacKenzie M, Berkman L, Gupta S, et al. ADD-ASPIRIN: A phase III, double-blind, placebo controlled, randomised trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common non-metastatic solid tumours. Contemporary clinical trials. 2016;51:56-64.

197. Al Murri AM, Bartlett JM, Canney PA, Doughty JC, Wilson C, McMillan DC. Evaluation of an inflammation-based prognostic score (GPS) in patients with metastatic breast cancer. Br J Cancer. 2006;94(2):227-30.

198. Honecker F, Harbeck N, Schnabel C, Wedding U, Waldenmaier D, Saupe S, et al. Geriatric assessment and biomarkers in patients with metastatic breast cancer receiving first-line mono-chemotherapy: Results from the randomized phase III PELICAN trial. J Geriatr Oncol. 2018;9(2):163-9.

199. Ferro M, De Cobelli O, Buonerba C, Di Lorenzo G, Capece M, Bruzzese D, et al. Modified Glasgow Prognostic Score is Associated With Risk of Recurrence in Bladder Cancer Patients After Radical Cystectomy: A Multicenter Experience. Medicine (Baltimore). 2015;94(42):e1861.

200. Kimura S, D DA, Soria F, Foerster B, Abufaraj M, Vartolomei MD, et al. Prognostic value of modified Glasgow Prognostic Score in non-muscle-invasive bladder cancer. Urologic oncology. 2019;37(3):179.e19-.e28.

201. Hwang EC, Hwang IS, Yu HS, Kim SO, Jung SI, Hwang JE, et al. Utility of inflammation-based prognostic scoring in patients given systemic chemotherapy first-line for advanced inoperable bladder cancer. Jpn J Clin Oncol. 2012;42(10):955-60.

202. Hefler-Frischmuth K, Seebacher V, Polterauer S, Tempfer C, Reinthaller A, Hefler L. The inflammation-based modified Glasgow Prognostic Score in patients with vulvar cancer. Eur J Obstet Gynecol Reprod Biol. 2010;149(1):102-5.

203. Saijo M, Nakamura K, Masuyama H, Ida N, Haruma T, Kusumoto T, et al. Glasgow prognostic score is a prognosis predictor for patients with endometrial cancer. Eur J Obstet Gynecol Reprod Biol. 2017;210:355-9.

204. Liu Y, Chen S, Zheng C, Ding M, Zhang L, Wang L, et al. The prognostic value of the preoperative c-reactive protein/albumin ratio in ovarian cancer. BMC cancer. 2017;17(1):285.

205. Xiao Y, Ren YK, Cheng HJ, Wang L, Luo SX. Modified Glasgow prognostic score is an independent prognostic factor in patients with cervical cancer undergoing chemoradiotherapy. Int J Clin Exp Pathol. 2015;8(5):5273-81.

206. Roncolato FT, Berton-Rigaud D, O'Connell R, Lanceley A, Sehouli J, Buizen L, et al. Validation of the modified Glasgow Prognostic Score (mGPS) in recurrent ovarian cancer (ROC) - Analysis of patients enrolled in the GCIG Symptom Benefit Study (SBS). Gynecol Oncol. 2018;148(1):36-41.

207. Seebacher V, Sturdza A, Bergmeister B, Polterauer S, Grimm C, Reinthaller A, et al. Factors associated with post-relapse survival in patients with recurrent cervical cancer: the value of the inflammation-based Glasgow Prognostic Score. Arch Gynecol Obstet. 2019;299(4):1055-62.

208. Owari T, Miyake M, Nakai Y, Morizawa Y, Hori S, Anai S, et al. A Genitourinary Cancer-specific Scoring System for the Prediction of Survival in Patients with Bone Metastasis: A Retrospective Analysis of Prostate Cancer, Renal Cell Carcinoma, and Urothelial Carcinoma. Anticancer Res. 2018;38(5):3097-103.

209. Kobayashi T, Teruya M, Kishiki T, Endo D, Takenaka Y, Tanaka H, et al. Inflammation-based prognostic score, prior to neoadjuvant chemoradiotherapy, predicts postoperative outcome in patients with esophageal squamous cell carcinoma. Surgery. 2008;144(5):729-35.

210. Kobayashi T, Teruya M, Kishiki T, Kaneko S, Endo D, Takenaka Y, et al. Inflammation-based prognostic score and number of lymph node metastases are independent prognostic factors in esophageal squamous cell carcinoma. Dig Surg. 2010;27(3):232-7.

211. Dutta S, Crumley AB, Fullarton GM, Horgan PG, McMillan DC. Comparison of the prognostic value of tumour- and patient-related factors in patients undergoing potentially curative resection of oesophageal cancer. World journal of surgery. 2011;35(8):1861-6.

212. Dutta S, Al-Mrabt NM, Fullarton GM, Horgan PG, McMillan DC. A comparison of POSSUM and GPS models in the prediction of post-operative outcome in patients

undergoing oesophago-gastric cancer resection. Annals of surgical oncology. 2011;18(10):2808-17.

213. Crumley AB, Going JJ, Hilmy M, Dutta S, Tannahill C, McKernan M, et al. Interrelationships between tumor proliferative activity, leucocyte and macrophage infiltration, systemic inflammatory response, and survival in patients selected for potentially curative resection for gastroesophageal cancer. Annals of surgical oncology. 2011;18(9):2604-12.

214. Vashist YK, Loos J, Dedow J, Tachezy M, Uzunoglu G, Kutup A, et al. Glasgow Prognostic Score is a predictor of perioperative and long-term outcome in patients with only surgically treated esophageal cancer. Annals of surgical oncology. 2011;18(4):1130-8.

215. Dutta S, Going JJ, Crumley AB, Mohammed Z, Orange C, Edwards J, et al. The relationship between tumour necrosis, tumour proliferation, local and systemic inflammation, microvessel density and survival in patients undergoing potentially curative resection of oesophageal adenocarcinoma. Br J Cancer. 2012;106(4):702-10.

216. Feng JF, Zhao Q, Chen QX. Prognostic significance of Glasgow prognostic score in patients undergoing esophagectomy for esophageal squamous cell carcinoma. Saudi J Gastroenterol. 2014;20(1):48-53.

217. Matsuda S, Takeuchi H, Kawakubo H, Fukuda K, Nakamura R, Takahashi T, et al. Cumulative prognostic scores based on plasma fibrinogen and serum albumin levels in esophageal cancer patients treated with transthoracic esophagectomy: comparison with the Glasgow prognostic score. Annals of surgical oncology. 2015;22(1):302-10.

218. Hirahara N, Matsubara T, Hayashi H, Takai K, Fujii Y, Tajima Y. Impact of inflammation-based prognostic score on survival after curative thoracoscopic esophagectomy for esophageal cancer. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2015;41(10):1308-15.

219. Walsh SM, Casey S, Kennedy R, Ravi N, Reynolds JV. Does the modified Glasgow Prognostic Score (mGPS) have a prognostic role in esophageal cancer? Journal of surgical oncology. 2016;113(7):732-7.

220. Otowa Y, Nakamura T, Takiguchi G, Tomono A, Yamamoto M, Kanaji S, et al. Changes in modified Glasgow prognostic score after neoadjuvant chemotherapy is a prognostic factor in clinical stage II/III esophageal cancer. Dis Esophagus. 2016;29(2):146-51.

221. Nozoe T, Iguchi T, Egashira A, Adachi E, Matsukuma A, Ezaki T. Significance of modified Glasgow prognostic score as a useful indicator for prognosis of patients with gastric carcinoma. American journal of surgery. 2011;201(2):186-91.

222. Kubota T, Hiki N, Nunobe S, Kumagai K, Aikou S, Watanabe R, et al. Significance of the inflammation-based Glasgow prognostic score for short- and long-term outcomes after curative resection of gastric cancer. J Gastrointest Surg. 2012;16(11):2037-44.

223. Dutta S, Crumley AB, Fullarton GM, Horgan PG, McMillan DC. Comparison of the prognostic value of tumour and patient related factors in patients undergoing potentially curative resection of gastric cancer. American journal of surgery. 2012;204(3):294-9.

224. Wang DS, Ren C, Qiu MZ, Luo HY, Wang ZQ, Zhang DS, et al. Comparison of the prognostic value of various preoperative inflammation-based factors in patients with stage III gastric cancer. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2012;33(3):749-56.

225. Jiang X, Hiki N, Nunobe S, Kumagai K, Kubota T, Aikou S, et al. Prognostic importance of the inflammation-based Glasgow prognostic score in patients with gastric cancer. Br J Cancer. 2012;107(2):275-9.

226. Melling N, Gruning A, Tachezy M, Nentwich M, Reeh M, Uzunoglu FG, et al. Glasgow Prognostic Score may be a prognostic index for overall and perioperative survival in gastric cancer without perioperative treatment. Surgery. 2016;159(6):1548-56.

227. Crumley AB, McMillan DC, McKernan M, McDonald AC, Stuart RC. Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. Br J Cancer. 2006;94(5):637-41.

228. Crumley AB, Stuart RC, McKernan M, McDonald AC, McMillan DC. Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG-ps) in patients receiving palliative chemotherapy for gastroesophageal cancer. J Gastroenterol Hepatol. 2008;23(8 Pt 2):e325-e9.

229. Zhang P, Xi M, Li QQ, He LR, Liu SL, Zhao L, et al. The modified glasgow prognostic score is an independent prognostic factor in patients with inoperable thoracic esophageal squamous cell carcinoma undergoing chemoradiotherapy. J Cancer. 2014;5(8):689-95.

230. Elahi MM, McMillan DC, McArdle CS, Angerson WJ, Sattar N. Score based on hypoalbuminemia and elevated C-reactive protein predicts survival in patients with advanced gastrointestinal cancer. Nutr Cancer. 2004;48(2):171-3.

231. Hwang JE, Kim HN, Kim DE, Choi HJ, Jung SH, Shim HJ, et al. Prognostic significance of a systemic inflammatory response in patients receiving first-line palliative chemotherapy for recurred or metastatic gastric cancer. BMC Cancer. 2011;11:489.

232. Jeong JH, Lim SM, Yun JY, Rhee GW, Lim JY, Cho JY, et al. Comparison of two inflammation-based prognostic scores in patients with unresectable advanced gastric cancer. Oncology. 2012;83(5):292-9.

233. Sachlova M, Majek O, Tucek S. Prognostic value of scores based on malnutrition or systemic inflammatory response in patients with metastatic or recurrent gastric cancer. Nutr Cancer. 2014;66(8):1362-70.

234. Namikawa T, Munekage E, Munekage M, Maeda H, Yatabe T, Kitagawa H, et al. Evaluation of Systemic Inflammatory Response Biomarkers in Patients Receiving Chemotherapy for Unresectable and Recurrent Advanced Gastric Cancer. Oncology. 2016;90(6):321-6.

235. Arigami T, Uenosono Y, Ishigami S, Okubo K, Kijima T, Yanagita S, et al. A Novel Scoring System Based on Fibrinogen and the Neutrophil-Lymphocyte Ratio as a Predictor of Chemotherapy Response and Prognosis in Patients with Advanced Gastric Cancer. Oncology. 2016;90(4):186-92.

236. Hsieh MC, Wang SH, Chuah SK, Lin YH, Lan J, Rau KM. A Prognostic Model Using Inflammation- and Nutrition-Based Scores in Patients With Metastatic Gastric Adenocarcinoma Treated With Chemotherapy. Medicine (Baltimore). 2016;95(17):e3504.

237. Chou WC, Kao CY, Wang PN, Chang H, Wang HM, Chang PH, et al. The application of the Palliative Prognostic Index, charlson comorbidity index, and Glasgow Prognostic Score in predicting the life expectancy of patients with hematologic malignancies under palliative care. BMC Palliat Care. 2015;14:18.

238. Jung SH, Yang DH, Ahn JS, Kim YK, Kim HJ, Lee JJ. Serum lactate dehydrogenase with a systemic inflammation score is useful for predicting response and survival in patients with newly diagnosed diffuse large B-cell lymphoma. Acta Haematol. 2015;133(1):10-7.

239. Qayyum T, McArdle PA, Lamb GW, Going JJ, Orange C, Seywright M, et al. Prospective study of the role of inflammation in renal cancer. Urol Int. 2012;88(3):277-81.

240. Lamb GW, Aitchison M, Ramsey S, Housley SL, McMillan DC. Clinical utility of the Glasgow Prognostic Score in patients undergoing curative nephrectomy for renal clear cell cancer: basis of new prognostic scoring systems. Br J Cancer. 2012;106(2):279-83.

241. Tsujino T, Komura K, Matsunaga T, Yoshikawa Y, Takai T, Uchimoto T, et al. Preoperative Measurement of the Modified Glasgow Prognostic Score Predicts Patient Survival in Non-Metastatic Renal Cell Carcinoma Prior to Nephrectomy. Annals of surgical oncology. 2017;24(9):2787-93.

242. Fukuda H, Takagi T, Kondo T, Yoshida K, Shimizu S, Nagashima Y, et al. Prognostic value of the Glasgow Prognostic Score for patients with metastatic renal cell carcinoma treated by cytoreductive nephrectomy. Int J Clin Oncol. 2018;23(3):539-46.

243. Inamoto T, Matsuyama H, Sakano S, Ibuki N, Takahara K, Komura K, et al. The systemic inflammation-based Glasgow Prognostic Score as a powerful prognostic factor in patients with upper tract urothelial carcinoma. Oncotarget. 2017;8(68):113248-57.

244. Son S, Hwang EC, Jung SI, Kwon DD, Choi SH, Kwon TG, et al. Prognostic value of preoperative systemic inflammation markers in localized upper tract urothelial cell carcinoma: a large, multicenter cohort analysis. Minerva Urol Nefrol. 2018;70(3):300-9.

245. Ramsey S, Aitchison M, Graham J, McMillan DC. The longitudinal relationship between the systemic inflammatory response, circulating T-lymphocytes, interleukin-6 and -10 in patients undergoing immunotherapy for metastatic renal cancer. BJU Int. 2008;102(1):125-9.

246. Ishizuka M, Nagata H, Takagi K, Horie T, Kubota K. Inflammation-based prognostic score is a novel predictor of postoperative outcome in patients with colorectal cancer. Annals of surgery. 2007;246(6):1047-51.

247. Leitch EF, Chakrabarti M, Crozier JE, McKee RF, Anderson JH, Horgan PG, et al. Comparison of the prognostic value of selected markers of the systemic inflammatory response in patients with colorectal cancer. Br J Cancer. 2007;97(9):1266-70.

248. Roxburgh CS, Salmond JM, Horgan PG, Oien KA, McMillan DC. Comparison of the prognostic value of inflammation-based pathologic and biochemical criteria in patients undergoing potentially curative resection for colorectal cancer. Annals of surgery. 2009;249(5):788-93.

249. Ishizuka M, Kita J, Shimoda M, Rokkaku K, Kato M, Sawada T, et al. Systemic inflammatory response predicts postoperative outcome in patients with liver metastases from colorectal cancer. Journal of surgical oncology. 2009;100(1):38-42.

250. Crozier JE, Leitch EF, McKee RF, Anderson JH, Horgan PG, McMillan DC. Relationship between emergency presentation, systemic inflammatory response, and cancer-specific survival in patients undergoing potentially curative surgery for colon cancer. American journal of surgery. 2009;197(4):544-9.

251. Roxburgh CS, Wallace AM, Guthrie GK, Horgan PG, McMillan DC. Comparison of the prognostic value of tumour- and patient-related factors in patients undergoing potentially curative surgery for colon cancer. Colorectal Dis. 2010;12(10):987-94.

252. Richards CH, Leitch EF, Horgan PG, Anderson JH, McKee RF, McMillan DC. The relationship between patient physiology, the systemic inflammatory response and survival in patients undergoing curative resection of colorectal cancer. Br J Cancer. 2010;103(9):1356-61.

253. Kobayashi T, Teruya M, Kishiki T, Endo D, Takenaka Y, Miki K, et al. Elevated C-reactive protein and hypoalbuminemia measured before resection of colorectal liver metastases predict postoperative survival. Dig Surg. 2010;27(4):285-90.

254. Moug SJ, McColl G, Lloyd SM, Wilson G, Saldanha JD, Diament RH. Comparison of positive lymph node ratio with an inflammation-based prognostic score in colorectal cancer. The British journal of surgery. 2011;98(2):282-6.

255. Roxburgh CS, Platt JJ, Leitch EF, Kinsella J, Horgan PG, McMillan DC. Relationship between preoperative comorbidity, systemic inflammatory response, and survival in patients undergoing curative resection for colorectal cancer. Annals of surgical oncology. 2011;18(4):997-1005.

256. Roxburgh C, McDonald A, Salmond J, Oien K, Anderson J, McKee R, et al. Adjuvant chemotherapy for resected colon cancer: comparison of the prognostic value of tumour and patient related factors. International journal of colorectal disease. 2011;26(4):483-92.

257. Richards CH, Roxburgh CS, Anderson JH, McKee RF, Foulis AK, Horgan PG, et al. Prognostic value of tumour necrosis and host inflammatory responses in colorectal cancer. The British journal of surgery. 2012;99(2):287-94.

258. Sugimoto K, Komiyama H, Kojima Y, Goto M, Tomiki Y, Sakamoto K. Glasgow prognostic score as a prognostic factor in patients undergoing curative surgery for colorectal cancer. Dig Surg. 2012;29(6):503-9.

259. Powell AG, Wallace R, McKee RF, Anderson JH, Going JJ, Edwards J, et al. The relationship between tumour site, clinicopathological characteristics and cancer-specific survival in patients undergoing surgery for colorectal cancer. Colorectal Dis. 2012;14(12):1493-9.

260. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Inflammation-based prognostic system predicts postoperative survival of colorectal cancer patients with a normal preoperative serum level of carcinoembryonic antigen. Annals of surgical oncology. 2012;19(11):3422-31.

261. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Inflammation-based prognostic system predicts survival after surgery for stage IV colorectal cancer. American journal of surgery. 2013;205(1):22-8.

262. Son HJ, Park JW, Chang HJ, Kim DY, Kim BC, Kim SY, et al. Preoperative plasma hyperfibrinogenemia is predictive of poor prognosis in patients with nonmetastatic colon cancer. Annals of surgical oncology. 2013;20(9):2908-13.

263. Nozoe T, Matono R, Ijichi H, Ohga T, Ezaki T. Glasgow Prognostic Score (GPS) can be a useful indicator to determine prognosis of patients with colorectal carcinoma. Int Surg. 2014;99(5):512-7.

264. Forrest R, Guthrie GJ, Orange C, Horgan PG, McMillan DC, Roxburgh CS. Comparison of visual and automated assessment of tumour inflammatory infiltrates in patients with colorectal cancer. European journal of cancer (Oxford, England : 1990). 2014;50(3):544-52.

265. Sun ZQ, Han XN, Wang HJ, Tang Y, Zhao ZL, Qu YL, et al. Prognostic significance of preoperative fibrinogen in patients with colon cancer. World journal of gastroenterology. 2014;20(26):8583-91.

266. Nakagawa K, Tanaka K, Nojiri K, Kumamoto T, Takeda K, Ueda M, et al. The modified Glasgow prognostic score as a predictor of survival after hepatectomy for colorectal liver metastases. Annals of surgical oncology. 2014;21(5):1711-8.

267. Shibutani M, Maeda K, Nagahara H, Ohtani H, Iseki Y, Ikeya T, et al. The prognostic significance of a postoperative systemic inflammatory response in patients with colorectal cancer. World journal of surgical oncology. 2015;13:194.

268. Park JH, Powell AG, Roxburgh CS, Horgan PG, McMillan DC, Edwards J. Mismatch repair status in patients with primary operable colorectal cancer: associations with the local and systemic tumour environment. Br J Cancer. 2016;114(5):562-70.

269. Chan JC, Chan DL, Diakos CI, Engel A, Pavlakis N, Gill A, et al. The Lymphocyte-to-Monocyte Ratio is a Superior Predictor of Overall Survival in Comparison to Established Biomarkers of Resectable Colorectal Cancer. Annals of surgery. 2016.

270. Read JA, Choy ST, Beale PJ, Clarke SJ. Evaluation of nutritional and inflammatory status of advanced colorectal cancer patients and its correlation with survival. Nutr Cancer. 2006;55(1):78-85.

271. Ishizuka M, Nagata H, Takagi K, Kubota K. Influence of inflammation-based prognostic score on mortality of patients undergoing chemotherapy for far advanced or recurrent unresectable colorectal cancer. Ann Surg. 2009;250(2):268-72.

272. Inoue Y, Iwata T, Okugawa Y, Kawamoto A, Hiro J, Toiyama Y, et al. Prognostic significance of a systemic inflammatory response in patients undergoing multimodality therapy for advanced colorectal cancer. Oncology. 2013;84(2):100-7.

273. Dreanic J, Dhooge M, Barret M, Brezault C, Mir O, Chaussade S, et al. Anti-epidermal or anti-vascular endothelial growth factor as first-line metastatic colorectal cancer in modified Glasgow prognostic score 2' patients. J Cachexia Sarcopenia Muscle. 2015;6(3):231-6.

274. Song A, Eo W, Lee S. Comparison of selected inflammation-based prognostic markers in relapsed or refractory metastatic colorectal cancer patients. World J Gastroenterol. 2015;21(43):12410-20.

275. Farhan-Alanie OM, McMahon J, McMillan DC. Systemic inflammatory response and survival in patients undergoing curative resection of oral squamous cell carcinoma. Br J Oral Maxillofac Surg. 2015;53(2):126-31.

276. Li XH, Chang H, Xu BQ, Tao YL, Gao J, Chen C, et al. An inflammatory biomarker-based nomogram to predict prognosis of patients with nasopharyngeal carcinoma: an analysis of a prospective study. Cancer medicine. 2017;6(1):310-9.

277. Chang PH, Yeh KY, Wang CH, Chen EY, Yang SW, Huang JS, et al. Impact of the pretreatment Glasgow prognostic score on treatment tolerance, toxicities, and survival in patients with advanced head and neck cancer undergoing concurrent chemoradiotherapy. Head Neck. 2017;39(10):1990-6.

278. Chang PH, Wang CH, Chen EY, Yang SW, Chou WC, Hsieh JC, et al. Glasgow prognostic score after concurrent chemoradiotherapy is a prognostic factor in advanced head and neck cancer. Chin J Cancer Res. 2017;29(3):172-8.

279. Jamieson NB, Denley SM, Logue J, MacKenzie DJ, Foulis AK, Dickson EJ, et al. A prospective comparison of the prognostic value of tumor- and patient-related factors in patients undergoing potentially curative surgery for pancreatic ductal adenocarcinoma. Annals of surgical oncology. 2011;18(8):2318-28.

280. La Torre M, Nigri G, Cavallini M, Mercantini P, Ziparo V, Ramacciato G. The glasgow prognostic score as a predictor of survival in patients with potentially resectable pancreatic adenocarcinoma. Annals of surgical oncology. 2012;19(9):2917-23.

281. Jamieson NB, Mohamed M, Oien KA, Foulis AK, Dickson EJ, Imrie CW, et al. The relationship between tumor inflammatory cell infiltrate and outcome in patients with pancreatic ductal adenocarcinoma. Annals of surgical oncology. 2012;19(11):3581-90.

282. Stotz M, Gerger A, Eisner F, Szkandera J, Loibner H, Ress AL, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer. 2013;109(2):416-21.

283. Wu XS, Shi LB, Li ML, Ding Q, Weng H, Wu WG, et al. Evaluation of two inflammation-based prognostic scores in patients with resectable gallbladder carcinoma. Annals of surgical oncology. 2014;21(2):449-57.

284. Shiba H, Misawa T, Fujiwara Y, Futagawa Y, Furukawa K, Haruki K, et al. Glasgow prognostic score predicts outcome after surgical resection of gallbladder cancer. World journal of surgery. 2015;39(3):753-8.

285. Oshiro Y, Sasaki R, Fukunaga K, Kondo T, Oda T, Takahashi H, et al. Inflammation-based prognostic score is a useful predictor of postoperative outcome in patients with extrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Sci. 2013;20(3):389-95.

286. Shiba H, Misawa T, Fujiwara Y, Futagawa Y, Furukawa K, Haruki K, et al. Glasgow prognostic score predicts therapeutic outcome after pancreaticoduodenectomy for carcinoma of the ampulla of vater. Anticancer Res. 2013;33(6):2715-21.

287. Ishizuka M, Kubota K, Kita J, Shimoda M, Kato M, Sawada T. Impact of an inflammation-based prognostic system on patients undergoing surgery for hepatocellular carcinoma: a retrospective study of 398 Japanese patients. American journal of surgery. 2012;203(1):101-6.

288. Horino K, Beppu T, Kuroki H, Mima K, Okabe H, Nakahara O, et al. Glasgow Prognostic Score as a useful prognostic factor after hepatectomy for hepatocellular carcinoma. Int J Clin Oncol. 2013;18(5):829-38.

289. Huang J, Xu L, Luo Y, He F, Zhang Y, Chen M. The inflammation-based scores to predict prognosis of patients with hepatocellular carcinoma after hepatectomy. Medical oncology (Northwood, London, England). 2014;31(4):883.

290. Ni XC, Yi Y, Fu YP, He HW, Cai XY, Wang JX, et al. Prognostic Value of the Modified Glasgow Prognostic Score in Patients Undergoing Radical Surgery for Hepatocellular Carcinoma. Medicine (Baltimore). 2015;94(36):e1486.

291. Okamura Y, Ashida R, Ito T, Sugiura T, Mori K, Uesaka K. Preoperative neutrophil to lymphocyte ratio and prognostic nutritional index predict overall survival after hepatectomy for hepatocellular carcinoma. World journal of surgery. 2015;39(6):1501-9.

292. Abe T, Tashiro H, Hattori M, Kuroda S, Tahara H, Ohira M, et al. Prediction of long-term survival by using the Glasgow Prognostic Score in patients with hepatocellular carcinoma after liver transplantation. Hepatol Res. 2016;46(7):622-33.

293. Fu YP, Ni XC, Yi Y, Cai XY, He HW, Wang JX, et al. A Novel and Validated Inflammation-Based Score (IBS) Predicts Survival in Patients With Hepatocellular Carcinoma Following Curative Surgical Resection: A STROBE-Compliant Article. Medicine (Baltimore). 2016;95(7):e2784.

294. Glen P, Jamieson NB, McMillan DC, Carter R, Imrie CW, McKay CJ. Evaluation of an inflammation-based prognostic score in patients with inoperable pancreatic cancer. Pancreatology. 2006;6(5):450-3.

295. Martin HL, Ohara K, Kiberu A, Van HT, Davidson A, Khattak MA. Prognostic value of systemic inflammation-based markers in advanced pancreatic cancer. Intern Med J. 2014;44(7):676-82.

296. Kasuga A, Okano N, Naruge D, Kitamura H, Takasu A, Nagashima F, et al. Retrospective analysis of fixed dose rate infusion of gemcitabine and S-1 combination therapy (FGS) as salvage chemotherapy in patients with gemcitabine-refractory advanced pancreatic cancer: inflammation-based prognostic score predicts survival. Cancer Chemother Pharmacol. 2015;75(3):457-64.

297. Mitsunaga S, Ikeda M, Shimizu S, Ohno I, Takahashi H, Okuyama H, et al. C-Reactive Protein Level Is an Indicator of the Aggressiveness of Advanced Pancreatic Cancer. Pancreas. 2016;45(1):110-6.

298. Moriwaki T, Ishige K, Araki M, Yoshida S, Nishi M, Sato M, et al. Glasgow Prognostic Score predicts poor prognosis among advanced biliary tract cancer patients with good performance status. Med Oncol. 2014;31(11):287.

299. Zhou DS, Xu L, Luo YL, He FY, Huang JT, Zhang YJ, et al. Inflammation scores predict survival for hepatitis B virus-related hepatocellular carcinoma patients after transarterial chemoembolization. World J Gastroenterol. 2015;21(18):5582-90.

300. Pinato DJ, Shiner RJ, Seckl MJ, Stebbing J, Sharma R, Mauri FA. Prognostic performance of inflammation-based prognostic indices in primary operable non-small cell lung cancer. Br J Cancer. 2014;110(8):1930-5.

301. Miyazaki T, Yamasaki N, Tsuchiya T, Matsumoto K, Kunizaki M, Taniguchi D, et al. Inflammation-based scoring is a useful prognostic predictor of pulmonary resection for elderly patients with clinical stage I non-small-cell lung cancer. Eur J Cardiothorac Surg. 2015;47(4):e140-5.

302. Fan H, Shao ZY, Xiao YY, Xie ZH, Chen W, Xie H, et al. Comparison of the Glasgow Prognostic Score (GPS) and the modified Glasgow Prognostic Score (mGPS) in evaluating the prognosis of patients with operable and inoperable non-small cell lung cancer. J Cancer Res Clin Oncol. 2016;142(6):1285-97.

303. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer. 2003;89(6):1028-30.

304. Leung EY, Scott HR, McMillan DC. Clinical utility of the pretreatment glasgow prognostic score in patients with advanced inoperable non-small cell lung cancer. J Thorac Oncol. 2012;7(4):655-62.

305. Gioulbasanis I, Pallis A, Vlachostergios PJ, Xyrafas A, Giannousi Z, Perdikouri IE, et al. The Glasgow Prognostic Score (GPS) predicts toxicity and efficacy in platinum-based treated patients with metastatic lung cancer. Lung cancer (Amsterdam, Netherlands). 2012;77(2):383-8.

306. Simmons CP, Koinis F, Fallon MT, Fearon KC, Bowden J, Solheim TS, et al. Prognosis in advanced lung cancer--A prospective study examining key clinicopathological factors. Lung Cancer. 2015;88(3):304-9.

307. Zhou T, Hong S, Hu Z, Hou X, Huang Y, Zhao H, et al. A systemic inflammation-based prognostic scores (mGPS) predicts overall survival of patients with small-cell lung cancer. Tumour Biol. 2015;36(1):337-43.

308. Jiang AG, Chen HL, Lu HY. The relationship between Glasgow Prognostic Score and serum tumor markers in patients with advanced non-small cell lung cancer. BMC Cancer. 2015;15:386.

309. Partridge M, Fallon M, Bray C, McMillan D, Brown D, Laird B. Prognostication in advanced cancer: a study examining an inflammation-based score. J Pain Symptom Manage. 2012;44(2):161-7.

310. Anshushaug M, Gynnild MA, Kaasa S, Kvikstad A, Gronberg BH. Characterization of patients receiving palliative chemo- and radiotherapy during end of life at a regional cancer center in Norway. Acta Oncol. 2015;54(3):395-402.

311. Miura T, Matsumoto Y, Hama T, Amano K, Tei Y, Kikuchi A, et al. Glasgow prognostic score predicts prognosis for cancer patients in palliative settings: a subanalysis of the Japan-prognostic assessment tools validation (J-ProVal) study. Support Care Cancer. 2015;23(11):3149-56.

312. de Paula PN, Paiva BS, Hui D, Paiva CE. Validation of the Modified Glasgow Prognostic Score in Advanced Cancer Patients Receiving Palliative Care. J Pain Symptom Manage. 2016;51(2):270-7.

313. Tan CS, Read JA, Phan VH, Beale PJ, Peat JK, Clarke SJ. The relationship between nutritional status, inflammatory markers and survival in patients with advanced cancer: a prospective cohort study. Support Care Cancer. 2015;23(2):385-91.

314. CRUK. Cancer Research UK statistics by cancer type London: Cancer Research UK; 2018 [updated 01/11/2017; cited 2018 28/02/2018]. 1:[Website]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type.

315. Fleming ID. American Joint Committee on Cancer, American Cancer Society. AJCC Cancer Staging Manual. 5 ed. Philadelphia: Lippincott Raven; 1997.

316. Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3(1):32-5.

317. Madden KS. Sympathetic neural-immune interactions regulate hematopoiesis, thermoregulation and inflammation in mammals. Developmental and comparative immunology. 2017;66:92-7.

318. Nagtegaal ID, Tot T, Jayne DG, McShane P, Nihlberg A, Marshall HC, et al. Lymph nodes, tumor deposits, and TNM: are we getting better? Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(18):2487-92.

319. Ueno H, Mochizuki H, Akagi Y, Kusumi T, Yamada K, Ikegami M, et al. Optimal colorectal cancer staging criteria in TNM classification. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(13):1519-26.

320. Lippitz BE. Cytokine patterns in patients with cancer: a systematic review. Lancet Oncol. 2013;14(6):e218-28.

321. Paulsen O, Klepstad P, Rosland JH, Aass N, Albert E, Fayers P, et al. Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using

opioids: a randomized, placebo-controlled, double-blind trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(29):3221-8.

322. Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. Brain, behavior, and immunity. 2007;21(4):413-27.

323. Wang XS, Williams LA, Krishnan S, Liao Z, Liu P, Mao L, et al. Serum sTNF-R1, IL-6, and the development of fatigue in patients with gastrointestinal cancer undergoing chemoradiation therapy. Brain, behavior, and immunity. 2012;26(5):699-705.

324. Makimura C, Arao T, Matsuoka H, Takeda M, Kiyota H, Tsurutani J, et al. Prospective study evaluating the plasma concentrations of twenty-six cytokines and response to morphine treatment in cancer patients. Anticancer Res. 2011;31(12):4561-8.

325. Seruga B, Zhang H, Bernstein LJ, Tannock IF. Cytokines and their relationship to the symptoms and outcome of cancer. Nature reviews Cancer. 2008;8(11):887-99.

326. Kleiner G, Marcuzzi A, Zanin V, Monasta L, Zauli G. Cytokine levels in the serum of healthy subjects. Mediators of inflammation. 2013;2013:434010.

327. Lippitz BE, Harris RA. Cytokine patterns in cancer patients: A review of the correlation between interleukin 6 and prognosis. Oncoimmunology. 2016;5(5):e1093722.

328. Pantano Nde P, Paiva BS, Hui D, Paiva CE. Validation of the Modified Glasgow Prognostic Score in Advanced Cancer Patients Receiving Palliative Care. Journal of pain and symptom management. 2016;51(2):270-7.

329. Kantola T, Klintrup K, Vayrynen JP, Vornanen J, Bloigu R, Karhu T, et al. Stage-dependent alterations of the serum cytokine pattern in colorectal carcinoma. Br J Cancer. 2012;107(10):1729-36.

330. Guthrie G, McMillan DC. Comment on 'Stage-dependent alterations of the serum cytokine pattern in colorectal carcinoma'. Br J Cancer. 2013;108(9):1915-6.

331. Laird BJ, Scott AC, Colvin LA, McKeon AL, Murray GD, Fearon KC, et al. Cancer pain and its relationship to systemic inflammation: an exploratory study. Pain. 2011;152(2):460-3.

332. Scott HR, McMillan DC, Crilly A, McArdle CS, Milroy R. The relationship between weight loss and interleukin 6 in non-small-cell lung cancer. Br J Cancer. 1996;73(12):1560-2.

333. Fearon KC, McMillan DC, Preston T, Winstanley FP, Cruickshank AM, Shenkin A. Elevated circulating interleukin-6 is associated with an acute-phase response but reduced fixed hepatic protein synthesis in patients with cancer. Annals of surgery. 1991;213(1):26-31.

334. Guthrie GJ, Roxburgh CS, Horgan PG, McMillan DC. Does interleukin-6 link explain the link between tumour necrosis, local and systemic inflammatory responses and outcome in patients with colorectal cancer? Cancer treatment reviews. 2013;39(1):89-96.

335. Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nature reviews Clinical oncology. 2018;15(4):234-48.

336. Coffelt SB, Wellenstein MD, de Visser KE. Neutrophils in cancer: neutral no more. Nature Reviews Cancer. 2016;16:431.

337. Wiedenmann B, Malfertheiner P, Friess H, Ritch P, Arseneau J, Mantovani G, et al. A multicenter, phase II study of infliximab plus gemcitabine in pancreatic cancer cachexia. J Support Oncol. 2008;6(1):18-25.

338. Jatoi A, Dakhil SR, Nguyen PL, Sloan JA, Kugler JW, Rowland KM, Jr., et al. A placebo-controlled double blind trial of etanercept for the cancer anorexia/weight loss syndrome: results from N00C1 from the North Central Cancer Treatment Group. Cancer. 2007;110(6):1396-403.

339. Bayliss TJ, Smith JT, Schuster M, Dragnev KH, Rigas JR. A humanized anti-IL-6 antibody (ALD518) in non-small cell lung cancer. Expert Opin Biol Ther. 2011;11(12):1663-8.

340. Hickish T, Andre T, Wyrwicz L, Saunders M, Sarosiek T, Kocsis J, et al. MABp1 as a novel antibody treatment for advanced colorectal cancer: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2017;18(2):192-201.

341. Dolan R, Laird B, Horgan PG, McMillan DC. The prognostic value of the systemic inflammatory response in randomised clinical trials in cancer: a systematic review. 2017.

342. Mantovani A, Barajon I, Garlanda C. IL-1 and IL-1 regulatory pathways in cancer progression and therapy. Immunological reviews. 2018;281(1):57-61.

343. Seyfried O, Hester J. Opioids and endocrine dysfunction. British journal of pain. 2012;6(1):17-24.

344. Wigmore T, Farquhar-Smith P. Opioids and cancer: friend or foe? Curr Opin Support Palliat Care. 2016;10(2):109-18.

345. Plein LM, Rittner HL. Opioids and the immune system - friend or foe. British journal of pharmacology. 2018;175(14):2717-25.

346. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. Clinical nutrition (Edinburgh, Scotland). 2017;36(5):1187-96.

347. Wagner D, DeMarco MM, Amini N, Buttner S, Segev D, Gani F, et al. Role of frailty and sarcopenia in predicting outcomes among patients undergoing gastrointestinal surgery. World journal of gastrointestinal surgery. 2016;8(1):27-40.

348. Gonzalez MC, Correia M, Heymsfield SB. A requiem for BMI in the clinical setting. Current opinion in clinical nutrition and metabolic care. 2017;20(5):314-21.

349. Dolan RD, Daly LE, Simmons C, Ryan A, Sim WS, Fallon M, et al. The relationship between ECOG-PS/mGPS (modified Glasgow prognostic score) framework, CT-derived body composition, physical function tests and survival in patients with advanced cancer. JAMA Oncology 2018;In Press.

350. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. European journal of cancer (Oxford, England : 1990). 2016;57:58-67.

351. Antoun S, Baracos VE, Birdsell L, Escudier B, Sawyer MB. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. Annals of oncology : official journal of the European Society for Medical Oncology. 2010;21(8):1594-8.

352. Bozzetti F. Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. Annals of oncology : official journal of the European Society for Medical Oncology. 2017;28(9):2107-18.

353. Caan BJ, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E, et al. Explaining the Obesity Paradox: The Association between Body Composition and Colorectal Cancer Survival (C-SCANS Study). Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2017;26(7):1008-15.

354. Malietzis G, Currie AC, Athanasiou T, Johns N, Anyamene N, Glynne-Jones R, et al. Influence of body composition profile on outcomes following colorectal cancer surgery. The British journal of surgery. 2016;103(5):572-80.

355. Douglas E, McMillan DC. Towards a simple objective framework for the investigation and treatment of cancer cachexia: the Glasgow Prognostic Score. Cancer treatment reviews. 2014;40(6):685-91.

356. Richards CH, Roxburgh CS, MacMillan MT, Isswiasi S, Robertson EG, Guthrie GK, et al. The relationships between body composition and the systemic inflammatory response in patients with primary operable colorectal cancer. PloS one. 2012;7(8):e41883.

357. Kim EY, Kim YS, Seo JY, Park I, Ahn HK, Jeong YM, et al. The Relationship between Sarcopenia and Systemic Inflammatory Response for Cancer Cachexia in Small Cell Lung Cancer. PloS one. 2016;11(8):e0161125.

358. Rollins KE, Tewari N, Ackner A, Awwad A, Madhusudan S, Macdonald IA, et al. The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. Clinical nutrition (Edinburgh, Scotland). 2016;35(5):1103-9.

359. Black D, Mackay C, Ramsay G, Hamoodi Z, Nanthakumaran S, Park KGM, et al. Prognostic Value of Computed Tomography: Measured Parameters of Body Composition in Primary Operable Gastrointestinal Cancers. Annals of surgical oncology. 2017;24(8):2241-51.

360. Feliciano EMC, Kroenke CH, Meyerhardt JA, Prado CM, Bradshaw PT, Kwan ML, et al. Association of Systemic Inflammation and Sarcopenia With Survival in Nonmetastatic Colorectal Cancer: Results From the C SCANS Study. JAMA Oncol. 2017;3(12):e172319.

361. Budczies J, Klauschen F, Sinn BV, Gyorffy B, Schmitt WD, Darb-Esfahani S, et al. Cutoff Finder: a comprehensive and straightforward Web application enabling rapid biomarker cutoff optimization. PloS one. 2012;7(12):e51862.

362. Xiao J, Caan BJ, Weltzien E, Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA, et al. Associations of pre-existing co-morbidities with skeletal muscle mass and radiodensity in patients with non-metastatic colorectal cancer. J Cachexia Sarcopenia Muscle. 2018.

363. Kroenke CH, Prado CM, Meyerhardt JA, Weltzien EK, Xiao J, Cespedes Feliciano EM, et al. Muscle radiodensity and mortality in patients with colorectal cancer. Cancer. 2018.

364. Government TS. The Scottish Index of Multiple Deprivation 2016. In: Group MDA, editor. 5 ed. Edinburgh The Scottish Government 2016.

365. Martin L, Hopkins J, Malietzis G, Jenkins JT, Sawyer MB, Brisebois R, et al. Assessment of Computed Tomography (CT)-Defined Muscle and Adipose Tissue Features in Relation to Short-Term Outcomes After Elective Surgery for Colorectal Cancer: A Multicenter Approach. Annals of surgical oncology. 2018.

366. Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. Lancet Oncol. 2016;17(4):519-31.

367. Simmons C, McMillan DC, Tuck S, Graham C, McKeown A, Bennett M, et al. "How Long Have I Got?"-A Prospective Cohort Study Comparing Validated Prognostic Factors for Use in Patients with Advanced Cancer. The oncologist. 2019.

368. Martin L. Diagnostic criteria for cancer cachexia: data versus dogma. Current opinion in clinical nutrition and metabolic care. 2016;19(3):188-98.

369. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(1):90-9.

370. Martin L, Senesse P, Gioulbasanis I, Lundholm K, Bosaeus I, Voss AC, et al. The combination of weight loss grade, performance status, and Glasgow Prognostic Score contribute to survival discrimination in advanced cancer patients at risk for cachexia. 8th Cachexia Conference 4-6 December 2015; Paris Journal of Cachexia, Sarcopenia and Muscle: Journal of Cachexia, Sarcopenia and Muscle; 2015. p. 446.

371. Solheim TS, Laird BJA, Balstad TR, Bye A, Stene G, Baracos V, et al. Cancer cachexia: rationale for the MENAC (Multimodal-Exercise, Nutrition and Anti-inflammatory medication for Cachexia) trial. BMJ Support Palliat Care. 2018;8(3):258-65.

372. McDonald JJ, McMillan DC, Laird BJ. Targeting IL-1alpha in cancer cachexia: a narrative review. Curr Opin Support Palliat Care. 2018.

373. Morley JE. Editorial: Screening for Malnutrition (Undernutrition) in Primary Care. J Nutr Health Aging. 2019;23(1):1-3.

374. Zimmermann C, Burman D, Swami N, Krzyzanowska MK, Leighl N, Moore M, et al. Determinants of quality of life in patients with advanced cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2011;19(5):621-9.

375. Vano YA, Oudard S, By MA, Tetu P, Thibault C, Aboudagga H, et al. Optimal cut-off for neutrophil-to-lymphocyte ratio: Fact or Fantasy? A prospective cohort study in metastatic cancer patients. PloS one. 2018;13(4):e0195042.

376. Simmons CP, Koinis F, Fallon MT, Fearon KC, Bowden J, Solheim TS, et al. Prognosis in advanced lung cancer--A prospective study examining key clinicopathological factors. Lung cancer (Amsterdam, Netherlands). 2015;88(3):304-9.

377. Kaasa S, Loge JH, Aapro M, Albreht T, Anderson R, Bruera E, et al. Integration of oncology and palliative care: a Lancet Oncology Commission. Lancet Oncol. 2018.

378. Fairclough DL, Cella DF. Eastern Cooperative Oncology Group (ECOG). Journal of the National Cancer Institute Monographs. 1996(20):73-5.

379. Simmons CPL, McMillan DC, McWilliams K, Sande TA, Fearon KC, Tuck S, et al. Prognostic Tools in Patients With Advanced Cancer: A Systematic Review. Journal of pain and symptom management. 2017;53(5):962-70 e10.

380. van Vugt JL, Levolger S, Gharbharan A, Koek M, Niessen WJ, Burger JW, et al. A comparative study of software programmes for cross-sectional skeletal muscle and adipose tissue measurements on abdominal computed tomography scans of rectal cancer patients. J Cachexia Sarcopenia Muscle. 2017;8(2):285-97.

381. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. The journals of gerontology Series A, Biological sciences and medical sciences. 2014;69(5):547-58.

382. Williams GR, Deal AM, Muss HB, Weinberg MS, Sanoff HK, Nyrop KA, et al. Skeletal muscle measures and physical function in older adults with cancer: sarcopenia or myopenia? Oncotarget. 2017;8(20):33658-65.

383. Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle. 2017;8(5):778-88.

384. Almasaudi AS, Dolan RD, McSorley ST, Horgan PG, Edwards C, McMillan DC. Relationship between computed tomography-derived body composition, sex, and post-operative complications in patients with colorectal cancer. Eur J Clin Nutr. 2019.

385. Lennon H, Sperrin M, Badrick E, Renehan AG. The Obesity Paradox in Cancer: a Review. Curr Oncol Rep. 2016;18(9):56-.

386. Charette N, Vandeputte C, Ameye L, Bogaert CV, Krygier J, Guiot T, et al. Prognostic value of adipose tissue and muscle mass in advanced colorectal cancer: a post hoc analysis of two non-randomized phase II trials. BMC cancer. 2019;19(1):134-.

387. Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Diabetologia. 2011;54(9):2263-71.

388. Renehan AG, Crosbie EJ, Campbell PT. Re: Prediagnosis body mass index, physical activity, and mortality in endometrial cancer patients. Journal of the National Cancer Institute. 2014;106(2):djt375.

389. Nagle CM, Dixon SC, Jensen A, Kjaer SK, Modugno F, deFazio A, et al. Obesity and survival among women with ovarian cancer: results from the Ovarian Cancer Association Consortium. British journal of cancer. 2015;113(5):817-26.

390. Wong AL, Seng KY, Ong EM, Wang LZ, Oscar H, Cordero MT, et al. Body fat composition impacts the hematologic toxicities and pharmacokinetics of doxorubicin in Asian breast cancer patients. Breast cancer research and treatment. 2014;144(1):143-52.

391. Gurunathan U, Myles PS. Limitations of body mass index as an obesity measure of perioperative risk. British journal of anaesthesia. 2016;116(3):319-21.

392. Demark-Wahnefried W, Platz EA, Ligibel JA, Blair CK, Courneya KS, Meyerhardt JA, et al. The role of obesity in cancer survival and recurrence. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2012;21(8):1244-59.

393. Brown JC, Caan BJ, Meyerhardt JA, Weltzien E, Xiao J, Cespedes Feliciano EM, et al. The deterioration of muscle mass and radiodensity is prognostic of poor survival in stage I-III colorectal cancer: a population-based cohort study (C-SCANS). J Cachexia Sarcopenia Muscle. 2018;9(4):664-72.

394. Trépanier M, Minnella EM, Paradis T, Awasthi R, Kaneva P, Schwartzman K, et al. Improved Disease-free Survival After Prehabilitation for Colorectal Cancer Surgery. Annals of surgery. 2019;270(3):493-501.

395. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100(1):57-70.

396. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74.

397. Balkwill FR, Capasso M, Hagemann T. The tumor microenvironment at a glance. J Cell Sci. 2012;125(Pt 23):5591-6.

398. Warburg O. On the origin of cancer cells. Science. 1956;123(3191):309-14.

399. Maguire D, Neytchev O, Talwar D, McMillan D, Shiels PG. Telomere Homeostasis: Interplay with Magnesium. International journal of molecular sciences. 2018;19(1).

400. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nat Med. 2013;19(11):1423-37.

401. Kijima S, Sasaki T, Nagata K, Utano K, Lefor AT, Sugimoto H. Preoperative evaluation of colorectal cancer using CT colonography, MRI, and PET/CT. World journal of gastroenterology. 2014;20(45):16964-75.

402. Inoue K, Goto R, Okada K, Kinomura S, Fukuda H. A bone marrow F-18 FDG uptake exceeding the liver uptake may indicate bone marrow hyperactivity. Annals of nuclear medicine. 2009;23(7):643-9.

403. Prevost S, Boucher L, Larivee P, Boileau R, Benard F. Bone marrow hypermetabolism on 18F-FDG PET as a survival prognostic factor in non-small cell lung cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2006;47(4):559-65.

404. Cicone F, Loose D, Deron P, Vermeersch H, Signore A, Van de Vyvere F, et al. Prognostic value of FDG uptake by the bone marrow in squamous cell carcinoma of the head and neck. Nucl Med Commun. 2008;29(5):431-5.

405. Chang PY, Kuo YB, Wu TL, Liao CT, Sun YC, Yen TC, et al. Association and prognostic value of serum inflammation markers in patients with leukoplakia and oral cavity cancer. Clin Chem Lab Med. 2013;51(6):1291-300.

406. Chen HH, Wang HM, Fan KH, Lin CY, Yen TC, Liao CT, et al. Pre-treatment levels of C-reactive protein and squamous cell carcinoma antigen for predicting the aggressiveness of pharyngolaryngeal carcinoma. PloS one. 2013;8(1):e55327.

407. Jeong E, Hyun SH, Moon SH, Cho YS, Kim BT, Lee KH. Relation between tumor FDG uptake and hematologic prognostic indicators in stage I lung cancer patients following curative resection. Medicine (Baltimore). 2017;96(5):e5935.

408. Zhong L, Li C, Ren Y, Wu D. Prognostic value of (18)F-fluorodeoxyglucose PET parameters and inflammation in patients with nasopharyngeal carcinoma. Oncol Lett. 2017;14(4):5004-12.

409. Lee JW, Na JO, Kang DY, Lee SY, Lee SM. Prognostic Significance of FDG Uptake of Bone Marrow on PET/CT in Patients With Non-Small-Cell Lung Cancer After Curative Surgical Resection. Clin Lung Cancer. 2017;18(2):198-206.

410. Lee JW, Seo KH, Kim ES, Lee SM. The role of (18)F-fluorodeoxyglucose uptake of bone marrow on PET/CT in predicting clinical outcomes in non-small cell lung cancer patients treated with chemoradiotherapy. Eur Radiol. 2017;27(5):1912-21.

411. Lee JW, Lee MS, Chung IK, Son MW, Cho YS, Lee SM. Clinical implication of FDG uptake of bone marrow on PET/CT in gastric cancer patients with surgical resection. World journal of gastroenterology. 2017;23(13):2385-95.

412. McSorley ST, Khor BY, Tsang K, Colville D, Han S, Horgan PG, et al. The relationship between 18F FDG-PETCT derived markers of tumour metabolism and systemic inflammation in patients with recurrent disease following surgery for colorectal cancer. Colorectal Dis. 2017.

413. Lee JW, Baek MJ, Ahn TS, Lee SM. Fluorine-18-fluorodeoxyglucose uptake of bone marrow on PET/CT can predict prognosis in patients with colorectal cancer after curative surgical resection. Eur J Gastroenterol Hepatol. 2018;30(2):187-94.

414. van Pelt GW, Sandberg TP, Morreau H, Gelderblom H, van Krieken J, Tollenaar R, et al. The tumour-stroma ratio in colon cancer: the biological role and its prognostic impact. Histopathology. 2018.

415. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. Nature Reviews Clinical Oncology. 2017;14:399.

416. Kudo-Saito C. Cancer-associated mesenchymal stem cells aggravate tumor progression. Frontiers in Cell and Developmental Biology. 2015;3.

417. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000Prime Reports. 2014;6.

418. Shreve PD. Focal fluorine-18 fluorodeoxyglucose accumulation in inflammatory pancreatic disease. European journal of nuclear medicine. 1998;25(3):259-64.

419. Rosenberg R, Herrmann K, Gertler R, Kunzli B, Essler M, Lordick F, et al. The predictive value of metabolic response to preoperative radiochemotherapy in locally advanced rectal cancer measured by PET/CT. International journal of colorectal disease. 2009;24(2):191-200.

420. Mezquita L, Auclin E, Ferrara R, Charrier M, Remon J, Planchard D, et al. Association of the Lung Immune Prognostic Index With Immune Checkpoint Inhibitor Outcomes in Patients With Advanced Non-Small Cell Lung Cancer. JAMA Oncol. 2018;4(3):351-7.

421. Uneno Y, Taneishi K, Kanai M, Okamoto K, Yamamoto Y, Yoshioka A, et al. Development and validation of a set of six adaptable prognosis prediction (SAP) models based on time-series real-world big data analysis for patients with cancer receiving chemotherapy: A multicenter case crossover study. PloS one. 2017;12(8):e0183291.

422. Ferris RL, Lenz HJ, Trotta AM, Garcia-Foncillas J, Schulten J, Audhuy F, et al. Rationale for combination of therapeutic antibodies targeting tumor cells and immune checkpoint receptors: Harnessing innate and adaptive immunity through IgG1 isotype immune effector stimulation. Cancer treatment reviews. 2018;63:48-60.

423. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015;65(2):87-108.

424. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(12):1539-47.

425. Prado CM, Cushen SJ, Orsso CE, Ryan AM. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. The Proceedings of the Nutrition Society. 2016;75(2):188-98.

426. McSorley ST, Black DH, Horgan PG, McMillan DC. The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer. Clinical nutrition (Edinburgh, Scotland). 2017.

427. Friesen DE, Baracos VE, Tuszynski JA. Modeling the energetic cost of cancer as a result of altered energy metabolism: implications for cachexia. Theoretical biology & medical modelling. 2015;12:17.

428. Guthrie GJ, Roxburgh CS, Richards CH, Horgan PG, McMillan DC. Circulating IL-6 concentrations link tumour necrosis and systemic and local inflammatory responses in patients undergoing resection for colorectal cancer. Br J Cancer. 2013;109(1):131-7.

429. O'Callaghan DS, O'Donnell D, O'Connell F, O'Byrne KJ. The role of inflammation in the pathogenesis of non-small cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2010;5(12):2024-36.

430. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol. 2014;15(11):e493-503.

431. Galon J, Mlecnik B, Bindea G, Angell HK, Berger A, Lagorce C, et al. Towards the introduction of the 'Immunoscore' in the classification of malignant tumours. The Journal of pathology. 2014;232(2):199-209.

432. Mesker WE, Junggeburt JM, Szuhai K, de Heer P, Morreau H, Tanke HJ, et al. The carcinoma-stromal ratio of colon carcinoma is an independent factor for survival compared to lymph node status and tumor stage. Cellular oncology : the official journal of the International Society for Cellular Oncology. 2007;29(5):387-98.

433. Park JH, McMillan DC. Outcome in colorectal cancer-tumour, stroma and so much more. Annals of oncology : official journal of the European Society for Medical Oncology. 2018;29(3):534-5.

434. Dolan RD, McSorley ST, McMillan DC, Horgan PG. Attitudes of surgeons to the use of postoperative markers of the systemic inflammatory response following elective surgery. Ann Med Surg (Lond). 2017;21:14-9.

435. McSorley ST, Horgan PG, McMillan DC. The impact of preoperative corticosteroids on the systemic inflammatory response and postoperative complications following surgery for gastrointestinal cancer: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2016;101:139-50.

436. Moug SJ, Mutrie N, Barry SJE, Mackay G, Steele RJC, Boachie C, et al. Prehabilitation is feasible in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy and may minimize physical deterioration: results from the REx trial. Colorectal Dis. 2019;21(5):548-62.

437. Mansouri D, McMillan DC, Crearie C, Morrison DS, Crighton EM, Horgan PG. Temporal trends in mode, site and stage of presentation with the introduction of colorectal cancer screening: a decade of experience from the West of Scotland. Br J Cancer. 2015;113(3):556-61.

438. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. The New England journal of medicine. 2010;363(8):733-42.

439. Huemer F, Schlintl V, Hecht S, Hackl H, Melchardt T, Rinnerthaler G, et al. Regorafenib Is Associated With Increased Skeletal Muscle Loss Compared to TAS-102 in Metastatic Colorectal Cancer. Clinical colorectal cancer. 2019;18(2):159-66.e3.

440. Degens J, Sanders KJC, de Jong EEC, Groen HJM, Smit EF, Aerts JG, et al. The prognostic value of early onset, CT derived loss of muscle and adipose tissue during

chemotherapy in metastatic non-small cell lung cancer. Lung cancer (Amsterdam, Netherlands). 2019;133:130-5.

441. Köstek O, Demircan NC, Gökyer A, Küçükarda A, Sunal BS, Hacıoğlu MB, et al. Skeletal muscle loss during anti-EGFR combined chemotherapy regimens predicts poor prognosis in patients with RAS wild metastatic colorectal cancer. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2019;21(11):1510-7.

442. Stene GB, Helbostad JL, Amundsen T, Sørhaug S, Hjelde H, Kaasa S, et al. Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. Acta Oncol. 2015;54(3):340-8.

443. He J, Blair AB, Groot VP, Javed AA, Burkhart RA, Gemenetzis G, et al. Is a Pathological Complete Response Following Neoadjuvant Chemoradiation Associated With Prolonged Survival in Patients With Pancreatic Cancer? Annals of surgery. 2018.

444. Gemenetzis G, Groot VP, Blair AB, Laheru DA, Zheng L, Narang AK, et al. Survival in Locally Advanced Pancreatic Cancer After Neoadjuvant Therapy and Surgical Resection. Annals of surgery. 2018.

445. Murphy JE, Wo JY, Ryan DP, Jiang W, Yeap BY, Drapek LC, et al. Total Neoadjuvant Therapy With FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma: A Phase 2 Clinical Trial. JAMA Oncol. 2018;4(7):963-9.

446. Dreyer SB, Pinese M, Jamieson NB, Scarlett CJ, Colvin EK, Pajic M, et al. Precision Oncology in Surgery: Patient Selection for Operable Pancreatic Cancer. Ann Surg. 2018.

447. Dunne DF, Jack S, Jones RP, Jones L, Lythgoe DT, Malik HZ, et al. Randomized clinical trial of prehabilitation before planned liver resection. Br J Surg. 2016;103(5):504-12.

448. Ueno H, Okada S, Okusaka T, Ikeda M. Prognostic factors in patients with metastatic pancreatic adenocarcinoma receiving systemic chemotherapy. Oncology. 2000;59(4):296-301.

449. McMillan DC, Elahi MM, Sattar N, Angerson WJ, Johnstone J, McArdle CS. Measurement of the systemic inflammatory response predicts cancer-specific and non-cancer survival in patients with cancer. Nutr Cancer. 2001;41(1-2):64-9.

450. Scott HR, McMillan DC, Forrest LM, Brown DJ, McArdle CS, Milroy R. The systemic inflammatory response, weight loss, performance status and survival in patients with inoperable non-small cell lung cancer. Br J Cancer. 2002;87(3):264-7.

451. Bromwich E, McMillan DC, Lamb GW, Vasey PA, Aitchison M. The systemic inflammatory response, performance status and survival in patients undergoing alpha-interferon treatment for advanced renal cancer. Br J Cancer. 2004;91(7):1236-8.

452. Elahi MM, McMillan DC, McArdle CS, Angerson WJ, Soukop M, Johnstone J, et al. The systemic inflammatory response predicts overall and cancer specific survival in patients with malignant lymphoma. Med Sci Monit. 2005;11(2):CR75-CR8.

453. Casamassima A, Picciariello M, Quaranta M, Berardino R, Ranieri C, Paradiso A, et al. C-reactive protein: a biomarker of survival in patients with metastatic renal cell carcinoma treated with subcutaneous interleukin-2 based immunotherapy. J Urol. 2005;173(1):52-5.

454. McArdle PA, Mir K, Almushatat AS, Wallace AM, Underwood MA, McMillan DC. Systemic inflammatory response, prostate-specific antigen and survival in patients with metastatic prostate cancer. Urol Int. 2006;77(2):127-9.

455. Sawaki A, Kanemitsu Y, Mizuno N, Takahashi K, Nakamura T, Ioka T, et al. Practical prognostic index for patients with metastatic pancreatic cancer treated with gemcitabine. J Gastroenterol Hepatol. 2008;23(8 Pt 1):1292-7.

456. Nakachi K, Furuse J, Ishii H, Suzuki E, Yoshino M. Prognostic factors in patients with gemcitabine-refractory pancreatic cancer. Jpn J Clin Oncol. 2007;37(2):114-20.

457. Tanaka T, Ikeda M, Okusaka T, Ueno H, Morizane C, Hagihara A, et al. Prognostic factors in japanese patients with advanced pancreatic cancer treated with single-agent gemcitabine as first-line therapy. Jpn J Clin Oncol. 2008;38(11):755-61.

458. Beer TM, Lalani AS, Lee S, Mori M, Eilers KM, Curd JG, et al. C-reactive protein as a prognostic marker for men with androgen-independent prostate cancer: results from the ASCENT trial. Cancer. 2008;112(11):2377-83.

459. Papadoniou N, Kosmas C, Gennatas K, Polyzos A, Mouratidou D, Skopelitis E, et al. Prognostic factors in patients with locally advanced (unresectable) or metastatic pancreatic adenocarcinoma: a retrospective analysis. Anticancer Res. 2008;28(1B):543-9.

460. Yoshida S, Saito K, Koga F, Yokoyama M, Kageyama Y, Masuda H, et al. C-reactive protein level predicts prognosis in patients with muscle-invasive bladder cancer treated with chemoradiotherapy. BJU Int. 2008;101(8):978-81.

461. Koch A, Fohlin H, Sorenson S. Prognostic significance of C-reactive protein and smoking in patients with advanced non-small cell lung cancer treated with first-line palliative chemotherapy. J Thorac Oncol. 2009;4(3):326-32.

462. Hashimoto K, Ueno H, Ikeda M, Kojima Y, Hagihara A, Kondo S, et al. Do recurrent and metastatic pancreatic cancer patients have the same outcomes with gemcitabine treatment? Oncology. 2009;77(3-4):217-23.

463. Zacharakis M, Xynos ID, Lazaris A, Smaro T, Kosmas C, Dokou A, et al. Predictors of survival in stage IV metastatic colorectal cancer. Anticancer Res. 2010;30(2):653-60.

464. Iwasa S, Nakajima TE, Nakamura K, Takashima A, Kato K, Hamaguchi T, et al. Systemic chemotherapy for peritoneal disseminated gastric cancer with inadequate oral intake: a retrospective study. Int J Clin Oncol. 2011;16(1):57-62.

465. Falkensammer CE, Thurnher M, Leonhartsberger N, Ramoner R. C-reactive protein is a strong predictor for anaemia in renal cell carcinoma: role of IL-6 in overall survival. BJU Int. 2011;107(12):1893-8.

466. Masago K, Fujita S, Togashi Y, Kim YH, Hatachi Y, Fukuhara A, et al. Clinical significance of pretreatment C-reactive protein in patients with advanced nonsquamous, non-small cell lung cancer who received gefitinib. Oncology. 2010;79(5-6):355-62.

467. Shimoda M, Katoh M, Kita J, Sawada T, Kubota K. The Glasgow Prognostic Score is a good predictor of treatment outcome in patients with unresectable pancreatic cancer. Chemotherapy. 2010;56(6):501-6.

468. Shinohara N, Abe T, Mochizuki T, Kashiwagi A, Kanagawa K, Maruyama S, et al. Is Memorial Sloan-Kettering Cancer Center risk classification appropriate for Japanese patients with metastatic renal cell carcinoma in the cytokine era? Urol Oncol. 2013;31(7):1276-82.

469. Yi JH, Lee J, Park SH, Lee KT, Lee JK, Lee KH, et al. A prognostic model to predict clinical outcomes with first-line gemcitabine-based chemotherapy in advanced pancreatic cancer. Oncology. 2011;80(3-4):175-80.

470. Kume H, Kakutani S, Yamada Y, Shinohara M, Tominaga T, Suzuki M, et al. Prognostic factors for renal cell carcinoma with bone metastasis: who are the long-term survivors? J Urol. 2011;185(5):1611-4.

471. Lee JS, Kwon OY, Choi HS, Hong HP, Ko YG. Serum C-reactive protein level is a predictive factor for 14-day mortality of patients with advanced cancer who present to the emergency department with acute symptoms. Acad Emerg Med. 2011;18(4):440-2.

472. Bystrom P, Berglund A, Nygren P, Wernroth L, Johansson B, Larsson A, et al. Evaluation of predictive markers for patients with advanced colorectal cancer. Acta Oncol. 2012;51(7):849-59.

473. Ishioka J, Saito K, Sakura M, Yokoyama M, Matsuoka Y, Numao N, et al. Development of a nomogram incorporating serum C-reactive protein level to predict overall survival of patients with advanced urothelial carcinoma and its evaluation by decision curve analysis. Br J Cancer. 2012;107(7):1031-6.

474. Prins RC, Rademacher BL, Mongoue-Tchokote S, Alumkal JJ, Graff JN, Eilers KM, et al. C-reactive protein as an adverse prognostic marker for men with castration-resistant prostate cancer (CRPC): confirmatory results. Urol Oncol. 2012;30(1):33-7.

475. Zeng YC, Xue M, Chi F, Xu ZG, Fan GL, Wu R, et al. C-reactive protein level predicts prognosis in patients with locoregionally advanced laryngeal carcinoma treated with chemoradiotherapy. Tumour Biol. 2012;33(3):891-5.

476. Pond GR, Armstrong AJ, Wood BA, Leopold L, Galsky MD, Sonpavde G. Ability of C-reactive protein to complement multiple prognostic classifiers in men with metastatic castration resistant prostate cancer receiving docetaxel-based chemotherapy. BJU Int. 2012;110(11 Pt B):E461-E8.

477. Kinoshita A, Onoda H, Takano K, Imai N, Saeki C, Fushiya N, et al. Pretreatment serum C-reactive protein level predicts poor prognosis in patients with hepatocellular carcinoma. Medical oncology (Northwood, London, England). 2012;29(4):2800-8.

478. Morizane S, Iwamoto H, Yao A, Isoyama T, Sejima T, Takenaka A. Serum C-reactive protein level is a significant prognostic indicator in patients with advanced urothelial cancer treated with gemcitabine-cisplatin or carboplatin - preliminary results. Cent European J Urol. 2012;65(2):62-6.

479. Haas M, Heinemann V, Kullmann F, Laubender RP, Klose C, Bruns CJ, et al. Prognostic value of CA 19-9, CEA, CRP, LDH and bilirubin levels in locally advanced and metastatic pancreatic cancer: results from a multicenter, pooled analysis of patients receiving palliative chemotherapy. J Cancer Res Clin Oncol. 2013;139(4):681-9.

480. Xia WX, Zhang HB, Shi JL, Lu X, Wang L, Ye YF, et al. A prognostic model predicts the risk of distant metastasis and death for patients with nasopharyngeal carcinoma based on pre-treatment serum C-reactive protein and N-classification. Eur J Cancer. 2013;49(9):2152-60.

481. Yasuda Y, Saito K, Yuasa T, Kitsukawa S, Urakami S, Yamamoto S, et al. Prognostic impact of pretreatment C-reactive protein for patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors. Int J Clin Oncol. 2013;18(5):884-9.

482. Shirakawa T, Kato K, Nagashima K, Nishikawa A, Sawada R, Takahashi N, et al. A retrospective study of docetaxel or paclitaxel in patients with advanced or recurrent

esophageal squamous cell carcinoma who previously received fluoropyrimidine- and platinum-based chemotherapy. Cancer Chemother Pharmacol. 2014;74(6):1207-15.

483. Teishima J, Kobatake K, Hayashi T, Seno Y, Ikeda K, Nagamatsu H, et al. Prognostic significance of C-reactive protein in patients with intermediate-risk metastatic renal cell carcinoma treated with molecular targeted therapy. Oncol Lett. 2014;8(2):881-5.

484. Deberne M, Ropert S, Billemont B, Daniel C, Chapron J, Goldwasser F. Inaugural bone metastases in non-small cell lung cancer: a specific prognostic entity? BMC Cancer. 2014;14:416.

485. Beuselinck B, Vano YA, Oudard S, Wolter P, De SR, Depoorter L, et al. Prognostic impact of baseline serum C-reactive protein in patients with metastatic renal cell carcinoma (RCC) treated with sunitinib. BJU Int. 2014;114(1):81-9.

486. Xue P, Kanai M, Mori Y, Nishimura T, Uza N, Kodama Y, et al. Comparative outcomes between initially unresectable and recurrent cases of advanced pancreatic cancer following palliative chemotherapy. Pancreas. 2014;43(3):411-6.

487. Formica V, Luccchetti J, Cunningham D, Smyth EC, Ferroni P, Nardecchia A, et al. Systemic inflammation, as measured by the neutrophil/lymphocyte ratio, may have differential prognostic impact before and during treatment with fluorouracil, irinotecan and bevacizumab in metastatic colorectal cancer patients. Med Oncol. 2014;31(9):166.

488. Kim YJ, Kim SJ, Lee JK, Choi WS, Park JH, Kim HJ, et al. Prediction of survival in terminally ill cancer patients at the time of terminal cancer diagnosis. J Cancer Res Clin Oncol. 2014;140(9):1567-74.

489. Ni XF, Wu P, Wu CP, Ji M, Wu J, Gu XF, et al. Elevated serum C-reactive protein, carcinoembryonic antigen and N2 disease are poor prognostic indicators in non-small cell lung cancer. Asia Pac J Clin Oncol. 2015;11(4):e22-e30.

490. Fiala O, Pesek M, Finek J, Topolcan O, Racek J, Minarik M, et al. High serum level of C-reactive protein is associated with worse outcome of patients with advanced-stage NSCLC treated with erlotinib. Tumour Biol. 2015;36(12):9215-22.

491. Adams HJ, de Klerk JM, Fijnheer R, Heggelman BG, Dubois SV, Nievelstein RA, et al. Prognostic Value of Anemia and C-Reactive Protein Levels in Diffuse Large B-Cell Lymphoma. Clin Lymphoma Myeloma Leuk. 2015;15(11):671-9.

492. Ito M, Saito K, Yasuda Y, Sukegawa G, Kubo Y, Numao N, et al. Prognostic impact of C-reactive protein for determining overall survival of patients with castration-resistant prostate cancer treated with docetaxel. Urology. 2011;78(5):1131-5.

493. Li X, Tian F, Wang F, Li Y. Serum C-reactive protein and overall survival of patients with osteosarcoma. Tumour Biol. 2015;36(7):5663-6.

494. Tang LQ, Hu DP, Chen QY, Zhang L, Lai XP, He Y, et al. Elevated high-sensitivity C-reactive protein levels predict decreased survival for nasopharyngeal carcinoma patients in the intensity-modulated radiotherapy era. PLoS One. 2015;10(4):e0122965.

495. Thurner EM, Krenn-Pilko S, Langsenlehner U, Stojakovic T, Pichler M, Gerger A, et al. The elevated C-reactive protein level is associated with poor prognosis in prostate cancer patients treated with radiotherapy. Eur J Cancer. 2015;51(5):610-9.

496. Zeng YC, Wu R, Xiao YP, Chi F, Xue M, Zhang ZY, et al. Serum C-reactive protein predicts poor prognosis in patients with locoregionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy. Curr Oncol. 2015;22(1):20-4.

497. Xu L, Zhao Q, Huang S, Li S, Wang J, Li Q. Serum C-reactive protein acted as a prognostic biomarker for overall survival in metastatic prostate cancer patients. Tumour Biol. 2015;36(2):669-73.

498. Go SI, Kim RB, Song HN, Kang MH, Lee US, Choi HJ, et al. Prognostic significance of the absolute monocyte counts in lung cancer patients with venous thromboembolism. Tumour Biol. 2015;36(10):7631-9.

499. Kim HW, Lee JC, Paik KH, Lee YS, Hwang JH, Kim J. Initial Metastatic Site as a Prognostic Factor in Patients With Stage IV Pancreatic Ductal Adenocarcinoma. Medicine (Baltimore). 2015;94(25):e1012.

500. Yao A, Sejima T, Iwamoto H, Masago T, Morizane S, Honda M, et al. High neutrophil-to-lymphocyte ratio predicts poor clinical outcome in patients with castration-resistant prostate cancer treated with docetaxel chemotherapy. Int J Urol. 2015;22(9):827-33.

501. Wu G, Yao Y, Bai C, Zeng J, Shi D, Gu X, et al. Combination of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio is a useful prognostic factor in advanced non-small cell lung cancer patients. Thorac Cancer. 2015;6(3):275-87.

502. Middleton G, Greenhalf W, Costello E, Shaw V, Cox T, Ghaneh P, et al. Immunobiological effects of gemcitabine and capecitabine combination chemotherapy in advanced pancreatic ductal adenocarcinoma. Br J Cancer. 2016;114(5):510-8.

503. Casadei GA, Carloni S, Scarpi E, Maltoni P, Dorizzi RM, Passardi A, et al. Prognostic role of serum concentrations of high-sensitivity C-reactive protein in patients with metastatic colorectal cancer: results from the ITACa trial. Oncotarget. 2016;7(9):10193-202.

504. Sheng J, Yang YP, Ma YX, Qin T, Hu ZH, Hong SD, et al. Low Prognostic Nutritional Index Correlates with Worse Survival in Patients with Advanced NSCLC following EGFR-TKIs. PLoS One. 2016;11(1):e0147226.

505. Kou T, Kanai M, Yamamoto M, Xue P, Mori Y, Kudo Y, et al. Prognostic model for survival based on readily available pretreatment factors in patients with advanced pancreatic cancer receiving palliative chemotherapy. Int J Clin Oncol. 2016;21(1):118-25.

506. Ahn HK, Hwang IC, Lee JS, Sym SJ, Cho EK, Shin DB. Neutrophil-Lymphocyte Ratio Predicts Survival in Terminal Cancer Patients. J Palliat Med. 2016;19(4):437-41.

507. Axdorph U, Sjoberg J, Grimfors G, Landgren O, Porwit-Macdonald A, Bjorkholm M. Biological markers may add to prediction of outcome achieved by the International Prognostic Score in Hodgkin's disease. Ann Oncol. 2000;11(11):1405-11.

508. Vigano A, Bruera E, Jhangri GS, Newman SC, Fields AL, Suarez-Almazor ME. Clinical survival predictors in patients with advanced cancer. Arch Intern Med. 2000;160(6):861-8.

509. Marechal R, Demols A, Gay F, De M, V, Arvanitaki M, Hendlisz A, et al. Prognostic factors and prognostic index for chemonaive and gemcitabine-refractory patients with advanced pancreatic cancer. Oncology. 2007;73(1-2):41-51.

510. Lam PT, Leung MW, Tse CY. Identifying prognostic factors for survival in advanced cancer patients: a prospective study. Hong Kong Med J. 2007;13(6):453-9.

511. Paralkar VR, Li T, Langer CJ. Population characteristics and prognostic factors in metastatic non-small-cell lung cancer: a Fox Chase Cancer Center retrospective. Clin Lung Cancer. 2008;9(2):116-21.

512. Ngo L, Hee SW, Lim LC, Tao M, Quek R, Yap SP, et al. Prognostic factors in patients with diffuse large B cell lymphoma: Before and after the introduction of rituximab. Leuk Lymphoma. 2008;49(3):462-9.

513. Shim HJ, Yun JY, Hwang JE, Bae WK, Cho SH, Chung IJ. Prognostic factor analysis of third-line chemotherapy in patients with advanced gastric cancer. Gastric Cancer. 2011;14(3):249-56.

514. Tredan O, Ray-Coquard I, Chvetzoff G, Rebattu P, Bajard A, Chabaud S, et al. Validation of prognostic scores for survival in cancer patients beyond first-line therapy. BMC Cancer. 2011;11:95.

515. Lim KH, Han SW, Oh DY, Im SA, Kim TY, Bang YJ. Outcome of infusional 5-fluorouracil, doxorubicin, and mitomycin-C (iFAM) chemotherapy and analysis of prognostic factors in patients with refractory advanced biliary tract cancer. Oncology. 2012;83(2):57-66.

516. Prakash G, Sharma A, Raina V, Kumar L, Sharma MC, Mohanti BK. B cell non-Hodgkin's lymphoma: experience from a tertiary care cancer center. Ann Hematol. 2012;91(10):1603-11.

517. Kang EJ, Choi YJ, Kim JS, Park KH, Oh SC, Seo JH, et al. Prognostic Factors for the Selection of Patients Eligible for Second-Line Chemotherapy in Advanced Biliary Tract Cancer. Chemotherapy. 2014;60(2):91-8.

518. Ulas A, Turkoz FP, Silay K, Tokluoglu S, Avci N, Oksuzoglu B, et al. A laboratory prognostic index model for patients with advanced non-small cell lung cancer. PLoS One. 2014;9(12):e114471.

519. Imedio ER, Beveridge RD, Urtasun JA, Campos GB, Estelles DL, Esparcia MF, et al. Safety and efficacy of sorafenib in the treatment of advanced hepatocellular carcinoma: a single center experience. Med Oncol. 2014;31(5):948.

520. Malik L, Parsons H, Mahalingam D, Ehler B, Goros M, Mejia A, et al. Clinical outcomes and survival of advanced renal cancer patients in phase I clinical trials. Clin Genitourin Cancer. 2014;12(5):359-65.

521. Tsai HJ, Hsieh MY, Tsai YC, Liu ZY, Hsieh HY, Lee CM, et al. Liver function tests may be useful tools for advanced cancer patient care: a preliminary single-center result. Kaohsiung J Med Sci. 2014;30(3):146-52.

522. Stenman M, Laurell A, Lindskog M. Prognostic significance of serum albumin in patients with metastatic renal cell carcinoma. Med Oncol. 2014;31(3):841.

523. Koo DH, Ryu MH, Ryoo BY, Seo J, Lee MY, Chang HM, et al. Improving trends in survival of patients who receive chemotherapy for metastatic or recurrent gastric cancer: 12 years of experience at a single institution. Gastric Cancer. 2015;18(2):346-53.

524. Kao J, Gold KD, Zarrili G, Copel E, Silverman AJ, Ramsaran SS, et al. Clinical Predictors of Survival for Patients with Stage IV Cancer Referred to Radiation Oncology. PLoS One. 2015;10(4):e0124329.

525. Wild AT, Ye X, Ellsworth SG, Smith JA, Narang AK, Garg T, et al. The Association Between Chemoradiation-related Lymphopenia and Clinical Outcomes in Patients With Locally Advanced Pancreatic Adenocarcinoma. Am J Clin Oncol. 2015;38(3):259-65.

526. Helissey C, Berger F, Cottu P, Dieras V, Mignot L, Servois V, et al. Circulating tumor cell thresholds and survival scores in advanced metastatic breast cancer: the observational step of the CirCe01 phase III trial. Cancer Lett. 2015;360(2):213-8.

527. Narwani V, Gabriel J, Boyd K, Chevassut T. Absolute lymphocyte count at day 29 of treatment is a powerful predictor of outcome in multiple myeloma. Clin Lymphoma Myeloma Leuk. 2015;15(4):222-6.

528. Moon H, Roh JL, Lee SW, Kim SB, Choi SH, Nam SY, et al. Prognostic value of nutritional and hematologic markers in head and neck squamous cell carcinoma treated by chemoradiotherapy. Radiother Oncol. 2016;118(2):330-4.

529. Uemura K, Miyoshi Y, Kawahara T, Yoneyama S, Hattori Y, Teranishi J, et al. Prognostic value of a computer-aided diagnosis system involving bone scans among men treated with docetaxel for metastatic castration-resistant prostate cancer. BMC Cancer. 2016;16:109.

530. Dorajoo SR, Tan WJ, Koo SX, Tan WS, Chew MH, Tang CL, et al. A scoring model for predicting survival following primary tumour resection in stage IV colorectal cancer patients with unresectable metastasis. Int J Colorectal Dis. 2016;31(2):235-45.

531. Choi Y, Oh DY, Park H, Kim TY, Lee KH, Han SW, et al. More Accurate Prediction of Metastatic Pancreatic Cancer Patients' Survival with Prognostic Model Using Both Host Immunity and Tumor Metabolic Activity. PLoS One. 2016;11(1):e0145692.

532. Mandrekar SJ, Schild SE, Hillman SL, Allen KL, Marks RS, Mailliard JA, et al. A prognostic model for advanced stage nonsmall cell lung cancer. Pooled analysis of North Central Cancer Treatment Group trials. Cancer. 2006;107(4):781-92.

533. Tibaldi C, Vasile E, Bernardini I, Orlandini C, Andreuccetti M, Falcone A. Baseline elevated leukocyte count in peripheral blood is associated with poor survival in patients with advanced non-small cell lung cancer: a prognostic model. J Cancer Res Clin Oncol. 2008;134(10):1143-9.

534. Lee CK, Hudson M, Stockler M, Coates AS, Ackland S, Gebski V, et al. A nomogram to predict survival time in women starting first-line chemotherapy for advanced breast cancer. Breast Cancer Res Treat. 2011;129(2):467-76.

535. Kawashima A, Tsujimura A, Takayama H, Arai Y, Nin M, Tanigawa G, et al. Impact of hyponatremia on survival of patients with metastatic renal cell carcinoma treated with molecular targeted therapy. Int J Urol. 2012;19(12):1050-7.

536. Luo XL, He W, Huang H, Chen QY, Liang Y, Mai HQ, et al. Design of a prognostic score model for nasopharyngeal carcinoma. Head Neck. 2015;37(5):624-9.

537. Iacovelli R, Farcomeni A, Sternberg CN, Carteni G, Milella M, Santoni M, et al. Prognostic factors in patients receiving third line targeted therapy for metastatic renal cell carcinoma. J Urol. 2015;193(6):1905-10.

538. Ferrucci PF, Ascierto PA, Pigozzo J, Del VM, Maio M, Antonini Cappellini GC, et al. Baseline neutrophils and derived neutrophil-to-lymphocyte ratio: prognostic relevance in metastatic melanoma patients receiving ipilimumab. Ann Oncol. 2016;27(4):732-8.

539. Bille A, Krug LM, Woo KM, Rusch VW, Zauderer MG. Contemporary Analysis of Prognostic Factors in Patients with Unresectable Malignant Pleural Mesothelioma. J Thorac Oncol. 2016;11(2):249-55.

540. Zaragoza J, Caille A, Beneton N, Bens G, Christiann F, Maillard H, et al. High neutrophil to lymphocyte ratio measured before starting ipilimumab treatment is associated with reduced overall survival in patients with melanoma. Br J Dermatol. 2016;174(1):146-51.

541. Oki Y, Yamamoto K, Kato H, Kuwatsuka Y, Taji H, Kagami Y, et al. Low absolute lymphocyte count is a poor prognostic marker in patients with diffuse large B-cell lymphoma and suggests patients' survival benefit from rituximab. Eur J Haematol. 2008;81(6):448-53.

542. Furukawa K, Uwagawa T, Iwase R, Haruki K, Fujiwara Y, Gocho T, et al. Prognostic factors of unresectable pancreatic cancer treated with nafamostat mesilate combined with gemcitabine chemotherapy. Anticancer Res. 2012;32(11):5121-6.

543. Lin GN, Peng JW, Xiao JJ, Liu DY, Xia ZJ. Prognostic impact of circulating monocytes and lymphocyte-to-monocyte ratio on previously untreated metastatic non-small cell lung cancer patients receiving platinum-based doublet. Med Oncol. 2014;31(7):70.

544. Lin GN, Peng JW, Liu DY, Xiao JJ, Chen YQ, Chen XQ. Increased lymphocyte to monocyte ratio is associated with better prognosis in patients with newly diagnosed metastatic nasopharyngeal carcinoma receiving chemotherapy. Tumour Biol. 2014;35(11):10849-54.

545. Lin GN, Liu PP, Liu DY, Peng JW, Xiao JJ, Xia ZJ. Prognostic significance of the pre-chemotherapy lymphocyte-to-monocyte ratio in patients with previously untreated metastatic colorectal cancer receiving FOLFOX chemotherapy. Chin J Cancer. 2016;35:5.

546. Wu ES, Oduyebo T, Cobb LP, Cholakian D, Kong X, Fader AN, et al. Lymphopenia and its association with survival in patients with locally advanced cervical cancer. Gynecol Oncol. 2016;140(1):76-82.

547. Bari A, Tadmor T, Sacchi S, Marcheselli L, Liardo EV, Pozzi S, et al. Monocytosis has adverse prognostic significance and impacts survival in patients with T-cell lymphomas. Leuk Res. 2013;37(6):619-23.

548. Cho KS, Choi YD, Kim SJ, Kim CI, Chung BH, Seong dH, et al. A comprehensive prognostic stratification for patients with metastatic renal clear cell carcinoma. Yonsei Med J. 2008;49(3):451-8.

549. Chen YP, Zhao BC, Chen C, Shen LJ, Gao J, Mai ZY, et al. Pretreatment platelet count improves the prognostic performance of the TNM staging system and aids in planning therapeutic regimens for nasopharyngeal carcinoma: a single-institutional study of 2,626 patients. Chin J Cancer. 2015;34(3):137-46.

550. Hong X, Cui B, Wang M, Yang Z, Wang L, Xu Q. Systemic Immune-inflammation Index, Based on Platelet Counts and Neutrophil-Lymphocyte Ratio, Is Useful for Predicting Prognosis in Small Cell Lung Cancer. Tohoku J Exp Med. 2015;236(4):297-304.

551. Shoultz-Henley S, Garden AS, Mohamed AS, Sheu T, Kroll MH, Rosenthal DI, et al. Prognostic value of pretherapy platelet elevation in oropharyngeal cancer patients treated with chemoradiation. Int J Cancer. 2016;138(5):1290-7.

552. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. Oncology. 2007;73(3-4):215-20.

553. Teramukai S, Kitano T, Kishida Y, Kawahara M, Kubota K, Komuta K, et al. Pretreatment neutrophil count as an independent prognostic factor in advanced non-small-cell lung cancer: an analysis of Japan Multinational Trial Organisation LC00-03. Eur J Cancer. 2009;45(11):1950-8.

554. Kao SC, Pavlakis N, Harvie R, Vardy JL, Boyer MJ, van ZN, et al. High blood neutrophil-to-lymphocyte ratio is an indicator of poor prognosis in malignant mesothelioma patients undergoing systemic therapy. Clin Cancer Res. 2010;16(23):5805-13.

555. An X, Ding PR, Li YH, Wang FH, Shi YX, Wang ZQ, et al. Elevated neutrophil to lymphocyte ratio predicts survival in advanced pancreatic cancer. Biomarkers. 2010;15(6):516-22.

556. An X, Ding PR, Wang FH, Jiang WQ, Li YH. Elevated neutrophil to lymphocyte ratio predicts poor prognosis in nasopharyngeal carcinoma. Tumour Biol. 2011;32(2):317-24.

557. Chua W, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. Br J Cancer. 2011;104(8):1288-95.

558. Wang S, Zhang Z, Fang F, Gao X, Sun W, Liu H. The neutrophil/lymphocyte ratio is an independent prognostic indicator in patients with bone metastasis. Oncol Lett. 2011;2(4):735-40.

559. Kaneko M, Nozawa H, Sasaki K, Hongo K, Hiyoshi M, Tada N, et al. Elevated neutrophil to lymphocyte ratio predicts poor prognosis in advanced colorectal cancer patients receiving oxaliplatin-based chemotherapy. Oncology. 2012;82(5):261-8.

560. Pinato DJ, Stebbing J, Ishizuka M, Khan SA, Wasan HS, North BV, et al. A novel and validated prognostic index in hepatocellular carcinoma: the inflammation based index (IBI). J Hepatol. 2012;57(5):1013-20.

561. He W, Yin C, Guo G, Jiang C, Wang F, Qiu H, et al. Initial neutrophil lymphocyte ratio is superior to platelet lymphocyte ratio as an adverse prognostic and predictive factor in metastatic colorectal cancer. Med Oncol. 2013;30(1):439.

562. Unal D, Eroglu C, Kurtul N, Oguz A, Tasdemir A. Are neutrophil/lymphocyte and platelet/lymphocyte rates in patients with non-small cell lung cancer associated with treatment response and prognosis? Asian Pac J Cancer Prev. 2013;14(9):5237-42.

563. Yao Y, Yuan D, Liu H, Gu X, Song Y. Pretreatment neutrophil to lymphocyte ratio is associated with response to therapy and prognosis of advanced non-small cell lung cancer patients treated with first-line platinum-based chemotherapy. Cancer Immunol Immunother. 2013;62(3):471-9.

564. Cetin B, Berk V, Kaplan MA, Afsar B, Tufan G, Ozkan M, et al. Is the pretreatment neutrophil to lymphocyte ratio an important prognostic parameter in patients with metastatic renal cell carcinoma? Clin Genitourin Cancer. 2013;11(2):141-8.

565. Jafri SH, Shi R, Mills G. Advance lung cancer inflammation index (ALI) at diagnosis is a prognostic marker in patients with metastatic non-small cell lung cancer (NSCLC): a retrospective review. BMC Cancer. 2013;13:158.

566. Troppan K, Deutsch A, Gerger A, Stojakovic T, Beham-Schmid C, Wenzl K, et al. The derived neutrophil to lymphocyte ratio is an independent prognostic factor in patients with diffuse large B-cell lymphoma. Br J Cancer. 2014;110(2):369-74.

567. Kang MH, Go SI, Song HN, Lee A, Kim SH, Kang JH, et al. The prognostic impact of the neutrophil-to-lymphocyte ratio in patients with small-cell lung cancer. Br J Cancer. 2014;111(3):452-60.

568. Templeton AJ, Pezaro C, Omlin A, McNamara MG, Leibowitz-Amit R, Vera-Badillo FE, et al. Simple prognostic score for metastatic castration-resistant prostate cancer with incorporation of neutrophil-to-lymphocyte ratio. Cancer. 2014;120(21):3346-52.

569. Nuhn P, Vaghasia AM, Goyal J, Zhou XC, Carducci MA, Eisenberger MA, et al. Association of pretreatment neutrophil-to-lymphocyte ratio (NLR) and overall survival (OS)

in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with first-line docetaxel. BJU Int. 2014;114(6b):E11-E7.

570. Sonpavde G, Pond GR, Armstrong AJ, Clarke SJ, Vardy JL, Templeton AJ, et al. Prognostic impact of the neutrophil-to-lymphocyte ratio in men with metastatic castration-resistant prostate cancer. Clin Genitourin Cancer. 2014;12(5):317-24.

571. Keizman D, Gottfried M, Ish-Shalom M, Maimon N, Peer A, Neumann A, et al. Active smoking may negatively affect response rate, progression-free survival, and overall survival of patients with metastatic renal cell carcinoma treated with sunitinib. The oncologist. 2014;19(1):51-60.

572. Li X, Chen ZH, Ma XK, Chen J, Wu DH, Lin Q, et al. Neutrophil-to-lymphocyte ratio acts as a prognostic factor for patients with advanced hepatocellular carcinoma. Tumour Biol. 2014;35(11):11057-63.

573. Kacan T, Babacan NA, Seker M, Yucel B, Bahceci A, Eren AA, et al. Could the neutrophil to lymphocyte ratio be a poor prognostic factor for non small cell lung cancers? Asian Pac J Cancer Prev. 2014;15(5):2089-94.

574. Lin GN, Peng JW, Liu PP, Liu DY, Xiao JJ, Chen XQ. Elevated neutrophil-to-lymphocyte ratio predicts poor outcome in patients with advanced non-small-cell lung cancer receiving first-line gefitinib or erlotinib treatment. Asia Pac J Clin Oncol. 2014.

575. Yoo EJ, Park JC, Kim EH, Park CH, Shim CN, Lee HJ, et al. Prognostic value of neutrophil-to-lymphocyte ratio in patients treated with concurrent chemoradiotherapy for locally advanced oesophageal cancer. Dig Liver Dis. 2014;46(9):846-53.

576. Langsenlehner T, Thurner EM, Krenn-Pilko S, Langsenlehner U, Stojakovic T, Gerger A, et al. Validation of the neutrophil-to-lymphocyte ratio as a prognostic factor in a cohort of European prostate cancer patients. World J Urol. 2015;33(11):1661-7.

577. Jiang L, Jiang S, Situ D, Lin Y, Yang H, Li Y, et al. Prognostic value of monocyte and neutrophils to lymphocytes ratio in patients with metastatic soft tissue sarcoma. Oncotarget. 2015;6(11):9542-50.

578. Luo G, Guo M, Liu Z, Xiao Z, Jin K, Long J, et al. Blood neutrophil-lymphocyte ratio predicts survival in patients with advanced pancreatic cancer treated with chemotherapy. Ann Surg Oncol. 2015;22(2):670-6.

579. Chen ZY, Raghav K, Lieu CH, Jiang ZQ, Eng C, Vauthey JN, et al. Cytokine profile and prognostic significance of high neutrophil-lymphocyte ratio in colorectal cancer. Br J Cancer. 2015;112(6):1088-97.

580. Santoni M, Buti S, Conti A, Porta C, Procopio G, Sternberg CN, et al. Prognostic significance of host immune status in patients with late relapsing renal cell carcinoma treated with targeted therapy. Target Oncol. 2015;10(4):517-22.

581. Ho CL, Lu CS, Chen JH, Chen YG, Huang TC, Wu YY. Neutrophil/Lymphocyte Ratio, Lymphocyte/Monocyte Ratio, and Absolute Lymphocyte Count/Absolute Monocyte Count Prognostic Score in Diffuse Large B-Cell Lymphoma: Useful Prognostic Tools in the Rituximab Era. Medicine (Baltimore). 2015;94(24):e993.

582. Mitchell P, Thatcher N, Socinski MA, Wasilewska-Tesluk E, Horwood K, Szczesna A, et al. Tecemotide in unresectable stage III non-small-cell lung cancer in the phase III START study: updated overall survival and biomarker analyses. Ann Oncol. 2015;26(6):1134-42.

583. Wang YY, Bai ZL, He JL, Yang Y, Zhao R, Hai P, et al. Prognostic Value of Neutrophil-Related Factors in Locally Advanced Cervical Squamous Cell Carcinoma Patients Treated with Cisplatin-Based Concurrent Chemoradiotherapy. Dis Markers. 2016;2016:3740794.

584. Beltran BE, Aguilar C, Quinones P, Morales D, Chavez JC, Sotomayor EM, et al. The neutrophil-to-lymphocyte ratio is an independent prognostic factor in patients with peripheral T-cell lymphoma, unspecified. Leuk Lymphoma. 2016;57(1):58-62.

585. Zhang GM, Zhu Y, Gu WJ, Zhang HL, Shi GH, Ye DW. Pretreatment neutrophil-to-lymphocyte ratio predicts prognosis in patients with metastatic renal cell carcinoma receiving targeted therapy. Int J Clin Oncol. 2016;21(2):373-8.

586. Lee BS, Lee SH, Son JH, Jang DK, Chung KH, Lee YS, et al. Neutrophil-lymphocyte ratio predicts survival in patients with advanced cholangiocarcinoma on chemotherapy. Cancer Immunol Immunother. 2016;65(2):141-50.

587. Li ZM, Peng YF, Du CZ, Gu J. Colon cancer with unresectable synchronous metastases: the AAAP scoring system for predicting the outcome after primary tumour resection. Colorectal Dis. 2016;18(3):255-63.

588. Li J, Jiang R, Liu WS, Liu Q, Xu M, Feng QS, et al. A large cohort study reveals the association of elevated peripheral blood lymphocyte-to-monocyte ratio with favorable prognosis in nasopharyngeal carcinoma. PLoS One. 2013;8(12):e83069.

589. Rambaldi A, Boschini C, Gritti G, Delaini F, Oldani E, Rossi A, et al. The lymphocyte to monocyte ratio improves the IPI-risk definition of diffuse large B-cell lymphoma when rituximab is added to chemotherapy. Am J Hematol. 2013;88(12):1062-7.

590. Go SI, Kim RB, Song HN, Kang MH, Lee US, Choi HJ, et al. Prognostic significance of the lymphocyte-to-monocyte ratio in patients with small cell lung cancer. Med Oncol. 2014;31(12):323.

591. Koh YW, Jung SJ, Yoon DH, Suh C, Cha HJ, Go H, et al. The absolute lymphocyte to monocyte ratio is associated with poor prognosis in classical Hodgkin lymphoma patients younger than 60 years of age. Hematol Oncol. 2015;33(3):133-40.

592. Jiang R, Cai XY, Yang ZH, Yan Y, Zou X, Guo L, et al. Elevated peripheral blood lymphocyte-to-monocyte ratio predicts a favorable prognosis in the patients with metastatic nasopharyngeal carcinoma. Chin J Cancer. 2015;34(6):237-46.

593. Simon Z, Barna S, Miltenyi Z, Husi K, Magyari F, Jona A, et al. Combined prognostic value of absolute lymphocyte/monocyte ratio in peripheral blood and interim PET/CT results in Hodgkin lymphoma. Int J Hematol. 2016;103(1):63-9.

594. Liu H, Wu Y, Wang Z, Yao Y, Chen F, Zhang H, et al. Pretreatment platelet-to-lymphocyte ratio (PLR) as a predictor of response to first-line platinum-based chemotherapy and prognosis for patients with non-small cell lung cancer. J Thorac Dis. 2013;5(6):783-9.

595. Li X, Chen ZH, Xing YF, Wang TT, Wu DH, Wen JY, et al. Platelet-to-lymphocyte ratio acts as a prognostic factor for patients with advanced hepatocellular carcinoma. Tumour Biol. 2015;36(4):2263-9.

596. Jiang R, Zou X, Hu W, Fan YY, Yan Y, Zhang MX, et al. The elevated pretreatment platelet-to-lymphocyte ratio predicts poor outcome in nasopharyngeal carcinoma patients. Tumour Biol. 2015;36(10):7775-87.

597. Nakamura K, Nishida T, Haruma T, Haraga J, Omichi C, Ogawa C, et al. Pretreatment platelet-lymphocyte ratio is an independent predictor of cervical cancer

recurrence following concurrent chemoradiation therapy. Mol Clin Oncol. 2015;3(5):1001-6.

598. Langsenlehner T, Pichler M, Thurner EM, Krenn-Pilko S, Stojakovic T, Gerger A, et al. Evaluation of the platelet-to-lymphocyte ratio as a prognostic indicator in a European cohort of patients with prostate cancer treated with radiotherapy. Urol Oncol. 2015;33(5):201-16.

599. Cannon NA, Meyer J, Iyengar P, Ahn C, Westover KD, Choy H, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as prognostic factors after stereotactic radiation therapy for early-stage non-small-cell lung cancer. J Thorac Oncol. 2015;10(2):280-5.

600. Watt DG, Martin JC, Park JH, Horgan PG, McMillan DC. Neutrophil count is the most important prognostic component of the differential white cell count in patients undergoing elective surgery for colorectal cancer. American journal of surgery. 2015;210(1):24-30.

601. Halazun KJ, Aldoori A, Malik HZ, Al-Mukhtar A, Prasad KR, Toogood GJ, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2008;34(1):55-60.

602. Gomez D, Morris-Stiff G, Toogood GJ, Lodge JP, Prasad KR. Impact of systemic inflammation on outcome following resection for intrahepatic cholangiocarcinoma. Journal of surgical oncology. 2008;97(6):513-8.

603. Sarraf KM, Belcher E, Raevsky E, Nicholson AG, Goldstraw P, Lim E. Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. J Thorac Cardiovasc Surg. 2009;137(2):425-8.

604. Kishi Y, Kopetz S, Chun YS, Palavecino M, Abdalla EK, Vauthey JN. Blood neutrophil-to-lymphocyte ratio predicts survival in patients with colorectal liver metastases treated with systemic chemotherapy. Annals of surgical oncology. 2009;16(3):614-22.

605. Cho H, Hur HW, Kim SW, Kim SH, Kim JH, Kim YT, et al. Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. Cancer Immunol Immunother. 2009;58(1):15-23.

606. Smith RA, Bosonnet L, Raraty M, Sutton R, Neoptolemos JP, Campbell F, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. American journal of surgery. 2009;197(4):466-72.

607. Halazun KJ, Hardy MA, Rana AA, Woodland DCt, Luyten EJ, Mahadev S, et al. Negative impact of neutrophil-lymphocyte ratio on outcome after liver transplantation for hepatocellular carcinoma. Annals of surgery. 2009;250(1):141-51.

608. Jagdev SP, Gregory W, Vasudev NS, Harnden P, Sim S, Thompson D, et al. Improving the accuracy of pre-operative survival prediction in renal cell carcinoma with C-reactive protein. Br J Cancer. 2010;103(11):1649-56.

609. Ubukata H, Motohashi G, Tabuchi T, Nagata H, Konishi S, Tabuchi T. Evaluations of interferon-gamma/interleukin-4 ratio and neutrophil/lymphocyte ratio as prognostic indicators in gastric cancer patients. Journal of surgical oncology. 2010;102(7):742-7.

610. Shimada H, Takiguchi N, Kainuma O, Soda H, Ikeda A, Cho A, et al. High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric

cancer. Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association. 2010;13(3):170-6.

611. Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. American journal of surgery. 2010;200(2):197-203.

612. Mohri Y, Tanaka K, Ohi M, Yokoe T, Miki C, Kusunoki M. Prognostic significance of host- and tumor-related factors in patients with gastric cancer. World journal of surgery. 2010;34(2):285-90.

613. Liu H, Liu G, Bao Q, Sun W, Bao H, Bi L, et al. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in rectal carcinoma. J Gastrointest Cancer. 2010;41(2):116-20.

614. Kao SC, Klebe S, Henderson DW, Reid G, Chatfield M, Armstrong NJ, et al. Low calretinin expression and high neutrophil-to-lymphocyte ratio are poor prognostic factors in patients with malignant mesothelioma undergoing extrapleural pneumonectomy. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2011;6(11):1923-9.

615. Jung MR, Park YK, Jeong O, Seon JW, Ryu SY, Kim DY, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts poor survival following resection in late stage gastric cancer. Journal of surgical oncology. 2011;104(5):504-10.

616. Sharaiha RZ, Halazun KJ, Mirza F, Port JL, Lee PC, Neugut AI, et al. Elevated preoperative neutrophil:lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. Annals of surgical oncology. 2011;18(12):3362-9.

617. Tomita M, Shimizu T, Ayabe T, Yonei A, Onitsuka T. Preoperative neutrophil to lymphocyte ratio as a prognostic predictor after curative resection for non-small cell lung cancer. Anticancer Res. 2011;31(9):2995-8.

618. Hung HY, Chen JS, Yeh CY, Changchien CR, Tang R, Hsieh PS, et al. Effect of preoperative neutrophil-lymphocyte ratio on the surgical outcomes of stage II colon cancer patients who do not receive adjuvant chemotherapy. International journal of colorectal disease. 2011;26(8):1059-65.

619. Neal CP, Mann CD, Garcea G, Briggs CD, Dennison AR, Berry DP. Preoperative systemic inflammation and infectious complications after resection of colorectal liver metastases. Arch Surg. 2011;146(4):471-8.

620. Asher V, Lee J, Innamaa A, Bali A. Preoperative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2011;13(7):499-503.

621. Wang GY, Yang Y, Li H, Zhang J, Jiang N, Li MR, et al. A scoring model based on neutrophil to lymphocyte ratio predicts recurrence of HBV-associated hepatocellular carcinoma after liver transplantation. PloS one. 2011;6(9):e25295.

622. Bertuzzo VR, Cescon M, Ravaioli M, Grazi GL, Ercolani G, Del Gaudio M, et al. Analysis of factors affecting recurrence of hepatocellular carcinoma after liver transplantation with a special focus on inflammation markers. Transplantation. 2011;91(11):1279-85.

623. Idowu OK, Ding Q, Taktak AF, Chandrasekar CR, Yin Q. Clinical implication of pretreatment neutrophil to lymphocyte ratio in soft tissue sarcoma. Biomarkers. 2012;17(6):539-44.

624. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Shibuya N, Kubota K. Clinical significance of tumor pathology for postoperative survival of patients undergoing surgery for stage IV colorectal cancer. Anticancer Res. 2012;32(8):3291-7.

625. Gondo T, Nakashima J, Ohno Y, Choichiro O, Horiguchi Y, Namiki K, et al. Prognostic value of neutrophil-to-lymphocyte ratio and establishment of novel preoperative risk stratification model in bladder cancer patients treated with radical cystectomy. Urology. 2012;79(5):1085-91.

626. Kwon HC, Kim SH, Oh SY, Lee S, Lee JH, Choi HJ, et al. Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers. 2012;17(3):216-22.

627. Wang L, Lin Y, Long H, Liu H, Rao H, He Y, et al. Esophageal carcinosarcoma: a unique entity with better prognosis. Annals of surgical oncology. 2013;20(3):997-1004.

628. Choi ES, Kim HS, Han I. Elevated preoperative systemic inflammatory markers predict poor outcome in localized soft tissue sarcoma. Annals of surgical oncology. 2014;21(3):778-85.

629. Szkandera J, Absenger G, Liegl-Atzwanger B, Pichler M, Stotz M, Samonigg H, et al. Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients. Br J Cancer. 2013;108(8):1677-83.

630. Krane LS, Richards KA, Kader AK, Davis R, Balaji KC, Hemal AK. Preoperative neutrophil/lymphocyte ratio predicts overall survival and extravesical disease in patients undergoing radical cystectomy. J Endourol. 2013;27(8):1046-50.

631. Pichler M, Hutterer GC, Stoeckigt C, Chromecki TF, Stojakovic T, Golbeck S, et al. Validation of the pre-treatment neutrophil-lymphocyte ratio as a prognostic factor in a large European cohort of renal cell carcinoma patients. Br J Cancer. 2013;108(4):901-7.

632. Jankova L, Dent OF, Chan C, Chapuis P, Clarke SJ. Preoperative neutrophil/lymphocyte ratio predicts overall survival but does not predict recurrence or cancer-specific survival after curative resection of node-positive colorectal cancer. BMC cancer. 2013;13:442.

633. Fu SJ, Shen SL, Li SQ, Hua YP, Hu WJ, Liang LJ, et al. Prognostic value of preoperative peripheral neutrophil-to-lymphocyte ratio in patients with HBV-associated hepatocellular carcinoma after radical hepatectomy. Medical oncology (Northwood, London, England). 2013;30(4):721.

634. Shibutani M, Maeda K, Nagahara H, Noda E, Ohtani H, Nishiguchi Y, et al. A high preoperative neutrophil-to-lymphocyte ratio is associated with poor survival in patients with colorectal cancer. Anticancer Res. 2013;33(8):3291-4.

635. Forget P, Machiels JP, Coulie PG, Berliere M, Poncelet AJ, Tombal B, et al. Neutrophil:lymphocyte ratio and intraoperative use of ketorolac or diclofenac are prognostic factors in different cohorts of patients undergoing breast, lung, and kidney cancer surgery. Annals of surgical oncology. 2013;20 Suppl 3:S650-60.

636. Absenger G, Szkandera J, Pichler M, Stotz M, Arminger F, Weissmueller M, et al. A derived neutrophil to lymphocyte ratio predicts clinical outcome in stage II and III colon cancer patients. Br J Cancer. 2013;109(2):395-400.

637. Mano Y, Shirabe K, Yamashita Y, Harimoto N, Tsujita E, Takeishi K, et al. Preoperative neutrophil-to-lymphocyte ratio is a predictor of survival after hepatectomy for hepatocellular carcinoma: a retrospective analysis. Annals of surgery. 2013;258(2):301-5.

638. Azuma T, Matayoshi Y, Odani K, Sato Y, Sato Y, Nagase Y, et al. Preoperative neutrophil-lymphocyte ratio as an independent prognostic marker for patients with upper urinary tract urothelial carcinoma. Clin Genitourin Cancer. 2013;11(3):337-41.

639. Dumitrascu T, Chirita D, Ionescu M, Popescu I. Resection for hilar cholangiocarcinoma: analysis of prognostic factors and the impact of systemic inflammation on long-term outcome. J Gastrointest Surg. 2013;17(5):913-24.

640. Perisanidis C, Kornek G, Poschl PW, Holzinger D, Pirklbauer K, Schopper C, et al. High neutrophil-to-lymphocyte ratio is an independent marker of poor disease-specific survival in patients with oral cancer. Medical oncology (Northwood, London, England). 2013;30(1):334.

641. Noh H, Eomm M, Han A. Usefulness of pretreatment neutrophil to lymphocyte ratio in predicting disease-specific survival in breast cancer patients. J Breast Cancer. 2013;16(1):55-9.

642. Liao Y, Ni Y, He R, Liu W, Du J. Clinical implications of fibroblast activation protein-alpha in non-small cell lung cancer after curative resection: a new predictor for prognosis. J Cancer Res Clin Oncol. 2013;139(9):1523-8.

643. Bambury RM, Teo MY, Power DG, Yusuf A, Murray S, Battley JE, et al. The association of pre-treatment neutrophil to lymphocyte ratio with overall survival in patients with glioblastoma multiforme. J Neurooncol. 2013;114(1):149-54.

644. Toiyama Y, Inoue Y, Saigusa S, Kawamura M, Kawamoto A, Okugawa Y, et al. C-reactive protein as predictor of recurrence in patients with rectal cancer undergoing chemoradiotherapy followed by surgery. Anticancer Res. 2013;33(11):5065-74.

645. Szkandera J, Gerger A, Liegl-Atzwanger B, Absenger G, Stotz M, Friesenbichler J, et al. The lymphocyte/monocyte ratio predicts poor clinical outcome and improves the predictive accuracy in patients with soft tissue sarcomas. International journal of cancer. 2014;135(2):362-70.

646. Dalpiaz O, Ehrlich GC, Mannweiler S, Hernandez JM, Gerger A, Stojakovic T, et al. Validation of pretreatment neutrophil-lymphocyte ratio as a prognostic factor in a European cohort of patients with upper tract urothelial carcinoma. BJU international. 2014;114(3):334-9.

647. Luo HL, Chen YT, Chuang YC, Cheng YT, Lee WC, Kang CH, et al. Subclassification of upper urinary tract urothelial carcinoma by the neutrophil-to-lymphocyte ratio (NLR) improves prediction of oncological outcome. BJU international. 2014;113(5b):E144-9.

648. Zhang T, Jiang Y, Qu X, Shen H, Liu Q, Du J. Evaluation of preoperative hematologic markers as prognostic factors and establishment of novel risk stratification in resected pN0 non-small-cell lung cancer. PloS one. 2014;9(10):e111494.

649. Ying HQ, Deng QW, He BS, Pan YQ, Wang F, Sun HL, et al. The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. Medical oncology (Northwood, London, England). 2014;31(12):305.

650. Linton A, Pavlakis N, O'Connell R, Soeberg M, Kao S, Clarke S, et al. Factors associated with survival in a large series of patients with malignant pleural mesothelioma in New South Wales. Br J Cancer. 2014;111(9):1860-9.

651. Kubo T, Ono S, Ueno H, Shinto E, Yamamoto J, Hase K. Impact of the perioperative neutrophil-to-lymphocyte ratio on the long-term survival following an elective resection of colorectal carcinoma. International journal of colorectal disease. 2014;29(9):1091-9.

652. Viers BR, Houston Thompson R, Boorjian SA, Lohse CM, Leibovich BC, Tollefson MK. Preoperative neutrophil-lymphocyte ratio predicts death among patients with localized clear cell renal carcinoma undergoing nephrectomy. Urologic oncology. 2014;32(8):1277-84.

653. Koh YW, Lee HJ, Ahn JH, Lee JW, Gong G. Prognostic significance of the ratio of absolute neutrophil to lymphocyte counts for breast cancer patients with ER/PR-positivity and HER2-negativity in neoadjuvant setting. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2014;35(10):9823-30.

654. Hermanns T, Bhindi B, Wei Y, Yu J, Noon AP, Richard PO, et al. Pre-treatment neutrophil-to-lymphocyte ratio as predictor of adverse outcomes in patients undergoing radical cystectomy for urothelial carcinoma of the bladder. Br J Cancer. 2014;111(3):444-51.

655. Tanaka N, Kikuchi E, Kanao K, Matsumoto K, Shirotake S, Miyazaki Y, et al. A multi-institutional validation of the prognostic value of the neutrophil-to-lymphocyte ratio for upper tract urothelial carcinoma treated with radical nephroureterectomy. Annals of surgical oncology. 2014;21(12):4041-8.

656. Jiang N, Deng JY, Liu Y, Ke B, Liu HG, Liang H. The role of preoperative neutrophil-lymphocyte and platelet-lymphocyte ratio in patients after radical resection for gastric cancer. Biomarkers. 2014;19(6):444-51.

657. Yuan D, Zhu K, Li K, Yan R, Jia Y, Dang C. The preoperative neutrophil-lymphocyte ratio predicts recurrence and survival among patients undergoing R0 resections of adenocarcinomas of the esophagogastric junction. Journal of surgical oncology. 2014;110(3):333-40.

658. Ozdemir Y, Akin ML, Sucullu I, Balta AZ, Yucel E. Pretreatment neutrophil/lymphocyte ratio as a prognostic aid in colorectal cancer. Asian Pacific journal of cancer prevention : APJCP. 2014;15(6):2647-50.

659. Feng JF, Huang Y, Chen QX. Preoperative platelet lymphocyte ratio (PLR) is superior to neutrophil lymphocyte ratio (NLR) as a predictive factor in patients with esophageal squamous cell carcinoma. World journal of surgical oncology. 2014;12:58.

660. Viers BR, Boorjian SA, Frank I, Tarrell RF, Thapa P, Karnes RJ, et al. Pretreatment neutrophil-to-lymphocyte ratio is associated with advanced pathologic tumor stage and increased cancer-specific mortality among patients with urothelial carcinoma of the bladder undergoing radical cystectomy. Eur Urol. 2014;66(6):1157-64.

661. McNamara MG, Templeton AJ, Maganti M, Walter T, Horgan AM, McKeever L, et al. Neutrophil/lymphocyte ratio as a prognostic factor in biliary tract cancer. European journal of cancer (Oxford, England : 1990). 2014;50(9):1581-9.

662. Malietzis G, Giacometti M, Askari A, Nachiappan S, Kennedy RH, Faiz OD, et al. A preoperative neutrophil to lymphocyte ratio of 3 predicts disease-free survival after curative elective colorectal cancer surgery. Annals of surgery. 2014;260(2):287-92.

663. Grivas N, Kafarakis V, Tsimaris I, Raptis P, Hastazeris K, Stavropoulos NE. Clinico-pathological prognostic factors of renal cell carcinoma: A 15-year review from a single center in Greece. Urology annals. 2014;6(2):116-21.

664. Shen L, Zhang H, Liang L, Li G, Fan M, Wu Y, et al. Baseline neutrophil-lymphocyte ratio (>/=2.8) as a prognostic factor for patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation. Radiation oncology (London, England). 2014;9:295.

665. Neofytou K, Smyth EC, Giakoustidis A, Khan AZ, Cunningham D, Mudan S. Elevated platelet to lymphocyte ratio predicts poor prognosis after hepatectomy for liver-only colorectal metastases, and it is superior to neutrophil to lymphocyte ratio as an adverse prognostic factor. Medical oncology (Northwood, London, England). 2014;31(10):239.

666. Song Y, Liu H, Gao L, Liu X, Ma L, Lu M, et al. Preoperative neutrophil-to-lymphocyte ratio as prognostic predictor for hypopharyngeal squamous cell carcinoma after radical resections. J Craniofac Surg. 2015;26(2):e137-40.

667. Takahashi Y, Horio H, Hato T, Harada M, Matsutani N, Morita S, et al. Prognostic Significance of Preoperative Neutrophil-Lymphocyte Ratios in Patients with Stage I Non-small Cell Lung Cancer After Complete Resection. Annals of surgical oncology. 2015;22 Suppl 3:S1324-31.

668. Tu XP, Qiu QH, Chen LS, Luo XN, Lu ZM, Zhang SY, et al. Preoperative neutrophil-to-lymphocyte ratio is an independent prognostic marker in patients with laryngeal squamous cell carcinoma. BMC cancer. 2015;15:743.

669. Shin JS, Suh KW, Oh SY. Preoperative neutrophil to lymphocyte ratio predicts survival in patients with T1-2N0 colorectal cancer. Journal of surgical oncology. 2015;112(6):654-7.

670. Que Y, Qiu H, Li Y, Chen Y, Xiao W, Zhou Z, et al. Preoperative platelet-lymphocyte ratio is superior to neutrophil-lymphocyte ratio as a prognostic factor for soft-tissue sarcoma. BMC cancer. 2015;15:648.

671. Hsu JT, Liao CK, Le PH, Chen TH, Lin CJ, Chen JS, et al. Prognostic Value of the Preoperative Neutrophil to Lymphocyte Ratio in Resectable Gastric Cancer. Medicine (Baltimore). 2015;94(39):e1589.

672. Shimizu K, Okita R, Saisho S, Maeda A, Nojima Y, Nakata M. Preoperative neutrophil/lymphocyte ratio and prognostic nutritional index predict survival in patients with non-small cell lung cancer. World journal of surgical oncology. 2015;13:291.

673. Han S, Liu Y, Li Q, Li Z, Hou H, Wu A. Pre-treatment neutrophil-to-lymphocyte ratio is associated with neutrophil and T-cell infiltration and predicts clinical outcome in patients with glioblastoma. BMC cancer. 2015;15:617.

674. Liao R, Tang ZW, Li DW, Luo SQ, Huang P, Du CY. Preoperative neutrophil-to-lymphocyte ratio predicts recurrence of patients with single-nodule small hepatocellular carcinoma following curative resection: a retrospective report. World journal of surgical oncology. 2015;13:265.

675. Aldemir MN, Turkeli M, Simsek M, Yildirim N, Bilen Y, Yetimoglu H, et al. Prognostic Value of Baseline Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratios in Local and Advanced Gastric Cancer Patients. Asian Pacific journal of cancer prevention : APJCP. 2015;16(14):5933-7.

676. Kadota K, Nitadori J, Ujiie H, Buitrago DH, Woo KM, Sima CS, et al. Prognostic Impact of Immune Microenvironment in Lung Squamous Cell Carcinoma: Tumor-

Infiltrating CD10+ Neutrophil/CD20+ Lymphocyte Ratio as an Independent Prognostic Factor. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2015;10(9):1301-10.

677. Neofytou K, Smyth EC, Giakoustidis A, Khan AZ, Williams R, Cunningham D, et al. The Preoperative Lymphocyte-to-Monocyte Ratio is Prognostic of Clinical Outcomes for Patients with Liver-Only Colorectal Metastases in the Neoadjuvant Setting. Annals of surgical oncology. 2015;22(13):4353-62.

678. Bagante F, Tran TB, Postlewait LM, Maithel SK, Wang TS, Evans DB, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratio as predictors of disease specific survival after resection of adrenocortical carcinoma. Journal of surgical oncology. 2015;112(2):164-72.

679. Wang Q, Blank S, Fiel MI, Kadri H, Luan W, Warren L, et al. The Severity of Liver Fibrosis Influences the Prognostic Value of Inflammation-Based Scores in Hepatitis B-Associated Hepatocellular Carcinoma. Annals of surgical oncology. 2015;22 Suppl 3:S1125-32.

680. Pine JK, Morris E, Hutchins GG, West NP, Jayne DG, Quirke P, et al. Systemic neutrophil-to-lymphocyte ratio in colorectal cancer: the relationship to patient survival, tumour biology and local lymphocytic response to tumour. Br J Cancer. 2015;113(2):204-11.

681. Li J, Lin J, Luo Y, Kuang M, Liu Y. Multivariate Analysis of Prognostic Biomarkers in Surgically Treated Endometrial Cancer. PloS one. 2015;10(6):e0130640.

682. Zhang H, Xia H, Zhang L, Zhang B, Yue D, Wang C. Clinical significance of preoperative neutrophil-lymphocyte vs platelet-lymphocyte ratio in primary operable patients with non-small cell lung cancer. American journal of surgery. 2015;210(3):526-35.

683. Zhang Y, Jiang C, Li J, Sun J, Qu X. Prognostic significance of preoperative neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in patients with gallbladder carcinoma. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2015;17(10):810-8.

684. Qu JL, Qu XJ, Li Z, Zhang JD, Liu J, Teng YE, et al. Prognostic Model Based on Systemic Inflammatory Response and Clinicopathological Factors to Predict Outcome of Patients with Node-Negative Gastric Cancer. PloS one. 2015;10(6):e0128540.

685. Zhang WW, Liu KJ, Hu GL, Liang WJ. Preoperative platelet/lymphocyte ratio is a superior prognostic factor compared to other systemic inflammatory response markers in ovarian cancer patients. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2015;36(11):8831-7.

686. Yu L, Lv CY, Yuan AH, Chen W, Wu AW. Significance of the preoperative neutrophil-to-lymphocyte ratio in the prognosis of patients with gastric cancer. World journal of gastroenterology. 2015;21(20):6280-6.

687. Duan H, Zhang X, Wang FX, Cai MY, Ma GW, Yang H, et al. Prognostic role of neutrophil-lymphocyte ratio in operable esophageal squamous cell carcinoma. World journal of gastroenterology. 2015;21(18):5591-7.

688. Wen RM, Zhang YJ, Ma S, Xu YL, Chen YS, Li HL, et al. Preoperative Neutrophil to Lymphocyte Ratio as a Prognostic Factor in Patients with Non-metastatic Renal Cell Carcinoma. Asian Pacific journal of cancer prevention : APJCP. 2015;16(9):3703-8.

689. Choi WJ, Cleghorn MC, Jiang H, Jackson TD, Okrainec A, Quereshy FA. Preoperative Neutrophil-to-Lymphocyte Ratio is a Better Prognostic Serum Biomarker than Platelet-to-Lymphocyte Ratio in Patients Undergoing Resection for Nonmetastatic Colorectal Cancer. Annals of surgical oncology. 2015;22 Suppl 3:S603-13.

690. Deng Q, He B, Liu X, Yue J, Ying H, Pan Y, et al. Prognostic value of pre-operative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model. Journal of translational medicine. 2015;13:66.

691. Spolverato G, Maqsood H, Kim Y, Margonis G, Luo T, Ejaz A, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratio in patients after resection for hepato-pancreatico-biliary malignancies. Journal of surgical oncology. 2015;111(7):868-74.

692. Han LH, Jia YB, Song QX, Wang JB, Wang NN, Cheng YF. Prognostic significance of preoperative lymphocyte-monocyte ratio in patients with resectable esophageal squamous cell carcinoma. Asian Pacific journal of cancer prevention : APJCP. 2015;16(6):2245-50.

693. Kim EY, Lee JW, Yoo HM, Park CH, Song KY. The Platelet-to-Lymphocyte Ratio Versus Neutrophil-to-Lymphocyte Ratio: Which is Better as a Prognostic Factor in Gastric Cancer? Annals of surgical oncology. 2015;22(13):4363-70.

694. Chan AW, Chan SL, Wong GL, Wong VW, Chong CC, Lai PB, et al. Prognostic Nutritional Index (PNI) Predicts Tumor Recurrence of Very Early/Early Stage Hepatocellular Carcinoma After Surgical Resection. Annals of surgical oncology. 2015;22(13):4138-48.

695. Choi JE, Villarreal J, Lasala J, Gottumukkala V, Mehran RJ, Rice D, et al. Perioperative neutrophil:lymphocyte ratio and postoperative NSAID use as predictors of survival after lung cancer surgery: a retrospective study. Cancer medicine. 2015;4(6):825-33.

696. Lee SK, Choi MY, Bae SY, Lee JH, Lee HC, Kil WH, et al. Immediate postoperative inflammation is an important prognostic factor in breast cancer. Oncology. 2015;88(6):337-44.

697. Wuxiao ZJ, Zhou HY, Wang KF, Chen XQ, Hao XB, Lu YD, et al. A prognostic model to predict survival in stage III colon cancer patients based on histological grade, preoperative carcinoembryonic antigen level and the neutrophil lymphocyte ratio. Asian Pacific journal of cancer prevention : APJCP. 2015;16(2):747-51.

698. Chen Q, Yang LX, Li XD, Yin D, Shi SM, Chen EB, et al. The elevated preoperative neutrophil-to-lymphocyte ratio predicts poor prognosis in intrahepatic cholangiocarcinoma patients undergoing hepatectomy. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2015;36(7):5283-9.

699. Kim M, Moon KC, Choi WS, Jeong CW, Kwak C, Kim HH, et al. Prognostic value of systemic inflammatory responses in patients with upper urinary tract urothelial carcinoma. World journal of urology. 2015;33(10):1439-57.

700. Szkandera J, Gerger A, Liegl-Atzwanger B, Stotz M, Samonigg H, Friesenbichler J, et al. The derived neutrophil/lymphocyte ratio predicts poor clinical outcome in soft tissue sarcoma patients. American journal of surgery. 2015;210(1):111-6.

701. Ben Q, An W, Wang L, Wang W, Yu L, Yuan Y. Validation of the pretreatment neutrophil-lymphocyte ratio as a predictor of overall survival in a cohort of patients with pancreatic ductal adenocarcinoma. Pancreas. 2015;44(3):471-7.

702. Graziosi L, Marino E, De Angelis V, Rebonato A, Cavazzoni E, Donini A. Prognostic value of preoperative neutrophils to lymphocytes ratio in patients resected for gastric cancer. American journal of surgery. 2015;209(2):333-7.

703. Takahashi R, Mabuchi S, Kawano M, Sasano T, Matsumoto Y, Kuroda H, et al. Prognostic significance of systemic neutrophil and leukocyte alterations in surgically treated endometrial cancer patients: a monoinstitutional study. Gynecol Oncol. 2015;137(1):112-8.

704. Shirai Y, Shiba H, Sakamoto T, Horiuchi T, Haruki K, Fujiwara Y, et al. Preoperative platelet to lymphocyte ratio predicts outcome of patients with pancreatic ductal adenocarcinoma after pancreatic resection. Surgery. 2015;158(2):360-5.

705. Chen Q, Dai Z, Yin D, Yang LX, Wang Z, Xiao YS, et al. Negative impact of preoperative platelet-lymphocyte ratio on outcome after hepatic resection for intrahepatic cholangiocarcinoma. Medicine (Baltimore). 2015;94(13):e574.

706. Lian L, Xia YY, Zhou C, Shen XM, Li XL, Han SG, et al. Application of platelet/lymphocyte and neutrophil/lymphocyte ratios in early diagnosis and prognostic prediction in patients with resectable gastric cancer. Cancer biomarkers : section A of Disease markers. 2015;15(6):899-907.

707. Xie X, Luo KJ, Hu Y, Wang JY, Chen J. Prognostic value of preoperative platelet-lymphocyte and neutrophil-lymphocyte ratio in patients undergoing surgery for esophageal squamous cell cancer. Dis Esophagus. 2016;29(1):79-85.

708. Mohri Y, Tanaka K, Toiyama Y, Ohi M, Yasuda H, Inoue Y, et al. Impact of Preoperative Neutrophil to Lymphocyte Ratio and Postoperative Infectious Complications on Survival After Curative Gastrectomy for Gastric Cancer: A Single Institutional Cohort Study. Medicine (Baltimore). 2016;95(11):e3125.

709. Takahashi Y, Kawamura M, Hato T, Harada M, Matsutani N, Horio H. Neutrophil-Lymphocyte Ratio as a Prognostic Marker for Lung Adenocarcinoma After Complete Resection. World journal of surgery. 2016;40(2):365-72.

710. Cheng YC, Huang CN, Wu WJ, Li CC, Ke HL, Li WM, et al. The Prognostic Significance of Inflammation-Associated Blood Cell Markers in Patients with Upper Tract Urothelial Carcinoma. Annals of surgical oncology. 2016;23(1):343-51.

711. Turner N, Wong HL, Templeton A, Tripathy S, Whiti Rogers T, Croxford M, et al. Analysis of local chronic inflammatory cell infiltrate combined with systemic inflammation improves prognostication in stage II colon cancer independent of standard clinicopathologic criteria. International journal of cancer. 2016;138(3):671-8.

712. Fu Y, Liu W, OuYang D, Yang A, Zhang Q. Preoperative Neutrophil-to-lymphocyte Ratio Predicts Long-term Survival in Patients Undergoing Total Laryngectomy With Advanced Laryngeal Squamous Cell Carcinoma: A Single-center Retrospective Study. Medicine (Baltimore). 2016;95(6):e2689.

713. Lu SD, Wang YY, Peng NF, Peng YC, Zhong JH, Qin HG, et al. Preoperative Ratio of Neutrophils to Lymphocytes Predicts Postresection Survival in Selected Patients With Early or Intermediate Stage Hepatocellular Carcinoma. Medicine (Baltimore). 2016;95(5):e2722.

714. Chen PC, Feng JF. A Novel Inflammation-Based Stage (I Stage) in Patients with Resectable Esophageal Squamous Cell Carcinoma. Mediators of inflammation. 2016;2016:5396747.

715. Wang SC, Chou JF, Strong VE, Brennan MF, Capanu M, Coit DG. Pretreatment Neutrophil to Lymphocyte Ratio Independently Predicts Disease-specific Survival in

Resectable Gastroesophageal Junction and Gastric Adenocarcinoma. Annals of surgery. 2016;263(2):292-7.

716. Hodek M, Sirak I, Ferko A, Orhalmi J, Hovorkova E, Hadzi Nikolov D, et al. Neoadjuvant chemoradiotherapy of rectal carcinoma : Baseline hematologic parameters influencing outcomes. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]. 2016;192(9):632-40.

717. Morizawa Y, Miyake M, Shimada K, Hori S, Tatsumi Y, Nakai Y, et al. Neutrophil-to-lymphocyte ratio as a detection marker of tumor recurrence in patients with muscle-invasive bladder cancer after radical cystectomy. Urologic oncology. 2016;34(6):257.e11-7.

718. Kosumi K, Baba Y, Ishimoto T, Harada K, Nakamura K, Ohuchi M, et al. Neutrophil/lymphocyte ratio predicts the prognosis in esophageal squamous cell carcinoma patients. Surgery today. 2016;46(4):405-13.

719. Kawahara T, Furuya K, Nakamura M, Sakamaki K, Osaka K, Ito H, et al. Neutrophil-to-lymphocyte ratio is a prognostic marker in bladder cancer patients after radical cystectomy. BMC cancer. 2016;16:185.

720. Kang M, Jeong CW, Kwak C, Kim HH, Ku JH. The Prognostic Significance of the Early Postoperative Neutrophil-to-Lymphocyte Ratio in Patients with Urothelial Carcinoma of the Bladder Undergoing Radical Cystectomy. Annals of surgical oncology. 2016;23(1):335-42.

721. Bhindi B, Hermanns T, Wei Y, Yu J, Richard PO, Wettstein MS, et al. Identification of the best complete blood count-based predictors for bladder cancer outcomes in patients undergoing radical cystectomy. Br J Cancer. 2016;114(2):207-12.

722. Raungkaewmanee S, Tangjitgamol S, Manusirivithaya S, Srijaipracharoen S, Thavaramara T. Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer. Journal of gynecologic oncology. 2012;23(4):265-73.

723. Feng JF, Huang Y, Zhao Q, Chen QX. Clinical significance of preoperative neutrophil lymphocyte ratio versus platelet lymphocyte ratio in patients with small cell carcinoma of the esophagus. ScientificWorldJournal. 2013;2013:504365.

724. Baranyai Z, Krzystanek M, Josa V, Dede K, Agoston E, Szasz AM, et al. The comparison of thrombocytosis and platelet-lymphocyte ratio as potential prognostic markers in colorectal cancer. Thrombosis and haemostasis. 2014;111(3):483-90.

725. Krenn-Pilko S, Langsenlehner U, Thurner EM, Stojakovic T, Pichler M, Gerger A, et al. The elevated preoperative platelet-to-lymphocyte ratio predicts poor prognosis in breast cancer patients. Br J Cancer. 2014;110(10):2524-30.

726. Szkandera J, Pichler M, Absenger G, Stotz M, Arminger F, Weissmueller M, et al. The elevated preoperative platelet to lymphocyte ratio predicts decreased time to recurrence in colon cancer patients. American journal of surgery. 2014;208(2):210-4.

727. Zhang GM, Zhu Y, Luo L, Wan FN, Zhu YP, Sun LJ, et al. Preoperative lymphocyte-monocyte and platelet-lymphocyte ratios as predictors of overall survival in patients with bladder cancer undergoing radical cystectomy. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2015;36(11):8537-43.

728. Messager M, Neofytou K, Chaudry MA, Allum WH. Prognostic impact of preoperative platelets to lymphocytes ratio (PLR) on survival for oesophageal and junctional carcinoma treated with neoadjuvant chemotherapy: A retrospective monocentric study on 153 patients. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2015;41(10):1316-23.

729. Pang Q, Zhang LQ, Wang RT, Bi JB, Zhang JY, Qu K, et al. Platelet to lymphocyte ratio as a novel prognostic tool for gallbladder carcinoma. World journal of gastroenterology. 2015;21(21):6675-83.

730. Ozawa T, Ishihara S, Nishikawa T, Tanaka T, Tanaka J, Kiyomatsu T, et al. The preoperative platelet to lymphocyte ratio is a prognostic marker in patients with stage II colorectal cancer. International journal of colorectal disease. 2015;30(9):1165-71.

731. Saito H, Noji T, Okamura K, Tsuchikawa T, Shichinohe T, Hirano S. A new prognostic scoring system using factors available preoperatively to predict survival after operative resection of perihilar cholangiocarcinoma. Surgery. 2016;159(3):842-51.

732. Stotz M, Pichler M, Absenger G, Szkandera J, Arminger F, Schaberl-Moser R, et al. The preoperative lymphocyte to monocyte ratio predicts clinical outcome in patients with stage III colon cancer. Br J Cancer. 2014;110(2):435-40.

733. Hu P, Shen H, Wang G, Zhang P, Liu Q, Du J. Prognostic significance of systemic inflammation-based lymphocyte- monocyte ratio in patients with lung cancer: based on a large cohort study. PloS one. 2014;9(9):e108062.

734. Zhou X, Du Y, Xu J, Huang Z, Qiu T, Wang X, et al. The preoperative lymphocyte to monocyte ratio predicts clinical outcomes in patients with stage II/III gastric cancer. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2014;35(11):11659-66.

735. Hutterer GC, Stoeckigt C, Stojakovic T, Jesche J, Eberhard K, Pummer K, et al. Low preoperative lymphocyte-monocyte ratio (LMR) represents a potentially poor prognostic factor in nonmetastatic clear cell renal cell carcinoma. Urologic oncology. 2014;32(7):1041-8.

736. Wen J, Ye F, Huang X, Li S, Yang L, Xiao X, et al. Prognostic Significance of Preoperative Circulating Monocyte Count in Patients With Breast Cancer: Based on a Large Cohort Study. Medicine (Baltimore). 2015;94(49):e2266.

737. Lin ZX, Ruan DY, Li Y, Wu DH, Ma XK, Chen J, et al. Lymphocyte-to-monocyte ratio predicts survival of patients with hepatocellular carcinoma after curative resection. World journal of gastroenterology. 2015;21(38):10898-906.

738. Yoshida T, Kinoshita H, Yoshida K, Yanishi M, Inui H, Komai Y, et al. A novel risk stratification model, involving preoperative lymphocyte-monocyte ratio and standard pathological factors, for overall survival in patients with bladder cancer undergoing radical cystectomy. Japanese journal of clinical oncology. 2015;45(12):1162-7.

739. Yamagishi T, Fujimoto N, Nishi H, Miyamoto Y, Hara N, Asano M, et al. Prognostic significance of the lymphocyte-to-monocyte ratio in patients with malignant pleural mesothelioma. Lung cancer (Amsterdam, Netherlands). 2015;90(1):111-7.

740. Ozawa T, Ishihara S, Kawai K, Kazama S, Yamaguchi H, Sunami E, et al. Impact of a lymphocyte to monocyte ratio in stage IV colorectal cancer. The Journal of surgical research. 2015;199(2):386-92.

741. Hutterer GC, Sobolev N, Ehrlich GC, Gutschi T, Stojakovic T, Mannweiler S, et al. Pretreatment lymphocyte-monocyte ratio as a potential prognostic factor in a cohort of patients with upper tract urothelial carcinoma. Journal of clinical pathology. 2015;68(5):351-5.

742. Huang Y, Feng JF. Low preoperative lymphocyte to monocyte ratio predicts poor cancer-specific survival in patients with esophageal squamous cell carcinoma. OncoTargets and therapy. 2015;8:137-45.

743. Chen L, Zhang F, Sheng XG, Zhang SQ. Decreased pretreatment lymphocyte/monocyte ratio is associated with poor prognosis in stage Ib1-IIa cervical cancer patients who undergo radical surgery. OncoTargets and therapy. 2015;8:1355-62.

744. Peng W, Li C, Zhu WJ, Wen TF, Yan LN, Li B, et al. Prognostic value of the platelet to lymphocyte ratio change in liver cancer. The Journal of surgical research. 2015;194(2):464-70.

745. Peng W, Li C, Wen TF, Yan LN, Li B, Wang WT, et al. Neutrophil to lymphocyte ratio changes predict small hepatocellular carcinoma survival. The Journal of surgical research. 2014;192(2):402-8.

17. APPENDIX 1

17.1 Tables and Footnotes:

Table 17.1: Studies investigating the prognostic value of CRP in an unselected cohort of patients with advanced cancer

No: CRP	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Systemic Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer Survival (HR, 95% CI)	Overall survival (HR, 95% CI)	Independent Prognostic Factors
1.	Ueno et al 2000 (448)	Retrospective	Prostate	Japan	103	CRP: ≥50mg/L	Active Chemotherapy	N/A	98	N/A	Multivariate: 3.140 (1.51–6.55) p<0.010	Performance Status, CA19-9
2.	McMillan et al 2001 (449)	Retrospective	Multiple	UK	772	CRP (Continuous per 10-fold increase in CRP)	Multiple treatments including platinum chemo and radio	596	671	Multivariate: 2.21 (1.92-2.56) P< 0.0001	Multivariate: (Non-cancer survival) 5.48 (3.55-8.46) P < 0.001	Age, Albumin
3.	Scott et al 2002 (450)	Retrospective	Lung	UK	106	CRP>10mg/l CRP>100mg/l	Palliative chemo with supportive treatment but no mention of either specifically	N/A	106	N/A	Multivariate: >10mg/l: 1.78 (1.01-3.15) P=0.047 Multivariate: >100mg/l: 1.94 (1.41 – 2.65) P<0.001	Age, Tumour Type, Weight Loss, Karnofsky performance status, fatigue
4.	Bromwich et al 2004 (451)	Retrospective	Renal	UK	58	CRP >10mg/l	α-interferon treatment	N/A	55	N/A	Multivariate: 2.03 (1.09-3.80) P=0.026	CRP Only
5.	Elahi et al 2005 (452)	Retrospective	Lymphoma	UK	147	CRP (≤10/11-100/>100mg/L)	No mention of treatment but usually treated with chemo	82	147	Multivariate: 8.18 (4.80-13.95) p<0.001	Multivariate: 2.11 (1.22-3.64) P<0.001	CRP Only

6.	Casamassima et al 2005 (453)	Retrospective	Renal	Italy	110	CRP: 8mg/L	IL-2 plus gemcitabine and vinorelbine.	N/A	38	N/A	Multivariate: 4.13 (1.68–10.15) p=0.002	DFI less vs. greater than 12
7.	McArdle et al 2006 (454)	Prospective	Prostate	UK	62	CRP>10mg/L	Androgen Deprivation therapy +/- radio	38	41	Multivariate: 1.97 (0.99-3.92) p = 0.052	N/A	PSA
8.	Sawaki et al 2008 (455)	Retrospective	Pancreatic	Japan	66	CRP: 10-30mg/L >30mg/L	Gemcitabine 1st line therapy	N/A	56	N/A	Multivariate: 10–30mg/L: 3.08 (1.18–8.00) p=0.002 >30mg/L 5.99 (2.33–15.45) p=0.002	Location, diameter of tumour, Liver Mets
9.	Al Murri et al 2006 (197)	Retrospective	Breast	UK	96	CRP>10mg/l	Chemotherapy and endocrine therapy	51	N/A	Multivariate: 2.50 (1.40–4.48) p=0.002	N/A	GPS
10.	Nakach et al 2007 (456)	Retrospective	Pancreatic	Japan	74	CRP>50mg/L	Second line palliative chemo	71	74	N/A	Multivariate: 3.291 (1.681–6.444) p=0.001	Performance Status, Peritoneal Dissemination
11.	Ramsey et al 2007 (31)	Retrospective	Renal Cell	UK	119	CRP: >10mg/L	Active Immunotherapy	102	N/A	Multivariate: 2.85 (1.49-5.45) P = 0.002	N/A	MSKCC, MRCCPS, GPS, Calcium, Albumin
12.	Tanaka et al 2008 (457)	Retrospective	Pancreatic	Japan	264	CRP>50mg/L	Single-agent gemcitabine therapy	235	264	N/A (PFS given but not CSS)	Multivariate: 1.86 (1.22–2.85) p<0.001	Karnofsky performance status, TNM stage, Hb, CA19-9
13.	Beer et al 2008 (458)	Prospective	Prostate	USA	160	CRP: 8mg/L	Docetaxel-based chemotherapy	N/A	63	N/A	Multivariate: 1.41 (1.20–1.65) p<0.001	CRP Only
14.	Papadoniou et al 2008 (459)	Retrospective	Pancreatic	Greece	215	CRP-5-15mg/L >15mg/L	Multiple treatments but all palliative	N/A	215	N/A	Univariate: 5-15mg/l: 8.08 (4.26-15.26) p<0.001	Tumour location in tail, Lymph node spread, Treatment, Performance status,

											Univariate: >15mg/l: 18.69 (8.23-42.40) p<0.001	Weight loss, CEA and Jaundice
15.	Yoshida et al 2008 (460)	Retrospective	Muscle-invasive bladder cancer	Japan	88	CRP > 5mg/L	ChRT: External beam radio and two cycles of cisplatin	23	N/A	Multivariate: 1.80 (1.01–2.97) p=0.046	N/A	T-stage
16.	Koch et al 2009 (461)	Retrospective	NSCLC	Sweden	289	CRP >10mg/L	Palliative supportive care and platinum based chemo	N/A	272	N/A	Multivariate: 1.50 (1.11–2.02) p<0.010	Stage, Performance Status, Smoking, Alb
17.	Hashimoto et al 2009 (462)	Retrospective	Pancreatic	Japan	326	CRP>10mg/L	Gemcitabine treatment with palliative intent	N/A	326	N/A	Multivariate: 0.56 (0.42–0.75) p=0.001 Inverse HR: 1.79 (1.33-2.38)	KPS, Liver Mets, Peritoneal Mets, ALP, LDH
18.	Zacharakis et al 2010 (463)	Retrospective	Colorectal	Greece	541	CRP: 5-15mg/l >15mg/l	Combination Chemotherapy	N/A	541	N/A	Multivariate: 5-15mg 1.374 (1.051 1.797) p=0.020 >15mg: 1.483 (1.077 2.040) p=0.016	low Hb, Low Alb, Fatigue, Blood transfusions, Combination Chemo, PS change
19.	Iwasa et al 2011 (464)	Retrospective	Gastric cancer	Japan	79	CRP≥20mg/L	5-FU based chemo	N/A	79	N/A	Multivariate: 2.03 (1.25–3.31) p<0.01	ECOG, Ascites, Alb,
20.	Falkensammer et al 2011 (465)	Retrospective	Renal Cell	Austria	86	CRP: >7mg/L	Active Chemotherapy	N/A	N/A (never given in text just HR)	N/A	Univariate: 2.92 (1.58–5.83) p=0.001	Anaemia, Erythropoietin, LDH, Neopeterin
21.	Masago et al 2010 (466)	Retrospective	Lung	Japan	79	CRP>10mg/L	Gefitinib chemotherapy	N/A	60	N/A	Multivariate: 1.48 (1.15–1.95) p=0.0073	EGFR
22.	Shimoda et al 2010 (467)	Retrospective	Pancreatic	Japan	83	CRP>10mg/L	50 patients received single-agent treatment with gemcitabine (GEM), 9 patients GEM combined with	N/A	83	N/A	Univariate: CRP: 0.92 (0.67–1.27) p=0.6099	Albumin

							radiotherapy (GEM+R) and 24 patients had best supportive care (BSC).				Inverse HR: 1.09 (0.79-1.50)	
23.	Shinohara et al 2013 (468)	Retrospective	Renal Cell	Japan	407	CRP>3mg/L	Multiple treatments including Cytokine 362 77 IFN-α, IL-2, Chemo & mastectomy Generally poor outcome	307	323	N/A	Multivariate: 2.1 (1.5–3.0) p<0.001	Time from initial diagnosis to metastasis, Hb, corrected Ca, LDH, Liver metastasis, Bone Metastasis, Lymph Node Metastasis
24.	Yi et al 2011 (469)	Retrospective	Pancreatic	Korea	298	CRP>12mg/L	Gemcitabine-based chemotherapy	N/A	298 (Not specifically mentioned)	N/A	Multivariate: 1.57: (1.07-2.30) p= 0.021	Metastasis to the liver, Ascites or carcinomatosis, Albumin
25.	Kume et al 2011 (470)	Retrospective	Renal Cell	Japan	94	CRP>3mg/l	Palliative chemo	N/A	86	N/A	Multivariate: 2.11 (1.13–3.93) p=0.018	Sarcomatid differentiation, Vertebral Bone Involvement, Extraosseous metastasis, ALP
26.	Lee et al 2011 (471)	Prospective	Multiple	Korea	126	CRP≥92mg/L	Palliative symptomatic control and chemotherapy	N/A	36	N/A	Multivariate: 2.44 (1.30-4.60) p=0.006	Chemotherapy
27.	Byström et al 2012 (472)	Retrospective	Colorectal	Sweden	106	CRP>5mg/L	Active Chemotherapy	N/A	60	N/A	Univariate: 1.46 (1.176-1.822) p=0.001 Multivariate: 1.11 (0.86-1.44) p=0.435	TPA, TIMP
28.	Ishioka et al 2012 (473)	Retrospective	Urothelial	Japan	223	CRP: Continuous	Palliative Chemo and radiotherapy for half with 45% treated with best supportive care	184	184	N/A	Multivariate: 1.60 (1.19–2.15) p=0.001	Age, ECOG PS≥2, Haemoglobin, Log (LDH) Visceral Metastasis, Lymph Node Metastasis

29.	Prins et al 2012 (474)	Retrospective	Prostate	USA	119	CRP: continuous, per each doubling of CRP)	End of life symptom care and palliative chemo	N/A	106	N/A	Multivariate: 1.11 (1.02–1.20) p=0.013	Alkaline phosphatase, Haemoglobin
30.	Zeng et al 2012 (475)	Retrospective	Laryngeal	China	57	CRP>8mg/L	Palliative chemo-radiotherapy including platinum chemo	29	N/A	Multivariate: 2.66 (1.22–5.82) p=0.014	N/A	Tumour site (glottic vs. supraglottic vs. subglottic)
31.	Pond et al 2012 (476)	Retrospective	Prostate	USA and Canada	116	CRP: ≥8 mg/L	Docetaxel-based chemotherapy	N/A	108	N/A	Multivariate: 1.37 (1.13 – 1.66) p=0.002	PCWG-2 Subtype, Risk groups, Halabi nomogram, Smaletz nomogram
32.	Kinoshita et al 2012 (477)	Prospective	HCC	Japan	135	CRP>10mg/L	Multimodal treatment including platinum chemo	N/A	123	N/A	Multivariate: 3.31 (1.73–6.32) p<0.001	a-Fetoprotein level, Tumour Numbers, Alb, CRP
33.	Morizane et al 2012 (478)	Retrospective	Urothelial	Japan	30	CRP>10mg/L	Gemcitabine-cisplatin or carboplatin	21	N/A	Multivariate: 4.61 (1.76-12.05) p=0.002	N/A	CRP Only
34.	Haas et al 2013 (479)	Retrospective	Pancreatic	Germany	291	CRP>10 mg/L but expressed as Log [80]	Palliative Chemo	N/A	237	N/A	Multivariate: 1.32 (1.06–1.63) p=0.011	Stage of Disease, Tumour Grading, KPS, Log
35.	Xia et al 2013 (480)	Prospective	Nasopharyngeal	China	335	CRP>2.46mg/L	Chemo, Radio and combined therapies	37	42	N/A	Multivariate: 2.114 (1.10-4.08) p=0.026	Node classification
36.	Yasuda et al 2013 (481)	Retrospective	RCC	Japan	52	CRP≥8mg/l	31 and 21 patients were administered sunitinib and sorafenib, respectively	20	22	N/A	Multivariate: 1.79 (1.15–2.86) p=0.0099	Neutrophils
37.	Shirakawa et al 2014 (482)	Retrospective	Oesophageal	Japan	163	CRP>10mg/L	Palliative Chemotherapy, which is platinum, based	N/A	163	N/A	Multivariate: 1.631 (1.119–2.376) p=0.011	Performance status, Number of Mets ≥3 versus <3
38.	Teishima et al 2014 (483)	Retrospective	Renal Cell	Japan	140	CRP>3mg/L	Active Molecular Therapy	70	73	N/A	Multivariate: 3.90 (2.06-7.37) P<0.001	Number of Mets, Prior nephrectomy

39.	Deberne et al 2014 (484)	Retrospective	Lung	France	55	CRP>7mg/L	Multiple treatments including chemotherapy, radiotherapy, and best supportive care some palliative surgery as well	N/A	50	N/A	Univariate: 4.3 (2.38-7.8) p<0.001	Leucocytes, Neutrophils, Hb, Alb, ALk P, Corrected Ca
40.	Beuselinck et al 2014 (485)	Retrospective	Renal Cell	Belgium	200	CRP>5mg/L	Active sunitinib treatment				Univariate: 3.17 (2.20-4.68) p<0.001	CRP Only
41.	Xue et al 2014 (486)	Retrospective	Pancreatic	Japan	269	CRP<5mg/l	Palliative Chemotherapy	231	N/A	N/A	Multivariate: 0.63 (0.41-0.89) p=0.01 Inverse HR: 1.58 (1.12-2.44)	The status of initially unresectable/recurrent, Distant Mets, ECOG PS, CA19-9, CEA, LDH
42.	Formica et al 2014 (487)	Retrospective	Colorectal	USA	106	CRP (Continuous)	Fluorouracil, irinotecan and bevacizumab	N/A	60	N/A	Multivariate: 1.01 (1.00-1.02) p=0.0138	NLR
43.	Kim et al 2014 (488)	Prospective	Multiple	Korea	141	CRP>10mg/L	End of life best supportive care	N/A	141	N/A	Multivariate: 1.64 (1.07–2.52) p=0.023	KPS, Time to terminal cancer<12 months, NLR>5
44.	Xue-Feng et al 2015 (489)	Retrospective	Lung	China	127	CRP>10mg/L	Palliative Chemotherapy	N/A	127	N/A	Multivariate: 1.80 (1.19-2.71) p=0.005	CEA, Lymph Node N2
45.	Fiala et al 2015 (490)	Retrospective	NSCLC	Czech Rep	595	CRP≥10mg/L	Erlotinib	N/A	395	N/A	Multivariate: 1.63 (1.30-2.03) P<0.001	EGFR Status, Stage, ECOG
46.	Adams et al 2015 (491)	Retrospective	Diffuse large B cell lymphoma	Netherlands	104	CRP>10mg/L	Rituximab, Hydroxydaunorubicin, Oncovin, and prednisolone (R-CHOP).	N/A	34	N/A	Univariate: 2.60 (1.07-6.30) p=0 .036	NCCN-IPI
47.	Ito et al 2011 (492)	Retrospective	Prostate	Japan	80	CRP>5mg/L	Docetaxel and active chemotherapy	37	38	N/A	Multivariate: 1.95 (1.33-2.96) p<0.001	Hb

48.	Li et al 2015 (493)	Retrospective	Osteosarcoma	China	85	CRP>10mg/L	Active Chemotherapy multiple types	N/A	N/A	N/A	Multivariate: 2.39 (1.22–4.67) p=0.01	Tumour size, poor response to chemo, Metastatic disease
49.	Tang et al 2015 (494)	Retrospective	Nasopharyngeal	China	1589	hs-CRP>1.96 mg/L	Chemoradiotherapy with chemo being platinum based	N/A	153	N/A	Multivariate: 1.72 (1.24-2.40) p=0.001	Age, Tumour Stage, BMI, EBV DNA
50.	Thurner et al 2015 (495)	Retrospective	Prostate	Austria	261	CRP≥8.6mg/L	Confocal Radiotherapy with ADT therapy	24	59	Multivariate: 4.31 (1.22-15.1) p=0.023	Multivariate: 3.24 (1.84-5.71) p<0.001	PSA (10-20)
51.	Zeng et al 2015 (496)	Retrospective	Nasopharyngeal	China	79	CRP>8mg/L	Chemoradiotherapy with platinum-based chemo	23	N/A	Multivariate: 3.04 (1.22-7.55) p=0.017	N/A	CRP Only
52.	Xu et al 2015 (497)	Retrospective	Prostate	China	135	CRP>10mg/L	Palliative care treatment with no mention of type	N/A	124	N/A	Multivariate: 2.39 (1.56-3.69) p<0.001	Gleason Score
53.	Go et al 2015 (498)	Retrospective	Lung	Korea	134	CRP≥19mg/L	Palliative chemo in patients with advanced Lung Ca developing VTE	N/A	N/A (Probability of survival given in months)	N/A	Multivariate: 1.596 (0.888-2.865) p=0.118	Stage, Alb, AMC
54.	Martin et al 2014 (295)	Retrospective	Pancreatic	Australia	124	CRP>10mg/L	Chemo for metastatic disease and radio for locally advanced	N/A	114	N/A	Multivariate: 1.42 (0.89-2.01) p=0.15	CA19-9, ALC, ANC, Platelet, NLR, PLR, mGPS, Alb, ECOG
55.	Mitsunaga et al 2016 (297)	Retrospective and Prospective	Pancreas	Japan	280 (Prospective: 141)	CRP: Inter: >5-20mg/L and High: >20mg/L	GEM chemotherapy	N/A	280 (141 prospective)	N/A	Retrospective Multivariate: Inter: 1.5 (1.1-2.0) p=0.02 High: 2.6 (1.9-3.6) p<0.01 Prospective Multivariate: Inter: 1.5 (0.8-2.8) p=0.19 High: 4.0 (1.6-10.3) p<0.01	Sex, Age, ECOG-PS, UICC stage, CA 19-9, mGPS, NLR

56.	Kim et al 2015 (499)	Retrospective	Pancreatic Ductal Ca	Korea	343 (212 underwent palliative chemo)	CRP>10mg/L	FOLFIRINOX and Gemcitabine based chemo	N/A	343	N/A	Multivariate: Whole Group: 2.313 (1.658-3.228) p<0.001 Palliative Chemo: 2.449 (1.635-3.667) p<0.001	ECOG, Alb, NLR Initial site of Mets, No initial chemotherapy
57.	Yao et al 2105 (500)	Retrospective	Prostate	Japan	57	CRP>18mg/L	Docetaxel Chemotherapy	N/A	55	N/A	Multivariate: 1.312 (0.428-4.015) p=0.635	Biopsy Gleason Score, PSA values, NLR
58.	Wu et al 2015 (501)	Prospective	Lung	China	366	CRP>10.4mg/L	Combination Chemotherapy	N/A	366	N/A	Multivariate: 1.774 (1.270-2.477) p=0.001	Metastasis, NLR
59.	Middleton et al 2016 (502)	Retrospective	Pancreatic Ductal Ca	UK	38	CRP (Continuous)	Combination gemcitabine and capecitabine chemo	N/A	38	N/A	Multivariate: 1.55 (1.00-2.39) p=0.049	Log CA19-9
60.	Casadei et al 2016 (503)	Prospective	Metastatic Colorectal Ca	Italy	132	hs-CRP (Continuous)	Combination chemotherapy including bevacizumab	N/A	124	N/A	Univariate: 1.006 (1.004-1.009) p<0.0001	N/A
61.	Sheng et al 2016 (504)	Retrospective	NSCLC	China	144	CRP (Relatively High vs. Relatively Low)	Combination Chemotherapy	N/A	144	N/A	Univariate 1.43 (0.83-2.47) p=0.204	Current or ex-smoker, stage, ECOG-PS, PNI
62.	Kou et al 2016 (505)	Retrospective	Pancreatic	Japan	306	CRP≥5mg/L	Combination chemotherapy with palliative intent	N/A	249	N/A	Multivariate: 1.24 (0.93-1.65) p=0.15	ECOG PS, Distant Metastasis, Initially unresectable, CEA, CA19-9, NLR
63.	Ahn et al 2016 (506)	Retrospective	Multiple Cancer Types	Korea	187	CRP≥8.4mg/L	Best supportive care	N/A	187	N/A	Univariate: 1.37 (1.03-1.82) p=0.028	ECOG PS≥3, High PPI score≥6, hyperbilirubinemia

Table 17.2: Studies investigating the prognostic value of Albumin in an unselected cohort of patients with advanced cancer

No: Albumin	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Systemic Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer Survival (HR, 95% CI)	Overall Survival (HR, 95% CI)	Independent Prognostic Factors
1.	Axdorph et al 2000 (507)	Retrospective	Hodgkin's disease	UK	145	Alb<40g/L	Multiple treatments including MOPP chemo and radio	48	57	Multivariate: 2.56 (1.05-6.25) p=0.037	N/A	IL-10, Hb<105g/dL
2.	Viganó et al 2000 (508)	Retrospective	Multiple palliative cancers	Canada	227	Alb<35g/L	Symptomatic palliative treatment	N/A	208	N/A	Univariate: 1.9 (1.4-2.8) p<0.01	Weight loss, Lymphocyte, Alk Phos, Karnofsky Performance status, ECOG
3.	Maréchal et al 2007 (509)	Retrospective	Pancreatic Cancer	Belgium	99	Alb<35g/L	Gemcitabine based chemo as 2nd line	N/A	90	N/A	Multivariate: 4.06 (1.88–8.77) p<0.001	CA19-9
4.	Lam et al 2007 (510)	Prospective	Multiple	Hong Kong	170	Alb (No threshold)	Palliative supportive treatment	N/A	167	N/A	Multivariate: 0.95 (0.92-0.98) p=0.001 Inverse HR: 1.05 (1.02-1.09)	Age, Number of Mets, Karnofsky Performance Status, Edmonton Symptom Assessment System
5.	Ramsey et al 2007 (31)	Retrospective	Renal Cell cancer Metastatic	UK	119	Alb:<35g/L	Active Immunotherapy	102	N/A	Multivariate: 2.63 (1.38-5.03) P=0.003	N/A	MSKCC, MRCCPS, GPS, Calcium, CRP
6.	Paralkar et al 2008 (511)	Retrospective	NSCLC	USA	172	Alb≤30g/L	Palliative chemotherapy	N/A	159	N/A	Multivariate: 1.7 (1.11-2.76) p=0.02	ECOG PS, Number of Mets
7.	Ngo et al 2008 (512)	Retrospective	B-cell lymphoma	Singapore	183	Alb<37g/L	CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)	N/A	71 (2-year death rates)	N/A	Multivariate: 2.29 (1.28–4.10) p=0.005	Age, LDH, Stage

8.	Iwasa et al 2011 (464)	Retrospective	Disseminated gastric cancer	Japan	79	Alb<30mg/L	5-FU based chemo	N/A	79	N/A	Multivariate 1.69 (1.05-2.73) p=0.03	ECOG, Ascites, CRP
9.	Shimoda et al 2010 (467)	Retrospective	Pancreatic	Japan	83	Alb<35g/L	50 patients received single-agent treatment with gemcitabine (GEM), 9 patients GEM combined with radiotherapy (GEM+R) and 24 patients had best supportive care (BSC).	N/A	83	N/A	Univariate: 7.15 (1.08–47.43) P=0.042	Albumin Only
10.	Shim et al 2011 (513)	Retrospective	Gastric Cancer	Korea	502	Alb<40g/L	Taxanes and cisplatin as first line. 2nd line oral fluoropyrimidine monotherapy	N/A	502	N/A	Multivariate: 1.82 (1.32-2.53) P < 0.001	ECOG, Histological grade, PFS< 2.7 months
11.	Yi et al 2011 (469)	Retrospective	Pancreatic	Korea	298	Alb<35mg/L	Gemcitabine-based chemotherapy	N/A	298	N/A	Multivariate: 1.701: (1.085-2.667) p=0.021	Metastasis to the liver, Ascites or carcinomatosis, CRP
12.	Trédan et al 2011 (514)	Prospective	Multiple	France	299	Alb<38 g/l	Patients treated with palliative chemo but no specific mention of the type	N/A	264	N/A	Multivariate: 1.47 (1.02-2.11) p=0.0374	ECOG, IL-6, LDH, Lymphocyte Count, Platelet Count
13.	Lim et al 2012 (515)	Prospective	Biliary Tract Cancer	Korea	50	Alb<35g/L	iFAM chemotherapy in advanced biliary cancer	N/A	49	N/A	Multivariate: 2.11 (1.057–4.22) p=0.034	ECOG, Response to chemotherapy
14.	Prakash et al 2012 (516)	Retrospective	B-cell lymphoma	India	486	Alb<40g/L	CHOP Chemo and IFRT chemo in resistant disease	N/A	314	N/A	Univariate: 2.36 (1.32–4.22) p=0.004	Elevated LDH, LR: Not attained, Age≥60, PS (2,3,4), IPI: Intermediate and high risk, Cycles <6, Hb<10
15.	Kang et al 2014 (517)	Retrospective	Biliary Tract	Korea	168	Alb<35g/L	Chemotherapy ultimately palliative. Chemo was platinum based	N/A	168	N/A	Multivariate: 2.0 (1.0–3.8) p=0.036	ECOG, Site of Mets

16.	Ulas et al 2014 (518)	Retrospective	Lung Cancer	Turkey	462	Alb<30g/L	Platinum based chemotherapy as both 1st and 2nd line treat	N/A	391	N/A	Multivariate: 1.28 (0.98-1.67) p=0.037	LDH, ECOG, Calcium, Liver Mets, Malignant Pleural effusion, Chemotherapy, No of Mets, LPI
17.	Imedio et al 2014 (519)	Retrospective	HCC	Spain	62	ALB<35g/L	TACE chemotherapy sorafenib, followed by second line erlotinib	N/A	44	N/A	Multivariate: 2.99 (1.03–8.66) P=0.044	PS, Alcohol ethology
18.	Malik et al 2014 (520)	Retrospective	Renal	USA	70	Alb<34g/L	Bio/chemo or combination therapy	N/A	51	N/A	Multivariate: 2.82 (1.04-7.65) p=0.042	Age, Sex, ECOG, Mets, LDH
19.	Tsai et al 2014 (521)	Prospective	Multiple	Taiwan	522	Alb<30g/L	Palliative and supportive care	N/A	479	N/A	Multivariate: 1.98 (1.01-3.88) p<0.05	AST
20.	Stenman et al 2014 (522)	Retrospective	Renal Cell Cancer	Sweden	84	Alb<30 g/L	Chemotherapy, Radiotherapy and 20% had Mastectomy	N/A	84	N/A	Multivariate: 2.72 (1.22-6.09) P=0.015	Albumin Only
21.	Koo et al 2015 (523)	Retrospective	Gastric Cancer	Korea	3888	Alb<33g/L	Palliative Chemotherapy	N/A	3494	N/A	Multivariate: 1.32 (1.22-1.44) p<0.001	ECOG, No gastronomy, Peritoneal, Bone and Liver Mets, Bilirubin, ALP
22.	Xue-Feng et al 2015 (489)	Retrospective	Lung	China	127	Alb: Normal vs. Low	Palliative Chemotherapy	N/A	127	N/A	Multivariate: 0.928 (0.531-1.622) p=0.793 Inverse: 1.078 (0.617-1.883)	CRP, CEA, Lymph Node N2
23.	Kao et al 2015 (524)	Retrospective	Multiple	USA	143	Alb≥34g/L vs. 24mg/L to 33mg/L vs. <24mg/L	Palliative Radiotherapy	N/A	69	N/A	Multivariate: 2.09 (1.25-3.48) p=0.005	ECOG, Number of Active Tumours, Tumour site
24.	Wild et al 2015 (525)	Retrospective	Pancreatic Adenocarcinoma	USA	101	Baseline Alb: continuous	Palliative chemoradiation	86	88	N/A	Multivariate: 3.584 (1.832-6.993) p=0.0002	Lymph Node Count, Baseline Bun and platelets both continuous, PTV: continuous

25.	Helissey et al 2015 (526)	Retrospective	Breast Cancer	France	56	Alb<35g/L	CirCe01 phase III trial using platinum chemotherapy	N/A	26	N/A	Multivariate: 11.1 (3.6–34) p<0.001	CTC >5, Receptor Status, Performance Status
26.	Narwani et al 2015 (527)	Retrospective	Multiple Myeloma	UK	38	Alb<35g/L	Chemo consists of oral cyclophosphamide 500 mg once weekly: thalidomide 100 mg/d	N/A	22	N/A	Multivariate: 9.34 (2.82-30.92) p<0.001	ALC, Age
27.	Go et al 2015 (498)	Retrospective	Lung	Korea	134	Alb<35g/L	Palliative chemo in patients with advanced Lung Ca developing VTE	N/A	N/A (Probability of survival given in months)	N/A	Multivariate: 1.92 (1.07-3.44) p=0.029	Stage, AMC
28.	Martin et al 2015 (295)	Retrospective	Pancreatic Cancer	Australia	124	Alb<35g/L vs. >35g/L	Chemo for metastatic disease and radio for locally advanced	N/A	114	N/A	Multivariate: 0.47 (0.31-0.72) p <0.001 Inverse: 2.12 (1.39-3.23)	CA19-9, ALC, ANC, Platelet, NLR, PLR, mGPS, ECOG
29.	Kou et al 2016 (505)	Retrospective	Pancreatic Cancer	Japan	306	Alb<35g/L	Combination chemotherapy with palliative intent	N/A	249	N/A	Multivariate: 0.80 (0.59-1.09) p=0.15	ECOG PS, Distant Metastasis, Initially unresectable, CEA, CA19-9, NLR
30.	Moon et al 2016 (528)	Prospective	Neck Squamous Cell Ca	Korea	153	Alb<33g/L	Combination chemotherapy and chemoradiotherapy	24	27	Multivariate: 3.80 (1.57-9.19) p=0.003	N/A	ECOG 1/0, BMI <18.5/others, NLR
31.	Uemura et a 2016 (529)	Retrospective	Prostate	Japan	41	Alb<39g/L	Combination chemotherapy including docetaxel	22	22 (All patients died of prostate Ca)	Multivariate: 3.776 (1.238-11.516) p=0.02	Multivariate: 3.776 (1.238-11.516) p=0.02	BSI (>1% vs. ≤1%)

32.	Dorajoo et al 2016 (530)	Retrospective	Colorectal	Singapore	482	Alb<35g/L	Combination chemo for Mets after previous resection of primary tumour	N/A	480	N/A	Multivariate: 1.295 (1.039-1.614) p=0.022	Age≥65, Poorly differentiated Ca, Met site: Live r, Lung, Carcinomatosis, Bone, Carcinoembryonic antigen
33.	Choi et al 2016 (531)	Retrospective	Pancreatic	Korea	396	Alb: Decreased	Palliative Chemotherapy	N/A	396	N/A	Univariate: 1.380 (1.098-1.735) p=0.006	ECOG PS, CA19-9

Table 17.3: Studies investigating the prognostic value of WCC in an unselected cohort of patients with advanced cancer

No: White Blood Cells	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Systemic Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer Survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Mandreka et al 2006 (532)	Retrospective	Lung	USA	1053	WCC> (>10.2x10^9 /L for males and >10.6x10^9 /L for females Low)	Chemotherapy majority platinum based	N/A	1011	N/A	Multivariate: 1.44 (1.23–1.69) p=0.001	ECOG, Stage, BMI Underweight, High Hb
2.	Ramsey et al 2007 (31)	Retrospective	Renal Cell	UK	119	WCC>11x10^9/L	Active Immunotherapy	102	N/A	Multivariate: 1.66 (1.17-2.35) P = 0.004	N/A	MSKCC, MRCCPS, GPS, Calcium, CRP, Albumin
3.	Tibaldi et al 2008 (533)	Retrospective	Lung	Italy	320	WCC>10 (>10 x 10^9/L)	Chemo Active with cisplatin + gemcitabine or gemcitabine alone	N/A	280	N/A	Multivariate: 1.79 (1.37–2.33) p=0.0001	Performance status, Histology, Brain metastasis
4.	Partridge et al 2012 (309)	Retrospective	Multiple	UK	101 (GPS 2)	WCC>10x10^9/L	Palliative end of life supportive care	N/A	47 (4-week mortality)	N/A	Multivariate: 1.015 (1.004-1.026) p=0.005	mGPS 2, Age, Primary cancer site: Breast

Table 17.4: Studies investigating the prognostic value of Neutrophils in an unselected cohort of patients with advanced cancer

No: Neutrophils	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Systemic Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Lee et al 2011 (534)	Retrospective	Breast	Australia	693	Neutrophil (log scale) above baseline of $\geq 7x10^9/L$	Active chemotherapy as part of two trials	N/A	577	N/A	Multivariate: 1.34 (1.11–1.62) p=0.003	ECOG, ER Status, Number of visceral Mets, Age, Alk Phos, Hb
2.	Kawashima et al 2012 (535)	Retrospective	Renal Cell	Japan	87	Neutrophil>ULN	Active Chemotherapy	87	N/A	Multivariate: 3.597 (1.046–12.364) P=0.042	N/A	Serum Sodium, CRP
3.	Deberne et al 2014 (484)	Retrospective	Lung	France	55	Neutrophil: >8000 /mm3	Multiple treatments including chemotherapy, radiotherapy, and best supportive care	N/A	50	N/A	Univariate: 3.08 (1.36-7) p=0.0001	Leucocytes, Hb, Alb, ALk P, Corrected Ca, CRP
4.	Luo et al 2015 (536)	Retrospective	Nasopharyngeal	China	419	Absolute Neutrophil Count (ANC) $>4.7x10^9L$	Chemotherapy which was active, and cisplatin based	180	N/A	Multivariate: 2.780 (1.819-4.247) p<0.001	N/A	Age, Stage III/IV, ANC, AER
5.	Lacovelli et al 2015 (537)	Retrospective	Renal Cell	Italy	281	Neutrophils >ULN Hb<LLN	Does not seem to mention specifics about chemo	N/A	131	N/A	Multivariate: 1.99 (1.21-3.27) p=0.006	Mets at Diagnosis, ECOG, Hb, Liver Mets
6.	Wu et al 2015 (501)	Prospective	Lung	China	366	Neutrophil $>3.41x10^9$cells/ml	Combination Chemotherapy	N/A	366	N/A	Multivariate: 1.020 (0.655-1.586) p=0.931	Metastasis, NLR, CRP
7.	Ferrucci et al 2016 (538)	Prospective	Metastatic Melanoma	Italy	720	ANC≥7500	Ipilimumab	N/A	662	N/A	Multivariate: 3.38 (2.62-4.36) p<0.0001	ECOG, Brain Mets, Liver Mets

8.	Bille et al 2016 (539)	Retrospective	Pleural Mesothelioma	USA	191	Neutrophils >ULN	First line combination chemotherapy	N/A	191	N/A	Multivariate: 1.27 (0.82-1.99) p=0.29	Platelet count, Performance status, Histological diagnosis
9.	Zaragoza et al 2016 (540)	Retrospective	Melanoma	France	58	Neutrophils: continuous Neutrophils: $\geq 7.5x10^9/L$	Chemotherapy including ipilimumab	N/A	22	N/A	Univariate: Continuous: 1.34 (1.17-1.53) p<0.0001 $\geq 7.5x10^9/L$: 3.28 (1.38-7.78) p=0.007	LDH IU, Performance Status

Table 17.5: Studies investigating the prognostic value of Lymphocytes in an unselected cohort of patients with advanced cancer

No: Lymphocytes	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Systemic Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR,95%CI)	Overall survival (HR,95%CI)	Independent Prognostic Factors
1.	Oki et al 2008 (541)	Retrospective	B-cell Lymphoma	Japan	221	ALC<1x10^9/L	Chemotherapy including Rituximab	N/A	N/A (percentage range given)	N/A	Multivariate: 2.51 (1.38–4.58) p=0.003	IPI as a linear parameter
2.	Trédan et al 2011 (514)	Prospective	Multiple	France	299	lymphocyte count ≤700/µL	Patients treated with palliative chemo but no specific mention of the type	N/A	264	N/A	Multivariate: 1.43 (1.04-1.95) p=0.0268	ECOG, IL-6, LDH, Alb, Platelet Count
3.	Furukawa et al 2012 (542)	Retrospective	Pancreatic	Japan	41	Lymph Count>2000/µl	Nafamostat Mesilate Combined with Gemcitabine Chemotherapy	N/A	41	N/A	Multivariate: 24.016 (5.003-115.278) p<0.0001	Jaundice, Ascites, CA19-9
4.	Lin et al 2014 (543)	Retrospective	SCLC	China	370	ALC≥0.45x10^9/L	Platinum based doublet chemotherapy	N/A	370	N/A	Multivariate: 2.039 (1.488-2.795) p<0.001	LMR, Histology, ECOG
5.	Lin et al 2014 (544)	Retrospective	Nasopharyngeal	China	281	ALC<2.25x10^9/L	Cisplatin based chemotherapy	N/A	255	N/A	Multivariate: 0.59 (0.43-0.81) p=0.001	Age, LMR
6.	Wild et al 2015 (525)	Retrospective	Pancreatic	USA	101	Lymph (<500 vs. ≥500)	Palliative chemoradiation	86	88	N/A	Multivariate: 2.879 (1.531-5.415) p=0.001	Baseline Alb, Baseline Bun and platelets both continuous, PTV: continuous

7.	Bille et al 2016 (539)	Retrospective	Pleural Mesothelioma	USA	191	lymphocyte (>1.4 vs. ≤1.4)	First line combination chemotherapy	N/A	191	N/A	Multivariate: 0.78 (0.54-1.12) P=0.17 Inverse HR: 1.282 (0.893-1.852)	Platelet count, Performance status, Histological diagnosis
8.	Lin et al 2016 (545)	Retrospective	Metastatic Colorectal	China	488	ALC ≥2.70x10^9/L	FOLFOX chemotherapy	N/A	479	N/A	Multivariate: 0.841 (0.676-1.047) p=0.391 Inverse HR: 1.189 (0.955-1.479)	Gender, ECOG Performance, Tumour differentiation, Pre-chemo AMC and LMR
9.	Wu et al 2016 (546)	Retrospective	Cervical Cancer	US	71	TLC≥1000 cells/mm^3	Platinum based chemoradiation	N/A	42	N/A	Multivariate: 0.23 (0.05-1.03) p=0.053 Inverse HR: 4.348 (0.971-20)	Stage III disease
10.	Choi et al 2016 (531)	Retrospective	Pancreatic	Korea	396	Lymphocytes <2000 cells/mm^3	Palliative Chemotherapy	N/A	396	N/A	Univariate: 1.410 (1.119-1.777) p=0.004	ECOG PS, CA19-9
11.	Zaragoza et al 2016 (540)	Retrospective	Melanoma	France	58	Lymphocytes: continuous	Chemotherapy including ipilimumab	N/A	22	N/A	Univariate; 0.88 (0.50-1.54) p<0.20 Inverse HR: 1.136 (0.649-2)	LDH IU, Performance Status

Table 17.6: Studies investigating the prognostic value of Monocytes in an unselected cohort of patients with advanced cancer

No: Monocytes	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Systemic Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Bari et al 2013 (547)	Retrospective	T-cell lymphoma	Italy	94	Mono>0.8x10^9/L	Active chemo including vincristine	N/A	48	N/A	Multivariate: 2.41, (1.19–4.89) p =0.015	PIT Score, Histopathology
2.	Lin et al 2014 (543)	Retrospective	SCLC	China	370	AMC≥0.45x10^9/L	Platinum based doublet chemotherapy	N/A	370	N/A	Multivariate: 0.928 (0.686-1.257) P=0.631	LMR, Histology, ECOG
3.	Lin et al 2014 (544)	Retrospective	Nasopharyngeal	China	281	AMC≥0.35x10^9/L	Cisplatin based chemotherapy	N/A	255	N/A	Multivariate: 1.20 (0.85-1.70) p=0.309	Age, ALC, LMR
4.	Go et al 2015 (498)	Retrospective	Lung	Korea	134	AMC≥640 cells/µL AMC= Absolute Mono Count	Palliative chemo in patients with advanced Lung Ca developing VTE	N/A	N/A (Probability of survival given in months)	N/A	Multivariate: 1.994 (1.137-3.498) p=0.016	Stage, Alb,
5.	Lin et al 2016 (545)	Retrospective	Metastatic Colorectal	China	488	AMC ≥0.55x10^9/L	FOLFOX chemotherapy	N/A	479	N/A	Multivariate: 1.514 (1.204-1.903) p<0.001	Gender, ECOG Performance, Tumour differentiation, Pre-chemo LMR

Table 17.7: Studies investigating the prognostic value of Platelets in an unselected cohort of patients with advanced cancer

No: Platelets	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Systemic Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Cho et al 2008 (548)	Retrospective	Renal Cell	Korea	197	Plate>450,000/mm^3	Immunotherapy [interferon-α, interleukin-2 (IL-2), or a combination thereof with or without 5-fluorouracil	127	129	Multivariate: 1.34 (0.74 – 2.41) p=0.333	N/A	ECOG-PS, N-stage, Sarcomatoid differentiation, Number of Mets
2.	Trédan et al 2011 (514)	Prospective	Multiple	France	299	Plate <130g/L	Patients treated with palliative chemo but no specific mention of the type	N/A	264	N/A	Multivariate: 1.70 (1.02-2.81) p=0.0402	ECOG, IL-6, LDH, Lymphocyte Count, Alb
3.	Stenman et al 2014 (522)	Retrospective	Renal Cell	Sweden	84	Plate: >360X 10^9/L	Chemo, Radio and 20% had Mastectomy	N/A	84	N/A	Multivariate: 1.62 (0.79–3.32) p=0.19	Albumin Only
4.	Chen et al 2015 (549)	Retrospective	Nasopharyngeal	China	2626	Plate>300×10^9 /L	Active radio and chemo or combination	N/A	774	N/A	Multivariate: 1.810 (1.531-2.140) p<0.001	Age, Sex, T-stage, N-stage
5.	Wild et al 2015 (525)	Retrospective	Pancreatic	USA	101	Baseline Plate: continuous	Palliative chemoradiation	86	88	N/A	Multivariate: 1.004 (1.001-1.007) p=0.005	Baseline Alb, LN Count, Baseline Bil both continuous, PTV: continuous
6.	Hong et al 2015 (550)	Retrospective	Lung Cancer	China	919	Plate≥ULN	Chemotherapy and radiotherapy	N/A	892	N/A	Multivariate: 1.016 (0.855-1.208) p=0.856	Stage, Response to treatment, LDH
7.	Shoultz-Henley et al 2016 (551)	Retrospective	Oropharyngeal	USA	433	Plate: 350x10^9/L	Combined chemo and radiotherapy	N/A	Not mentioned only % given	N/A	Multivariate: 1.9 (1.2-2.9) p<0.006	Anaemia, Dahstrom-Sturgis category, HPV status
8.	Bille et al 2016 (539)	Retrospective	Pleural Mesothelioma	USA	191	Plate>450,000 per mm^3	First line combination chemotherapy	N/A	191	N/A	Multivariate: 2.09 (1.33-3.35) p=0.002	Performance status, Histological diagnosis

Table 17.8: Studies investigating the prognostic value of GPS/mGPS in an unselected cohort of patients with advanced cancer

No: GPS/mGPS	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Systemic Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Forrest et al 2003 (303)	Retrospective	NSCLC	UK	161	GPS (0/1/2)	Chemotherapy mainly cisplatin and radical radio	N/A	118	N/A	Multivariate: 1.111(1.23–2.35) P= 0.001	Stage/ECOG score, CRP/Alb score
2.	Elahi et al 2004 (230)	Retrospective	Gastric and colorectal	UK	165	GPS (0/1/2)	Palliative Chemo and Supportive Care	N/A	165	N/A	Univariate: Gastric: 1.71 (1.15–2.25) P = 0.002 Colorectal: 1.77 (1.51–2.57) P < 0.001)	Age, Tumour Type
3.	Crumley et al 2006 (227)	Retrospective	Gastro-oesophageal	UK	258	GPS (0/1/2)	Chemotherapy and radiotherapy with palliative intent	202	211	Multivariate: 1.51 (1.22-1.86) p<0.001	N/A	GPS Only
4.	Al Murri et al 2006 (197)	Retrospective	Breast	UK	96	GPS (0/1/2)	Chemotherapy and endocrine therapy	51	N/A	Multivariate: 2.26 (1.45-3.52) p<0.001	N/A	CRP, Alb
5.	Glen et al 2006 (294)	Retrospective	Pancreatic	UK	187	GPS (0/1/2)	Palliative treatment with platinum based chemo	N/A	181	N/A	Multivariate: 1.72 (1.40-2.11) p< 0.001	Age, TNM
6.	Read et al 2006 (270)	Prospective	Colorectal	Australia	51	GPS (0/1/2)	Chemo and Radiotherapy as well as supportive care	N/A	32	N/A	Multivariate: 2.27 (1.09–4.73) P = 0.028	Type of treatment, PS, SAP

7.	Ramsey et al 2007 (31)	Retrospective	Renal Cell	UK	119	GPS: (0/1/2)	Active Immunotherapy	102	N/A	Multivariate: 2.35(1.51–3.67) P<0.001	N/A	MSKCC, MRCCPS, Calcium, CRP, Albumin
8.	Leitch et al 2007 (247)	Retrospective	Colorectal Liver Mets	UK	84	GPS (0,1,2)	Palliative chemotherapy	71	N/A	Multivariate: 1.44 (1.01–2.04) P =0.043	N/A	Age, Single liver metastasis, Extra-hepatic disease, chemotherapy treatment
9.	Crumley et al 2008 (228)	Retrospective	Gastro-oesophageal	UK	65	GPS (0/1/2)	Mostly cisplatin based chemotherapy	58	59	Multivariate: 1.69 (1.00-2.86) P=0.05	N/A	GPS Only
10.	Ramsey et al 2008 (245)	Prospective	Renal Cell	UK	23	GPS (0/1/2)	Palliative treatment with immunotherapy	N/A	15	N/A	Multivariate: 2.23 (1.06-4.57) p=0.029	GPS Only
11.	Ishizuka et al 2009 (271)	Retrospective	Colorectal	Japan	112	mGPS: 1/2	Active chemo in form of FOLFIRI and FOLFOX regimens	44	N/A	Multivariate: 6.071 (1.625–22.68) p=0.0073	N/A	mGPS only
12.	Shimoda et al 2010 (467)	Retrospective	Pancreatic	Japan	83	GPS (0 vs. 1 or 2)	50 patients received single-agent treatment with gemcitabine (GEM), 9 patients GEM combined with radiotherapy (GEM+R) and 24 patients had best supportive care (BSC).	N/A	83	N/A	Univariate: 0.513 (0.047–5.547) P=0.5825 Inverse: 1.949 (0.180-21.277)	Albumin
13.	Hwang et al 2011 (231)	Retrospective	Gastric	Korea	402	GPS: (1&2)	Mostly Cisplatin based chemotherapy general 1st line treat: taxanes and cisplatin	N/A	402	N/A	Multivariate: GPS 1: 1.75 (1.37-2.26) p=0.001 GPS 2: 1.79 (1.29-2.47) p=0.001	ECOG, Bone Mets

14.	Chua et al 2012 (163)	Prospective	Multiple	Australia	68	mGPS (1&2)	Single unit docetaxel treatment	N/A	68	N/A	Multivariate: 1.111(2.2–7.7) p<0.0001	NLR
15.	Inoue et al 2013 (272)	Retrospective	Colorectal	Japan	164 (chemo only)	mGPS (1-2 vs. 0)	FOLFOX and FOLFIRI chemo.	N/A (HR given only)	N/A	Multivariate: 1.858 (1.213-2.846) p=0.0044	N/A	Age, CEA
16.	Leung et al 2012 (304)	Retrospective	Lung	UK	261	mGPS (0/1/2)	Chemotherapy (mainly platinum based) and/or radical radiotherapy	246	248	Multivariate: 1.67 (1.28-2.19) P<0.0001	N/A	Age, ECOG, Tumour stage (III/IV)
17.	Jeong et al 2012 (232)	Retrospective	Gastric	Korea	104	mGPS: (1 & 2)	Treated with palliative chemo	N/A	94	N/A	Multivariate: mGPS 1: 3.77 (2.00–7.01) p<0.000 mGPS 2: 2.29 (1.21–4.32) p<0.010	Histology, LN Mets, NLR
18.	Partridge et al 2012 (309)	Retrospective	Multiple	UK	101 (GPS 2)	mGPS (1&2)	Palliative end of life supportive care	N/A	47 (4-week mortality)	N/A	Multivariate: mGPS 1: 1.346 (0.585-3.100) p=0.484 mGPS 2: 2.712 (1.252-5.875) p=0.011	Age, Primary cancer site: Breast, WBC
19.	Gioulbasanis et al 2012 (305)	Retrospective	Lung	Greece	96	GPS (1&2)	Platinum-based chemotherapy	N/A	89	N/A	Multivariate: GPS 1: 1.20 (0.68–2.13) p=0.529 GPS 2: 2.63 (1.29–5.34) p=0.008	PS Only
20.	Hwang et al 2012 (201)	Prospective	Bladder	Korea	67	GPS (1&2)	Treated with chemotherapy	N/A	67	N/A	Multivariate: GPS 1: 2.91 (0.96-8.75) P=0.057 GPS 2: 7.00 (2.53-19.36)	PS Only

											P=0.001	
21.	Laird et al 2013 (17)	Prospective	Multiple	UK	1825 (Test) 631 (Validation)	GPS: 1&2	Chemo, radio and BSC	N/A	1601(Test) 471 (Validation)	N/A	Multivariate: Test: mGPS 1: 1.62 (1.35-1.93) p<0.001 mGPS 2: 2.05 (1.72-2.44) p<0.001 Validation: mGPS 1: 1.58 (1.25-2.01) p<0.001 mGPS 2: 2.06 (1.62-2.63) p<0.001	Test: Dyspnoea, ECOG Validation: Quality of life, Physical Function, Pain, BMI, ECOG
22.	Linton et al 2013 (154)	Prospective	Prostate	Australia	112	mGPS (2 vs. 0) (1 vs. 0)	Docetaxel and prednisone treatment	N/A	84	N/A	Univariate: mGPS Categorical (2 vs. 0) 3.44 (1.75-6.76) p <0.001 (1.vs 0.) 1.97 (1.01-3.83) p=0.047	mGPS only
23.	Sachlova et al 2014 (233)	Retrospective	Gastric	Czech Rep	64 (treated with chemo)	GPS (1&2)	Palliative chemo mostly platinum based	N/A	64	N/A	Multivariate: GPS 1: 1.93 (0.85-4.40) p=0.12 GPS 2: 6.63 (2.42-18.17) p<0.001	OPNI

24.	Zhang et al 2014 (229)	Retrospective	Oesophageal	China	212	mGPS (0,1,2)	Radiotherapy and cisplatin based chemo	N/A	160	N/A	Multivariate: 1.694 (1.350-2.126) p<0.001	Location, T&M, stage
25.	Anshushaug et al 2015 (310)	Retrospective	Multiple	Norway	723	GPS (1 & 2)	Palliative radio and chemo	N/A	723	N/A	Multivariate: Chemo: GPS: 1: 1.69 (0.72-4.00) p=0.23 2: 3.00 (1.32-6.80) p=0.009 Radio: GPS 1: 2.90 (0.97-8.67) p=0.06 GPS 2: 3.98 (1.52-10.42) p=0.005	Age, Performance status, Referred to Palliative Care, Mets when diagnosed
26.	Moriwaki et al 2014 (298)	Retrospective	Biliary Tract	Japan	218	Continuous: GPS (0 vs. 1/2)	Chemo with GEM and CDDP regimens	N/A	218	N/A	Multivariate: 0.60 (0.40-0.90) P=0.012 Inverse: 1.666 (1.111-2.5)	ALP, LDH, No of Mets, Liver, Peritoneal/Other Mets
27.	Miura et al 2015 (311)	Prospective	Multiple	Japan	1160	GPS 1&2	Purely palliative care no active treatment	N/A	1160 (All end of life care)	N/A	Multivariate: GPS 1: 1.07 (0.78-1.49) P= 0.673 GPS 2: 1.36 (1.01-1.87) P= 0.046	Performance status, Liver Mets, PP >6I, NLR≥4, Dyspnea, Oedem0.308a
28.	de Paula Pantano et al 2016 (312)	Prospective	Multiple	USA	459	mGPS 1&2	Predominantly supportive treatment but some still receiving chemo	N/A	346	N/A	Multivariate: GPS 1: 2.066 (1.356-3.147) P= 0.001 GPS 2: 2.664 (1.929-2.680) P<0.001	Sex, Hepatic Mets, CNS Mets, Treatment Palliative care only, KPS (0-70%),

29.	Tan et al 2015 (313)	Prospective	Multiple	Australia	114	mGPS: 1/2	Chemotherapy but no specific mention of type	N/A	Followed up until the date of death or the date that data as last updated.	N/A	Multivariate: 1.68 (1.03-2.76) p=0.039	PG-SGA C, Required dose reduction +/- transfusion
30.	Jung et al 2015 (238)	Retrospective	B-cell Lymphoma	Korea	213	L-GPS: 1&2	R-CHOP chemotherapy.	50	58	N/A	Multivariate GPS 1: 2.135 (0.919-4.533) p=0.078 GPS 2: 5.898 (2.028-14.454) p=0.001	ECOG
31.	Xiao et al 2015 (205)	Retrospective	Cervical	China	238	mGPS (0/1/2)	Chemo in the form of Cisplatin plus 5-fluorouracil or cisplatin plus docetaxel. Also, treated with radio	N/A	124	N/A	Multivariate: 1.820 (1.378-2.404) p<0.001	PS, FIGO Stage, LN status
32.	Martin et al 2014 (295)	Retrospective	Pancreatic	Australia	124	mGPS: (0,1,2)	Chemo for metastatic disease and radio for locally advanced	N/A	114	N/A	Multivariate: mGPS 1.41 (1.10-1.80) p=0.01	CA19-9, ALC, ANC, Platelet, NLR, PLR, Alb, ECOG
33.	Kasuga et al 2015 (296)	Retrospective	Pancreatic	Japan	61	mGPS: 2	Gemcitabine and S−1 combination therapy (FGS) as salvage chemotherapy	N/A	61	N/A	Multivariate: 6.605 (2.965–14.709) p<0.001	CA19-9 > 2,000 ECOG>0
34.	Simmons et al 2015 (306)	Prospective	Lung	Greece	390	mGPS (0/1/2)	Best supportive care	N/A	283	N/A	Multivariate: 1.67 (1.40-2.00) p<0.001	ECOG
35.	Zhou et al 2015 (307)	Retrospective	Lung	China	359	mGPS 1&2	Radiotherapy and chemotherapy (Irinotecan, Etoposide)	N/A	180	N/A	Multivariate: mGPS 1: 1.52 (1.08-2.13) p=0.015 mGPS 2: 5.23 (2.36-11.58) p<0.001	Adjusted for age, sex, disease stage, ECOG-PS.

36.	Chou et al 2015 (237)	Retrospective	Haematological	China	217	GPS: (1&2)	Palliative care no specific mention of chemo	N/A	204	N/A	Multivariate: GPS 1: 2.12 (1.13–3.97) p=0.020 GPS 2: 1.71 (0.964–3.05) p=0.069	PPI :> 4.5.
37.	Jiang et al 2015 (308)	Prospective	Lung	China	138	GPS: 1&2	Cisplatin based chemo.	N/A	138	Multivariate: GPS 1: 0.8 (0.5-0.9) p=0.02 GPS 2: 0.6 (0.2-0.8) p=0.02 Inverse: GPS 1: 1.25 (1.111-2) GPS 2: 1.666 (1.25-5)	Multivariate: GPS 1: 0.8 (0.4-0.9) p=0.02 GPS 2: 0.5 (0.2-0.9) P=0.02 Inverse: GPS 1: 1.25 (1.111-2.5) GPS 2: 2 (1.111-5)	CYFRA21-1, CEA, TPS
38.	Dreanic et al 2015 (273)	Retrospective	Colorectal	France	27	mGPS: 2 Inverse mGPS: 2	5-fluorouracil-based systemic chemotherapy and anti-VEGF	N/A	27	N/A	Univariate in anti-VEGF group: 0.48 (0.18-1.29) p=0.15 Inverse: 2.083 (0.775-5.555)	GPS Only
39.	Mitsunaga et al 2016 (297)	Prospective	Pancreas	Japan	280 (Prospective: 141)	mGPS: 1 &2	GEM chemotherapy	N/A	280 (141 prospective)	N/A	Multivariate: mGPS: 1: 0.9(0.4-1.9) p=0.76 mGPS 2: 0.72 (0.3-1.7) p=0.47 Inverse: mGPS 1: 1.111 (0.526-2.5)	Sex, Age, ECOG-PS, UICC stage, CA 19-9, Prognostic CRP Classification, NLR

											mGPS 2: 1.388 (0.588-3.333)	
40.	Song et al 2015 (274)	Retrospective	Colorectal	Korea	177	mGPS: (0 vs. 1 or 2)	Best supportive care and herbal therapy	N/A	177	N/A	Multivariate: 0 vs 1: 1.135 (0.717-1.797) p=0.588 0 vs 2: 3.212 (1.437-7.716) p=0.004	LMR, CA19-9, AST, KM treatment
41.	Zhou et al 2015 (299)	Prospective	HCC	China	244	GPS (0/1/2)	TRACE chemotherapy	N/A	198	N/A	Multivariate: 1.697 (1.325-2.174) p< 0.001	ALT, CLIP score
42.	Namikawa et al 2016 (234)	Retrospective	Gastric	Japan	224	GPS (0/1 or 2) mGPS (0/1 or 2)	Combination chemotherapy including trastuzmab	N/A	223	N/A	Multivariate: GPS: 1.297 (0.667-2.552) p=0.444 mGPS: 0.68 (0.350-1.322) p=0.255	Histological type, NLR
43.	Arigami et al 2016 (235)	Retrospective	Gastric	Japan	68	GPS: 1&2	Chemotherapy and chemoradiotherapy	N/A	68	N/A	Multivariate: GPS 1: 0.830 (0.418-1.618) p=0.586 GPS 2: 2.608 (0.792-7.965) p=0.111	F-NLR score (combined fibrinogen and NLR)
44.	Hsieh et al 2016 (236)	Retrospective	Gastric	Taiwan	256	mGPS (>1)	Combination Chemotherapy	N/A	248	N/A	Multivariate: 2.78 (1.60–4.83) p<0.001	Peritoneal Mets, NLR, mGPS, PG-SGA

Table 17.9: Studies investigating the prognostic value of NLR in an unselected cohort of patients with advanced cancer

No: NLR	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Systemic Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Yamanaka et al 2008 (552)	Prospective	Gastric	Japan	1220	NLR>2.5	Patients receiving oral fluoropyrimidine	N/A	984	N/A	Multivariate: 1.52 (1.32–1.75) p=0.077	Age, ECOG, Advanced Disease, Liver Mets, WBC 9000-12000/mm3
2.	Teramukai et al 2009 (553)	Prospective	Lung	Japan	388	NLR≥4.744	Vinorelbine, gemcitabine, docetaxel, paclitaxel, carboplatin	N/A	276	N/A	Multivariate: 1.56 (1.09–2.24) p=0.015	Neutrophil count
3.	Kao et al 2010 (554)	Retrospective	Malignant mesothelioma	Australia	173	NLR≥5	Platinum based chemotherapy	N/A	131	N/A	Multivariate: 2.7 (1.8-3.9) p<0.001	Histological subtype
4.	An et al 2010 (555)	Retrospective	Pancreatic	China	95	NLR>5	Gemcitabine-based chemotherapy	N/A	95	N/A	Multivariate: 4.489 (1.372–14.692) p=0.013	CA19-9
5.	Chua et al 2012 (163)	Prospective	Multiple	Australia	68	NLR>5	Single unit docetaxel treatment	N/A	68	N/A	Multivariate: 2.0 (1.2–3.3) p=0.010	GPS: 1&2
6.	An et al 2011 (556)	Prospective	Nasopharyngeal	China	363	NLR>3.73	Local radio and cisplatin and/or 5-FU-based neoadjuvant	96	102	Multivariate: 1.74 (1.15–2.62) p=0.008	N/A	Age, sex and T-stage
7.	Chua et al 2011 (557)	Retrospective	Colorectal	Australia	349	NLR≥5	Chemotherapy and best supportive care	N/A	315	N/A	Multivariate: 1.7 (1.2-2.5) p=0.002	ECOG>1
8.	Wang et al 2011 (558)	Retrospective	Multiple	China	497	NLR>3	Multiple treatment modalities.	N/A	464	N/A	Multivariate: 1.348 (1.062-1.712) p=0.014	Gender, Tumour Type, Surgery, Other Mets, Adjuvant treatment

9.	Jeong et al 2012 (232)	Retrospective	Gastric	Korea	104	NLR>3	Treated with palliative chemo	N/A	94	N/A	Multivariate: 1.65 (1.03–2.64) p = 0.037	Histology, LN Mets, mGPS
10.	Lee et al 2012 (169)	Prospective	Lung adenocarcinoma	Korea	199	NLR >2.18	Gefitinib with gemcitabine plus cisplatin as first-line therapy.	N/A	N/A (Expressed in months)	N/A	Multivariate: 1.13 (1.06-1.21) p<0.001	ECOG
11.	Kaneko et al 2012 (559)	Retrospective	Colorectal	Japan	50	NLR ≥4	Palliative Oxaliplatin-based combination chemotherapy	27	27	N/A	Multivariate: 4.39 (1.82-10.7) p = 0.0013	Platelets
12.	Pinato et al 2012 (560)	Retrospective	HCC	USA	112	NLR>5	Active platinum based chemo	N/A	81	N/A	Multivariate: 2.06 (1.16-3.66) p=0.013	IBI, CLIP, BSC
13.	He et al 2013 (561)	Retrospective	Colorectal	China	243	NLR≤3 Inverted NLR NLR≥3	Combination chemotherapy including Oxaliplatin and Irinotecan	N/A	199	N/A	Multivariate: 0.678 (0.479-.0961) p=0.029 Inverted: 1.475 (1.041-2.088)	CEA
14.	Linton et al 2013 (154)	Prospective	Prostate	Australia	112	NLR: Continuous Categorical: (≥5 vs. <5)	Docetaxel and prednisone treatment	N/A	84	N/A	Univariate: NLR: Cont 1.08 (0.83-1.41) p=0.55 NLR (≥5 vs. <5): 0.98 (0.64-1.49) p=0.91	mGPS 2 vs. 0 and mGPS 1 vs. 0
15.	Unal et al 2013 (562)	Prospective	NSCLC	Turkey	94	NLR (low or high)	Chemoradiotherapy including platinum based treat	N/A	81	N/A	Univariate: 1.81 (1.16-2.81) p=0.0008	PLR, Response to chemoradiotherapy
16.	Yao et al 2013 (563)	Prospective	Lung	China	182	NLR>2.68	First-line platinum-based chemotherapy.	N/A	91	N/A	Multivariate: 1.761 (1.095-–2.832) p=0.020	Nodal spread N2, Metastasis M2.

17.	Fox et al 2013 (180)	Retrospective	Renal Cell	Australia	362	NLR>3	Patients treated with Lapatinib or hormonal therapy after prior failure of immunotherapy in a randomised phase III trial	N/A	357	N/A	Multivariate: 1.42 (1.10-1.84) p=0.008	Neutrophils, Platelets, KPS, Corrected Calcium, Low Hb
18.	Cetin et al 2013 (564)	Retrospective	Renal Cell	Turkey	100	NLR>3.04	Tyrosine Kinase Inhibitors	N/A	54	N/A	Multivariate: 2.406 (1.327-4.361) p=0.004	Male, PFS
19.	Jafri et al 2013 (565)	Retrospective	Lung	USA	173	NLR<5	Treated with active chemotherapy multiple types		173		Univariate: 0.57 (0.41-0.79) 0.0008 Inverted HR: 1.754 (1.266-2.439)	PS (0-1/ 2–4), Mets (1-2/ >2), No chemotherapy, ALC <1, ALI < 18
20.	Troppan et al 2014 (566)	Retrospective	B-cell Lymphoma	Austria	290	NLR≥4	Standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen every 3 weeks for six to eight cycles	N/A	92	N/A	Multivariate: 2.03 (1.17-3.50) p=0.011	Age ≥60, Clinical Stage III & IV, non-GCB, dNLR≥4
21.	Kim et al 2014 (488)	Prospective	Multiple	Korea	141	NLR>5	Best supportive care	N/A	141	N/A	Multivariate: 1.96 (1.17–3.31) p=0.011	KPS, Time to terminal cancer<12 months, CRP≥10mg/dl
22.	Kang et al 2014 (567)	Retrospective	Lung	UK	187	NLR≥4	platinum-based chemotherapy	N/A	187	N/A	Multivariate: 1.465 (1.012-2.119) p=0.043	Extensive Disease, LDH
23.	Cho et al 2014 (30)	Prospective	Gastric	Korea	268	NLR>3	Initial treatment with chest wall radiotherapy and FOLFOX and platinum based chemo	N/A	268	N/A	Multivariate: 1.569 (1.227–2.006) P<0.001	Undifferentiated, Progressive disease

24.	Templeton et al 2014 (568)	Retrospective	Prostate	Canada	357	NLR>3	Docetaxel and platinum based chemo	N/A	345	N/A	Multivariate: 1.89 (1.27-2.82) p=0.002	Liver Mets, Hb, Alb, Log (PSA, LDH, ALP)
25.	Nuhn et al 2014 (569)	Retrospective	Prostate	USA	238	NLR>3	First line docetaxel	N/A	237	N/A	Multivariate: 1.883 (1.248, 2.842) p=0.002	Number of chemo cycles, Hb, Alb, AST, Baseline PSA
26.	Sonpavde et al 2014 (570)	Retrospective	Prostate	Multinational (US and Canada)	784	NLR (Log transformed)	Patients treated with Sunitinib and prednisolone and docetaxel-based chemotherapy	N/A	516	N/A	Multivariate: 1.55 (1.32-1.83) p<0.001	Log (LDH), Hb, Organ Involvement
27.	Keizmann et al 2014 (571)	Prospective	Renal cell	Multinational (USA and Israel)	244	NLR>3	Sunitinib treatment	N/A	203	N/A	Multivariate: 2.95 (2–4.34) p<0.001	Sunitinib induced HTN, Pre-treatment, never having smoked
28.	Li et al 2014 (572)	Retrospective	HCC	China	205	NLR>2.43	Sorafenib based chemoembolization	N/A	132	N/A	Multivariate: 1.104 (1.044–1.167) p<0.001	AFP, Tumour Morphology, Child-Pugh Score, Platelets
29.	Formica et al 2014 (487)	Retrospective	Colorectal	USA	106	NLR (Continuous)	Fluorouracil, irinotecan and bevacizumab	N/A	60	N/A	Multivariate: 1.8012 (0.2833-1.6048) p=0.0019	CRP
30.	Kacan et al 2014 (573)	Retrospective	Lung	Turkey	299	NLR≥5	Chemo and Radiotherapy no mention of surgery	N/A	204 (2 Year survival)	N/A	Multivariate: 1.7 (1.0-2.7) p=0.017	Age, Anaemia at diagnosis, Stage, ECOG PS
31.	Lin et al 2014 (574)	Retrospective	Lung	China	81	NLR>3.5	EGFR-TKI treatment	56	56 (All deaths Ca related)	N/A	Multivariate: 3.29 (1.62–6.71) p<0.001	ECOG
32.	Yoo et al 2014 (575)	Retrospective	Lung	Korea	138	NLR≥2	Concurrent chemoradiotherapy	N/A	112	N/A	Multivariate: 2.115 (1.193-3.749) p=0.010	ECOG performance status

33.	Langsenlehner et al 2015 (576)	Retrospective	Prostate	Austria	415	NLR≥5	Androgen deprivation therapy, Chemotherapy	N/A	60	N/A	Multivariate: 2.16 (1.17-3.99) p=0.013	Intermediate risk group classification
34.	Jiang et al 2015 (577)	Retrospective	Soft Tissue Sarcoma	China	154	NLR>1	Treated with active chemotherapy and Ipilimumab	65	80	N/A	Multivariate: 2.477 (1.423-4.311) P= 0.033	Monocyte Ratio>1
35.	Lorente et al 2015 (178) 2015	Retrospective	Prostate	UK	755	NLR: Continuous NLR>3	Patients treated with cabazitaxel (25 mg/m2) versus 3-weekly mitoxantrone (12 mg/m2), both in combination with prednisone 10 mg daily	N/A	N/A (Does not give a figure)	N/A	Multivariate: Conti: 1.91 (1.31-2.79) p=0.001 NLR>3: 1.55 (1.3–1.84), P < 0.001	Measurable disease, Pain at baseline, Treatment arm
36.	Luo et al 2015 (578)	Retrospective	Pancreatic	China	403	NLR: ≥3.1	74.9% underwent gemcitabine-based chemotherapy	N/A	394	N/A	Multivariate: 1.42 (1.15-1.74) p=0.001	Age, CA19-9, Albumin, Tumour spread
37.	Kim et al 2015 (499)	Retrospective	Pancreatic Ductal	Korea	343 (212 palliative chemo)	NLR>5	FOLFIRINOX and Gemcitabine based chemo	N/A	343	N/A	Multivariate: Whole Group: 1.428 (1.014-2.012) p=0.042 Palliative Chemo: 1.038 (0.654-1.650) p=0.175	ECOG, Alb, CRP, Initial site of Mets, No initial chemotherapy
38.	Chen et al 2015 (579)	Retrospective	Colorectal	United States	166	NLR>5	Best supportive care after failure of other treatment in palliative group and Panitumumab in active treatment group	N/A	N/A (No specific numbers of deaths)	N/A	Multivariate: 1.73 (1.03-2.89) p=0.039	Metastatic Site numbers ≥1, LDH>ULN

39.	Santoni et al 2015 (580)	Retrospective	Renal Cell	Italy	151	NLR>3	Active treatment with VEGFR-TKI also treated with sunitinib, sorafenib, and pazopanib	N/A	53	N/A	Multivariate: 2.21 (1.21–4.04) p=0.010	MSKCC Prognostic Group
40.	Ho et al 2015 (581)	Retrospective	Large B Cell Lymphoma	Taiwan	148	NLR>4.35	Standard R-chemotherapy.	N/A	41	N/A	Multivariate: 1.624 (0.827-3.189) p=0.159	Age, B-symptoms, ECOG, ALC, AMC, ALC/AMC PS
41.	Mitchell et al 2015 (582)	Prospective	Lung	Canada	1239	NLR>5	Tecemotide in unresectable stage III non-small-cell lung cancer	N/A	1239	N/A	Univariate: 0.81 (0.66–0.99), P = 0.0383 Inverse HR: 1.235 (1.01-1.515)	High sMUC1, High ANA
42.	Martin et al 2014 (295)	Retrospective	Pancreatic	Australia	124	NLR≥5	Chemo for metastatic disease and radio for locally advanced	N/A	114	N/A	Multivariate: 1.60 (1.07-2.40) p=0.02	CA19-9, ALC, ANC, Platelet, PLR, mGPS, Alb, ECOG
43.	Mitsunaga et al 2016 (297)	Prospective	Pancreas	Japan	280 (Prospective: 141)	NLR≥5	GEM chemotherapy	N/A	280 (141 prospective)	N/A	Multivariate: 1.3 (0.8-2.2) p=0.32	Sex, Age, ECOG-PS, UICC stage, CA 19-9, Prognostic CRP Classification, mGPS
44.	Wu et al 2015 (501)	Prospective	Lung	China	366	NLR>2.68	Combination Chemotherapy	N/A	366	N/A	Multivariate: 1.778 (1.157-2.732) p=0.009	Metastasis, CRP
45.	Hong et al 2015 (550)	Retrospective	Lung Cancer	China	919	NLR<5 Inverse: NLR>5	Chemotherapy and radiotherapy	N/A	892	N/A	Multivariate: 0.908 (0.721-1.144) p=0.413 Inverse Multivariate: 1.101 (0.874-1.387)	Stage, Response to treatment, LDH

46.	Yao et al 2015 (500)	Retrospective	Prostate	Japan	57	NLR≥3.5	Docetaxel Chemotherapy	N/A	55	N/A	Multivariate: 2.728 (1.050-7.088) p=0.039	Biopsy Gleason Score, PSA value
47.	Wang et al 2016 (583)	Retrospective	Cervical	China	60	NLR<2 Inverse: NLR>2	Cisplatin-based chemoradiotherapy	N/A	23	N/A	Multivariate: 0.268 (0.078-0.924) p=0.037 Inverse Multivariate: 3.731 (1.082-12.821)	Nil
48.	Beltran et al 2016 (584)	Retrospective	T-cell lymphoma	Peru	83	NLR≥4	Combined Chemotherapy, Radiotherapy and Chemoradiotherapy	N/A	59	N/A	Multivariate: 4.73 (1.78-12.6) p<0.01	Performance Status
49.	Ferrucci et al 2016 (538)	Prospective	Metastatic Melanoma	Italy	720	NLR≥3	Ipilimumab	N/A	662	N/A	Multivariate: 2.29 (1.86-2.82) p<0.0001	Sex, ECOG, Brain Mets, Liver Mets
50.	Zhang et al 2016 (585)	Retrospective	RCC	China	373	NLR≥2.2	Combined Chemotherapy including Sorafenib and Sunitinib	N/A	373	N/A	Multivariate: 1.391 (1.022-1.894) p=0.036	Age, ECOG, IMDC Poor, Pathology, Fuhrman grade
51.	Kou et al 2016 (505)	Retrospective	Pancreatic	Japan	306	NLR≥5	Combination chemotherapy with palliative intent	N/A	249	N/A	Multivariate: 2.54 (1.75-3.69) p<0.01	ECOG PS, Distant Metastasis, Initially unresectable, CEA, CA19-9
52.	Namikawa et al 2016 (234)	Retrospective	Gastric	Japan	224	NLR≥4	Combination chemotherapy including trastuzmab	N/A	223	N/A	Multivariate: 1.651 (1.187-2.297) p=0.003	Histological type
53.	Moon et al 2016 (528)	Prospective	Neck Squamous Cell Ca	Korea	153	NLR: Continuous	Combination chemotherapy and chemoradiotherapy	24	27	Multivariate: 4.13 (1.57-9.19) p=0.003	Multivariate: 3.22 (1.41-7.09) p=0.005	ECOG 1/0, BMI <18.5/others

54.	Lee et al 2016 (586)	Retrospective	Cholangiocarcinoma	Korea	221	NLR>5	Combination chemotherapy including Gemcitabine and 5-Flurouracil based	N/A	197	N/A	Multivariate: 1.87 (1.33-2.62) p<0.001	Carcinoembryonic antigen, carbohydrate antigen 19-9, stage cholangiocarcinoma, number of cycles of chemotherapy
55.	Ahn et al 2016 (506)	Retrospective	Multiple Cancer Types	Korea	205	NLR≥10	Best supportive care	N/A	205	N/A	Multivariate: 1.54 (1.14-2.07) p=0.005	ECOG PS≥3, High PPI score≥6, hyperbilirubinemia
56.	Choi et al 2016 (531)	Retrospective	Pancreatic	Korea	396	NLR: 2.5-4.4 NLR: ≥4.5	Palliative Chemotherapy	N/A	396	N/A	Multivariate: 2.5-4.4: 1.659 (1.306-2.108) p<0.001 ≥4.5: 2.926 (2.181-3.927) p<0.001	ECOG PS, CA19-9
57.	Zaragoza et al 2016 (540)	Retrospective	Melanoma	France	58	NLR week 1: continuous NLR week 1: ≥4	Chemotherapy including ipilimumab	N/A	22	N/A	Multivariate; Continuous: 1.10 (1.01-1.19) p=0.026 ≥4: 2.20 (1.01-4.78) p=0.047	LDH IU, Performance Status
58.	Li et al 2016 (587)	Retrospective	Colorectal Ca Mets	China	110	NLR≤5 Inverse: NLR≥5	Combination chemotherapy including XELOX, FOLFOX and FOLFIRI	N/A	86	N/A	Multivariate: 0.99 (0.52-1.91) p=0.98 Inverse Multivariate: 1.01 (0.524-1.923)	Age, ALP Level, Ascites, PLR
59.	Hsieh et al 2016 (236)	Retrospective	Gastric	Taiwan	256	NLR>3	Combination Chemotherapy	N/A	248	N/A	Multivariate: 2.04 (1.22–3.40) p=0.007	Peritoneal Mets, NLR, mGPS, PG-SGA

Table 17.10: Studies investigating the prognostic value of LMR in an unselected cohort of patients with advanced cancer

No: LMR	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Systemic Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Li et al 2013 (588)	Retrospective	Nasopharyngeal	China	1547	LMR>5.220	Treatment with chemotherapy and radiotherapy	1457	1465	Multivariate: 0.669 (0.535–0.838) p=0.001 Inverse: 1.495 (1.193-1.869)	Multivariate: 0.558 (0.417–0.748) p=0.001 Inverse: 1.792 (1.337-2.398)	Sex, age, T stage, N stage, overall stage, treatment, prognostic measures.
2.	Rambaldi et al 2013 (589)	Retrospective	B-Cell Lymphoma	Italy	700	LMR≤2.6	Systemic chemotherapy including rituximab	N/A	392 (10 Year survival)	N/A	Multivariate: 1.88 (1.32–2.70) p=0.001	IPI>2
3.	Lin et al 2014 (543)	Retrospective	SCLC	China	370	LMR≥4.56 Inverse: LMR≤4.56	Platinum based doublet chemotherapy	N/A	370	N/A	Multivariate: 0.530 (0.409-2.795) p<0.001 Inverse: 1.887 (0.358-2.445)	ALC, Histology, ECOG
4.	Lin et al 2014 (544)	Retrospective	Nasopharyngeal	China	281	LMR≥5.07 Inverse: LMR≤5.07	Cisplatin based chemotherapy	N/A	255	N/A	Multivariate: 0.42 (0.30-0.59) p<0.001 Inverse: 2.381 (1.695-3.333)	Age, ALC
5.	Go et al 2014 (590)	Retrospective	SCLC	Korea	188	LMR: Low	Platinum based chemotherapy	N/A	152	N/A	Multivariate: 1.472 (1.029-2.106) p=0.034	Stage
6.	Koh et al 2015 (591)	Retrospective	Hodgkin Lymphoma	Korea	351	LMR<2.8	Active chemotherapy	38	48	N/A	Multivariate: 3.678 (1.008-13.41) p=0.049	LMR Only

7.	Jiang et al 2015 (592)	Retrospective	Nasopharyngeal	China	672	LMR (≥2.475 vs. <2.475)	Active chemotherapy multiple modalities	N/A	458	N/A	Multivariate: 0.50 (0.41-0.60) p<0.001 Inverse: 2 (1.666-2.439)	N-stage, Number of metastatic lesions, Liver Mets
8.	Ho et al 2015 (581)	Retrospective	Large B Cell Lymphoma	Taiwan	148	LMR<2.11	Standard R-chemotherapy.	N/A	41	N/A	Multivariate: 1.528 (0.751-3.111) p=0.242	Age, B-symptoms, ECOG, ALC, AMC, ALC/AMC PS
9.	Song et al 2015 (274)	Retrospective	Colorectal	Korea	177	LMR≤3.4	Best supportive care and herbal therapy	N/A	177	N/A	Multivariate: 1.658 (1.092-2.518) p=0.018	mGPS, CA19-9, AST, KM treatment
10.	Simon et al 2016 (593)	Retrospective	Hodgkin's Lymphoma	Hungary	121	LMR≤2.11	Combination of chemotherapy and radiotherapy	N/A	13	N/A	Multivariate: 5.57 (1.53-20.25) p=0.003	PET 2 (positive)
11.	Lin et al 2016 (545)	Retrospective	Metastatic Colorectal	China	488	LMR≥3.11 Inverse: LMR≤3.11	FOLFOX chemotherapy	N/A	479	N/A	Multivariate: 0.662 (0.501-0.875) p=0.004 Inverse: 1.511(1.143-1.996)	Gender, ECOG Performance, Tumour differentiation, Pre-chemo AMC

Table 17.11: Studies investigating the prognostic value of PLR in an unselected cohort of patients with advanced cancer

No: PLR	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Systemic Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Unal et al 2013 (562)	Prospective	Lung	Turkey	94	PLR>194	Chemoradiotherapy including platinum based chemotherapy	N/A	81	N/A	Multivariate: 1.87 (1.20-2.91) p=0.006	Response to chemoradiotherapy, NLR
2.	Liu et al 2013 (594)	Prospective	Lung	China	210	PLR≥152.6	First-line platinum-based chemotherapy	N/A	210	N/A	Multivariate: 2.025 (1.405-2.919) p<0.0001	Female sex, TNM stage IV, ECOG,
3.	Martin et al 2014 (295)	Retrospective	Pancreatic	Australia	124	PLR≥200	Chemo for metastatic disease and radio for locally advanced	N/A	114	N/A	Multivariate: 1.58 (1.07-2.33) p=0.02	CA19-9, ALC, ANC, Platelet, NLR, mGPS, Alb, ECOG
4.	Li et al 2015 (595)	Retrospective	HCC	China	243	PLR>111.23	Multiple Palliative Chemo	N/A	208	N/A	Univariate: 1.003 (1.002-1.004) p=0.002	White cell, Neutrophil, Platelets, NLR
5.	Jiang et al 2015 (596)	Retrospective	Nasopharyngeal	China	1261	PLR ≥153.64	Chemo and Radiotherapy	137	125	Multivariate: 1.84 (1.26-2.67) p=0.001	Multivariate: 1.83 (1.28-2.61) p=0.001	Age, Sex, Histology, TNM, EBV DNA
6.	Nakamura et al 2015 (597)	Retrospective	Cervical	Japan	32	PLR>322.0	All patients treated with external radiotherapy and concurrent cisplatin based chemo	N/A	32	N/A	Multivariate: 4.204 (1.158-15.268) p=0.029	2nd line chemotherapy, Pre-treatment
7.	Langsenehner et al 2015 (598)	Retrospective	Prostate	Austria	374	PLP≥190	Radiotherapy	18	65	Multivariate: 3.99 (1.19-13.4) p=0.025	Multivariate: 1.87 (1.02-3.42) p=0.044	Neoadjuvant ADT, Secondary ADT, Gleason score ≥7,

8.	Cannon et al 2015 (599)	Retrospective	Lung	USA	59	PLR>146	Stereotactic Radiation Therapy	N/A	28 (17 month follow up)	N/A	Multivariate: 4.0 (1.5–11.0) p = 0.006	PLR only
9.	Hong et al 2015 (550)	Retrospective	Lung Cancer	China	919	PLR≥250	Chemotherapy and radiotherapy	N/A	892	N/A	Multivariate: 0.975 (0.783-1.215) p=0.824	Stage, Response to treatment, LDH
10.	Wu et al 2015 (501)	Prospective	Lung	China	366	PLR>119.50	Combination Chemotherapy	N/A	366	N/A	Multivariate: 1.079 (0.729-1.596) p=0.705	Metastasis, NLR, CRP
11.	Kou et al 2016 (505)	Retrospective	Pancreatic	Japan	306	PLR≥150	Combination chemotherapy with palliative intent	N/A	249	N/A	Multivariate: 0.96 (0.72-1.28) p=0.78	ECOG PS, Distant Metastasis, Initially unresectable, CEA, CA19-9, NLR
12.	Li et al 2016 (587)	Retrospective	Colorectal Ca Mets	China	110	PLR>162	Combination chemotherapy including XELOX, FOLFOX and FOLFIRI	N/A	86	N/A	Multivariate: 2.27 (1.32-4.03) p=0.003	Age, ALP Level, Ascites

Table 17.12: Studies investigating the prognostic value of other markers of the SIR in an unselected cohort of patients with advanced cancer

No: Unassigned scores	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Systemic Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Yao et al 2014 (91)	Retrospective	Lung	China	316	GAR>0.58	Active platinum based chemo	N/A	209	N/A	Multivariate: 1.65 (1.20-2.26) p=0.002	Albumin
2.	Zhou et al 2015 (88)	Retrospective	Lung	China	367	CRP/Alb ratio (≥0.441)	Etoposide-based chemotherapy	N/A	258	N/A	Multivariate: 1.34 (1.04-1.73) p=0.025	Cancer stage, LDH level, PS
3.	Shibutani et al 2015 (90)	Retrospective	Colorectal	Japan	66	AGR (>1.25)	Active Chemotherapy including platinum chemo	N/A	N/A (Only HR reported)	N/A	Multivariate: 2.247 (1.069-4.722) p=0.033	NLR
4.	Chan et al 2015 (92)	Retrospective	HCC	Hong Kong	425	AAPR (>0.68)	Palliative chemo and radiotherapy	N/A	418	N/A	Multivariate: 2.185 (1.780-2.683) p<0.001	AJCC, BCLC, CLIP, CUPI, JIS
5.	Yamashita et al 2016 (89)	Retrospective	Prostate Ca	Japan	79	CRP/Alb ratio (CAR) ≥7	Docetaxel-based chemotherapy	36	42	NA	Multivariate: 2.34 (0.91-6.05) p=0.08	ECOG PS≥1, PSA at docetaxel initiation, Hb≥12g/dL
6.	Zhou et al 2016 (88)	Retrospective	SCLC	China	276: Testing 379: Validated	CRP/Globulin Ratio ≥1.29	Chemotherapy including etoposide based regimes as well as cranial radiotherapy	N/A	Testing: 213 Validated: 205	N/A	Testing Multivariate: 1.35 (1.61-1.81) p=0.046 Validated Multivariate: 1.43 (1.05-1.95) p=0.022	ECOG-PS, Disease stage

18. APPENDIX 2

18.1 Tables and Footnotes:

Table 18.1: Studies investigating the prognostic value of the GPS/mGPS in an unselected cohort of patients with operable cancer

No: GPS/ mGPS	Study	Type of Study	Cancer	Country	Patients (n)	Measure of Systemic Inflammatory Response (SIR)	Additional Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Ishizuka et al 2007 (246)	Retrospective	Colorectal	Japan	315	GPS (0/1/2)	No neoadjuvant treatments given	66	144	N/A	Multivariate: OR: 0.165 (0.037-0.732) p=0.0177	Multivariate: Nil else
2.	McMillan et al 2007 (118)	Retrospective	Colorectal	UK	316	mGPS (0/1/2)	Adjuvant therapy not specified	70	117	Univariate: Colon: p<0.0001 Rectal: p<0.0001 Multivariate: Dukes stage B 1.74 (1.20-2.51) p=0.0032	Univariate: Colon: p<0.0001 Rectal: p<0.0001	Multivariate: Age
3.	Leitch et al 2007 (247)	Retrospective	Colorectal	UK	149	mGPS (0/1/2)	43 patients in the GPS 0, 24 patients in the GPS1 and 4 patients in the GPS 4 group underwent adjuvant treatment	20	45	Multivariate: 2.21 (1.11-4.41) p=0.024	Multivariate: 2.08 (1.32-3.28) p=0.002	Multivariate: Age, TNM stage, monocyte count
4.	Kobayashi et al 2008 (209)	Retrospective	Oesophageal squamous cell carcinoma	Japan	48	GPS (0/ 1 and 2)	Neoadjuvant chemoradiotherapy (nCRT)	N/A	34	N/A	Multivariate: OR: 0.17 (0.06-0.52) p=0.019	Multivariate: Nil else
5.	Roxburgh et al 2009 (248)	Retrospective	Colorectal	UK	287	mGPS (0/1/2)	Adjuvant therapy not specified	67	116	Multivariate: 2.65 (1.66-4.25) p<0.001	N/A	Multivariate: Age, Dukes stage, Klintrup criteria

6.	Ishizuka et al 2009 (249)	Retrospective	Colorectal Liver Metastases	Japan	93	GPS (0/1/2)	No patients had neoadjuvant chemotherapy	48	51	Univariate: OR: 1.273 (0.269-6.030) p=0.7612	N/A	Multivariate: Number of tumours, number of hepatectomies, synchronous lung metastasis, CRP
7.	Crozier et al 2009 (250)	Prospective	Colon cancer	UK	188	mGPS (0/1/2)	54 patients received adjuvant therapy	47	67	Multivariate: TNM stage 2 patients (n=95) 2.22 (1.04-4.74) p=0.0391	N/A	Multivariate: Presentation (elective/ emergency)
8.	Roxburgh et al 2010 (251)	Retrospective	Colon	UK	287	mGPS (0/1/2)	Adjuvant chemotherapy	80	125	Multivariate: 1.96 (1.19-3.21) p=0.008	Multivariate: 1.73 (1.18-2.25) p=0.005	Multivariate: Dukes stage, vascular invasion
9.	Richards et al 2010 (252)	Prospective	Colorectal	UK	320	mGPS (0/1/2)	66 had adjuvant therapy	83	136	Multivariate: 1.78 (1.32-2.41) p<0.001	Multivariate: 1.60 (1.26-2.02) p<0.001	Multivariate: Age, Smoking, Dukes stage, POSSUM physiology score
10.	Hefler-Frischmuth et al 2010 (202)	Prospective	Vulval	Austria	93	GPS (0/1/2)	No mention of adjuvant treatment	23	27	N/A	Multivariate: 1.1 (0.5–2.4) p=0.8	Multivariate: Tumour stage, Positive lymph node
11.	Kobayashi et al 2010 (210)	Retrospective	Esophageal Squamous Cell Carcinoma	Japan	65	GPS (0 and 1)	39 patients received neoadjuvant chemoradiotherapy	57	N/A	Multivariate: GPS 0: 0.071 (0.011-0.470) p=0.0061 GPS 1: 0.367 (0.046-2.927) p=0.3442	N/A	Multivariate: Number of lymph node metastases
12.	Kobayashi et al 2010 (253)	Retrospective	Colorectal Liver Metastases	Japan	63	GPS (0/ 1 and 2)	53 patients received chemotherapy after hepatectomy	N/A	30 (5-year survival)	N/A	Multivariate: 3.07 (1.18-7.98) p= 0.0217	Multivariate: Liver metastases
13.	Moug et al 2011 (254)	Retrospective	Colorectal	UK	206	GPS (0/1/2)	9 had neoadjuvant and 48 had adjuvant	N/A	63	N/A	Multivariate: 1.56 (1.18-2.08) p=0.02	Multivariate: pLNR

14.	Dutta et al 2011 (211)	Retrospective	Oesophageal	UK	112	GPS (0/1/2)	31 had neoadjuvant and 14 adjuvant therapy	52	59	Multivariate: 4.31 (2.20-8.45) p<0.001	N/A	Multivariate: Positive to total lymph node ratio (0/≤0.2/>0.2)
15.	Dutta et al 2011 (212)	Retrospective	Oesphagogastric	UK	121	GPS (0/1/2)	67 patients have had neoadjuvant and 19 adjuvant therapy	39	44	Multivariate: 1.96 (1.09–3.54) p= 0.025	N/A	Multivariate: TNM stage
16.	Crumley et al 2012 (213)	Retrospective	Gastroesophageal	UK	100	GPS (0/1/2)	Adjuvant and neoadjuvant therapy administered chemo and radiotherapy, but numbers not given	51	55	Multivariate: 3.99 (1.96-8.11) p<0.001	N/A	Multivariate: Number of positive LN, Tumour differentiation, Klintrup score, Ki-67
17.	Jamieson et al 2011 (279)	Prospective	Pancreatic Ductal Cancer	UK	135	GPS (0/1/2)	74 patients had adjuvant therapy	107	109	N/A	Multivariate: 2.26 (1.43-3.57) p=0.0001	Multivariate: Tumour stage, tumour grade, margin involved, venous invasion, preoperative biliary drainage, adjuvant therapy
18.	Roxburgh et al 2011 (255)	Retrospective	Colorectal	UK	302	GPS (0/1/2)	71 patients had adjuvant therapy	85	135	Multivariate: 1.81 (1.32-2.48) p<0.001	Multivariate: 1.60 (1.25-2.05) p<0.001	Multivariate: Age, TNM, Peterson Index, Postoperative infective complications, ACE-27
19.	Vashist et al 2011 (214)	Retrospective	Oesophageal	Germany	495	GPS (0/1/2)	No adjuvant or neoadjuvant therapy	N/A	71	N/A	Multivariate: GPS 1: 1.7 (1.3–2.2) p<0.001 GPS 2: 2.5 (1.7-3.6) p<0.001	Multivariate: Tumour size, Node status, Mets, Cell type
20.	Nozoe et al 2011 (221)	Prospective	Gastric	Japan	232	GPS (0/1/2) mGPS (0/1/2)	No mention of adjuvant treatment	N/A	184	N/A	Multivariate: GPS: 3.425 (1.211–9.709) p=0.020 mGPS: 4.184 (1.792-9.804) p=0.0009	Multivariate: Tumour stage

21.	Ishizuka et al 2011 (146)	Retrospective	HCC	Japan	300	hGPS (0, 1/2) *CRP>0.3 mg/dl	No mention of adjuvant treatment	91	106	N/A	Univariate: OR: 2.107 (1.061-4.185) p=0.033	Univariate: CLIP score (0,1/ ≥2)
22.	Roxburgh et al 2011 (256)	Retrospective	Colon Cancer	UK	76	mGPS (0/1 or 2)	All patients received adjuvant chemotherapy	30	33	Multivariate: 3.24 (1.45-7.27) p=0.004	Multivariate: 3.23 (1.49-7.01) p=0.003	Multivariate: Petersen index, T category
23.	Dutta et al 2012 (215)	Retrospective	Oesophageal Cancer	UK	98	GPS (0/1/2)	47 underwent neoadjuvant therapy and 18 adjuvant	60	68	Multivariate: 2.91 (1.51-5.62) p=0.001	N/A	Multivariate: Age, Positive to total lymph node ratio, CD68 tertials
24.	Ishizuka et al 2012 (287)	Retrospective	HCC	Japan	398	GPS (0, 1/2)	No mention of neoadjuvant or adjuvant therapy	112	130	N/A	Multivariate: OR: 2.5 (1.124-5.561) p=0.025	Multivariate: CLIP score (0, 1/ ≥2)
25.	Richards et al 2012 (257)	Retrospective	Colorectal Cancer	UK	343	GPS (0/1/2)	No mention of adjuvant treatment	85	N/A	Multivariate: 1.74 (1.27-2.39) p=0.001	N/A	Multivariate: GPS, Local Inflammatory Cell Infiltrate, TNM, Paterson Index
26.	Qayyum et al 2012 (239)	Prospective	Renal Cell	UK	79	GPS (0/1/2)	No mention of adjuvant therapies	19	N/A	Multivariate: 8.64 (3.5–21.29) p<0.001	N/A	Multivariate: Nil else
27.	Suigimoto et al 2012 (258)	Retrospective	Colorectal	Japan	366	GPS (0/1/2)	Adjuvant chemotherapy administered	67	N/A	Multivariate: 3.09 (1.65-5.79) p=0.0004	N/A	Multivariate: Invasion Depth, Lymphatic Invasion, Lymph node metastasis
28.	Kubota et al 2012 (222)	Retrospective	Gastric	Japan	1017	GPS (0/1/2)	No mention of adjuvant treatment	66	92	Multivariate: GPS 1: 1.26 (0.54-2.56) p=0.5702 GPS 2: 5.07 (1.94-11.41) p=0.0018	Multivariate: GPS 1: 1.82 (1.00-3.11) p=0.0499 GPS 2: 5.23 (2.30-10.37) p=0.0003	Multivariate : Age≥75, Upper zone tumour, Lymph node mets, Surgical complications

29.	Powell et al 2012 (259)	Prospective	Colorectal	UK	411	mGPS (0/1/2)	Adjuvant therapy offered but no specific information on numbers given	114	191	Multivariate: 1.36 (1.03-1.79) p=0.028	N/A	Multivariate: Age, Lymph Node Ratio, Peterson Index, Klintrup score
30.	La Torre et al 2012 (280)	Retrospective	Pancreatic	Italy	101	GPS (0/1/2)	26 underwent adjuvant treatment including chemotherapy and radiotherapy	N/A	84	N/A	Multivariate: 1.7745 (1.1869-2.6532) p=0.005428	Multivariate: LNR, Node status, Margin status
31.	Dutta et al 2012 (223)	Retrospective	Gastric	UK	120	GPS (0/1/2)	Patients received both adjuvant and neoadjuvant therapy specific figures not given	44	51	Multivariate: 2.23 (1.40-3.54) p=0.001	N/A	Multivariate: Elevated lymph node ratio
32.	Wang et al 2012 (224)	Retrospective	Gastric	China	324	GPS (0/1/2)	210 patients had adjuvant chemotherapy	N/A	162	N/A	Multivariate: 1.397 (1.070-1.824) p=0.014	Multivariate: The 7th TNM stage, Adjuvant chemotherapy
33.	Lamb et al 2012 (240)	Retrospective	Renal	UK	169	GPS (0/1/2)	No mention of adjuvant therapies	35	59	Multivariate: 6.65 (3.71 – 11.93) p<0.001	Multivariate: 4.17 (2.48 – 7.03) p<0.001	Multivariate: Fuhmann grade, Necrosis, UISS, Leibovich, SSIGN,
34.	Ishizuka et al 2012 (260)	Retrospective	Colorectal	Japan	271	GPS (0/1/2)	Adjuvant chemotherapy in 76 cases	42	59	Univariate: OR: 1.986 (1.028-3.840) p=0.041	Multivariate: OR: 2.023 (1.046-3.915) p=0.036	Multivariate: Platelet Count
35.	Jiang et al 2012 (225)	Retrospective	Gastric	Japan	1710	mGPS (0/1/2)	No mention of adjuvant treatment	N/A	562	N/A	Multivariate: OR: 1.845 (1.184-2.875) p=0.007	Multivariate: Age, Tumour stage
36.	Jamieson et al 2012 (281)	Retrospective	Pancreatic Ductal Adenocarcinoma	UK	173	mGPS (0/1/2)	67 patients received adjuvant chemotherapy	N/A	173	N/A	Multivariate: 1.77 (1.19-2.62) p=0.005	Multivariate: Tumour stage, resection margin status, venous invasion, inflammatory cell infiltrate, adjuvant therapy

37.	Stoz et al 2013 (282)	Retrospective	Pancreatic Cancer	Austria	110	GPS (0/1/2)	88 Underwent chemotherapy	N/A	110	N/A	Univariate: 1.095 (0.791-1.574) p=0.585	Multivariate: Stage at diagnosis, NLR
38.	Guthrie et al 2013 (147)	Retrospective	Colorectal	UK	206	mGPS (0/1/2)	58 patients had adjuvant chemotherapy	29	41	Multivariate: Pre-Op: 1.97 (1.16–3.34) P<0.05	N/A	Multivariate: Pre-Op NLR
39.	Shiba et al 2013 (286)	Retrospective	Carcinoma of the ampulla of vater	Japan	30	GPS (0/1/2)	No specific mention of adjuvant therapy	N/A	25	N/A	Multivariate: 11.364 (1.017-126.9) p=0.048	Multivariate: Lymph node metastasis
40.	Oshiro et al 2013 (285)	Retrospective	Cholangiocarcinoma	Japan	62	GPS (0/1/2)	No mention of adjuvant treatment	N/A	46	N/A	Multivariate: 2.787 (1.153-6.735) p=0.022	Multivariate: Nil Else
41.	Horino et al 2013 (288)	Retrospective	HCC	Japan	352	GPS (0/1/2)	No mention of adjuvant treatment	N/A	128	N/A	Multivariate: 3.796 (2.050–7.031) p<0.001	Multivariate: Tumour size, Operation time, Vp
42.	Ishizuka et al 2013 (261)	Retrospective	Colorectal Stage IV	Japan	108	GPS 2 vs. 0,1	Majority had adjuvant chemotherapy	72	79	N/A	Multivariate: OR: 0.451 (0.271-0.753) p=0.002	Multivariate: Pathology others, Subclass of stage IV
43.	Ishizuka et al 2013 (119)	Retrospective	Colorectal	Japan	481	GPS (0/1/2)	Patients with stage IV disease had chemotherapy	120	150	Multivariate: OR: 2.604 (1.242-5.456) p=0.011	N/A	Multivariate: Pathology, LN Mets, CRP, Albumin, CEA, COP-NLR
44.	Son et al 2013 (262)	Retrospective	Colon Cancer	Korea	624	mGPS (2 vs. 0-1)	503 patients received chemotherapy	N/A	55 (5 yr. survival)	N/A	Multivariate: 2.217 (0.716-6.864) p=0.167	Multivariate: Fibrinogen, stage, CEA
45.	Nozoe et al 2014 (263)	Retrospective	Colorectal	Japan	272	GPS (0/1/2)	No mention of adjuvant treatment	N/A	49	N/A	Multivariate: OR: 7.41 (3.66-15.2) p<0.0001	Multivariate: Tumour stage, venous invasion

46.	Takeno et al 2014 (145)	Retrospective	Gastric	Japan	552	mGPS (0/1/2)	No mention of adjuvant treatment	N/A	215	N/A	Multivariate: 1.2391 (0.9188-1.6787) p=0.1598	Multivariate: HS-mGPS
47.	Pinato et al 2014 (300)	Retrospective	Lung	UK	220	GPS (0/1/2)	Adjuvant radio and chemotherapy administered	N/A	61	N/A	Univariate: 1.5 (1.0–2.0) p=0.02	Multivariate: NLR, Pleural Effusion
48.	Huang et al 2014 (289)	Prospective	HCC	China	349	GPS (0/1/2)	No mention of adjuvant treatment	N/A	153	N/A	Multivariate: 1.633 (1.226–2.174) p=0.001	Multivariate: CLIP score, BCLC stage
49.	Feng et al 2014 (216) 2014	Retrospective	Oesophageal	China	493	GPS (0/1/2)	Adjuvant chemo and radiotherapy administered	409 (1 year)	N/A	Univariate: 1.907 (1.608-2.262) p<0.001	N/A	Univariate: Tumour depth, Differentiation, Nodal Mets
50.	Forrest et al 2014 (264)	Retrospective	Colorectal	UK	134	GPS (0/1/2)	No mention of Adjuvant treatment	43	81	Univariate: 2.12 (1.41-3.20) p<0.001	N/A	Univariate: T-stage, N-stage, TNM stage, Venous invasion, Peritoneal involvement, Margin involvement, Manual and Automatic Klintrup–Makinen grade
51.	Wu et al 2014 (283)	Retrospective	Gallbladder	China	85	GPS (0 vs 1/2)	13 patients had post op chemotherapy	N/A	75	N/A	Multivariate: 10.877 (2.496-47.398) p=0.001	Multivariate: Tumour Invasion, Lymph node metastasis, Margin status
52.	Hirashima et al 2014 (143)	Retrospective	Gastric	Japan	294	mGPS (0/1/2)	9 patients had neoadjuvant chemotherapy	N/A	38	N/A	Multivariate: <75 Years: (n=195) 1.24 (0.41-3.75) p=0.70 >75 Years: (n=99) 2.26 (1.09-4.69) p=0.03	Multivariate: Age, Total Gastrectomy, Peritoneal mets, Stage

53.	Nakamura et al 2014 (141)	Retrospective	Oesophageal	Japan	168	mGPS (0/1/2)	13 had neoadjuvant treatment while 62 had adjuvant treatment	N/A	44 (3-year survival)	N/A	Multivariate: 2.726 (1.021–7.112) p=0.0449	Multivariate: N3: Lymph node, Residual Tumour
54.	Sun et al 2014 (265)	Retrospective	Colon cancer	China	255	mGPS (0/1/2)	No specific mention of neoadjuvant or adjuvant treatment	N/A	94	N/A	Multivariate: RR 2.968 (2.137-4.122) p=0.000	Multivariate: AFP, CEA,fibrinogen, TNM
55.	Nakagawa et al 2014 (266)	Retrospective	Colorectal Liver Metastases	Japan	343	mGPS (0/1/2)	69 patients received neoadjuvant chemotherapy, 216 received adjuvant chemotherapy	86	94	Multivariate: 1.595 (1.156-2.201) p=0.004	N/A	Multivariate: CEA (<30/ ≥30 ng/L)
56.	Aurello et al 2014 (135)	Retrospective	Gastric Cancer	Italy	102	mGPS (0/1/2)	68 patients received adjuvant chemotherapy after surgery	62	62	N/A	Multivariate: mGPS 1: 1.70 (1.20-3.42) p=0.005 mGPS 2: 1.91 (1.38-3.18) p=0.008	Multivariate: Prognostic index
57.	Miyazaki et al 2015 (301)	Retrospective	Non Small Cell Lung Cancer (NSCLC)	Japan	97	GPS (0/1/2)	No mention of adjuvant treatment	29	44	N/A	Multivariate: 2.13 (1.036-4.393) p=0.04	Multivariate: Patient factors, Inflammatory factors, stage factors
58.	Matsuda et al 2015 (217)	Retrospective	Oesophageal Cancer	Japan	199	GPS (0/1/2)	99 patients received neoadjuvant chemotherapy/ chemoradiotherapy	N/A	72	N/A	Multivariate: GPS 1: 0.562 (0.229-1.377) p=0.208 GPS 2: 0.969 (0.123-7.668) p=0.976	Multivariate: Clinical stage, fibrinogen and albumin score
59.	Farhan-Alanie et al 2015 (275)	Retrospective	Oral SCC	UK	178	GPS (0/1/2)	70 patients had adjuvant therapy	42	56	Multivariate: 2.12 (1.49-3.00) p<0.001	Multivariate: 1.69 (1.23-2.31) p=0.001	Multivariate: Male and AJCC stage 4
60.	Ferro et al 2015 (199)	Retrospective	Bladder Cancer	Italy	1037	mGPS (0/1/2)	799 received adjuvant chemotherapy	426	430	Multivariate: mGPS 1: 0.87 (0.54-1.40) p=0.565	Multivariate: mGPS 1: 1.19 (0.84-1.70) p=0.332	Multivariate: Pathologic stage T4, Node positive

										mGPS 2: 0.94 (0.49-1.81 p=0.853	mGPS 2: 1.25 (0.74-2.11) p=0.410	and adjuvant Chemotherapy
61.	Arigami et al 2015 (142)	Retrospective	Oesophageal Cancer	Japan	238	mGPS (0/1/2)	No mention of adjuvant therapy	N/A	98	N/A	Multivariate: 1.08 (0.49-2.19) p=0.830	Multivariate: F-NLR Score, Lymph node mets, Depth of tumour invasion
62.	Xu et al 2015 (127)	Retrospective	Oesophageal SCC	China	468	GPS/mGPS (0/1/2)	196 patient received adjuvant chemo and radiotherapy	N/A	259	N/A	Univariate: GPS 1: 1.33 (0.99-1.78) p=0.057 GPS 2: 1.83 (1.18-2.86) p=0.008 mGPS 1: 1.39 (1.01-1.91) p=0.046 mGPS 2: 1.82 (1.17-2.83) p=0.008	Multivariate: Lymph Node Mets, Venous/lymphatic invasion, CRP/Alb Ratio
63.	Ni et al 2015 (290)	Retrospective	HCC	China	367	mGPS (0/1/2)	No mention of adjuvant treatment	N/A	40	N/A	Multivariate: 4.356 (2.495-7.605) p<0.001	Multivariate: GGT≥60, AFP≥400, CLIP Score, Vascular Invasion
64.	Hirahara et al 2015 (218)	Retrospective	Oesophageal	Japan	141	GPS (0/1/2)	No mention of adjuvant treatment	N/A	16	N/A	Multivariate: 2.045 (1.032-3.928) p=0.041	Multivariate: p Stage
65.	Shibutani et al 2015 (267)	Retrospective	Colorectal	Japan	254	GPS (0/1/2)	Adjuvant chemotherapy	N/A	69	N/A	Multivariate: 7.238 (1.180-44.415) p=0.032	Multivariate: NLR (Pre & Post op), Number of lymph node mets
66.	Shiba et al 2015 (284)	Retrospective	Gallbladder Ca	Japan	51	GPS (0/1/2)	No mention of adjuvant treatment	N/A	16	N/A	Multivariate: 3.782 (1.119-12.786) p=0.032	Multivariate: Lymph node metastasis
67.	Kawashima et al 2015 (144)	Retrospective	Lung Cancer	Japan	1043	GPS (0/1/2)	No mention of adjuvant treatment	N/A	227	N/A	Multivariate: GPS 1 1.63 (1.09-2.42) p=0.02 GPS 2 1.44 (0.80-2.60)	Multivariate: Age, smoking, preoperative co-morbidity, CEA, pathological stage, histological

											p=0.22	tumour type, LVI, surgical procedure
68.	Watt et al 2015 (600)	Retrospective	Colorectal cancer	UK	508	mGPS (0/1/2)	108 patients had adjuvant chemotherapy following resection.	172	292	Multivariate: 1.54 (1.25-1.90) p< 0.001	Multivariate: 1.32 (1.12-1.56) p=0.001	Multivariate: Age, site, TNM stage, margin involvement, peritoneal involvement, sex, venous invasion, tumour perforation
69.	Okamura et al 2015 (291)	Retrospective	HCC	Japan	256	GPS (0/1/2)	No mention of adjuvant treatment	N/A	86	N/A	Multivariate: 1.71 (0.92-3.16) p=0.089	Multivariate: AFP, des-gamma-carboxy prothrombin, high NLR, low PNI.
70.	Abe et al 2016 (292)	Retrospective	HCC	Japan	46	GPS (0/ 1,2)	No mention of adjuvant treatment	N/A	17	N/A	Multivariate: 7.718 (1.710-34.840) p=0.008	Multivariate: Milan criteria
71.	Ishizuka et al 2016 (126)	Retrospective	Colorectal Cancer	Japan	627	GPS (2/0, 1)	No mention of adjuvant treatment	110	142	N/A	Multivariate: 1.809 (1.181-2.772) p=0.006	Multivariate: Pathological differentiation, CEA, stage, CAR, NLR
72.	Park et al 2016 (268)	Retrospective	Colorectal Cancer	UK	228	GPS (0/1/2)	131 received adjuvant therapy	66	N/A	Multivariate: 1.59 (1.12–2.27) p=0.010	N/A	Multivariate: CD3 cancer cells nest density (low/high), NPS
73.	Park et al 2016 (7)	Retrospective	Colorectal	UK	1000	mGPS (0/1/2)	Adjuvant therapy: 248 Neoadjuvant therapy: 98	242	435	Multivariate: 1.28 (1.09-1.52) p=0.003	Multivariate: 1.28 (1.13-1.45) p<0.001	Multivariate: Age, Adjuvant therapy, T stage, N stage, Differentiation, Margins involved
74.	Fu et al 2016 (293)	Retrospective	HCC	China	Training: 772	GPS (0/1/2) mGPS (0/1/2)	No mention of adjuvant treatment	N/A	377 (4-year survival)	N/A	Multivariate: Training cohort: mGPS 3.508 (1.384-8.890) p=0.008	Multivariate: AFP, GGT, IBS, PLR, PI, tumour size, tumour number, microscopic

												vascular invasion, differentiation, BCLC.
75.	Fan et al 2016 (302)	Retrospective	Non-small Cell Lung Cancer	China	1243	GPS (0/1/2) mGPS (0/1/2)	684 patients received chemotherapy, 220 patients received radiotherapy	N/A	373	N/A	Multivariate: GPS: 2.228 (1.447-3.431) p< 0.0001 mGPS: 0.958 (0.633-1.452) p=0.841	Multivariate: Gender, age, TNM stage, chemotherapy, radiotherapy
76.	Chan et al 2016 (269)	Retrospective	Colorectal Cancer	Australia	386	mGPS (0/1/2)	Patients with high-risk stage II and III colon cancer disease were generally offered standard adjuvant chemotherapy, whereas those with stage II or III rectal cancers were usually treated with neoadjuvant	N/A	353	N/A	Univariate: mGPS 1: 1.552 (0.892-2.700) P=0.001 mGPS 2: 2.214 (1.454-3.369) p=0.001	Multivariate: Age, T stage, grade, LMR
77.	Walsh et al 2016 (219)	Retrospective	Esophageal Cancer	Ireland	223	mGPS (0 vs. 1/2)	109 patients received neoadjuvant chemoradiotherapy, 66 patients received chemotherapy	N/A	104 (5-year survival)	N/A	Multivariate: 1.24 (0.69-2.22) p=0.47	Multivariate: TNM stage, nodal status
78.	Otowa et al 2016 (220)	Retrospective	Oesophageal Cancer	Japan	100	Pre-NAC mGPS (0/1-2) Post-NAC mGPS (0/2) NAC=neoadjuvant chemotherapy	All patients underwent NAC followed by surgery	N/A	36	N/A	Multivariate: Pre-NAC mGPS: 0.043 (0.001–1.311) p=0.067 Post-NAC mGPS: 0.020 (0.018–0.621) p=0.018	Multivariate: Grade of response to chemotherapy
79.	Melling et al 2016 (226)	Retrospective	Gastric Cancer	Germany	88	GPS (0/1/2)	Any neoadjuvant/adjuvant therapy was an exclusion criterion	N/A	57	N/A	Multivariate: OR 1.6 (1.0-2.4) p=0.033	Multivariate: Nil else

80.	Toyokawa et al 2016 (140)	Retrospective	Thoracic Oesophageal Squamous Cell Carcinoma	Japan	185	GPS (0 vs 1/2)	46 patients received neoadjuvant treatment (39 chemotherapy, 6 chemoradiotherapy, 1 radiotherapy)	N/A	77	N/A	Multivariate: 1.021 (0.465-2.245) p=0.958	Multivariate: Sex, performance status, America Society of Anaesthesiologist Physical Status Classification (ASA), cTNM stage, CONUT score

Table 18.2: Studies investigating the prognostic value of the NLR in an unselected cohort of patients with operable cancer

No: NLR	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Additional Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Halazun et al 2008 (601)	Retrospective	Colorectal Liver Metastases	UK	440	NLR >5	Adjuvant therapy of 5-FU/folinic acid	N/A	395 (5-year survival)	N/A	Multivariate: 2.275 (1.654-3.129) p<0.0001	Multivariate: Age, tumour number
2.	Gomez et al 2008 (602)	Retrospective	Intrahepatic cholangiocarcinoma	UK	27	NLR ≥5	No mention of adjuvant or neoadjuvant treatment	N/A	21	N/A	Multivariate: RR: 1.778 (0.558-5.668) p=0.331	Multivariate: Nil else
3.	Sarraf et al 2009 (603)	Retrospective	Non-Small Cell Lung Cancer	UK	177	NLR (tertiles)	No mention of adjuvant or neoadjuvant treatment	N/A	81 (5-year survival)	N/A	Multivariate: 1.10 (1.03-1.17) p= 0.005	Multivariate: Stage of disease
4.	Kishi et al 2009 (604)	Retrospective	Colorectal Liver Metastases	US	200	NLR >5	Neoadjuvant chemotherapy	N/A	118 (5-year survival)	N/A	Multivariate: 2.0 (1.0-3.8) p= 0.048	Multivariate: Postoperative factors namely concomitant radiofrequency ablation (RFA) and surgical margin
5.	Cho et al 2009 (605)	Retrospective	Epithelial Ovarian Cancer	South Korea	192	NLR >2.6	Adjuvant chemotherapy	N/A	20	N/A	Multivariate: 8.42 (1.09-64.84) p=0.041	Multivariate: Age, stage
6.	Smith et al 2009 (606)	Retrospective	Pancreatic Ductal Adenocarcinoma	UK	110	NLR continuous	33 patients had adjuvant therapy	N/A	106	N/A	Univariate: 1.047 (0.985-1.113) p=0.14	Multivariate: Lymphocyte count, PLR
7.	Halazun et al 2009 (607)	Retrospective	HCC	US	150	NLR ≥5	116 patients received pretransplant tumour therapy	N/A	61	N/A	Multivariate: 6.102 (2.286-16.290) p<0.0001	Multivariate: Preoperative AFP

8.	Jagdev et al 2010 (608)	Retrospective	Renal Cell Carcinoma	UK	286	Log (NLR)	No mention of adjuvant or neoadjuvant treatment	63 (5-year survival)	111 (5-year survival)	Multivariate: 4.2 (1.6-11) p=0.004	Univariate: 2.1 (1.5-2.8) p<0.001	Multivariate: Log CRP, stage, grade, RBC, WBC, M stage, necrosis, micro vascular invasion
9.	Ubukata et al 2010 (609)	Retrospective	Gastric Cancer	Japan	157	NLR ≥5	No neoadjuvant therapy.	N/A	77	N/A	Multivariate: RR: 5.779 (0.950-35.170) p=0.0001	Multivariate: Th1/ Th2 ratio, pathological stage, depth of invasion, tumour size, lymph node metastasis
10.	Shimada et al 2010 (610)	Retrospective	Gastric Cancer	Japan	1028	NLR ≥4	No mention of adjuvant or neoadjuvant treatment	128	147	N/A	Multivariate: 1.845 (1.236-2.747) p=0.003	Multivariate: Tumour depth, N factor, distant/ peritoneal metastasis, histology, platelet count
11.	Bhatti et al 2010 (611)	Retrospective	Pancreatic ductal adenocarcinoma	UK	84	NLR (continuous)	30 patients received adjuvant chemotherapy	N/A	66 (3-year survival)	N/A	Multivariate: 1.210 (1.010-1.449) p=0.039	Multivariate: Lymphocyte count, resection margin
12.	Mohri et al 2010 (612)	Retrospective	Gastric Cancer	Japan	357	NLR >2.2	No neoadjuvant therapy	N/A	98	N/A	Multivariate: 2.78 (1.79-4.36) p<0.0001	Multivariate: Tumour size, clinical T stage
13.	Liu et al 2010 (613)	Retrospective	Rectal carcinoma	China	123	NLR >2	Stage II cancers received adjuvant chemotherapy	N/A	123	N/A	Multivariate: 2.615 (1.152-5.933) p=0.021	Multivariate: Depth of invasion, tumour size, CA12-5 level, stage
14.	Miyata et al 2011 (128)	Retrospective	Oesophageal Cancer	Japan	152	NLR ≥4	All patients received neoadjuvant chemotherapy	N.A.	92 (5-year survival)	N/A	Multivariate: 1.30 (0.76-2.22) p=0.3362	Multivariate: Clinical response, SI score, number of metastatic lymph nodes, operative complication

15.	Dutta et al 2011 (211)	Retrospective	Oesophagus	UK	112	NLR (<2.5/ 2.5-5/ >5)	31 had neoadjuvant and 14 adjuvant therapy	52	59	Univariate: 1.08 (0.75-1.56) p=0.686	N/A	Multivariate: Positive to total lymph node ratio (0/≤0.2/>0.2), mGPS
16.	Kao et al 2011 (614)	Retrospective	Malignant pleural mesothelioma	Australia	85	NLR ≥3	19 patients received neoadjuvant chemotherapy	N/A	72 (5-year survival)	N/A	Multivariate: 1.79 (1.04-3.07) p=0.04	Multivariate: Gender, histological subtype, calretinin score, D2-40 score
17.	Jung et al 2011 (615)	Retrospective	Gastric cancer	Korea	293	NLR ≥2	183 patients received adjuvant chemotherapy	N/A	166	N/A	Multivariate: 1.462 (1.033-2.068) p=0.032	Multivariate: Combined resection radicalism, Lauren classification, postoperative chemotherapy
18.	Sharaiha et al 2011 (616)	Retrospective	Esophageal cancer	US	295	NLR ≥5	127 received neoadjuvant therapy (chemo/ radiotherapy)	N/A	160 (5-year survival)	N/A	Multivariate: 2.32 (1.53-3.50) p<0.0001	Multivariate: Age, sex, stage, tumour differentiation, comorbidities
19.	Tomita et al 2011 (617)	Retrospective	Non-small Cell Lung Cancer	Japan	284	NLR≥2.5	No mention of adjuvant or neoadjuvant treatment	N/A	109 (5-year survival)	N/A	Multivariate: RR: 1.2863 (1.0462-1.5738) p=0.0173	Multivariate: Age, histology, pT, pN, pleural lavage cytology
20.	Hung et al 2011 (618)	Retrospective	Colon cancer	Taiwan	1040	NLR ≥5	No neoadjuvant therapy administered	122	334	N/A	Multivariate: 1.29 (1.07-1.80) p=0.012	Multivariate: Age, CEA, examined lymph node no. <12, T stage, tumour obstruction/ perforation
21.	Neal et al 2011 (619)	Retrospective	Colorectal Liver Metastases	UK	202	NLR ≥5	84 patients had systemic chemotherapy in the 6 months before liver resection	N/A	127 (5-year survival)	N/A	Univariate: 2.51 (1.56-4.02) p<0.001	Multivariate: Clinical risk score, neutrophil count, serum albumin
22.	Asher et al 2011 (620)	Retrospective	Ovarian Cancer	UK	235	NLR>4	170 patients received chemotherapy	N/A	169 (survival after 150 months)	N/A	Multivariate: 0.865 (0.521-1.437) p=0.575	Multivariate: Age, stage, residual disease, PLR

23.	Wang et al 2011 (621)	Retrospective	HCC	China	101	NLR≥3	35 patients received pre-transplant tumour therapy	N/A	51	N/A	Multivariate: 2.654 (1.419-4.964) p<0.001	Multivariate: Tumour numbers, vascular invasion
24.	Bertuzzo et al 2011 (622)	Retrospective	HCC	Italy	219	NLR ≥5	159 patients received neoadjuvant treatments (TACE, PEI, RFA)	27	61	N/A	Multivariate: OR: 4.868 (2.473-9.582) p< 0.0001	Multivariate: Microvascular invasion
25.	Idowu et al 2012 (623)	Retrospective	Soft Tissue Sarcoma	UK	223	NLR ≥5	No mention of adjuvant or neoadjuvant treatment	N/A	44 (5-year survival)	N/A	Multivariate: 5.125 (1.245-21.086) p=0.024	Multivariate: Grade, surgical margin.
26.	Ishizuka et al 2012 (624)	Retrospective	Colorectal Cancer	Japan	169	NLR (continuous)	Adjuvant chemotherapy in most patients	86	96	N/A	Multivariate: OR: 0.980 (0.870-1.106) p=0.747	Multivariate: Tumour pathology
27.	Wang et al 2012 (224)	Retrospective	Gastric	China	324	NLR >5	210 patients had adjuvant chemotherapy	N/A	162	N/A	Multivariate: 1.866 (0.901-3.866) p=0.093	Multivariate: The 7th TNM stage, adjuvant chemotherapy
28.	Gondo et al 2012 (625)	Retrospective	Bladder cancer	Japan	189	NLR ≥2.5	38 received intravesical chemotherapy	54	N/A	Multivariate: 1.946 (1.035-3.663) p=0.0387	N/A	Multivariate: Tumour size, Hb
29.	Kwon et al 2012 (626)	Retrospective	Colorectal cancer	Korea	200	NLR ≥5	150 patients received adjuvant chemotherapy/ chemoradiation	N/A	39	N/A	Multivariate: 1.520 (0.613-3.772) p=0.367	Multivariate: Stage, CEA, PLR
30.	Carruthers et al 2012 (102)	Retrospective	Rectal cancer	UK	115	NLR ≥5	Neoadjuvant chemoradiation	N/A	43	N/A	Multivariate: 7.0 (2.6-19.2) p<0.001	Multivariate: Total WBC, platelet count, R status, down staging
31.	Dutta et al 2012 (223)	Retrospective	Gastric	UK	120	NLR (<2.5/ 2.5-5/ >5)	Patients received both adjuvant and neoadjuvant therapy specific figures not given	44	51	Univariate: 1.19 (0.76-1.87) p=0.454	N/A	Multivariate: Positive lymph node ratio

32.	Wang et al 2013 (627)	Retrospective	Oesophageal Cacinosarcoma	China	33	NLR≥5	4 patients received adjuvant chemotherapy, 3 received adjuvant radiotherapy	N/A	14	N/A	Multivariate: 138.47 (6.772-2831.214) p=0.001	Multivariate: Nil else
33.	Choi et al 2014 (628)	Retrospective	Soft Tissue Sarcoma	Korea	162	NLR >2.5	7 patients received neoadjuvant chemotherapy, 72 patients received adjuvant radiation, 36 patients received adjuvant chemotherapy	20	20	Multivariate: OR: 1.32 (0.55-3.21) p=0.096	N/A	Multivariate: CRP, ESR, number of elevated markers
34.	Szkandera et al 2013 (629)	Retrospective	Soft Tissue Sarcoma	Austria	260	NLR <3.58vs. ≥3.58	167 patients received adjuvant radiotherapy, 35 received adjuvant chemotherapy	N/A	86	N/A	Multivariate: 1.88 (1.14-3.12) P=0.014	Multivariate: Sex, tumour necrosis, tumour stage
35.	Krane et al 2013 (630)	Retrospective	Bladder Cancer	US	68	NLR >2.5	10 patients received neoadjuvant chemotherapy	25	40	Multivariate: RR 2.68 (1.01-8.59)	Multivariate: RR 2.49 (1.14-6.09)	Multivariate: Hypoalbuminaemia, pT3, nodal disease.
36.	Pichler et al 2013 (631)	Retrospective	Renal Cell Carcinoma	Austria	678	NLR <3.3vs. ≥3.3	No mention of adjuvant or neoadjuvant treatment	59	123	Multivariate: 1.59 (0.84-2.99) P=0.148	Multivariate: 1.59 (1.10-2.31) P=0.014	Multivariate: Age, T stage, tumour grade, presence of tumour necrosis
37.	Jankova et al 2013 (632)	Retrospective	Colorectal cancer	Australia	322	NLR (continuous)	7 patients received adjuvant radiotherapy, 197 received adjuvant chemotherapy	86	141	Multivariate: 1.01 (0.92-1.12) P=0.782	Multivariate: 1.06 (1.01-1.12) P=0.013	Multivariate: Age, direct spread beyond muscularis propria, nodes involvement, adjacent structure infiltrated, postoperative chemotherapy, sex
38.	Fu et al 2013 (633)	Retrospective	Hepatocellular Carcinoma	China	282	NLR>2	No mention of adjuvant or neoadjuvant treatment	N/A	173	N/A	Multivariate: 1.434 (1.044-1.970) P=0.026	Multivariate: Tumour size, tumour number, macroscopic vascular invasion, Child-Pugh class

39.	Shibutani et al 2013 (634)	Retrospective	Colorectal Cancer	Japan	674	NLR ≥2.5	No mention of adjuvant or neoadjuvant treatment	136	177	Multivariate: 1.609 (1.117-2.319) P=0.011	N/A	Multivariate: Tumour diameter, lymph node metastasis, distant metastasis
40.	Forget et al 2013 (635)	Retrospective	Breast Cancer	Belgium	Centre 1: n=172 Centre 2: n=162	Centre 1: NLR. ≥4 Centre 2: NLR. ≥3	No mention of adjuvant or neoadjuvant treatment	N/A	Centre 1: 17 (at 60 months) Centre 2: 8 (at 24 months)	N/A	Centre 1: Univariate 0.51 (0.35-8.58) P=0.47 Centre 2: Univariate 4.00 (1.12-14.3) P=0.03	Univariate: Ketorolac or diclofenac use
41.	Forget et al 2013 (635)	Retrospective	NSCLC	Belgium	255	NLR≥5	No mention of adjuvant or neoadjuvant treatment	N/A	109 (at 60 months)	N/A	Univariate: 1.52 (1.07-2.17) P=0.02	Multivariate: Pneumonectomy, Ketorolac (vs. no NSAIDS)
42.	Forget et al 2013 (635)	Retrospective	Kidney Cancer	Belgium	227	NLR≥5	No mention of adjuvant or neoadjuvant treatment	N/A	64 (at 60 months)	N/A	Multivariate: 1.67 (1.0-2.81) p=0.05	Multivariate: Node status, stage, histological stage
43.	Absenger et al 2013 (636)	Retrospective	Colon Cancer	Austria	372	dNLR (≤2.2 vs. >2.2) preoperative NLR >4 preoperative NLR ≥5	230 patients received adjuvant chemotherapy	N/A	72	N/A	Multivariate: dNLR 1.78 (1.07-2.97) p=0.026 Preoperative NLR >4 2.22 (1.36-3.62) p=0.002 Preoperative NLR ≥5 1.68 (1.03-2.73) p=0.037	Multivariate: Clinical stage
44.	Feng et al 2013 (123)	Retrospective	Oesophageal Squamous Cell Carcinoma	China	483	NLR >3.45	No mention of adjuvant or neoadjuvant treatment	N/A	244	N/A	Multivariate: 1.310 (0.997-1.722) p=0.053	Multivariate: Differentiation, depth of invasion, node metastasis, PLR, CNP
45.	Mano et al 2013 (637)	Retrospective	Hepatocellular Carcinoma	Japan	958	NLR ≥2.81	No mention of adjuvant or neoadjuvant treatment	N/A	310 (5-year survival)	N/A	Multivariate: 3.745 (1.027-1.088) p=0.0002	Multivariate: Albumin, tumour size, portal vein thrombus, stage, multiple tumours

46.	Azuma et al 2013 (638)	Retrospective	Upper Urinary Tract Urothelial Carcinoma	Japan	137	NLR ≥2.5	No mention of adjuvant or neoadjuvant treatment	54 (5-year survival)	N/A	Multivariate: 3.06 (1.44-6.83) p=0.0035	N/A	Multivariate: pT stage, lymphovascular invasion
47.	Dumitrascu et al 2013 (639)	Retrospective	Hilar Cholangiocarcinoma	Romania	90	NLR <3.3	43 received adjuvant treatment (chemotherapy, radiotherapy or chemoradiotherapy)	51	56	N/A	Multivariate: RR 0.76 (0.57-1) p=0.053	Multivariate: Adjuvant chemotherapy with gemcitabine, R0 resection, caudate lobe invasion
48.	Perisanidis et al 2013 (640)	Retrospective	Oral Cancer	Austria	97	NLR >1.9	All patients treated with neoadjuvant chemoradiotherapy	17	35	Multivariate: 10.37 (1.28-84.08) p=0.029	N/A	Multivariate: ypTNM, perineural invasion
49.	Noh et al 2013 (641)	Retrospective	Breast Cancer	Korea	442	NLR ≥2.5	Triple negative cancers are treated with chemotherapy	25 (5-year survival)	32	Multivariate: 4.08 (1.62-10.28) p=0,003	N/A	Multivariate: Node status, ER status
50.	Liao et al 2013 (642)	Retrospective	Non-small Cell Lung Cancer	China	59	NLR continuous	Patients who underwent neoadjuvant chemotherapy and/or radiotherapy were excluded	N/A	23 (after 40 months)	N/A	Multivariate: 1.00 (0.40-2.49) p=0.98	Multivariate: Tumour differentiation, FAP-α percentage/ grade.
51.	Bambury et al 2013 (643)	Retrospective	Glioblastoma multiforme	Ireland	84	NLR >4	49 patients received complete Stupp protocol (using concurrent chemoradiotherapy followed by consolidation chemotherapy with temozolomide)	N/A	82	N/A	Multivariate: 1.81 (1.08-3.01) p=0.025	Multivariate: Age, gender, extent of resection, full Stupp protocol
52.	Toiyama et al 2013 (644)	Retrospective	Rectal Cancer	Japan	84	NLR >3	All patients received neoadjuvant chemoradiotherapy	N/A	37 (after 150 months)	N/A	Multivariate: 0.98 (0.37-2.56) p=0.96	Multivariate: Pathological TNM stage, CRP
53.	Son et al 2013 (262)	Retrospective	Colon Cancer	Korea	624	NLR ≥5	503 patients received chemotherapy	N/A	55 (5 yr. survival)	N/A	Multivariate: 1.841 (0.470-7.204) p=0.381	Multivariate: Fibrinogen, stage, CEA

54.	Stoz et al 2013 (282)	Retrospective	Pancreatic Cancer	Austria	110	NLR≥5	88 Underwent chemotherapy	N/A	110	Multivariate: 1.611 (1.024-2.534) p=0.039	N/A	Multivariate: Stage at diagnosis, NLR
55.	Guthrie et al 2013 (147)	Retrospective	Colorectal	UK	206	NLR>5	58 patients had adjuvant chemotherapy	29	41	Multivariate Pre-Op: 3.07 (1.23–7.63) P<0.05	N/A	Multivariate: Pre-Op and Post-Op mGPS
56.	Ishizuka et al 2013 (119)	Retrospective	Colorectal	Japan	481	NLR>3	Patients with stage IV disease had chemotherapy	120	150	Univariate: OR: 0.961 (0.843-1.096) p=0.554	N/A	Multivariate: Pathology, LN Mets, CRP, Albumin, CEA, GPS
57.	Szkandera et al 2014 (645)	Retrospective	Soft Tissue Sarcoma	Austria	340 Training set, n=170 Validation set, n=170	NLR ≥5	Training set: 16 received adjuvant chemotherapy, 102 received adjuvant radiotherapy Validation set: 22 received adjuvant chemotherapy, 107 received adjuvant radiotherapy	Training set: 30 Validation set: 22	Training set: 53 Validation set: 51	Univariate: Training set: 2.14 (0.81-5.66) p=0.124 Validation set: 1.98 (0.77-5.08) p=0.153	Multivariate: Training set: 1.68 (0.75-3.76) p=0.201 Validation set: 2.84 (1.37-5.87) p=0.005	Multivariate: Age, tumour grade, LMR, tumour size
58.	Dalpiaz et al 2014 (646)	Retrospective	Upper Tract Urothelial Carcinoma	Austria	202	NLR ≥2.7	No mention of adjuvant or neoadjuvant treatment	58	147	Multivariate: 2.718 (1.246-5.928) P=0.012	Multivariate: 2.480 (1.308-4.702) P=0.005	Multivariate: pT stage
59.	Luo et al 2014 (647)	Retrospective	Upper Urinary Tract Urothelial Carcinoma	Taiwan	234	NLR >3	Patients underwent RNU without neoadjuvant or adjuvant intervention.	24	N/A	Multivariate: 6.38 (1.75-23.31) p=0.006	N/A	Multivariate: Pathological stage, age, smoking
60.	Wu et al 2014 (283)	Retrospective	Gallbladder	China	85	NLR >2.3	13 patients had post op chemotherapy	N/A	75	N/A	Univariate: 1.769 (1.111-2.818) p=0.016	Multivariate: Tumour Invasion, Lymph node metastasis, Margin status
61.	Zhang et al 2014 (648)	Retrospective	Non-Small Cell Lung Cancer	China	400	NLR <3.3vs. ≥3.3	Patients treated with neoadjuvant and adjuvant therapy were excluded	86	N/A	N/A	Multivariate: 2.075 (1.317-3.271) p=0.002	Multivariate: Age, tumour size

62.	Ying et al 2014 (649)	Retrospective	Colorectal Cancer	China	205	NLR≥3.12	77 colon and 31 rectal cancer patients underwent chemotherapy	100	112	Multivariate: 2.77 (1.72-4.46) p<0.001	Multivariate: 2.73 (1.74-4.29) p<0.001	Multivariate: Grade (G3/G4), chemotherapy
63.	Linton et al 2014 (650)	Retrospective	Malignant Pleural Mesothelioma	Australia	59	NLR. ≥5	64% received adjuvant radiotherapy, 33% received induction or adjuvant chemotherapy	N/A	24 (survival >20 months)	N/A	Survival after 4 months Univariate: NLR≥5 0.86 (0.40-1.82) p=0.69	Multivariate: Nil else
64.	Ishizuka et al 2014 (120)	Retrospective	Gastric Cancer	Japan	544	NLR (≤3 vs. >3)	343 patients received adjuvant chemotherapy	55	108	N/A	Univariate: 1.990 (1.417-2.793) p<0.001	Multivariate: Age, tumour type, lymph node metastasis, albumin, COP-NLR
65.	Kubo et al 2014 (651)	Retrospective	Colorectal carcinoma	Japan	524	NLR (high/low)	Adjuvant chemotherapy in 156 patients with stage 3 cancer and 38 patients with stage 2 cancer	74	104	Multivariate: 1.71 (1.03-2.88) p=0.04	N/A	Multivariate: Cancer site, T stage, lymph node metastasis
66.	Viers et al 2014 (652)	Retrospective	Clear Cell Renal Carcinoma	US	827	NLR (continuous)	No mention of adjuvant or neoadjuvant treatment	233	436	Multivariate: 1.02 (1.01-1.04) p=0.009	Multivariate: 1.02 (1.01-1.03) p=0.004	Multivariate: ECOG performance status, tumour size, constitutional symptoms, age
67.	Koh et al 2014 (653)	Retrospective	Breast Cancer	South Korea	157	NLR >2.25)	All treated with neoadjuvant chemotherapy	N/A	25	N/A	Multivariate: 24.87 (3.075-201.3) p=0.003	Multivariate: Nil else
68.	Hermanns et al 2014 (654)	Retrospective	Bladder cancer	Canada	424	NLR ≥3	29 patients received neo-adjuvant chemotherapy, 87 received adjuvant chemotherapy, 55 received salvage chemotherapy	110	178	Multivariate: 1.88 (1.39-2.54) p<0.001	Multivariate: 1.67 (1.17-2.39) p=0.005	Multivariate: Charlson Comorbidity Index, Hb, platelets, N-stage, year of radical cystectomy, lymphovascular invasion

69.	Tanaka et al 2014 (655)	Retrospective	Upper Tract Urothelial Carcinoma	Japan	665	NLR >3	129 patients received adjuvant chemotherapy	129	N/A	Multivariate: 1.47 (1.03-2.11) p=0.036	N/A	Multivariate: Age, pathological T stage, lymphovascular invasion, lymph node involvement
70.	Jiang et al 2014 (656)	Retrospective	Gastric Cancer	China	377	NLR <1.44 vs. ≥1.44	219 patients received adjuvant chemotherapy post gastrectomy	N/A	223	N/A	Multivariate: 1.595 (1.045-2.435) p=0.030	Multivariate: Tumour size, serosal invasion, lymph node metastasis, post complication
71.	Yuan et al 2014 (657)	Retrospective	Adenocarcinoma of Esophagogastric Junction	China	327	NLR <5 vs. ≥5	18 patients received neoadjuvant chemotherapy, 59 patients received adjuvant chemotherapy	N/A	168	N/A	Multivariate: 2.551 (1.847-3.524) p<0.0001	Multivariate: pTNM stage, adjuvant treatment
72.	Ozdemir et al 2014 (658)	Retrospective	Colorectal Cancer	Turkey	281	NLR (≤2.2 vs. >2.2)	Patients with lymph node invasion, vascular invasion, perineural invasion and high neoadjuvant CEA were given adjuvant chemotherapy	N/A	134	N/A	Multivariate: 3.306 (1.713-6.378) p=0.005	Multivariate: pN stage, pTNM stage.
73.	Dalpiaz et al 2014 (646)	Retrospective	Upper Tract Urothelial Carcinoma	Austria	171	dNLR (continuous),	No mention of adjuvant or neoadjuvant treatment	54	79	Multivariate: 1.16 (1.01-1.35) p=0.045	Multivariate: 1.21 (1.09-1.34) p<0.001	Multivariate: Age at operation, pT-stage
74.	Feng et al 2014 (659)	Retrospective	Esophageal SCC	China	483	NLR ≥3.5	No mention of adjuvant or neoadjuvant treatment	N/A	244	N/A	Multivariate: 1.339 (1.015-1.768) p=0.039	Multivariate: Differentiation, depth of invasion, nodal metastasis, PLR
75.	Viers et al 2014 (660)	Retrospective	Bladder Cancer	USA	899	NLR (continuous)	117 patients received adjuvant therapy (radiation or chemotherapy)	345	615	Multivariate: 1.04 (1.01-1.08) p=0.01	Multivariate: 1.03 (1.01-1.06) p=0.01	Multivariate: Age at surgery, ECOG performance status, pathologic tumour stage, lymph node density,

												lymphovascular invasion
76.	McNamara et al 2014 (661)	Retrospective	Biliary Tract Cancer	Canada	326	NLR ≥3	90 received adjuvant chemotherapy	N/A	199	N/A	Multivariate: 1.15 (0.87-1.53) p=0.33	Multivariate: Site, stage, age
77.	East et al 2014 (133)	Retrospective	Colon Cancer	UK	436 Training set, n=386 Test set, n=50	NLR ≥3.4	26 patients received adjuvant chemotherapy	N/A	27	N/A	Multivariate: Training set: 1.43 (1.06-1.94) p=0.02 Test set: 3.40 (2.64-5.13) p<0.001	Multivariate: N stage, R0 resection, adjuvant treatment, T stage, WLR.
78.	Malietzis et al 2014 (662)	Retrospective	Colorectal Cancer	UK	506	NLR >3	All patients with neoadjuvant or adjuvant therapy were excluded	28	118	N/A	Multivariate: OR: 1.23 (0.80-1.90) p=0.347	Multivariate: Age at operation, T stage, N stage, surgical approach, ASA score, major complication
79.	Grivas et al 2014 (663)	Retrospective	Renal Cell Carcinoma	Greece	114	NLR ≥2.7	No patients received adjuvant therapy	10	14	N/A	Multivariate: 2.866 p=0.034	Multivariate: Hb level, Fuhrman grade
80.	Shen et al 2014 (664)	Retrospective	Rectal Cancer	China	199	NLR ≥2.8	All patients treated with neoadjuvant chemoradiotherapy followed by surgery, 184 patients received adjuvant chemotherapy.	N/A	43	N/A	Multivariate: 2.123 (1.140-3.954) p=0.018	Multivariate: ypTNM staging, adjuvant chemotherapy
81.	Sun et al 2014 (265)	Retrospective	Colon cancer	China	255	NLR ≥5	No specific mention of neoadjuvant or adjuvant treatment	N/A	94	N/A	Multivariate: RR 1.541 (0.724-3.282) p=0.262	Multivariate: AFP, CEA, fibrinogen, TNM, mGPS
82.	Neofytou et al 2014 (665)	Retrospective	Liver-only Colorectal Metastases	UK	140	NLR >2.4	All patients received neoadjuvant chemotherapy	N/A	59 (5-year survival)	N/A	Multivariate: 1.52 (0.78-2.99) p=0.216	Multivariate: No adjuvant chemotherapy

83.	Aurello et al 2014 (135)	Retrospective	Gastric Cancer	Italy	102	NLR ≥5	68 patients received adjuvant chemotherapy after surgery	62	62	N/A	Multivariate: 1.51 (0.69-3.28) p=0.29	Multivariate: Prognostic index, mGPS, Tumour stage IV, PI 1&2
84.	Pinato et al 2014 (300)	Retrospective	Lung	UK	220	NLR>5	Adjuvant radio and chemotherapy administered	N/A	61	N/A	Multivariate: 3.8 (1.6 –8.9) p=0.002	Multivariate: TNM stage, Pleural Effusion
85.	Forrest et al 2014 (264)	Retrospective	Colorectal	UK	134	NLR>5	No mention of Adjuvant treatment	43	81	Univariate: 2.27 (0.99-5.19) p=0.052	N/A	Univariate: T-stage, N-stage, TNM stage, Venous invasion, Peritoneal involvement, Margin involvement, Manual and Automatic Klintrup–Makinen grade
86.	Song et al 2015 (666)	Retrospective	Hypopharyngeal SCC	China	146	NLR ≥2.3	14 patients received adjuvant chemoradiotherapy 94 received adjuvant radiotherapy	N/A	75 (3-year survival)	N/A	Multivariate: 2.36 (1.33-4.18) p0.003	Multivariate: Treatment modalities
87.	Xu et al 2015 (127)	Retrospective	Oesophageal SCC	China	468	NLR>2.40	196 patient received adjuvant chemo and radiotherapy	N/A	259	N/A	Univariate: 1.50 (1.17-2.83) p=0.008	Multivariate: Lymph Node Mets, Venous/lymphatic invasion, CRP/Alb Ration
88.	Hirahara et al 2015 (218)	Retrospective	Oesophageal	Japan	141	NLR≥2.5	No mention of adjuvant treatment	N/A	16	N/A	Univariate: 1.164 (0.616-2.126) p=0.631	Multivariate: pStage, GPS
89.	Shibutani et al 2015 (267)	Retrospective	Colorectal	Japan	254	NLR>2.5	Adjuvant chemotherapy	N/A	69	N/A	Multivariate: 6.599 (0.928-46.914) p=0.059	Multivariate: NLR (Post op), Number of lymph node mets

90.	Takahashi et al 2015 (667)	Retrospective	Non-small Cell Lung Cancer	Japan	342	NLR ≥2.5	Patients who had received neoadjuvant chemotherapy or thoracic irradiation were not included.	N/A	51 (5-year survival)	N/A	Multivariate: 2.141 (1.306-3.515) p=0.003	Multivariate: Smoking, CEA, nonadenocarcinoma, pathological stage, presence of pleural invasion
91.	Tu et al 2015 (668)	Retrospective	Laryngeal Squamous Cell Carcinoma	China	141	NLR >2.17	No mention of adjuvant treatment	N/A	45	N/A	Multivariate: 2.177 (1.208-3.924) p=0.010	Multivariate: T classification, lymph node metastasis
92.	Shin et al 2015 (669)	Retrospective	Colorectal Cancer	Korea	269	NLR. ≥3	Patients treated with chemoradiation were excluded	5	N/A	Multivariate: 6.190 (1.034-37.047) p=0.046	N/A	Multivariate; Thrombocytosis
93.	Que et al 2015 (670)	Retrospective	Soft-tissue Sarcoma	China	222	NLR ≥2.5	39 patients received adjuvant chemotherapy, 65 patients received adjuvant radiotherapy	N/A	82 (after 150 months)	N/A	Multivariate: 1.06 (0.52-2.16) p=0.881	Multivariate: Tumour site, AJCC stage, PLR
94.	Hsu et al 2015 (671)	Retrospective	Gastric Cancer	Taiwan	989	NLR >3.44	499 patients with stage 2 to 4 tumour received chemotherapy	N/A	395 (5-year survival)	N/A	Multivariate: 1.565 (1.198-2.044) p=0.001	Multivariate: Resection margin, differentiation, T status, N status, LN ratio, M1 status
95.	Shimizu et al 2015 (672)	Retrospective	Non-small Cell Lung Cancer	Japan	334	NLR ≥2.5	Neither radiotherapy nor chemotherapy administered prior to the surgery	N/A	95 (3-year survival)	N/A	Multivariate: 1.60 (1.04-2.54) p=0.048	Multivariate: Age, nodal metastasis, PNI
96.	Han et al 2015 (673)	Retrospective	Glioblastoma	China	152	NLR ≥4	All patients received adjuvant radio-chemotherapy	N/A	118 (2-year survival)	N/A	Multivariate: 1.050 (1.003-1.100) p=0.037	Multivariate: KPS, resection, MGMT promoter, PLR
97.	Liao et al 2015 (674)	Retrospective	Hepatocellular Carcinoma	China	222	NLR >2.1	69 patients received transcatheter arterial chemoembolization (TACE) 1-month post surgery.	N/A	77 (5-year survival)	N/A	Multivariate: 3.013 (1.633-5.561) p=0.014	Multivariate: Neutrophil count, postoperative TACE

98.	Aldemir et al 2015 (675)	Retrospective	Gastric Cancer	Turkey	53	NLR ≥2.75	No mention of adjuvant treatment	N/A	19	N/A	Univariate: p=0.88	Univariate: ECOG performance status, platelet count
99.	Kadota et al 2015 (676)	Retrospective	Lung Squamous Cell Carcinoma	US	485 Training cohort n=331	NLR >5.5	80% patients received adjuvant therapy	N/A	Training cohort n=188	N/A	In training cohort Univariate: 1.82 (1.26-2.62) p=0.001	Multivariate: Smoking pack-year, pathological stage, CD10/CD20 risk index, age, lymphovascular invasion
100.	Neofytou et al 2015 (677)	Retrospective	Liver-Only Colorectal Metastases	UK	140	NLR (continuous)	All patients received neoadjuvant chemotherapy, 104 received adjuvant chemotherapy.	60	63	Univariate: 1.20 (1.06-1.36) p=0.003	N/A	Multivariate: Adjuvant chemotherapy, preoperative LMR.
101.	Bagante et al 2015 (678)	Retrospective	Adrenocortical Carcinoma	US	84	NLR >5	51 patients received peri-operative systemic chemotherapy, 38 patients received adjuvant mitotane	50 (5-year CSS)	N/A	Multivariate: 2.21 (1.10-4.43) p=0.025	N/A	Multivariate: AJCC tumour status and metastatic status
102.	Wang et al 2015 (679)	Retrospective	Hepatocellular Carcinoma	US	234	NLR >2.5	170 patients had antiviral treatment	N/A	88 (5-year survival)	N/A	Multivariate: 4.9 (1.8-13.2) p=0.002	Multivariate: Tumour size
103.	Pine et al 2015 (680)	Retrospective	Colorectal Cancer	UK	358	NLR ≥5	No mention of adjuvant treatment	N/A	157 (after 4 years)	N/A	Multivariate: 1.819 (1.310-2.526) p<0.001	Multivariate: Age, Dukes' stage C and stage D
104.	Li et al 2015 (681)	Retrospective	Endometrial Cancer	China	282	NLR ≥4.68	No mention of adjuvant treatment	N/A	38 (5-year survival)	N/A	Multivariate: 2.298 (0.679-7.781) p=0.181	Multivariate: CRP, D-dimer,
105.	Zhang et al 2015 (682)	Retrospective	Non-small Cell Lung Cancer	China	678	NLR >2.3	Adjuvant chemotherapy or/and radiotherapy	N/A	367	N/A	Multivariate: 1.624 (1.304-2.022) p<0.001	Multivariate: Pathological stage (I, II, IIIA)

106.	Zhang et al 2015 (683)	Retrospective	Gallbladder Carcinoma	China	145	NLR ≥1.94	No mention of adjuvant treatment	N/A	117 (5-year survival)	N/A	Multivariate: RR 2.059 (1.253-3.384) p=0.004	Multivariate: Nevin stages, operation modes, Hb
107.	Qu et al 2015 (684)	Retrospective	Gastric Cancer	China	1397 Development set: n=1123 Validation set: n=274	NLR >1.86	All patients underwent neoadjuvant chemotherapy or adjuvant radiotherapy	N/A	3-year survival Development set: 307 Validation set: 60	N/A	Multivariate: 1.379 (1.082-1.758) p=0.009	Multivariate: Age, tumour size, Lauren type, depth of invasion, number of metastatic lymph node.
108.	Zhang et al 2015 (685)	Retrospective	Ovarian Cancer	China	190	NLR >3.4)	Surgery was followed by platinum-based chemotherapy	N/A	170 (after 100-month)	N/A	Univariate: 2.172 (1.545-3.054) p<0.001	Multivariate: Stage (FIGO), postoperative residual tumour mass, PLR
109.	Yu et al 2015 (686)	Retrospective	Gastric Cancer	China	291	NLR <3.5	No mention of adjuvant treatment	N/A	199 (5-year survival)	N/A	Multivariate: 0.626 (0.460-0.852) p=0.003	Multivariate: N staging, TNM staging
110.	Sun et al 2015 (136)	Retrospective	Gastric Cancer	China	632	NLR. >1.83	395 patients received adjuvant chemotherapy	N/A	448	N/A	Multivariate: 1.056 (0.830-1.343) p=0.656	Multivariate: Age, respectability, distant metastasis, pathological stage, CEA, postoperative complications, PNI
111.	Duan et al 2015 (687)	Retrospective	Esophageal SCC	China	371	NLR >3	No mention of adjuvant treatment	192	N/A	Multivariate: 1.591 (1.132-2.235) p=0.007	N/A	Multivariate: pN status
112.	Wen et al 2015 (688)	Retrospective	Renal Cell Carcinoma	China	327	NLR ≥1.7	No mention of adjuvant treatment	N/A	230 (after 80 months)	N/A	Multivariate: 1.674 (1.103-2.539) p=0.019	Multivariate: Histological subtypes, pT stage
113.	Zhang et al 2015 (121)	Retrospective	Non-Small Cell Lung Cancer	China	1238	NLR >2.3	Adjuvant treatments including chemotherapy, radiotherapy and	N/A	686	N/A	Univariate: 1.533 (1.458-1.785) p<0.001	Multivariate: TNM stage, LDH, D-dimer, COP-NLR

							concurrent chemoradiotherapy					
114.	Choi et al 2015 (689)	Retrospective	Colorectal Cancer	Canada	549	NLR≥2.6	147 patients received adjuvant therapy: chemotherapy, radiation or both	N/A	120 (5-year survival)	N/A	Multivariate: 1.91 (1.26-2.9) p=0.002	Multivariate: Age>75, lymph nodes positive, ASA status
115.	Deng et al 2015 (690)	Retrospective	Gastric Cancer	China	389	NLR≥2.36	No mention of adjuvant treatment	235	270	Multivariate: 1.53 (1.11-2.11) p=0.010	Multivariate: 1.13 (0.68-1.87) p=0.648	Multivariate: Age, tumour stage, lymph node, distant metastasis, dNLR
116.	Spolverato et al 2015 (691)	Retrospective	Hepato-Pancreatico-Biliary Malignancies	US	452	NLR ≥5	189 patients received neoadjuvant chemotherapy.	N/A	192 (5-year survival)	N/A	Multivariate: 1.94 (1.03-3.64) p=0.040	Multivariate: Age, complications.
117.	Han et al 2015 (692)	Retrospective	Esophageal SCC	China	218	NLR< 2.60	Adjuvant treatment: 17 received chemotherapy 41 received radiotherapy 24 received chemoradiotherapy	N/A	138	N/A	Multivariate: 1.133 (0.762-1.685) p=0.538	Multivariate: Tumour length, pTNM stage, LMR.
118.	Kim et al 2015 (693)	Retrospective	Gastric Cancer	Korea	1986	NLR>2	No mention of adjuvant treatment	N/A	323 (5-year survival)	N/A	Multivariate: 1.403 (1.048-1.879) p=0.0230	Multivariate: Age, approach method, depth of invasion, node status
119.	Chan et al 2015 (694)	Retrospective	Hepatocellular Carcinoma	Hong Kong	324	NLR≥5	282 patients with chronic viral hepatitis received antiviral therapy	N/A	79 (5-year survival)	N/A	Univariate: 1.587 (0.817-3.086) p=0.173	Multivariate: Antiviral therapy, microvascular invasion, PNI.
120.	Choi et al 2015 (695) 2015	Retrospective	Lung Cancer	US	1139	NLR ≥5	Neoadjuvant: 245 received chemotherapy 18 received radiation Adjuvant: 285 received chemotherapy	N/A	752 (5-year survival)	N/A	Multivariate: Preoperative NLR 1.686 (1.274-2.230) p=0.0003	Multivariate: Age, stage, adjuvant radiation

							170 received radiation					
121.	Lee et al (696) 2015	Retrospective	Breast cancer	South Korea	3116	NLR ≥ 5.2	No mention of adjuvant treatment	300	N/A	Univariate: 1.09 (0.94-1.26) p=0.516	N/A	Multivariate: Post op NLR 1-week, Nuclear grade, AJCC stage, HR status.
122.	Chen et al 2015 (579)	Retrospective	Colorectal Cancer	US	274	NLR >5	No mention of adjuvant treatment	N/A	32 (3-year survival)	N/A	Univariate: 2.37 (1.10-5.10) p=0.023	Multivariate: Metastatic site, LDH
123.	Wuxiao et al 2015 (697)	Retrospective	Colon Cancer	China	548	NLR ≤3	All stage 3 patients received 5-fluorouracil based adjuvant chemotherapy	N/A	106	N/A	Multivariate: RR 0.384 (0.255-0.580) p<0.001 Inverted: 2.60 (1.72-3.92)	Multivariate: Histological grade, preoperative CEA levels
124.	Qing Chen et al 2015 (698)	Retrospective	Intrahepatic cholangiocarcinoma	China	322	NLR ≥2.49	Patients treated with chemoradiotherapy are removed from this study	N/A	204 (5-year survival)	N/A	Multivariate: 1.600 (1.178-2.174) p=0.003	Multivariate: CA199, tumour number, lymph node metastasis.
125.	Kim et al 2015 (699)	Retrospective	Upper Urinary Tract Urothelial Carcinoma	South Korea	277	NLR. ≥5:1	71 patients received adjuvant chemotherapy	73	96	Univariate: 1.179 (0.511-2.718) p=0.700	N/A	Multivariate: Bladder cuff excision, pathologic T stage, lymphovascular invasion, derived NLR
126.	Szkandera et al 2015 (700)	Retrospective	Soft Tissue Sarcoma	Austria	340	dNLR ≥2.39	No mention of adjuvant treatment	N/A	98	N/A	Multivariate: 1.60 (1.07-2.40) p=0.022	Multivariate: Tumour grade
127.	Ben et al 2015 (701)	Retrospective	Pancreatic Ductal Adenocarcinoma	China	381	NLR ≥2	No mention of adjuvant treatment	N/A	283	N/A	Multivariate: 1.51 (1.15-1.99) p=0.003	Multivariate: lymphoid node involvement, poor tumour differentiation, edge positive.

128.	Graziosi et al 2015 (702)	Retrospective	Gastric Cancer	Italy	156	NLR. ≥2.34	18 patients received neoadjuvant chemotherapy 70 patients received adjuvant chemotherapy	N/A	70	N/A	Multivariate: 1.70 (1.02-2.84) p<0.043	Multivariate: Mixed-type Lauren classification
129.	Takahashi et al 2015 (703)	Retrospective	Endometrial Cancer	Japan	508	NLR >3	215 patients received adjuvant therapy	50	55	N/A	Univariate: 2.47 (1.45-4.24) p=0.0009	Multivariate: Age, FIGO stage, LVSI, neutrophil count
130.	Shirai et al 2015 (704)	Retrospective	Pancreatic cancer	Japan	131	NLR ≥5	No mention of adjuvant treatment	N/A	103 (5-year survival)	N/A	Univariate: 0.984 (0.511-1.894) p=0.961	Multivariate: Tumour size, resection margin status, tumour differentiation, PLR
131.	Chen et al 2015 (705)	Retrospective	Intrahepatic Cholangiocarcinoma	China	322	NLR (continuous)	Adjuvant chemoradiotherapy used as well as radiofrequency ablation	N/A	197 (5-year survival)	N/A	Multivariate: 1.399 (1.006-1.947) p=0.046	Multivariate: CA19-9, tumour number, lymph node metastasis, PLR
132.	Neal et al 2015(122)	Retrospective	Colorectal Liver Metastases	UK	302	NLR ≥5	132 patients had systemic chemotherapy in the 6 months prior to liver resection, 126 patients received systemic chemotherapy following mastectomy	204 (5-year survival)	214 (5-year survival)	Multivariate: 1.927 (1.398-2.655) p<0.001	Multivariate: 1.769 (1.302-2.403) p<0.001	Multivariate: Clinical risk score
133.	Kawashima et al 2015 (144)	Retrospective	Lung Cancer	Japan	1043	NLR >5	No mention of adjuvant treatment	N/A	227	N/A	Univariate: 1.53 (1.00-2.34) p=0.05	Multivariate: Age, smoking, preoperative co-morbidity, CEA, pathological stage, histological tumour type, LVI, surgical procedure
134.	Cummings et al 2015 (124)	Retrospective	Endometrial Cancer	UK	605	NLR ≥2.4	33% of patients received adjuvant radiotherapy, 13% of patients received	96	166	Multivariate: 1.68 (1.03-2.76) p=0.04	Multivariate: 1.82 (1.27-2.62) p=0.001	Multivariate: PLR, combined NLR + PLR, age, FIGO stage,

							adjuvant chemotherapy					grade, histopathological subtype, LVSI
135.	Lian et al 2015 (706)	Retrospective	Gastric Cancer	China	162	NLR ≥4.02	No mention of adjuvant treatment	N/A	N/A (expressed in months)	N/A	Univariate: OR 2.58 (1.62-3.80) p=0.001	Multivariate: Depth of invasion, lymph node metastasis, AJCC stage, PLR
136.	Okamura et al 2015 (291)	Retrospective	Hepatocellular Carcinoma	Japan	256	NLR ≥2.81	No mention of adjuvant treatment	N/A	86	N/A	Multivariate: 2.41 (1.44-4.01) p=0.001	Multivariate: AFP, des-gamma-carboxy prothrombin, low PNI.
137.	Xie et al 2016 (707)	Retrospective	Oesophageal Squamous Cell Cancer	China	317	NLR. >2.1	76 patients received adjuvant chemotherapy after surgery	147	152	Multivariate: 1.196 (0.833-1.719) p=0.332	N/A	Multivariate: PLR, TNM stage
138.	Mohri et al 2016 (708)	Retrospective	Gastric Cancer	Japan	404	NLR >3	No mention of adjuvant treatment	65 (5-year survival)	82 (5-year survival)	Multivariate: 1.97 (1.08-3.58) p=0.03	Multivariate: 2.09 (1.10-3.94) p=0.02	Multivariate: Age, gender, ASA, tumour size, p-stage 2 and 3, infectious complication
139.	Ha et al 2016 (129)	Retrospective	Ampulla of Vater Cancer	South Korea	227	NLR >1.78	Adjuvant treatments including chemotherapy, radiotherapy and concurrent chemoradiotherapy	N/A	105	N/A	Multivariate: 1.280 (0.70-2.33) p=0.418	Multivariate: Vascular invasion, CA19-9.
140.	Li et al 2016 (137)	Retrospective	Colorectal Cancer	China	5336	NLR (≤2.72 vs. >2.72)	5-Fu based adjuvant chemotherapy for stage 2/3 patients	588	611	N/A	Multivariate: 1.227 (1.003-1.501) p=0.047	Multivariate: Age, T stage, N stage, differentiation, venous invasion, LMR, AGR
141.	Takahashi et al 2016 (709)	Retrospective	Lung adenocarcinoma	Japan	361	NLR ≥2.5	80 received adjuvant chemotherapy	N/A	74 (5-year survival)	N/A	Multivariate: 1.822 (1.133-2.931) p=0.013	Multivariate: Gender, smoking history, pathological stage, lymphatic/ vascular/ pleural invasion

142.	Cheng et al 2016 (710)	Retrospective	Upper Tract Urothelial Carcinoma	Taiwan	195	NLR ≥2.7	35 patients received adjuvant chemotherapy and 16 patients received adjuvant radiation therapy	N/A	55	Multivariate: 1.362 (0.652-2.847) p=0.411	Multivariate: 1.611 (0.890-2.916) p=0.115	Multivariate: WBC, pT stage, tumour grade, RDW
143.	Turner et al 2016 (711)	Retrospective	Colon Cancer	Australia	396	NLR >5	Neoadjuvant chemotherapy was an exclusion criteria	N/A	93	N/A	Multivariate: 1.75 (0.87-3.52) p=0.039	Multivariate: Low CIC density, age, ASA score, T4 stage
144.	Fu et al 2016 (712)	Retrospective	Laryngeal Squamous Cell Carcinoma	China	420	NLR ≥2.59	Patients needed to have no previous anti-cancer treatment to be included	171 (5-year CSS)	176 (5-year survival)	Multivariate: 1.42 (1.06-1.91) p=0.018	Multivariate: 1.31 (1.00-1.71) p=0.046	Multivariate: Age, drinking, N stage, histological type
145.	Lu et al 2016 (713)	Retrospective	Hepatocellular carcinoma	China	963	NLR>2.81	No mention of adjuvant treatment	N/A	553 (5-year survival)	N/A	Multivariate: 1.296 (1.074-1.563) p=0.007	Multivariate: Tumour number, incomplete capsule, serum albumin , ALT, macrovascular invasion
146.	Chen et al 2016 (714)	Retrospective	Esophageal Squamous Cell Carcinoma	China	323	NLR >3.5	No mention of adjuvant treatment	221 (5-year)	N/A	Multivariate: 1.050 (0.740-1.488) p=0.786	N/A	Multivariate: TNM stage, I stage
147.	Wang et al 2016 (715)	Retrospective	Gastroesophageal Junction and Gastric Adenocarcinoma	US	1498	NLR (continuous)	Neoadjuvant chemotherapy or radiotherapy	588 (5-years)	N/A	Multivariate: 1.10 (1.05-1.13) p<0.0001	N/A	Multivariate: T stage, N stage, tumour location
148.	Hodek et al 2016 (716)	Retrospective	Rectal Carcinoma	Czech Republic	173	NLR (continuous)	All patients received neoadjuvant chemoradiotherapy	N/A	22	N/A	Univariate: RR 1.21 (1.03-1.43) p=0.02	Univariate: WBC, RBC, Hb, platelet count, neutrophils, PLR
149.	Christina et al 2016 (138)	Retrospective	Oral cancer	Austria	144	NLR> 1.9	All patients received neoadjuvant radiotherapy in combination with systemic cytotoxic therapy	N/A	60 (5-year survival)	N/A	Univariate: 1.16 (0.65-2.06) p=0.62	Multivariate: Regression grade

150.	Morizawa et al 2016 (717)	Retrospective	Bladder cancer	Japan	110	NLR ≥2.6	37 patients received neoadjuvant chemotherapy	32	42	Multivariate: 2.6 (1.9-5.2) p=0.01	Multivariate: 2.8 (1.4-5.4) p=0.00	Multivariate: ECOG-PS, lymph node metastasis, tumour growth pattern
151.	Ishizuka et al 2016 (126)	Retrospective	Colorectal Cancer	Japan	627	NLR >2.9	No mention of adjuvant treatment	110	142	N/A	Multivariate: 1.811 (1.229-2.669) p=0.003	Multivariate: Pathological differentiation, CEA, stage, CAR, GPS
152.	Kosumi et al 2016 (718)	Retrospective	Oesophageal Squamous Cell Carcinoma	Japan	283	NLR ≥1.94	191 patients received adjuvant therapy; 10 patients received neoadjuvant chemoradiotherapy	65	91	Multivariate: 1.84 (1.07-3.21) p=0.028	Multivariate: 1.84 (1.17-2.93) p=0.0081	Multivariate: Nil else
153.	Kawahara et al 2016 (719)	Retrospective	Bladder Cancer	Japan	74	NLR ≥2.38	10 patients received neoadjuvant chemotherapy, 25 patients received adjuvant chemotherapy	N/A	29 (after 4000 days)	N/A	Multivariate: 4.62 (1.16-18.34) p=0.030	Multivariate: CRP, pathological lymph node metastasis.
154.	Wang et al 2016 (139)	Retrospective	Ovarian Cancer	China	143	NLR. >3.43)	No mention of adjuvant treatment	N/A	51	N/A	Multivariate: 3.37 (1.39-8.15) p=0.007	Multivariate: Metastasis, prognostic inflammation score
155.	Kang et al 2016 (720)	Retrospective	Bladder Cancer	Korea	385	Preop-NLR ≥2.1	96 patients received adjuvant chemotherapy	85	116	Multivariate: 1.16 (1.06-1.28) p=0.005	Multivariate: 1.13 (1.04-1.22) p=0.003	Multivariate: Postop-NLR, pT stage, number of lymph nodes removed, lymph node status, age, surgical margin status
156.	Chan et al 2016 (269)	Retrospective	Colorectal Cancer	Australia	1623	NLR. >3.19)	Patients with high-risk stage II and III colon cancer disease were generally offered standard adjuvant chemotherapy, whereas those with stage II or III rectal cancers were usually	N/A	941	N/A	Univariate: 1.830 (1.539-2.176) p< 0.001	Multivariate: Age, T stage, N stage, grade, LMR

							treated with neoadjuvant chemoradiotherapy					
157.	Toyokawa et al 2016 (140)	Retrospective	Thoracic Oesophageal Squamous Cell Carcinoma	Japan	185	NLR >3.612	46 patients received neoadjuvant treatment (39 chemotherapy, 6 chemoradiotherapy, 1 radiotherapy)	N/A	77	N/A	Multivariate: 1.194 (0.627-2.273) p=0.589	Multivariate: Sex, performance status, ASA, cTNM stage, CONUT score
158.	Bhindi et al 2016 (721)	Retrospective	Bladder Cancer	Canada	418	NLR (per 1-log unit)	28 received neo-adjuvant chemotherapy, 87 received adjuvant chemotherapy, 54 received salvage chemotherapy	107	177	Multivariate: 1.47 (1.20-1.80) p<0.001	Multivariate: 1.56 (1.16-2.10) p=0.004	Multivariate: T-stage, N-stage, haemoglobin, age, Charlson co-morbidity index, lymphovascular invasion

Table 18.3: Studies investigating the prognostic value of the PLR in an unselected cohort of patients with operable cancer

No: PLR	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Additional Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Smith et al 2009 (606)	Retrospective	Pancreatic Ductal Adenocarcinoma	UK	110	PLR (continuous)	33 patients had adjuvant therapy	N/A	93 (48-month survival)	N/A	Multivariate: 1.004 (1.002-1.006) p=0.0003	Multivariate: Tumour size, Lymph node ratio
2.	Bhatti et al 2010 (611)	Retrospective	Pancreatic ductal adenocarcinoma	UK	84	PLR ≤100, 100-200, >200	30 patients received adjuvant chemotherapy	N/A	66 (3-year survival)	N/A	Univariate: 0.978 (0.899-1.075) 0.642	Multivariate: NLR, Resection margin status
3.	Asher et al 2011 (620)	Retrospective	Ovarian Cancer	UK	235	PLR>300	170 patients received chemotherapy	N/A	169 (survival after 150 months)	N/A	Multivariate: 1.698 (1.031-2.797) p=0.03	Multivariate: Age, stage, residual disease
4.	Dutta et al 2011 (211)	Retrospective	Oesophagus	UK	112	PLR (<150/ 150-300/ >300)	31 had neoadjuvant and 14 adjuvant therapy	52	59	Univariate: 0.94 (0.60-1.48) p=0.781	N/A	Multivariate: mGPS (0/1/2) lymph node ratio (0/≤0.2/>0.2)
5.	Kwon et al 2012 (626)	Retrospective	Colorectal cancer	Korea	200	PLR <150, 150-300, >300	150 patients received adjuvant chemotherapy or chemoradiation	N/A	39	N/A	Multivariate: 1.953 (1.161-3.284) p=0.012	Multivariate: Stage, CEA
6.	Dutta et al 2012 (223)	Retrospective	Gastric	UK	120	PLR (<150/ 150-300/ >300)	Patients received both adjuvant and neoadjuvant therapy specific figures not given	44	51	Univariate: 0.83 (0.49-1.40) p=0.483	N/A	Multivariate: Positive lymph node ratio, mGPS,
7.	Carruthers et al 2012 (102)	Retrospective	Rectal cancer	UK	115	PLR<160	Neoadjuvant chemoradiation	N/A	43	N/A	Univariate: 1.5 (0.8-2.7) p=0.192	Multivariate: R status, NLR (<5)

8.	Raungkaewmanee et al 2012 (722)	Retrospective	Epithelial Ovarian Cancer	Thailand	166	PLR ≥200	145 patients had adjuvant chemotherapy	N/A	50	N/A	Multivariate: 1.41 (0.77-2.56) p=0.263	Multivariate: Stage, surgical outcomes
9.	Wang et al 2012 (224)	Retrospective	Gastric	China	324	PLR (<150/ 150-300/ >300)	210 patients had adjuvant chemotherapy	N/A	162	N/A	Univariate: 0.867 (0.665-1.132) p=0.296	Multivariate: The 7th TNM stage, Adjuvant chemotherapy, GPS
10.	Feng et al 2013 (123)	Retrospective	Oesophageal Squamous Cell Carcinoma	China	483	PLR >166.5	No mention of adjuvant or neoadjuvant treatment	N/A	244	N/A	Multivariate: 1.751 (1.345-2.280) p<0.001	Multivariate: Differentiation, depth of invasion, node metastasis, CNP
11.	Feng et al 2013 (723)	Retrospective	Small Cell Carcinoma of Oesophagus	China	43	PLR ≥150	26 patients received adjuvant chemoradiotherapy	N/A	35	N/A	Multivariate: 2.272 (1.035-4.984) p=0.041	Multivariate: Chemoradiotherapy
12.	Stoz et al 2013 (282)	Retrospective	Pancreatic Cancer	Austria	110	PLR≥150	88 Underwent chemotherapy	N/A	110	N/A	Univariate: 1.133 (0.815-1.574) p=0.458	Multivariate: Stage at diagnosis, NLR
13.	Toiyama et al 2013 (644)	Retrospective	Rectal Cancer	Japan	84	PLR >150	All patients received neoadjuvant chemoradiotherapy	N/A	37 (after 150 months)	N/A	Univariate: 2.17 (0.90-5.21) p=0.08	Multivariate: Pathological TNM stage, CRP
14.	Son et al 2013 (262)	Retrospective	Colon Cancer	Korea	624	PLR>300 vs. <150/ 150-300	503 patients received chemotherapy	N/A	55 (5 yr. survival)	N/A	Multivariate: 2.006 (0.530-7.589) p=0.305	Multivariate: Fibrinogen, stage, CEA
15.	Zhang et al 2014 (648)	Retrospective	Non-Small Cell Lung Cancer	China	400	PLR ≥171	Patients treated with neoadjuvant and adjuvant therapy were excluded	86	129	N/A	Univariate: 1.985 (1.269-3.104) p=0.003	Multivariate: Age, tumour size
16.	Ying et al 2014 (649)	Retrospective	Colorectal Cancer	China	205	PLR≥176	77 colon and 31 rectal cancer patients underwent chemotherapy	100	112	Multivariate: 1.15 (0.75-1.78) p=0.513	Multivariate: 1.15 (0.77-1.73) p=0.501	Multivariate: Grade (G3/G4), chemotherapy

17.	Szkandera et al 2014 (645)	Retrospective	Soft Tissue Sarcoma	Austria	340 Training set, n=170 Validation set, n=170	PLR ≥200	Training set: 16 received adjuvant chemotherapy, 102 received adjuvant radiotherapy Validation set: 22 received adjuvant chemotherapy, 107 received adjuvant radiotherapy	Training set: 30 Validation set: 22	Training set: 53 Validation set: 51	Univariate: Training set: 2.43 (0.99-5.90) p=0.051 Validation set: 1.52 (0.66-3.54) p=0.320	Univariate: Training set: 3.02 (0.94-9.70) p=0.019 Multivariate: Validation set: 0.61 (0.30-1.25) p=0.175	Multivariate: Age, tumour grade, LMR, tumour size
18.	Baranyai et al 2014 (724)	Retrospective	Colorectal Cancer	Hungary	336	PLR >300	No mention of adjuvant or neoadjuvant treatment	N/A	335	N/A	Multivariate: 3.5 (2.2-5.6) logrank P=3.6e-08 (insignificant)	Multivariate: Elevated platelet count
19.	Jiang et al 2014 (656)	Retrospective	Gastric Cancer	China	377	PLR ≥184	219 patients received adjuvant chemotherapy post gastrectomy	N/A	223	N/A	Multivariate: 1.068 (0.791-1.441) p=0.668	Multivariate: Tumour size, serosal invasion, lymph node metastasis, post complication, NLR
20.	Yuan et al 2014 (657)	Retrospective	Adenocarcinoma of Esophagogastric Junction	China	327	PLR <150, 150-300, ≥300	18 patients received neoadjuvant chemotherapy, 59 patients received adjuvant chemotherapy	N/A	185	N/A	Univariate: PLR 150-300: 1.284 (0.897-1.838) p=0.172 PLR ≥300: 1.398 (0.872-2.241) p=0.164	Multivariate: pTNM stage, adjuvant treatment
21.	Feng et al 2014 (659)	Retrospective	Esophageal SCC	China	483	PLR ≥150	No mention of adjuvant or neoadjuvant treatment	N/A	244	N/A	Multivariate: 1.840 (1.407-2.407) p<0.001	Multivariate: Differentiation, depth of invasion, nodal metastasis, NLR
22.	Sun et al 2014 (265)	Retrospective	Colon cancer	China	255	PLR<150, 150-300, >300	No specific mention of neoadjuvant or adjuvant treatment	N/A	94	N/A	Multivariate: RR 0.825 (0.560-1.215) p=0.330	Multivariate: AFP, CEA, fibrinogen, TNM, mGPS
23.	Neofytou et al 2014 (665)	Retrospective	Liver-only Colorectal Metastases	UK	140	PLR >150	All patients received neoadjuvant chemotherapy	N/A	59 (5-year survival)	N/A	Multivariate: 2.17 (1.09-4.32) p=0.027	Multivariate: No adjuvant chemotherapy

24.	Krenn-Pilko et al 2014 (725)	Retrospective	Breast cancer	Austria	793	PLR ≥292	712 patients received adjuvant radiotherapy, 93 received adjuvant chemotherapy, 378 received adjuvant hormonal treatment, and 202 received both adjuvant chemotherapy and hormonal therapy.	136	136	Multivariate: 2.03 (1.03-4.02) p=0.042	Multivariate: 1.92 (1.01-3.67) p=0.047	Multivariate: Tumour stage, lymph node involvement
25.	Szkandera et al 2014 (726)	Retrospective	Colon Cancer	Austria	372	PLR >225	No specific mention of neoadjuvant or adjuvant treatment	N/A	91	N/A	Multivariate: 1.49 (0.92-2.40) p=0.107	Multivariate: Nil else
26.	Pinato et al 2014 (300)	Retrospective	Lung	UK	220	PLR>300	Adjuvant radio and chemotherapy administered	N/A	61	N/A	Univariate: 1.6 (0.6–5.6) p=0.32	Multivariate: TNM I/II/III, Pleural Effusion, NLR
27.	Aurello et al 2014 (135)	Retrospective	Gastric Cancer	Italy	102	PLR <150, 150-300, >300 (0,1,2 respectively)	68 patients received adjuvant chemotherapy after surgery	62	62	N/A	Multivariate: PLR 1: 0.43 (0.10-1.73) p=0.23 PLR 2: 1.13 (0.45-2.79) p=0.79	Multivariate: Prognostic index, mGPS
28.	Que et al 2015 (670)	Retrospective	Soft-tissue Sarcoma	China	222	PLR ≥133.915	39 patients received adjuvant chemotherapy; 65 patients received adjuvant radiotherapy	N/A	82 (after 150 months)	N/A	Multivariate: 2.60 (1.17-5.74) p=0.019	Multivariate: Tumour site: Trunk & extremity, AJCC stage, PLR
29.	Hsu et al 2015 (671)	Retrospective	Gastric Cancer	Taiwan	989	PLR >132	499 patients with stage 2 to 4 tumour received chemotherapy	N/A	395 (5-year survival)	N/A	Multivariate: 0.898 (0.696-1.159) p=0.41	Multivariate: NLR, resection margins, differentiation, T status, N status, LN ratio, M1 status

30.	Sheng Han et al 2015 (673)	Retrospective	Glioblastoma	China	152	PLR >135	All patients received adjuvant radio-chemotherapy	N/A	118 (2-year survival)	N/A	Multivariate: 1.003 (0.999-1.007) p=0.152	Multivariate: KPS, MGMT promoter, pre-treatment NLR
31.	Aldemir et al 2015 (675)	Retrospective	Gastric Cancer	Turkey	53	PLR <170 vs. ≥170	No mention of adjuvant treatment	N/A	19	N/A	Univariate: p=0.55	Univariate: ECOG performance status, platelet count
32.	Bagante et al 2015 (678)	Retrospective	Adrenocortical Carcinoma	US	84	PLR >190	51 patients received peri-operative systemic chemotherapy, 38 patients received adjuvant mitotane	50 (5-year DSS)	N/A	Univariate: 0.90 (0.47-1.73) p=0.757	N/A	Multivariate: AJCC tumour site, T stage III-IV, Metastasis, NLR
33.	Wang et al 2015 (679)	Retrospective	HCC	US	234	PLR >118.5	170 patients had antiviral treatment	N/A	88 (5-year survival)	N/A	Multivariate: 1.6 (0.6-4.3) p=0.3	Multivariate: Tumour size, NLR
34.	Li et al 2015 (681)	Retrospective	Endometrial Cancer	China	282	PLR ≥250	No specific mention of neoadjuvant or adjuvant treatment	N/A	38 (5-year survival)	N/A	Multivariate: 0.993 (0.294-3.357) p=0.991	Multivariate: CRP, D-dimer,
35.	Zhang et al 2015 (682)	Retrospective	Non-small Cell Lung Cancer	China	678	PLR >106	Adjuvant chemotherapy or/and radiotherapy	N/A	367	N/A	Multivariate: 0.966 (0.761-1.228) p=0.780	Multivariate: Pathological stage (I, II, IIIA), NLR
36.	Zhang et al 2015 (683)	Retrospective	Gallbladder Carcinoma	China	145	PLR ≥113.34	No specific mention of neoadjuvant or adjuvant treatment	N/A	117 (5-year survival)	N/A	Univariate: RR 1.903 (1.309-2.767) p=0.001	Multivariate: Nevin stages, operation modes, Hb, NLR
37.	Qu et al 2015 (684)	Retrospective	Gastric Cancer	China	1397 Development set: n=1123 Validation set: n=274	PLR. >168	No specific mention of neoadjuvant or adjuvant treatment	N/A	3-year survival Development set: 307 Validation set: 60	N/A	Univariate: 1.762 (1.372-2.264) p<0.001	Multivariate: Age, tumour size, Lauren type, depth of invasion, number of metastatic lymph node, NLR

38.	Zhang et al 2015 (685)	Retrospective	Ovarian Cancer	China	190	PLR >203	Surgery was followed by platinum-based chemotherapy	N/A	170 (after 100-month)	N/A	Multivariate: 2.158 (1.468-3.171) p<0.001	Multivariate: Stage (FIGO), postoperative residual tumour mass
39.	Zhang et al 2015 (727)	Retrospective	Bladder cancer	China	124	PLR ≥140	No mention of adjuvant treatment	N/A	55 (5-year survival)	N/A	Multivariate: 1.161(0.605-2.226) p=0.654	Multivariate: Diabetes, T staging, distant metastasis, LMR
40.	Sun et al 2015 (136)	Retrospective	Gastric Cancer	China	632	PLR >140	395 patients received adjuvant chemotherapy	N/A	448	N/A	Multivariate: 1.190 (0.960-1.475) p=0.113	Multivariate: Age, respectability, distant metastasis, pathological stage, CEA, postoperative complications, PNI
41.	Choi et al 2015 (689)	Retrospective	Colorectal Cancer	Canada	549	PLR≥295	147 patients received adjuvant therapy: chemotherapy, radiation or both	N/A	120 (5-year survival)	N/A	Univariate: 1.81 (1.06-3.06) p=0.028	Multivariate: Age>75, lymph nodes positive, ASA status, NLR
42.	Deng et al 2015 (690)	Retrospective	Gastric Cancer	China	389	PLR≥132	No mention of adjuvant treatment	235	270	Multivariate: 0.96 (0.71-1.28) p=0.763	Multivariate: 1.03 (0.78-1.35) p=0.858	Multivariate: Age, tumour stage, lymph node, distant metastasis, dNLR
43.	Spolverato et al 2015 (691)	Retrospective	Hepato-Pancreatico-Biliary Malignancies	US	452	PLR ≥190	189 patients received neoadjuvant chemotherapy.	N/A	192 (5-year survival)	N/A	Multivariate: 1.79 (1.05-3.04) p=0.032	Multivariate: Age, complications, NLR
44.	Han et al 2015 (692)	Retrospective	Esophageal SCC	China	218	PLR<244	Adjuvant treatment: 17 received chemotherapy 41 received radiotherapy 24 received chemoradiotherapy	N/A	138	N/A	Multivariate: 1.014 (0.582-1.769) p=0.96	Multivariate: Tumour length, pTNM stage, LMR.

45.	Kim et al 2015 (693)	Retrospective	Gastric Cancer	Korea	1986	PLR>126	No mention of adjuvant treatment	N/A	323 (5-year survival)	N/A	Multivariate: 1.035 (0.805-1.330) p=0.7888	Multivariate: Age, approach method, depth of invasion, node status, NLR
46.	Anthony et al 2015 (694)	Retrospective	Hepatocellular Carcinoma	Hong Kong	324	PLR≥150	282 patients with chronic viral hepatitis received antiviral therapy	N/A	79 (5-year survival)	N/A	Univariate: 1.229 (0.756-1.998) p=0.405	Multivariate: Antiviral therapy, microvascular invasion, PNI.
47.	Kim et al 2015 (699)	Retrospective	Upper Urinary Tract Urothelial Carcinoma	South Korea	277	PLR <150, 150-300, >300	71 patients received adjuvant chemotherapy	73	96	Univariate: PLR 150-300 1.460 (0.887-2.405) p=0.137 PLR >300 1.202 (0.374-3.864) p=0.757	N/A	Multivariate: Bladder cuff excision, pathologic T stage, lymphovascular invasion, derived NLR
48.	Neofytou et al 2015 (677)	Retrospective	Liver-Only Colorectal Metastases	UK	140	PLR (continuous variable)	All patients received neoadjuvant chemotherapy, 104 received adjuvant chemotherapy.	60	63	Univariate: 1.006 (1.002-1.009) p<0.001	N/A	Multivariate: Adjuvant chemotherapy, neoadjuvant LMR.
49.	Messager et al 2015 (728)	Retrospective	Oesophageal and junctional carcinoma	UK	153	PLR >192	36.6% of patients received adjuvant chemotherapy after surgery	N/A	39	N/A	Multivariate: 2.47 (1.21-5.01) p=0.012	Multivariate: Differentiation, resection margin, ypN
50.	Pang et al 2015 (729)	Retrospective	Gallbladder carcinoma	China	316	PLR≥ 117.7	No mention of adjuvant or neoadjuvant treatment	N/A	254	N/A	Multivariate: 2.021 (1.243-3.278) p=0.005	Multivariate: CA-125, CA-199, TNM
51.	Ozawa et al 2015 (730)	Retrospective	Colorectal Cancer	Japan	234	PLR ≥25.4	15 patients excluded as underwent adjuvant chemotherapy	222	211	Multivariate: 3.61 (1.08-12.64) p=0.038	N/A	Multivariate: Nil else
52.	Shirai et al 2015 (704)	Retrospective	Pancreatic cancer	Japan	131	PLR ≥150	No mention of adjuvant treatment	N/A	103 (5-year survival)	N/A	Multivariate: 1.688 (1.045-2.726) p=0.032	Multivariate: Tumour size, resection margin status, tumour differentiation

53.	Chen et al 2015 (705)	Retrospective	Intrahepatic Cholangiocarcinoma	China	322	PLR ≥123	Adjuvant chemoradiotherapy used as well as radiofrequency ablation	N/A	197 (5-year survival)	N/A	Multivariate: 1.410 (1.026-1.938) p=0.034	Multivariate: CA19-9, tumour number, lymph node metastasis, NLR
54.	Neal et al 2015 (122)	Retrospective	Colorectal Liver Metastases	UK	302	PLR <150, 150-300, >300	132 patients had systemic chemotherapy in the 6 months prior to liver resection, 126 patients received systemic chemotherapy following mastectomy	204 (5-year survival)	214 (5-year survival)	Univariate: 1.244 (1.003-1.542) p=0.047	Univariate: 1.244 (1.015-1.525) p=0.036	Multivariate: Clinical risk score, NLR≥3
55.	Xu et al 2015 (127)	Retrospective	Oesophageal SCC	China	468	PLR>147	196 patient received adjuvant chemo and radiotherapy	N/A	259	N/A	Univariate: 1.12 (0.87-1.43) p=0.39	Multivariate: Lymph Node Mets, Venous/lymphatic invasion, CRP/Alb Ratio
56.	Kawashima et al 2015 (144)	Retrospective	Lung Cancer	Japan	1043	PLR >300	No mention of adjuvant treatment	N/A	227	N/A	Univariate: 2.35 (1.45-3.82) p<0.01	Multivariate: Age, smoking, neoadjuvant therapy, co-morbidity, CEA, pathological stage, histological tumour type, LVI, surgical procedure
57.	Cummings et al 2015 (124)	Retrospective	Endometrial Cancer	UK	605	PLR. ≥240	33% of patients received adjuvant radiotherapy, 13% of patients received adjuvant chemotherapy	96	166	Multivariate: 1.76 (1.09-2.87) p=0.022	Multivariate: 1.89 (1.30-2.75) p=0.001	Multivariate: NLR, Combined NLR + PLR, age, FIGO stage, grade, histopathological subtype, LVSI
58.	Lian et al 2015 (706)	Retrospective	Gastric Cancer	China	162	PLR ≥208	No mention of adjuvant treatment	N/A	N/A (expressed in months)	N/A	Multivariate: OR 2.55 (1.37-3.84) p=0.001	Multivariate: Depth of invasion, lymph node metastasis, AJCC stage

59.	Saito et al 2016 (731)	Retrospective	Perihilar cholangiocarcinoma	Japan	115	PLR >150	1 patient received neoadjuvant chemotherapy, 1 patient received neoadjuvant radiation, 1 patient received neoadjuvant chemotherapy and radiation, 21 patients received adjuvant therapy	N/A	59 (5-year survival)	Multivariate: 2.207 (1.200-4.060) p=0.011	N/A	Multivariate: Preoperative factors (CEA, albumin, CRP), N category, portal vein invasion, surgical margin
60.	Xie et al 2016 (707)	Retrospective	Oesophageal Squamous Cell Cancer	China	317	PLR >103	76 patients received adjuvant chemotherapy	147	152	Multivariate: 1.776 (1.224-2.578) p=0.003	N/A	Multivariate: TNM stage
61.	Bhindi et al 2016 (721)	Retrospective	Bladder Cancer	Canada	418	PLR per 100 units	28 received neo-adjuvant chemotherapy, 87 received adjuvant chemotherapy, 54 received salvage chemotherapy	107	177	Univariate: 1.21 (1.05-1.41) p=0.01	Univariate: 1.16 (1.02-1.33) p=0.03	Multivariate: T-stage, N-stage, haemoglobin, NLR, age, Charlson co-morbidity index, lymphovascular invasion
62.	Ha et al 2016 (129)	Retrospective	Ampulla of Vater Cancer	South Korea	227	PLR >192	Adjuvant treatments including chemotherapy, radiotherapy and concurrent chemoradiotherapy	N/A	105	N/A	Multivariate: 0.686 (0.35-1.34) p=0.268	Multivariate: Vascular invasion, CA19-9.
63.	Li et al 2016 (137)	Retrospective	Colorectal Cancer	China	5336	PLR >219	5-Fu based adjuvant chemotherapy for stage 2/3 patients	588	611	N/A	Multivariate: 1.175 (0.946-1.460) p=0.144	Multivariate: Age, T stage, N stage, differentiation, venous invasion, NLR, LMR, AGR
64.	Chen et al 2016 (714)	Retrospective	Esophageal Squamous Cell Carcinoma	China	323	PLR >150	No mention of adjuvant treatment	221 (5-year)	N/A	Multivariate: 1.440 (0.978-2.121) p=0.064	N/A	Multivariate: TNM stage, I stage

65.	Hodek et al 2016 (716)	Retrospective	Rectal Carcinoma	Czech Republic	173	PLR (continuous)	All patients received neoadjuvant chemoradiotherapy	N/A	22	N/A	Univariate: RR: 1.01 (1.00-1.01) p=0.02	Univariate: Clinical T stage, circular vs semi-circular, stenosing tumour, LVSI, angioinvasion, perineural invasion, R0 resection, positive lymph nodes, tumour stage, WBC, RBC, Hb, platelet count, neutrophils, NLR
66.	Wang et al 2016 (139)	Retrospective	Ovarian Cancer	China	143	PLR >201	No mention of adjuvant treatment	N/A	51	N/A	Univariate: 1.76 (1.02-3.06) p=0.043	Multivariate: Metastasis, prognostic inflammation score
67.	Chan et al 2016 (269)	Retrospective	Colorectal Cancer	Australia	1623	PLR >258	Patients with high-risk stage II and III colon cancer disease received adjuvant chemotherapy. Stage II or III rectal cancers received neoadjuvant chemoradiotherapy	N/A	941	N/A	Univariate: 1.592 (1.343-1.886) p< 0.001	Multivariate: Age, T stage, N stage, grade, LMR
68.	Toyokawa et al 2016 (140)	Retrospective	Thoracic Oesophageal Squamous Cell Carcinoma	Japan	185	PLR >193	46 patients received neoadjuvant treatment (39 chemotherapy, 6 chemoradiotherapy, 1 radiotherapy)	N/A	77	N/A	Multivariate: 1.213 (0.696-2.115) p=0.496	Multivariate: Sex, performance status, ASA, cTNM stage, CONUT score

Table 18.4: Studies investigating the prognostic value of the LMR in an unselected cohort of patients with operable cancer

No: LMR	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Additional Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Stotz et al 2014 (732)	Retrospective	Colon Cancer	Austria	372	LMR ≥ 2.14	230 patients received adjuvant chemotherapy	N/A	72	N/A	Multivariate: 0.51 (0.31-0.83) p=0.007	Multivariate: Tumour invasion depth, lymph node involvement, tumour stage
2.	Szkandera et al 2014 (645)	Retrospective	Soft Tissue Sarcoma	Austria	340 Training set, n=170 Validation set, n=170	LMR ≥2.85	Training set: 16 received adjuvant chemotherapy, 102 received adjuvant radiotherapy Validation set: 22 received adjuvant chemotherapy, 107 received adjuvant radiotherapy	Training set: 30 Validation set: 22	Training set: 53 Validation set: 51	Multivariate: Training set: 0.41 (0.18-0.97) p=0.043 Validation set: 0.33 (0.12-0.90) p=0.030	Multivariate: Training set: 0.72 (0.34-1.52) p=0.390 Validation set: 0.35 (0.17-0.75) p=0.007	Multivariate: Age, tumour grade, LMR, tumour size
3.	Hu et al 2014 (733)	Retrospective	Lung Cancer	China	1453	LMR ≤3.68	No mention of adjuvant treatment	N/A	509	N/A	Multivariate: 1.510 (1.265-1.803) p<0.001	Multivariate: Age, TNM stage
4.	Zhou et al 2014 (734)	Retrospective	Gastric Cancer	China	426	LMR ≥4.32	306 patients received adjuvant chemotherapy	N/A	250	N/A	Multivariate: 0.688 (0.521-0.908) p=0.008	Multivariate: Size, vascular/ nerve infiltration, TNM stage, adjuvant chemotherapy
5.	Hutterer et al 2014 (735)	Retrospective	Clear Cell Renal Cell Carcinoma	Austria	678	LMR <3	No mention of adjuvant treatment	68	123	Multivariate: 2.332 (1.100-4.942) p=0.027	Multivariate: 1.373 (0.929-2.031) p=0.112	Multivariate: Age, pathologic T category, tumour grade, tumour necrosis
6.	Zhang et al 2015 (727)	Retrospective	Bladder cancer	China	124	LMR ≥4	No mention of adjuvant treatment	N/A	55 (5-year survival)	N/A	Multivariate: 0.674 (0.412-0.890) p=0.003	Multivariate: Diabetes, T staging, distant metastasis, PLR

7.	Han et al 2015 (692)	Retrospective	Esophageal SCC	China	218	LMR<2.57	Adjuvant treatment: 17 received chemotherapy 41 received radiotherapy 24 received chemoradiotherapy	N/A	138	N/A	Multivariate: 1.759 (1.201-2.576) p=0.004	Multivariate: Tumour length, pTNM stage.
8.	Deng et al 2015 (690)	Retrospective	Gastric Cancer	China	389	LMR≥4.95	No mention of adjuvant treatment	235	270	Multivariate: 1.00 (0.71-1.40) p=0.995	Multivariate: 1.00 (0.73-1.35) p=0.977	Multivariate: Age, tumour stage, lymph node, distant metastasis, dNLR
9.	Neofytou et al 2015 (677)	Retrospective	Liver-Only Colorectal Metastases	UK	140	Preoperative LMR ≤3	All patients received neoadjuvant chemotherapy, 104 received adjuvant chemotherapy.	60	63	Multivariate: 2.15 (1.13-4.10) p=0.020	Multivariate: 2.43 (1.32-4.48) p=0.004	Multivariate: Adjuvant chemotherapy, preoperative
10.	Neal et al 2015 (122)	Retrospective	Colorectal Liver Metastases	UK	302	LMR >2.35	132 patients had systemic chemotherapy in the 6 months prior to liver resection, 126 patients received systemic chemotherapy following mastectomy	204 (5-year survival)	214 (5-year survival)	Univariate: 0.624 (0.455-0.855) p=0.003	Univariate: 0.638 (0.473-0.860) p=0.003	Multivariate: Clinical risk score
11.	Wen et al 2015 (736)	Retrospective	Breast Cancer	China	2000	LMR cut-off 3.80 (low or high-LMR)	No mention of adjuvant therapy but likely triple negative cancers had chemo	N/A	326	N/A	Multivariate: 0.840 (0.629-1.121) p=0.236	Multivariate: Menstrual status, tumour size, lymph node status ER, HER-2, monocyte count
12.	Lin et al 2015 (737)	Retrospective	HCC	China	210	LMR >3.23	Antiviral therapy for all patients after surgery	47	48	N/A	Multivariate: 0.398 (0.219-0.725) p=0.003	Multivariate: Liver cirrhosis, ALP, microvascular invasion, histological differentiation, BCLC stage

13.	Yoshida et al 2015 (738)	Retrospective	Bladder Cancer	Japan	181	LMR <3.51	44 patients received adjuvant chemotherapy	58	70	N/A	Multivariate: 3.77 (2.19-6.48) p<0.001	Multivariate: pT-stage, pN-stage, positive margin
14.	Yamagishi et al 2015 (739)	Retrospective	Malignant Pleural Mesothelioma	Japan	44	LMR <2.74	Chemotherapy administered in 57.3% of people	N/A	28	N/A	Multivariate: 2.34 (1.58-3.47) p<0.0001	Multivariate: Histological subtype, ECOG, Stage, Surgery
15.	Ozawa et al 2015 (740)	Retrospective	Colorectal Cancer	Japan	117	LMR <3	53 patients received adjuvant chemotherapy	24 (3-year death rate)	N/A	Multivariate: 2.75 (1.40-5.44) p=0.004	N/A	Multivariate: Nil Else
16.	Hutterer et al 2015 (741)	Retrospective	Upper Tract Urothelial Carcinoma	Austria	182	LMR ≥2	No mention of adjuvant treatment	N/A	82	N/A	Multivariate: 0.56 (0.35-0.92) p=0.021	Multivariate: Age, pathological T stage
17.	Huang et al 2015 (742)	Retrospective	Oesophageal Squamous Cell Carcinoma	China	348	LMR >2.93	105 patients received adjuvant therapy	129	N/A	Multivariate: 0.600 (0.407-0.885) p=0.010	N/A	Multivariate: Depth of invasion, nodal metastasis, lymphocyte count
18.	Chen et al 2015 (743)	Retrospective	Cervical Cancer	China	485	LMR >2.87	63 patients received radiotherapy, 315 received chemoradiotherapy	N/A	64	N/A	Multivariate: 0.417 (0.244-0.714) p=0.001	Multivariate: Lymph node metastasis
19.	Bhindi et al 2016 (721)	Retrospective	Bladder Cancer	Canada	418	LMR per 1-log unit	28 received neo-adjuvant chemotherapy, 87 received adjuvant chemotherapy, 54 received salvage chemotherapy	107	177	Univariate: 0.69 (0.53-0.91) p=0.009	Univariate: 0.70 (0.55-0.88) p=0.002	Multivariate: T-stage, N-stage, haemoglobin, NLR, age, Charlson co-morbidity index, lymphovascular invasion
20.	Li et al 2016 (137)	Retrospective	Colorectal Cancer	China	5336	LMR >2.83	5-Fu based adjuvant chemotherapy for stage 2/3 patients	588	611	N/A	Multivariate: 0.761 (0.621-0.932) p=0.008	Multivariate: Age, T stage, N stage, differentiation, venous invasion, NLR, AGR

21.	Chan et al 2016 (269)	Retrospective	Colorectal Cancer	Australia	1623	LMR >2.38	Patients with high-risk stage II and III colon cancer disease were generally offered standard adjuvant chemotherapy, whereas those with stage II or III rectal cancers were usually treated with neoadjuvant chemoradiotherapy	N/A	941	N/A	Multivariate: 0.569 (0.478-0.677) p< 0.001	Multivariate: Age, T stage, N stage, grade

Table 18.5: Studies investigating the prognostic value of the other markers of inflammation in an unselected cohort of patients with operable cancer

No: Other	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	Additional Treatment	Cancer deaths (n)	Overall deaths (n)	Cancer survival (HR, 95%CI)	Overall survival (HR, 95%CI)	Independent Prognostic Factors
1.	Miyata et al 2011 (128)	Retrospective	Esophageal Cancer	Japan	152	Systemic inflammation score (0-1 vs. 2-3) involving leucocyte count, serum albumin and haemoglobin level	All patients received pre-operative chemotherapy	N. A	92 (5-year survival)	N/A	Multivariate: 3.17 (1.74-5.78) p=0.0002	Multivariate: Clinical response, number of metastatic lymph nodes, operative complication
2.	Tomita et al 2012 (130)	Retrospective	Non-Small Cell Lung Cancer	Japan	301	NLR and CRP combined	No mention of adjuvant treatment	N/A	N/A (expressed in %)	N/A	Multivariate: Both low/ both high Risk ratio 0.403 (0.240-0.689) p=0.0012 Either high/ both high Risk ratio 0.452 (0.225-0.872) p=0.0177	Multivariate: pT status, pN status, CEA.
3.	Feng et al 2013 (123)	Retrospective	Oesophageal Squamous Cell Carcinoma	China	483	CNP (1-2 vs. 0) involving NLR and PLR	No mention of adjuvant or neoadjuvant treatment	N/A	244	N/A	Multivariate: 1.964 (1.371-2.814) p<0.001	Multivariate: Differentiation, depth of invasion, node metastasis, PLR
4.	Ishizuka et al 2013 (119)	Retrospective	Colorectal	Japan	481	COP-NLR (1, 2/0)	Patients with stage IV disease had chemotherapy	120	150	Multivariate: OR: 0.464 (0.267-0.807) p=0.007	N/A	Pathology, LN Mets, CRP, Albumin, CEA, GPS
5.	Peng et al 2015 (744)	Retrospective	HCC	China	219	ΔPLR ≥2.875	No specific mention of neoadjuvant or adjuvant treatment	N/A	40	N/A	Multivariate: 5.929 (2.823-12.448) p<0.001	Multivariate: Vascular invasion
6.	Peng et al 2014 (745)	Retrospective	Small hepatocellular carcinoma	China	189	ΔNLR (postoperative minus preoperative NLR)	68 patients received adjuvant therapy after operation (TACE, RFA, sorafenib)	N/A	37	N/A	Multivariate: 2.637 (1.356-5.128) p=0.004	Vascular invasion, postoperative NLR.
7.	Ishizuka et al 2014 (120)	Retrospective	Gastric Cancer	Japan	544	COP-NLR (0, 1/2)	343 patients received adjuvant chemotherapy	55	108	N/A	Multivariate: 1.781 (1.094-2.899) p=0.020	Multivariate: Age, tumour type, lymph node

												metastasis, albumin, COP-NLR
8.	Sung et al 2015 (132)	Retrospective	Upper Urinary Tract Urothelial Carcinoma	Korea	410	Inflammation risk score (none, I, II) involving NLR and ESR	91 patients received adjuvant chemotherapy post operation	67	118	Multivariate: Score I 2.785 (1.343-5.776) p=0.006 Score II 4.367 (1.987-9.597) p<0.001	Multivariate: Score I 2.513 (1.434-4.405) p=0.001 Score II 3.521 (1.888-6.567) p<0.001	Multivariate: Age, tumour stage, lymph node, margin, micropapillary variant
9.	East et al 2014 (133)	Retrospective	Colon Cancer	UK	436 Training set, n=386 Test set, n=50	White cell count/ lymphocyte ratio (WLR) ≥3.4	26 patients received adjuvant chemotherapy	N/A	27	N/A	Multivariate: Training set: 1.40 (1.04-1.89) p=0.03 Test set: 4.10 (3.13-7.42) p=0.03	Multivariate: N stage, R0 resection, adjuvant treatment, T stage, NLR.
10.	Shen et al 2014 (134)	Retrospective	HCC	China	332	AST-platelet ratio index (APRI) <0.62 vs. ≥0.62	No mention of adjuvant or neoadjuvant treatment	N/A	209	N/A	Multivariate: 1.508 (1.127-2.016) p=0.006	Multivariate: APRI, tumour size, noncapsulation, tumour number
11.	Aurello et al 2014 (135)	Retrospective	Gastric Cancer	Italy	102	Prognostic index (PI) 0/1/2 involving CRP and white cell count Prognostic nutrition index (PNI) 0/1 involving albumin and total lymphocyte count	68 patients received adjuvant chemotherapy after surgery	62	62	N/A	Multivariate: PI 1: 0.04 (0.01-0.20) p< 0.001 PI 2: 0.37 (0.16-0.82) p=0.01 Univariate: PNI 0/1: 0.52 (0.26-1.04) p=0.06	Multivariate: mGPS
12.	Takeno et al 2014 (145)	Retrospective	Gastric	Japan	552	HS-mGPS (0/1/2)	No mention of adjuvant treatment	N/A	215	N/A	Multivariate: 1.6748 (1.2867-2.1314) p= 0.0002	Multivariate: HS-mGPS
13.	Cummings et al 2015 (124)	Retrospective	Endometrial Cancer	UK	605	MLR <0.19 vs. ≥0.19	33% of patients received adjuvant radiotherapy, 13% of patients received	96	166	Multivariate: 1.26 (0.73-2.15) p=0.409	Multivariate: 1.23 (0.84-1.82) p=0.294	Multivariate: PLR, combined NLR + PLR, age, FIGO stage, grade,

							adjuvant chemotherapy					histopathological subtype, LVSI
14.	Shimizu et al 2015 (672)	Retrospective	Non-small Cell Lung Cancer	Japan	334	Prognostic nutritional index <50 vs. ≥50	Neither radiotherapy nor chemotherapy administered prior to the surgery	N/A	95 (3-year survival)	N/A	Multivariate: 2.40 (1.39-4.14 p=0.002	Multivariate: Age, nodal metastasis, NLR
15.	Wang et al 2015 (679)	Retrospective	Hepatitis B-Associated Hepatocellular Carcinoma	US	234	Prognostic nutritional index >50.5	170 patients had antiviral treatment	N/A	88 (5-year survival)	N/A	Multivariate: 1.3 (0.5-3.4) p=0.5	Multivariate: Tumour size, NLR
16.	Sun et al 2015 (136)	Retrospective	Gastric Cancer	China	632	Prognostic nutritional index <48.2 vs. ≥48.2	395 patients received adjuvant chemotherapy	N/A	448	N/A	Multivariate: 1.668 (1.368-2.035) p=0.656	Multivariate: Age, respectability, distant metastasis, pathological stage, CEA, postoperative complications
17.	Sun et al 2015 (136)	Retrospective	Gastric Cancer	China	632	Canton score (0/1/2/3)	395 patients received adjuvant chemotherapy	N/A	448	N/A	Multivariate: Canton score 1 1.076 (0.796-1.454) p=0.633 Canton score 2 1.554 (1.151-2.097) p=0.004 Canton score 3 1.643 (1.142-2.364) p=0.007	Multivariate: Resectability,
18.	Zhang et al 2015 (121)	Retrospective	Non-Small Cell Lung Cancer	China	1238	Combination of neoadjuvant platelet count and neutrophil-lymphocyte ratio COP-NLR (0/1/2)	Adjuvant treatments including chemotherapy, radiotherapy and concurrent chemoradiotherapy	N/A	686	N/A	Multivariate: 1.810 (1.587-2.056) p<0.001	Multivariate: TNM stage, LDH, D-dimer, COP-NLR
19.	Chan et al 2015 (694)	Retrospective	Hepatocellular Carcinoma	Hong Kong	324	Prognostic nutritional index < 45	282 patients with chronic viral hepatitis received antiviral therapy	N/A	79 (5-year survival)	N/A	Multivariate: 2.778 (1.630-4.813) p<0.001	Multivariate: Antiviral therapy, microvascular invasion

20.	Kim et al 2015 (699)	Retrospective	Upper Urinary Tract Urothelial Carcinoma	South Korea	277	PNI ≥45 vs. <45	71 patients received adjuvant chemotherapy	73	96	Multivariate: 0.947 (0.491-1.826) p=0.870	N/A	Multivariate: Bladder cuff excision, pathologic T stage, lymphovascular invasion, derived NLR
21.	Neal et al 2015 (122)	Retrospective	Colorectal Liver Metastases	UK	302	COP-NLR (2/1/0): Combination of platelet count and NLR	132 patients had systemic chemotherapy in the 6 months prior to liver resection, 126 patients received systemic chemotherapy following mastectomy	204 (5-year survival)	214 (5-year survival)	Univariate: 1.243 (1.003-1.541) p=0.047	Univariate: 1.230 (1.005-1.505) p=0.045	Multivariate: Clinical risk score
22.	Neal et al 2015 (122)	Retrospective	Colorectal Liver Metastases	UK	302	Prognostic nutritional index (0/1)	132 patients had systemic chemotherapy in the 6 months prior to liver resection, 126 patients received systemic chemotherapy following mastectomy	204 (5-year survival)	214 (5-year survival)	Univariate: 0.657 (0.437-0.988) p=0.043	Univariate: 0.707 (0.475-1.053) p=0.088	Multivariate: Clinical risk score
23.	Cummings et al 2015 (124)	Retrospective	Endometrial Cancer	UK	605	Combined NLR + PLR (both low, either high, both high)	33% of patients received adjuvant radiotherapy, 13% of patients received adjuvant chemotherapy	96	166	Multivariate: Either high: 1.46 (0.87-2.47) p=0.156 Both high: 2.26 (1.24-4.13) p=0.008	Multivariate: Either high: 1.59 (1.08-2.35) p=0.018 Both high: 2.54 (1.61-4.01) p<0.001	Multivariate: Age, FIGO stage, grade, histopathological subtype, LVSI
24.	Ishizuka et al 2016 (126)	Retrospective	Colorectal Cancer	Japan	627	CRP/ albumin ratio (CAR) >0.038 vs. ≤0.038	No mention of adjuvant treatment	110	142	N/A	Multivariate: 2.613 (1.621-4.212) p< 0.001	Multivariate: Pathological differentiation, CEA, stage, GPS, NLR
25.	Chen et al 2015 (131)	Retrospective	Gastric Carcinoma	China	1332	Neoadjuvant haemoglobin, albumin,	No mention of adjuvant treatment	N/A	581	N/A	Multivariate: Training set: 0.782 (0.617-0.993)	Multivariate: Age, longitudinal location, tumour

					Training set: 888 Validation set: 444	lymphocyte and platelet (HALP) <56.8 vs. ≥56.8					p=0.043 Validation set: 0.700 (0.496-0.987) p=0.042	size, N stage, M stage
26.	Okamura et al 2015 (291)	Retrospective	Hepatocellular Carcinoma	Japan	256	Prognostic nutritional index <48.5 vs. ≥48.5	No mention of adjuvant treatment	N/A	86	N/A	Multivariate: 1.96 (1.21-3.18) p=0.006	Multivariate: AFP, des-gamma-carboxy prothrombin, high NLR
27.	Xu et al 2015 (127)	Retrospective	Oesophageal SCC	China	468	CRP/Albumin Ratio >0.50	196 patient received adjuvant chemo and radiotherapy	N/A	259	N/A	Multivariate: 2.44 (1.82-3.26) p<0.0001	Multivariate: Lymph Node Mets, Venous/lymphatic invasion, CRP/Alb Ration
28.	Chuan Li et al 2015 (125)	Retrospective	Hepatocellular Carcinoma	China	236	Postoperative NLR-PLR (0/1/2) NLR> 2.3 and PLR>116 score 2, either 1 score 1, none score 0	Antiviral drug (entecavir or lamivudine) were given to patients with positive HBV-DNA	N/A	41	N/A	Multivariate: 2.894 (1.992-4.2) p<0.001	Multivariate: Microvascular invasion, transfusion
29.	Arigami et al 2015 (142)	Retrospective	Oesophageal Squamous Cell Carcinoma	Japan	238	F-NLR (0-1/2)	Patients who have undergone neoadjuvant treatment were excluded	N/A	100	N/A	Multivariate: 1.94 (1.04-3.53) p=0.037	Multivariate: Depth of tumour invasion, lymph node metastasis
30.	Ha et al 2016 (129)	Retrospective	Ampulla of Vater Cancer	South Korea	227	Systemic inflammatory index (≤780 vs. >780)	Adjuvant treatments including chemotherapy, radiotherapy and concurrent chemoradiotherapy	N/A	105	N/A	Multivariate: 0.924 (0.44-1.93) p=0.833	Multivariate: Vascular invasion, CA19-9.
31.	Li et al 2016 (137)	Retrospective	Colorectal Cancer	China	5336	Albumin/ globulin ratio (<1.50 vs. ≥1.50)	5-Fu based adjuvant chemotherapy for stage 2/3 patients	588	611	N/A	Multivariate: 0.646 (0.543-0.767) p<0.001	Multivariate: Age, T stage, N stage, differentiation, venous invasion, LMR, NLR

32.	Christina et al 2016 (138)	Retrospective	Oral cancer	Austria	144	CRP/ Neutrophils (low/high)	All patients received neoadjuvant radiotherapy in combination with systemic cytotoxic therapy	N/A	60 (5-year survival)	N/A	Multivariate: 2.7 (0.68-10.75) p=0.16	Multivariate: Regression grade
33.	Wang et al 2016 (139)	Retrospective	Ovarian Cancer	China	143	Prognostic Inflammation Score (0/1/2) involving NLR and serum albumin	No mention of adjuvant treatment	N/A	51	N/A	Multivariate: PIS 1: 0.33 (0.16-0.67) p=0.002 PIS 2: 0.18 (0.09-0.38) p<0.001	Multivariate: Metastasis, prognostic inflammation score
34.	Toyokawa et al 2016 (140)	Retrospective	Thoracic Oesophageal Squamous Cell Carcinoma	Japan	185	CONUT score (≥3, ≤2) involving serum albumin concentration, total lymphocyte count, total cholesterol concentration	46 patients received neoadjuvant treatment (39 chemotherapy, 6 chemoradiotherapy, 1 radiotherapy)	N/A	77	N/A	Multivariate: 2.303 (1.191-4.455) p=0.013	Multivariate: Sex, performance status, ASA, cTNM stage
35.	Fu et al 2016 (293)	Retrospective	Hepatocellular Carcinoma	China	Training: 772 Validation: 349	Inflammation-based score (IBS)	No mention of adjuvant treatment	N/A	377 (4-year survival)	N/A	Multivariate: Training 4.247 (2.786-6.473) p<0.001	Multivariate: GGT, mGPS, tumour number, microscopic vascular invasion, BCLC.