The role of the systematic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: systematic review and meta analysis

Abstract:

Introduction: Cancer remains a leading cause of death worldwide. 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 their limited life expectancy appropriate allocation of treatment is vital. It is recognised that systemic chemoradiotherapy may shorten the quality/quantity of life in patients with advanced cancer. It is against this background that the present systematic review and meta-analysis of the prognostic value of markers of the systemic inflammatory response in patients with advanced cancer was conducted.

Methods: An extensive literature review using targeted medical subject headings was carried out in the MEDLINE, EMBASE, and CDSR databases until the end of 2016. Titles were examined for relevance and studies relating to duplicate datasets, that were not published in English and that did not have full text availability were excluded. Full texts of relevant articles were obtained and were then examined to identify any further relevant articles.

Results: The majority of studies were retrospective. The systemic inflammatory response, as evidenced by a number of markers at clinical thresholds, was reported to have independent prognostic value, across tumour types and geographical locations. In particular, C-reactive protein (CRP, 63 studies), albumin (33 studies) the Glasgow Prognostic Score (GPS, 44 studies) and the Neutrophil Lymphocyte Ratio (NLR, 59 articles) were consistently validated across tumour types and geographical locations. There was considerable variation in the thresholds reported to have prognostic value when CRP and albumin were examined. There was less variation in the thresholds reported for NLR and still less for the GPS.

Discussion: The systemic inflammatory response, especially as evidenced by the GPS and NLR, has reliable prognostic value in patients with advanced cancer. Further prospective studies of their clinical utility in randomised clinical trials and in treatment allocation are warranted.

Introduction:

Cancer remains one of the leading cause of death worldwide and is responsible for 7.6 million deaths per year. Therefore, 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.[1]

However, optimal allocation of treatment remains elusive. There is increasing evidence that inappropriate anti-cancer treatment does not improve quality of life or survival[2-5]. 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[4]. 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*[5]. 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[5]. 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[6]. 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[7]. 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 (Glasgow Prognostic Score), 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[8-10]. Indeed, studies have shown a direct relationship between systemic inflammation measured by the GPS and NLR (Neutrophil Lymphocyte Ratio) and elevation of inflammatory cytokines, adipokines and other biochemical disturbances associated with loss of lean muscle mass and reduced performance status[8;11-14]. 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 (SIR) as measured by the mGPS (modified Glasgow Prognostic Score) improved the prediction of outcomes of patients with advanced cancer[15]. Furthermore, they showed that quality of life was independently associated with both performance and the GPS[16].

Therefore, from the above and with the introduction of immunotherapeutic agents for advanced inoperable cancer it is timely to review the role of the markers of systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer.

Methods:

The present systematic review and meta-analysis of published literature was undertaken according to a pre-defined protocol described in the PRISMA-P statement. The primary outcome was to assess the prognostic value of the SIR 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. Medical subject heading (MeSH) terms (Advanced Cancer, CRP, C-Reactive Protein, Albumin, White Cell Count, Neutrophil Count, Lymphocyte Count, Monocyte Count, Platelet Count, Red Blood Cell Count), were used 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 relating to duplicate datasets, studies not available in English and those published in abstract form only were excluded. 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 or odds ratios with associated confidence intervals were included in the review. Studies with patients who had failed resections and patients who underwent palliative symptom control procedures were also included.

Statistics

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.

Interstudy heterogeneity among included studies was evaluated by I^2 statistics using the random-effects (DerSimonian – Laird method) model. All P values were 2-sided and $P < 0.05$ were considered statistical 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.

Results

Study selection process

Initial search strategy identified 9546 articles whose titles and abstracts were reviewed (Figure 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.

Figure 1:

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

Sixty-three articles with both overall survival (OS) and/or cancer specific survival (CSS) as their primary outcome measures were identified comprising data on 13,498 patients (8,466 deaths) (Supplementary Table). Fifty-four studies were carried out in a retrospective manner while eight were prospective with one study having both prospective and retrospective arms (Supplementary Table). Fifty-four studies used multivariate and nine used univariate survival analysis (Supplementary Table). 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%CI 1.31-2.26, 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 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) (Supplementary Table). Twenty-eight studies were conducted in a retrospective manner while five were prospective. Twenty-nine articles used multivariate and four univariate survival analysis (Supplementary Table).

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). 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% on Taiwan, 39% in the 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) (Supplementary Table). 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 $>11 \times 10^9$ /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) (Supplementary Table). Seven studies were conducted in a retrospective manner while two were prospective. (Supplementary Table). 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 $\geq$ 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 x 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) (Supplementary Table). 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. (Supplementary Table). 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) , <1x10^9/L (n=2), ≥0.45x10^9/L (n=1), <2.25x10^9/L (n=1), <1.4x1x10^9/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) (Supplementary Table). 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) (Supplementary Table). Seven studies were conducted in a retrospective manner while one was prospective (Supplementary Table). 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) (Supplementary Table). Thirty-two studies were conducted in a retrospective manner while twelve were prospective

(Supplementary Table). Forty studies reported multivariate and four reported univariate survival analysis (Supplementary Table). 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 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) (Supplementary Table). 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 (Supplementary Table). 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%). 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%).

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%, Fig 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) (Supplementary Table). 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 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) (Supplementary Table). 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 (Supplementary Table). 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 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 (Supplementary Table). Two studies focused on the CRP/Albumin ratio (CAR). The first such study was by Zhou et al[17] 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[18] 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[19] 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[20] 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[21] 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[17] 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.

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, C-reactive protein, 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 end-point. However, for some markers of the systemic inflammatory response such as C-reactive protein and GPS there were also multiple studies using cancer specific survival as an end-point. 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 (C-reactive protein 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[22;23]. Therefore, it would appear that the optimal prognostic utility of markers of the systemic inflammatory response such as C-reactive protein and the GPS is 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. C-reactive protein 90% (all) vs. 35% (>10mg/l), albumin 84% (all) vs. 79% (<35g/l) and NLR 79% (all) vs. 57% (≥5)

respectively). In studies with these specific thresholds (e.g. in C-reactive protein 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, it would appear that 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 C-reactive protein and NLR where a number of 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[24] and therefore are likely to have reproducible clinical utility in the context of randomized 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. In particular, 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, there are well known ethnic differences in the normal range of neutrophils and lymphocytes[25-27]. Azab and co-workers recently reported that in a review of >9,000 patients, there were ethnic differences in NLR ratios in the United States[27]. Overall, the mean NLR was 2.15, whereas 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[27]. Also, within ethnicities, patients who had diabetes, cardiovascular disease, a high BMI and were smokers had a significantly higher NLR[27]. 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[28] in patients with advanced disease.

The systemic inflammatory response in patients with advanced cancer can be thought of as a result of a chronic inflammatory cascade. From the initial innate immune activation, as a result of the invasive tumour, due to the interaction of neutrophils and platelets at the site of tissue injury[29], to the chronic wounding of tissues around the body in metastatic disease. This chronic activation of inflammatory processes results in profound changes at the genomic, intracellular, cellular and systemic levels in the patient with cancer[9]. In particular, at the systemic level, markers of a systemic inflammatory response are associated with a progressive nutritional and functional decline[8] and a profound deterioration in quality of life[16].

A key pathway connecting the genomic, intracellular, cellular and systemic levels is the IL-6/JAK/STAT pathway[30]. Indeed, it is now increasingly recognised that genomic changes result in the chronic activation of the JAK/STAT pathway in the tumour and its microenvironment resulting in unregulated IL-6 production that produces an unregulated inflammatory cascade at cellular and systemic levels (increased C-reactive protein, neutrophil and platelet counts and decreased albumin). At the cellular and systemic level, IL-6 would appear to be the ideal marker of chronic systemic inflammation activation. Indeed, IL-6 in the circulation reflects the magnitude of tissue injury following surgery.[31] However, the strong correlation of IL-6 and C-reactive protein, 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. Indeed, in the use of anti-IL-6 treatments, inhibition of the production and the fall in circulating concentrations of C-reactive protein is often used as a surrogate for IL-6 activity. Finally, that IL-6 is produced in most tissues including the tumour means that compared with C-reactive protein and albumin (produced in the liver only) and

The development of immune-oncology medications such as iplimumab provides a potential means to target the activated inflammatory cascades to treat patients[44;45]. Indeed in a recent study in pancreatic cancer ruxolitinib, a strong downregulator 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[46]. This suggests a possible innovative means to treat patients with advanced cancers[46].

The present systematic review and meta-analysis has a number of limitations. 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.

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Figure and Table Legends Section:

Figure 1: PRISMA flowchart demonstrating study selection

Figure 2: Forrest Plot of Studies investigating the prognostic value of CRP in an unselected cohort of patients with advanced cancer

Figure 3: Forrest Plot of Studies investigating the prognostic value of Albumin in an unselected cohort of patients with advanced cancer

Figure 4: Forrest Plot of Studies investigating the prognostic value of GPS/mGPS in an unselected cohort of patients with advanced cancer

Figure 5: Forrest Plot of Studies investigating the prognostic value of NLR in an unselected cohort of patients with advanced cancer

Figure 6: Forrest Plot of Studies investigating the prognostic value of LMR in an unselected cohort of patients with advanced cancer

Figure 7: Forrest Plot of Studies investigating the prognostic value of PLR in an unselected cohort of patients with advanced cancer

Supplementary Table: Studies investigating the prognostic value of all markers of the SIR in an unselected cohort of patients with advanced cancer

Supplementary Table: Studies investigating the prognostic value of all markers of the SIR 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[47] 2000	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[48] 2001	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[49] 2002	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[50] 2004	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[51] 2005	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[52] 2005	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[53] 2006	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[54] 2006	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[55] 2006	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[56] 2007	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[57] 2007	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[58] 2008	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[59] 2008	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[60] 2008	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 Univariate: >15mg/l: 18.69 (8.23-42.40) p<0.001	Tumour location in tail, Lymph node spread, Treatment, Performance status, Weight loss, CEA and Jaundice
15.	Yoshida et al[61] 2008	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[62] 2009	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[63] 2009	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[64] 2010	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[65] 2010	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[66] 2010	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[67] 2010	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[68] 2010	Retrospective	Pancreatic	Japan	83	CRP>10mg/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: CRP: 0.92 (0.67–1.27) p=0.6099 Inverse HR: 1.09 (0.79-1.50)	Albumin
23.	Shinohara et al[69] 2011	Retrospective	Renal Cell	Japan	407	CRP>3mg/L	Multiple treatments including Cytokine 362 77 IFN-α, IL-2, Chemo &	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

							metastasectomy Generally poor outcome					metastasis, Bone Metastasis, Lymph Node Metastasis
24.	Yi et al[70] 2011	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[71] 2011	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[72] 2011	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[73] 2012	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[74] 2012	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[75] 2012	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 [76] 2012	Retrospective	Laryngeal	China	57	CRP>8mg/L	Palliative chemo-radiotherapy including platinum	29	N/A	Multivariate: 2.66 (1.22–5.82)	N/A	Tumour site (glottic vs. supraglottic vs.

							chemo			p=0.014		subglottic)
31.	Pond et al[77] 2012	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[78] 2012	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[79] 2012	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[80] 2013	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[81] 2013	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[82] 2013	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[83] 2014	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[84] 2014	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[85] 2014	Retrospective	Lung	France	55	CRP>7mg/L	Multiple treatments including chemotherapy, radiotherapy, and	N/A	50	N/A	Univariate: 4.3 (2.38-7.8) p<0.001	Leucocytes, Neutrophils, Hb, Alb, ALk P, Corrected Ca

							best supportive care some palliative surgery as well					
40.	Beuselinck et al[86] 2014	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[87] 2014	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[88] 2014	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[89] 2014	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[90] 2015	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[91] 2015	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[92] 2015	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[93] 2015	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[94] 2015	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[95] 2015	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[96] 2015	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[97] 2015	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[98] 2015	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[99] 2015	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[100] 2015	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[101] 2015	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[102] 2015	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[103] 2015	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[104] 2015	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[105] 2016	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[106] 2016	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[107] 2016	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[108] 2016	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[109] 2016	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
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[210] 2000	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[111] 2000	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[112] 2007	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[113] 2007	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[57] 2007	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[114] 2008	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[115] 2008	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[65] 2010	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[68] 2010	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[116] 2011	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[70] 2011	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[117] 2011	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[118] 2012	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[119] 2012	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[120] 2014	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[121] 2014	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[122] 2014	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[123] 2014	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[124] 2014	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[125] 2014	Retrospective	Renal Cell Cancer	Sweden	84	Alb<30 g/L	Chemotherapy, Radiotherapy and 20% had Metastectomy	N/A	84	N/A	Multivariate: 2.72 (1.22-6.09) P=0.015	Albumin Only
21.	Koo et al[126] 2015	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[90] 2015	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[127] 2015	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[128] 2015	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[129] 2015	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[130] 2015	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[99] 2015	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[100] 2015	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[108] 2016	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[131] 2016	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 al[132] 2016	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[133] 2016	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: Liver, Lung, Carcinomatosis, Bone, Carcinoembryonic antigen
33.	Choi et al[134] 2016	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
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[135] 2006	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[57] 2007	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[136] 2008	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[137] 2012	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
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[138] 2011	Retrospective	Breast	Australia	693	Neut (log scale) above baseline of ≥7x10^9/L	Active chemotherapy as part of two trails	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[139] 2012	Retrospective	Renal Cell	Japan	87	Neut>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[65] 2014	Retrospective	Lung	France	55	Neut: >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[140] 2015	Retrospective	Nasopharyngeal	China	419	Absolute Neutrophil Count (ANC) >4.7x10^{9}L	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[141] 2015	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[104] 2015	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[142] 2016	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[143] 2016	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[144] 2016	Retrospective	Melanoma	France	58	Neutrophils: continuous Neutrophils: ≥7.5x10^9/L	Chemotherapy including ipilimumab	N/A	22	N/A	Univariate: Continuous: 1.34 (1.17-1.53) p<0.0001 ≥7.5x10^9/L : 3.28 (1.38-7.78) p=0.007	LDH IU, Performance Status
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[145] 2008	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[117] 2011	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[146] 2012	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[147] 2014	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[148] 2014	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[128] 2015	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[143] 2016	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[149] 2016	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[150] 2016	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[134] 2016	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[144] 2016	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
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[151] 2013	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[147] 2014	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[148] 2014	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[99] 2015	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[149] 2016	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
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[152] 2008	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[117] 2011	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[125] 2014	Retrospective	Renal Cell	Sweden	84	Plate: >360X 10^9/L	Chemo, Radio and 20% had Metastectomy	N/A	84	N/A	Multivariate: 1.62 (0.79–3.32) p=0.19	Albumin Only
4.	Chen et al[153] 2015	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[128] 2015	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[154] 2015	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[155] 2016	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[143] 2016	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
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[156] 2003	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[157] 2004	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[158] 2006	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[55] 2006	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[159] 2006	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[160] 2006	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[57] 2007	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[161] 2007	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[162] 2008	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[163] 2008	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[164] 2010	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[68] 2010	Retrospective	Pancreatic	Japan	83	GPS (0 vs. 1 or 2)	50 patients received single-agent treatment with gemcitabine (GEM), 9 patients GEM combined with	N/A	83	N/A	Univariate: 0.513 (0.047–5.547) P=0.5825 Inverse: 1.949 (0.180-21.277)	Albumin

							radiotherapy (GEM+R) and 24 patients had best supportive care (BSC).					
13.	Hwang et al[165] 2011	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[166] 2011	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[167] 2012	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[168] 2012	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[169] 2012	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[137] 2012	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[170] 2012	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[171] 2012	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	PS Only

											GPS 2: 7.00 (2.53-19.36) P=0.001	
21.	Laird et al[172] 2013	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[173] 2013	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[174] 2014	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[175] 2014	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[176] 2014	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	Age, Performance status, Referred to Palliative Care, Mets when diagnosed

											Radio: GPS 1: 2.90 (0.97-8.67) p=0.06 GPS 2: 3.98 (1.52-10.42) p=0.005	
26.	Moriwaki et al[177] 2014	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[178] 2015	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 >6l, NLR≥4, Dyspnea, Oedem0.308a
28.	De Paula Pantano et al[179] 2015	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[180] 2015	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[181] 2015	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[182] 2015	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[100] 2015	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[183] 2015	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[184] 2015	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[185] 2015	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[186] 2015	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[187] 2015	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[188] 2015	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-	GPS Only

											5.555)	
39.	Mitsunaga et al[101] 2015	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) mGPS 2: 1.388 (0.588-3.333)	Sex, Age, ECOG-PS, UICC stage, CA 19-9, Prognostic CRP Classification, NLR
40. S	Song et al[189] 2015	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[190] 2015	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[191] 2016	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. A r	Arigami et al[192] 2016	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[193] 2016	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

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[194] 2008	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[195] 2009	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[196] 2010	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[197] 2010	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[166] 2011	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[198] 2011	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[199] 2011	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[200] 2011	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[169] 2012	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[201] 2012	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[202] 2012	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[203] 2012	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 2012[204]	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[173] 2013	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[205] 2013	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[206] 2013	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[207] 2013	Retrospective	Renal Cell	Australia	362	NLR>3	Patients treated with Lapatinib or hormonal therapy after prior failure of immunotherapy in a	N/A	357	N/A	Multivariate: 1.42 (1.10- 1.84) p=0.008	Neutrophils, Platelets, KPS, Corrected Calcium, Low Hb

							randomised phase III trial					
18.	Cetin et al[208] 2013	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[209] 2013	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[210] 2014	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[89] 2014	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[211] 2014	Retrospective	Lung	United Kingdom	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[212] 2014	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[213] 2014	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[214] 2014	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[215] 2014	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[216] 2014	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[217] 2014	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[88] 2014	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[218] 2014	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[219] 2014	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[220] 2014	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[221] 2015	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[222] 2015	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[223] 2015	Retrospective	Prostate	United Kingdom	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[224] 2015	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[102] 2015	Retrospective	Pancreatic Ductal	Korea	343 (212 palliative chemo)	NLR>5	FOLFIRINOX and Gemcitabine based chemo	N/A	343	N/A	Multivariate: <u>Whole Group:</u> 1.428 (1.014-2.012) p=0.042 <u>Palliative Chemo:</u> 1.038 (0.654-1.650) p=0.175	ECOG, Alb, CRP, Initial site of Mets, No initial chemotherapy
38.	Chen et al[225] 2015	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[226] 2015	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[227] 2015	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[228] 2015	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[100] 2015	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[101] 2015	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[104] 2015	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[154] 2015	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[103] 2015	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[229] 2016	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

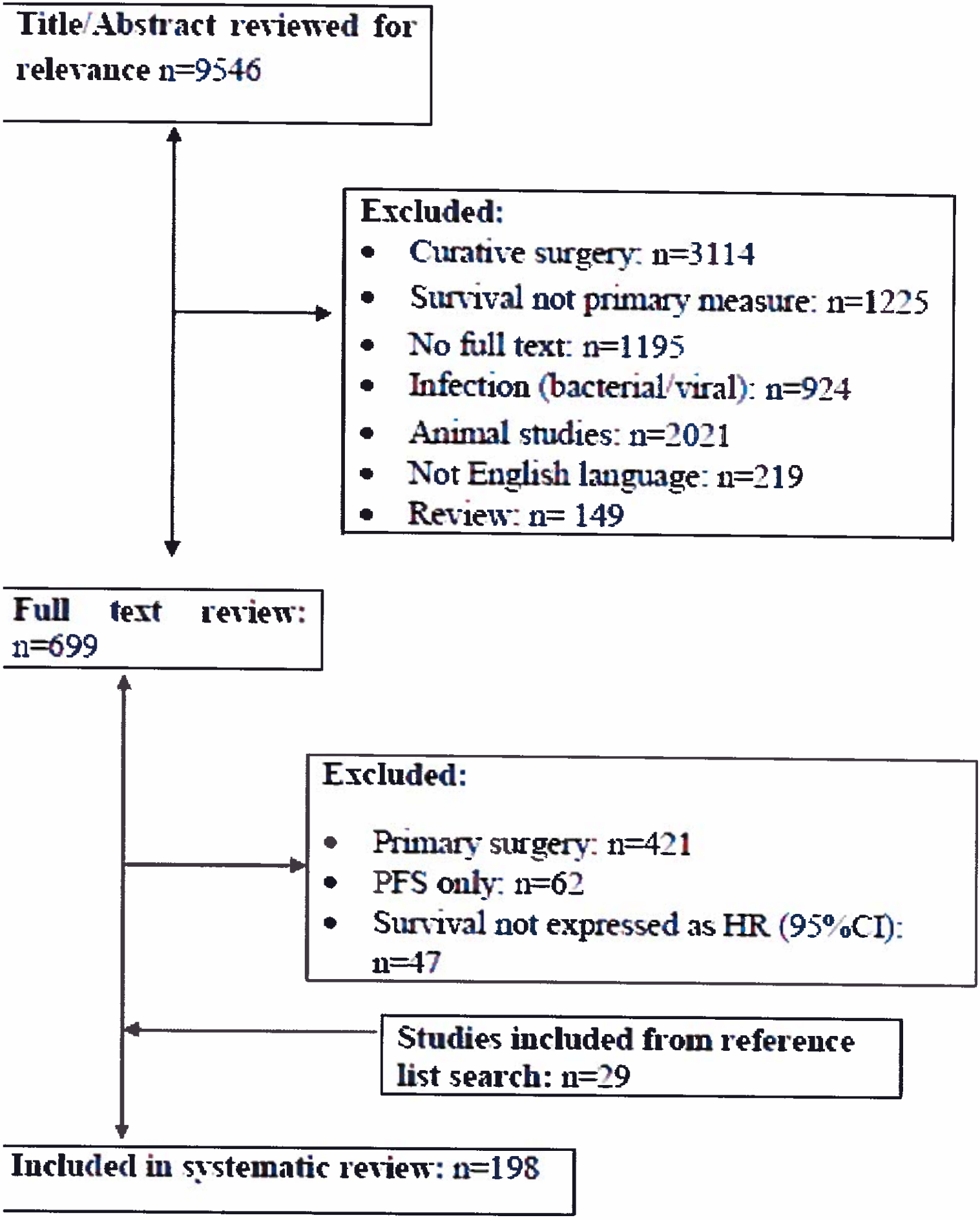
48.	Beltran et al[230] 2016	Retrospective	T-cell lymphoma	Peru	83	NLR≥4	Combined Chemotherapy, Radiotherapy and Chemoradiotherapy	N/A	59	N/A	Multivariate: 4.73 (1.78-12.6) p<0.01	Performance Status
49.	Ferrucci et al[142] 2016	Prospective	Metastatic Melanoma	Italy	720	NLR≥3	Ipilimumab	N/A	662	N/A	Multivariate: 2.29 (1.86-2.82) p<0.0001	Sex, ECOG, Brain Mets, Liver Mets
50.	Zhang et al[231] 2016	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[108] 2016	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[191] 2016	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[131] 2016	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[232] 2016	Retrospective	Cholangiocarcinoma	Korea	221	NLR>5	Combination chemotherapy including Gencitabine 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[109] 2016	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[134] 2016	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[144] 2016	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[233] 2016	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[193] 2016	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
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[234] 2013	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[235] 2013	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[147] 2014	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[148] 2014	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[236] 2014	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[237] 2015	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[238] 2015	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[227] 2015	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[189] 2015	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[239] 2016	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[149] 2016	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
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[205] 2013	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[240] 2013	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[100] 2015	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[241] 2015	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[242] 2015	Retrospective	Nasopharyngeal	China	1261	PLR ≥153.64	Chemo and Radio active	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[243] 2015	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[244] 2015	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[245] 2015	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[154] 2015	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	Wu et al[104] 2015	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[108] 2016	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[233] 2016	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
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[20] 2014	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[17] 2015	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[19] 2015	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[21] 2015	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[18] 2016	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[17] 2016	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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Not English language: n=219
Review: n= 149
Full text review: n=699
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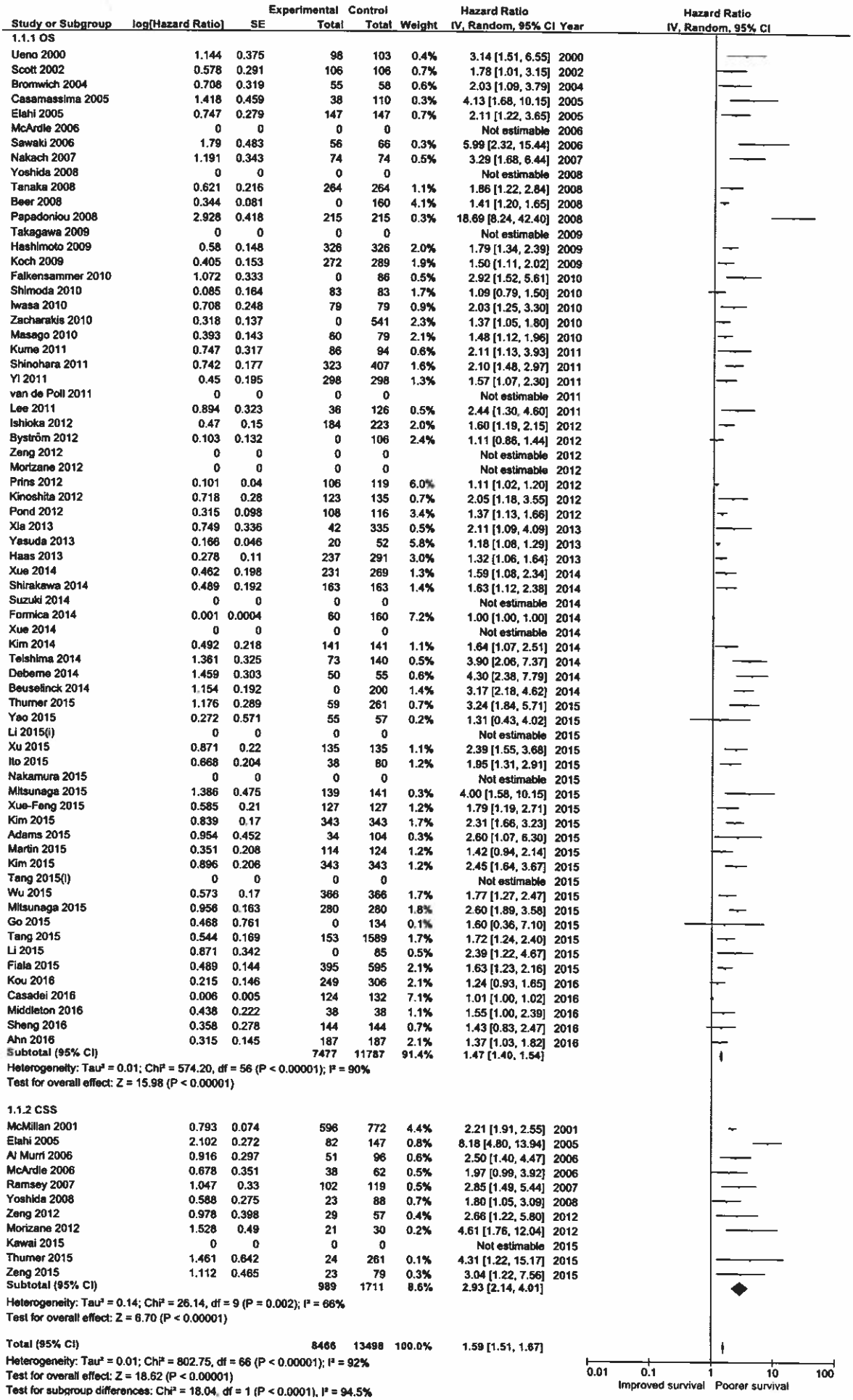
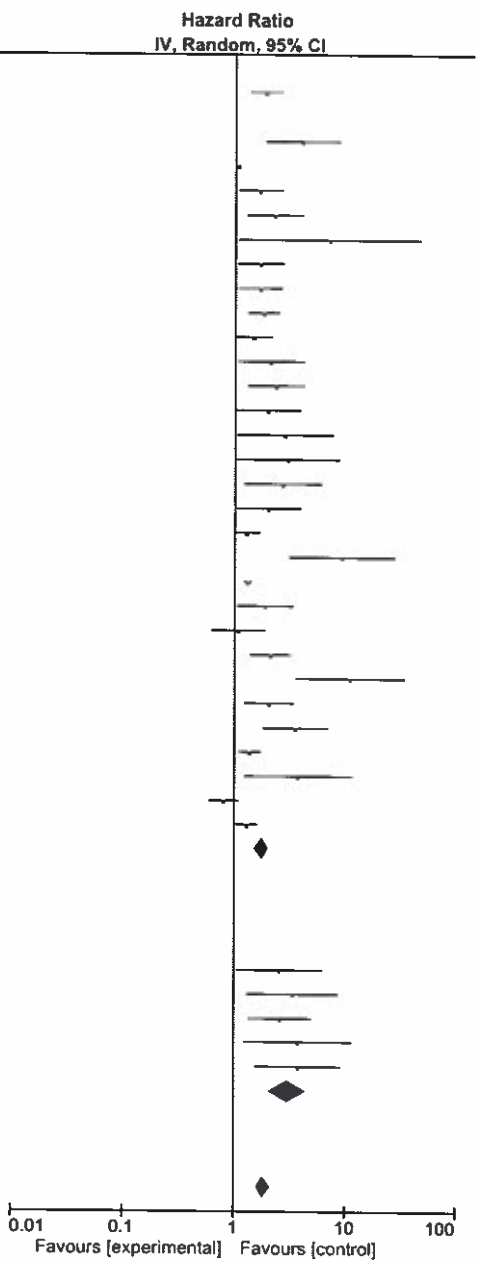
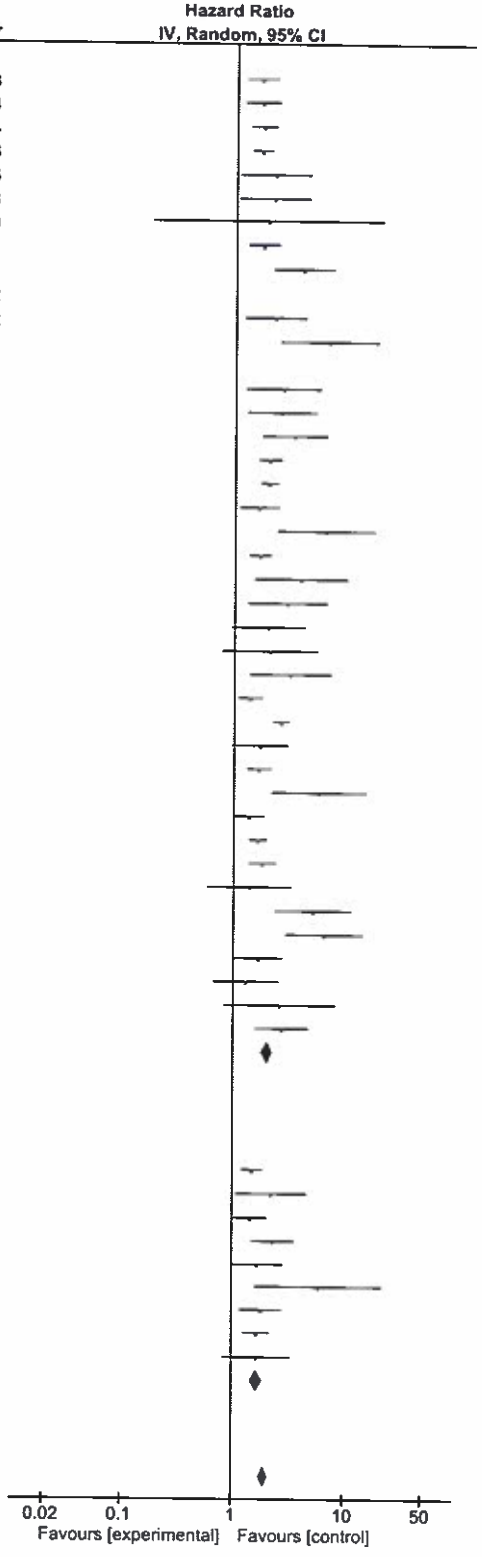
Studies included from reference list search: n=29
Included in systematic review: n=198

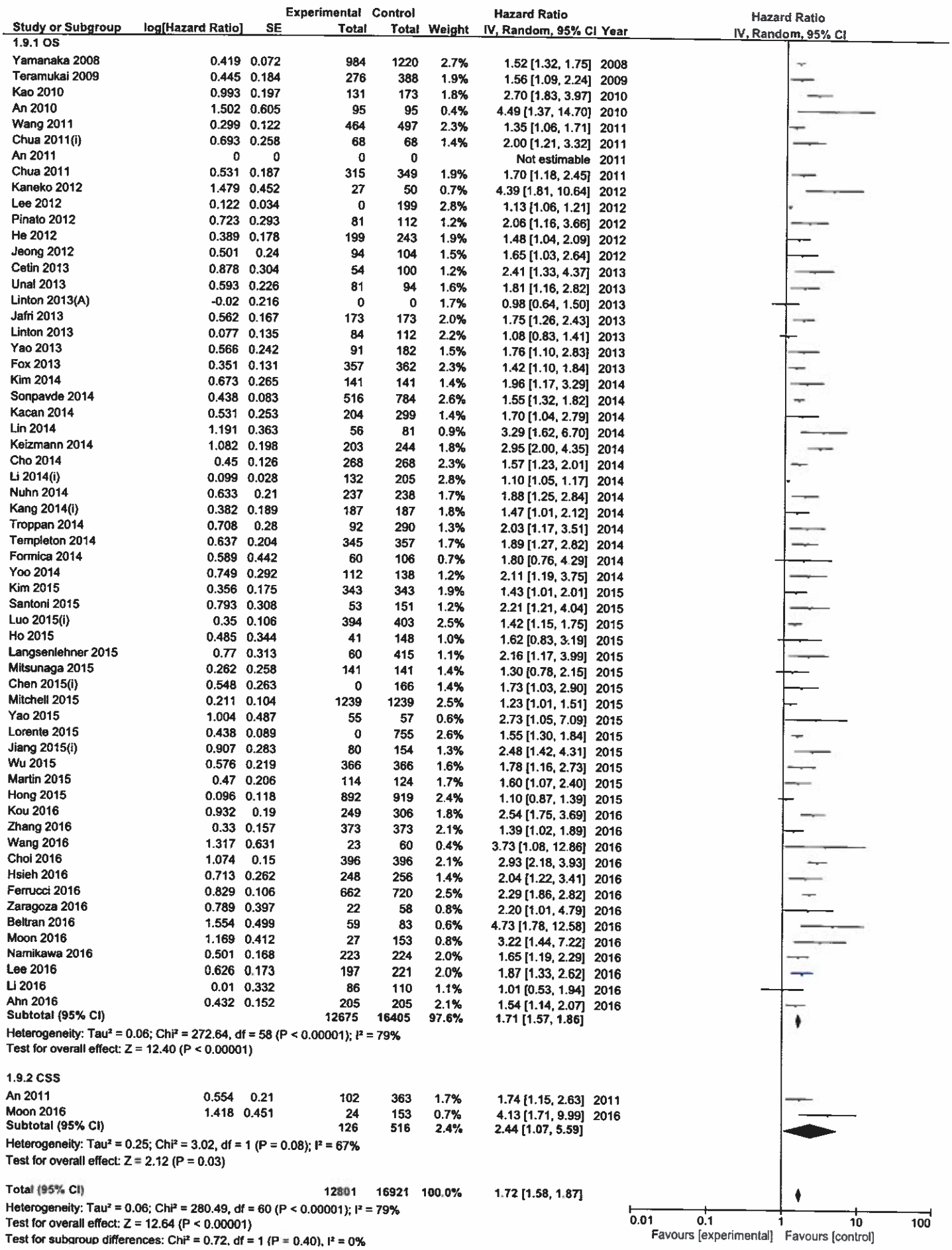

Experimental
Control
Hazard Ratio
Hazard Ratio
Study or Subgroup log[Hazard Ratio] SE Total Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
1.1.1 OS
Ueno 2000 1.144 0.375 98 103 0.4% 3.14 [1.51, 6.55] 2000
Scott 2002 0.578 0.291 106 106 0.7% 1.78 [1.01, 3.15] 2002
Bromwich 2004 0.708 0.319 55 58 0.6% 2.03 [1.09, 3.79] 2004
Casamassima 2005 1.418 0.459 38 110 0.3% 4.13 [1.68, 10.15] 2005
Elahi 2005 0.747 0.279 147 147 0.7% 2.11 [1.22, 3.65] 2005
McArdle 2006 0 0 0 0 Not estimable 2006
Sawaki 2006 1.79 0.483 56 66 0.3% 5.99 [2.32, 15.44] 2006
Nakach 2007 1.191 0.343 74 74 0.5% 3.29 [1.68, 6.44] 2007
Yoshida 2008 0 0 0 0 Not estimable 2008
Tanaka 2008 0.621 0.216 264 264 1.1% 1.86 [1.22, 2.84] 2008
Beer 2008 0.344 0.081 0 160 4.1% 1.41 [1.20, 1.65] 2008
Papadoniou 2008 2.928 0.418 215 215 0.3% 18.69 [8.24, 42.40] 2008
Takagawa 2009 0 0 0 0 Not estimable 2009
Hashimoto 2009 0.58 0.148 326 326 2.0% 1.79 [1.34, 2.39] 2009
Koch 2009 0.405 0.153 272 289 1.9% 1.50 [1.11, 2.02] 2009
Falkensammer 2010 1.072 0.333 0 86 0.5% 2.92 [1.52, 5.61] 2010
Shimoda 2010 0.085 0.164 83 83 1.7% 1.09 [0.79, 1.50] 2010
Iwasa 2010 0.708 0.248 79 79 0.9% 2.03 [1.25, 3.30] 2010
Zacharakis 2010 0.318 0.137 0 541 2.3% 1.37 [1.05, 1.80] 2010
Masago 2010 0.393 0.143 80 79 2.1% 1.48 [1.12, 1.96] 2010
Kume 2011 0.747 0.317 86 94 0.6% 2.11 [1.13, 3.93] 2011
Shinohara 2011 0.742 0.177 323 407 1.6% 2.10 [1.48, 2.97] 2011
Yi 2011 0.45 0.195 298 298 1.3% 1.57 [1.07, 2.30] 2011
van de Poll 2011 0 0 0 0 Not estimable 2011
Lee 2011 0.894 0.323 36 126 0.5% 2.44 [1.30, 4.60] 2011
Ishioka 2012 0.47 0.15 184 223 2.0% 1.60 [1.19, 2.15] 2012
Byström 2012 0.103 0.132 0 106 2.4% 1.11 [0.86, 1.44] 2012
Zeng 2012 0 0 0 0 Not estimable 2012
Morizane 2012 0 0 0 0 Not estimable 2012
Prins 2012 0.101 0.04 106 119 6.0% 1.11 [1.02, 1.20] 2012
Kinoshita 2012 0.718 0.28 123 135 0.7% 2.05 [1.18, 3.55] 2012
Pond 2012 0.315 0.098 108 116 3.4% 1.37 [1.13, 1.66] 2012
Xia 2013 0.749 0.336 42 335 0.5% 2.11 [1.09, 4.09] 2013
Yasuda 2013 0.166 0.046 20 52 5.8% 1.18 [1.08, 1.29] 2013
Haas 2013 0.278 0.11 237 291 3.0% 1.32 [1.06, 1.64] 2013
Xue 2014 0.462 0.198 231 269 1.3% 1.59 [1.08, 2.34] 2014
Shirakawa 2014 0.489 0.192 163 163 1.4% 1.63 [1.12, 2.38] 2014
Suzuki 2014 0 0 0 0 Not estimable 2014
Formica 2014 0.001 0.0004 60 160 7.2% 1.00 [1.00, 1.00] 2014
Xue 2014 0 0 0 0 Not estimable 2014
Kim 2014 0.492 0.218 141 141 1.1% 1.64 [1.07, 2.51] 2014
Telshima 2014 1.361 0.325 73 140 0.5% 3.90 [2.06, 7.37] 2014
Debeme 2014 1.459 0.303 50 55 0.6% 4.30 [2.38, 7.79] 2014
Beuselinck 2014 1.154 0.192 0 200 1.4% 3.17 [2.18, 4.62] 2014
Thumer 2015 1.176 0.289 59 261 0.7% 3.24 [1.84, 5.71] 2015
Yao 2015 0.272 0.571 55 57 0.2% 1.31 [0.43, 4.02] 2015
Li 2015(i) 0 0 0 0 Not estimable 2015
Xu 2015 0.871 0.22 135 135 1.1% 2.39 [1.55, 3.68] 2015
Ito 2015 0.668 0.204 38 80 1.2% 1.95 [1.31, 2.91] 2015
Nakamura 2015 0 0 0 0 Not estimable 2015
Mitsunaga 2015 1.386 0.475 139 141 0.3% 4.00 [1.58, 10.15] 2015
Xue-Feng 2015 0.585 0.21 127 127 1.2% 1.79 [1.19, 2.71] 2015
Kim 2015 0.839 0.17 343 343 1.7% 2.31 [1.66, 3.23] 2015
Adams 2015 0.954 0.452 34 104 0.3% 2.60 [1.07, 6.30] 2015
Martin 2015 0.351 0.208 114 124 1.2% 1.42 [0.94, 2.14] 2015
Kim 2015 0.896 0.206 343 343 1.2% 2.45 [1.64, 3.67] 2015
Tang 2015(i) 0 0 0 0 Not estimable 2015
Wu 2015 0.573 0.17 366 366 1.7% 1.77 [1.27, 2.47] 2015
Mitsunaga 2015 0.956 0.163 280 280 1.8% 2.60 [1.89, 3.58] 2015
Go 2015 0.468 0.761 0 134 0.1% 1.60 [0.36, 7.10] 2015
Tang 2015 0.544 0.169 153 1589 1.7% 1.72 [1.24, 2.40] 2015
Li 2015 0.871 0.342 0 85 0.5% 2.39 [1.22, 4.67] 2015
Fiala 2015 0.489 0.144 395 595 2.1% 1.63 [1.23, 2.16] 2015
Kou 2016 0.215 0.146 249 306 2.1% 1.24 [0.93, 1.65] 2016
Casadei 2016 0.006 0.005 124 132 7.1% 1.01 [1.00, 1.02] 2016
Middleton 2016 0.438 0.222 38 38 1.1% 1.55 [1.00, 2.39] 2016
Sheng 2016 0.358 0.278 144 144 0.7% 1.43 [0.83, 2.47] 2016
Ahn 2016 0.315 0.145 187 187 2.1% 1.37 [1.03, 1.82] 2016
Subtotal (95% CI) 7477 11787 91.4% 1.47 [1.40, 1.54]
Heterogeneity: Tau² = 0.01; Chi² = 574.20, df = 56 (P < 0.00001); I² = 90%
Test for overall effect: Z = 15.98 (P < 0.00001)
1.1.2 CSS
McMillan 2001 0.793 0.074 596 772 4.4% 2.21 [1.91, 2.55] 2001
Elahi 2005 2.102 0.272 82 147 0.8% 8.18 [4.80, 13.94] 2005
Al Murri 2006 0.916 0.297 51 96 0.6% 2.50 [1.40, 4.47] 2006
McArdle 2006 0.678 0.351 38 62 0.5% 1.97 [0.99, 3.92] 2006
Ramsey 2007 1.047 0.33 102 119 0.5% 2.85 [1.49, 5.44] 2007
Yoshida 2008 0.588 0.275 23 88 0.7% 1.80 [1.05, 3.09] 2008
Zeng 2012 0.978 0.398 29 57 0.4% 2.66 [1.22, 5.80] 2012
Morizane 2012 1.528 0.49 21 30 0.2% 4.61 [1.76, 12.04] 2012
Kawai 2015 0 0 0 0 Not estimable 2015
Thumer 2015 1.461 0.642 24 261 0.1% 4.31 [1.22, 15.17] 2015
Zeng 2015 1.112 0.465 23 79 0.3% 3.04 [1.22, 7.56] 2015
Subtotal (95% CI) 989 1711 8.6% 2.93 [2.14, 4.01]
Heterogeneity: Tau² = 0.14; Chi² = 26.14, df = 9 (P = 0.002); I² = 66%
Test for overall effect: Z = 6.70 (P < 0.00001)
Total (95% CI) 8466 13498 100.0% 1.59 [1.51, 1.67]
Heterogeneity: Tau² = 0.01; Chi² = 802.75, df = 66 (P < 0.00001); I² = 92%
Test for overall effect: Z = 18.62 (P < 0.00001)
Test for subgroup differences: Chi² = 18.04, df = 1 (P < 0.0001), I² = 94.5%
0.01 0.1 1 10 100
Improved survival Poorer survival

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
1.3.1 OS							
Viganó 2000	0.642	0.177	208	227	4.2%	1.90 [1.34, 2.69]	2000
Axdorph 2000	0	0	0	0		Not estimable	2000
Maréchal 2007	1.402	0.393	90	99	2.0%	4.06 [1.88, 8.78]	2007
Lam 2007	0.052	0.016	57	145	5.6%	1.05 [1.02, 1.09]	2007
Paralkar 2008	0.531	0.232	159	172	3.5%	1.70 [1.08, 2.68]	2008
Ngo 2008	0.83	0.296	71	183	2.8%	2.29 [1.28, 4.10]	2008
Shimoda 2010	1.967	0.966	83	83	0.5%	7.15 [1.08, 47.48]	2010
Iwasa 2010	0.525	0.244	79	79	3.4%	1.69 [1.05, 2.73]	2010
Yi 2011	0.531	0.229	278	278	3.5%	1.70 [1.09, 2.66]	2011
Shim 2011	0.599	0.166	502	502	4.3%	1.82 [1.31, 2.52]	2011
Trédan 2011	0.385	0.189	299	264	4.0%	1.47 [1.01, 2.13]	2011
Lim 2012	0.748	0.353	49	50	2.3%	2.11 [1.06, 4.22]	2012
Prakash 2012	0.859	0.296	314	486	2.8%	2.36 [1.32, 4.22]	2012
Tsai 2014	0.683	0.343	479	522	2.4%	1.98 [1.01, 3.88]	2014
Malik 2014	1.036	0.51	51	70	1.4%	2.82 [1.04, 7.66]	2014
Imedio 2014	1.095	0.543	44	62	1.3%	2.99 [1.03, 8.66]	2014
Stenman 2014	1.001	0.41	84	84	1.9%	2.72 [1.22, 6.08]	2014
Kang 2014	0.693	0.341	168	168	2.4%	2.00 [1.02, 3.90]	2014
Ulas 2014	0.247	0.136	391	462	4.7%	1.28 [0.98, 1.67]	2014
Narwani 2015	2.235	0.564	22	38	1.2%	9.35 [3.09, 28.23]	2015
Koo 2015	0.281	0.041	3494	3888	5.5%	1.32 [1.22, 1.44]	2015
Go 2015	0.651	0.298	0	134	2.8%	1.92 [1.07, 3.44]	2015
Xue-Feng 2015	0.075	0.285	127	127	2.9%	1.08 [0.62, 1.88]	2015
Martin 2015	0.753	0.215	114	124	3.7%	2.12 [1.39, 3.24]	2015
Helissey 2015	2.407	0.573	26	56	1.2%	11.10 [3.61, 34.13]	2015
Kao 2015	0.737	0.261	69	143	3.2%	2.09 [1.25, 3.49]	2015
Wild 2015	1.277	0.342	88	101	2.4%	3.59 [1.83, 7.01]	2015
Choi 2016	0.322	0.117	396	396	4.9%	1.38 [1.10, 1.74]	2016
Uemura 2016	1.329	0.569	22	22	1.2%	3.78 [1.24, 11.52]	2016
Kou 2016	-0.223	0.156	249	306	4.4%	0.80 [0.59, 1.09]	2016
Dorajoo 2016	0.259	0.112	480	482	4.9%	1.30 [1.04, 1.61]	2016
Subtotal (95% CI)			8493	9753	91.4%	1.77 [1.54, 2.03]	
Heterogeneity: Tau² = 0.08; Chi² = 181.16, df = 29 (P < 0.00001); I² = 84%							
Test for overall effect: Z = 8.05 (P < 0.00001)							
1.3.2 CSS							
Axdorph 2000	0.94	0.455	48	145	1.7%	2.56 [1.05, 6.25]	2000
Al Murri 2006	1.227	0.48	51	96	1.6%	3.41 [1.33, 8.74]	2006
Ramsey 2007	0.967	0.33	102	119	2.5%	2.63 [1.38, 5.02]	2007
Uemura 2016	1.329	0.569	22	22	1.2%	3.78 [1.24, 11.52]	2016
Moon 2016	1.335	0.451	24	153	1.7%	3.80 [1.57, 9.20]	2016
Subtotal (95% CI)			247	535	8.6%	3.05 [2.08, 4.47]	
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 4 (P = 0.94); I² = 0%							
Test for overall effect: Z = 5.73 (P < 0.00001)							
Total (95% CI)			8740	10288	100.0%	1.87 [1.63, 2.15]	
Heterogeneity: Tau² = 0.09; Chi² = 207.73, df = 34 (P < 0.00001); I² = 84%							
Test for overall effect: Z = 8.93 (P < 0.00001)							
Test for subgroup differences: Chi² = 6.93, df = 1 (P = 0.008), I² = 85.6%							

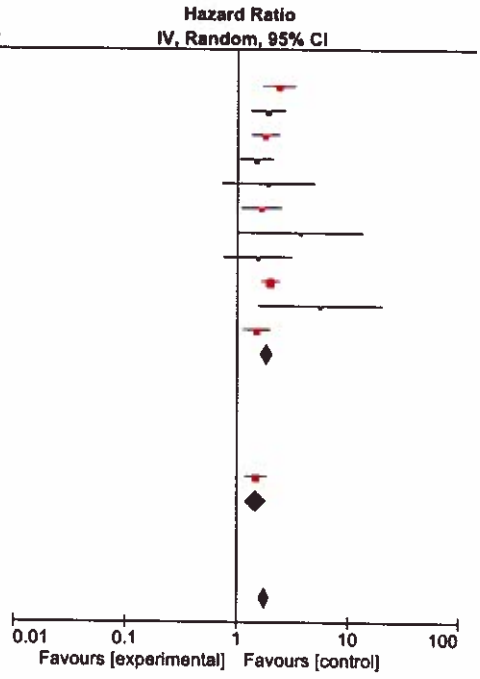


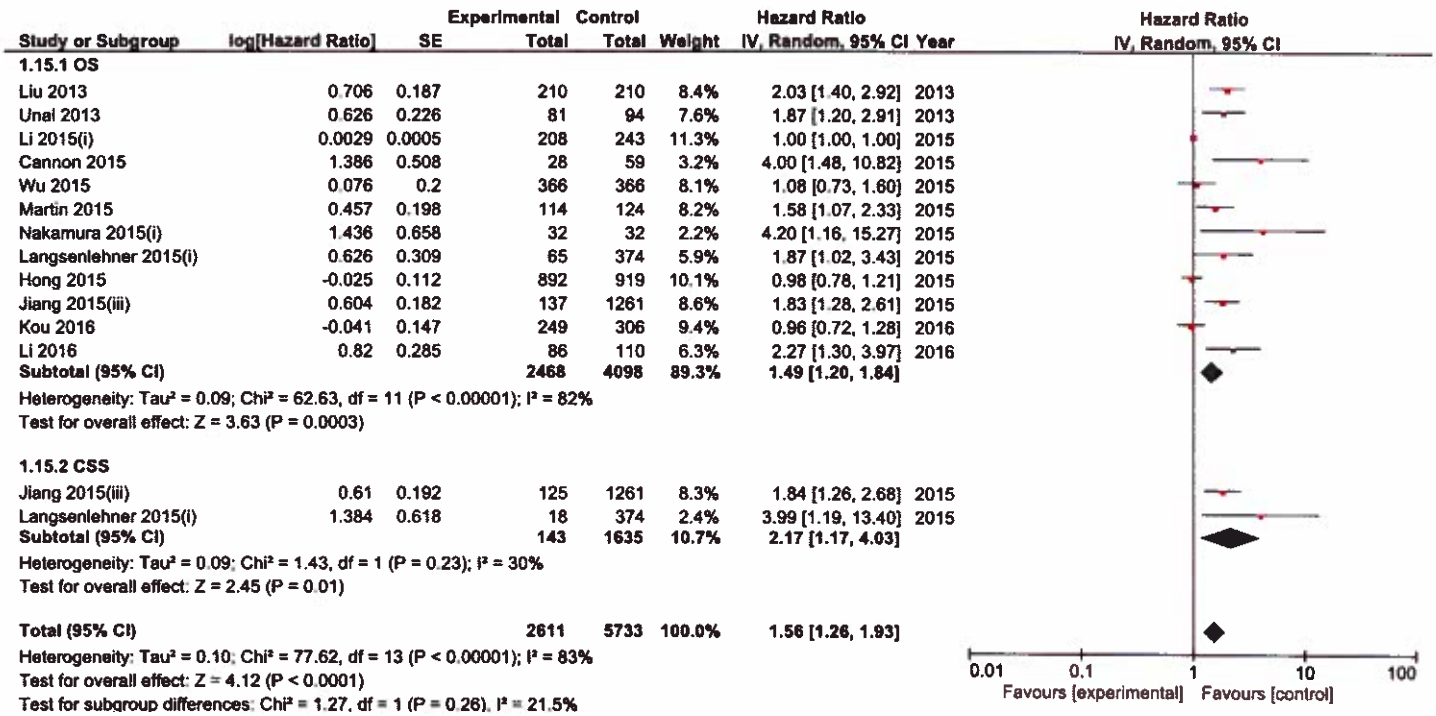
Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
1.8.1 OS							
Forrest 2003	0.531	0.165	118	161	3.1%	1.70 [1.23, 2.35]	2003
Elahi 2004 (A)	0.537	0.185	165	165	2.8%	1.71 [1.19, 2.46]	2004
Elahi 2004 (B)	0.571	0.136	165	165	3.6%	1.77 [1.36, 2.31]	2004
Glen 2006	0.542	0.105	181	187	4.1%	1.72 [1.40, 2.11]	2006
Read 2006	0.82	0.375	32	51	1.1%	2.27 [1.09, 4.74]	2006
Ramsey 2008	0.802	0.373	15	23	1.2%	2.23 [1.07, 4.63]	2008
Shimoda 2010	0.667	1.218	83	83	0.1%	1.95 [0.18, 21.20]	2010
Hwang 2011	0.582	0.166	402	402	3.1%	1.79 [1.29, 2.48]	2011
Chua 2011(i)	1.411	0.319	68	68	1.5%	4.10 [2.19, 7.66]	2011
Leung 2012	0	0	0	0		Not estimable	2012
Jeong 2012	0.828	0.325	94	104	1.4%	2.29 [1.21, 4.33]	2012
Hwang 2012	1.946	0.519	67	67	0.7%	7.00 [2.53, 19.36]	2012
Inoue 2012	0	0	0	0		Not estimable	2012
Partridge 2012	0.998	0.394	47	101	1.1%	2.71 [1.25, 5.87]	2012
Gioulbasanis 2012	0.967	0.362	89	96	1.2%	2.63 [1.29, 5.35]	2012
Linton 2013	1.236	0.345	84	112	1.3%	3.44 [1.75, 6.77]	2013
Laird 2013 (B)	0.723	0.124	471	631	3.8%	2.06 [1.62, 2.63]	2013
Laird 2013 (A)	0.718	0.089	1601	1825	4.4%	2.05 [1.72, 2.44]	2013
Moriwaki 2014	0.51	0.207	218	218	2.5%	1.67 [1.11, 2.50]	2014
Sachlova 2014	1.892	0.514	64	64	0.7%	6.63 [2.42, 18.16]	2014
Zhang 2014	0.527	0.116	723	723	3.9%	1.69 [1.35, 2.13]	2014
Anshushaug 2014 (B)	1.381	0.491	723	723	0.7%	3.98 [1.52, 10.42]	2014
Anshushaug 2014 (A)	1.099	0.418	723	723	1.0%	3.00 [1.32, 6.81]	2014
Jiang 2015(i)	0.693	0.384	138	138	1.1%	2.00 [0.94, 4.24]	2015
Dreanic 2015	0.734	0.503	27	27	0.7%	2.08 [0.78, 5.58]	2015
Song 2015	1.167	0.429	177	177	0.9%	3.21 [1.39, 7.45]	2015
Martin 2015	0.344	0.126	114	124	3.8%	1.41 [1.10, 1.81]	2015
De Paula Pantano 2015	0.98	0.084	346	459	4.5%	2.66 [2.26, 3.14]	2015
Chou 2015	0.537	0.294	204	217	1.6%	1.71 [0.96, 3.04]	2015
Zhou 2015(ii)	0.529	0.126	198	244	3.8%	1.70 [1.33, 2.17]	2015
Jung 2015	1.775	0.501	58	213	0.7%	5.90 [2.21, 15.75]	2015
Miura 2015	0.308	0.157	1160	1160	3.2%	1.36 [1.00, 1.85]	2015
Simmons 2015	0.513	0.091	283	390	4.4%	1.67 [1.40, 2.00]	2015
Xiao 2015	0.599	0.142	124	238	3.5%	1.82 [1.38, 2.40]	2015
Mitsunaga 2015	0.328	0.443	280	280	0.9%	1.39 [0.58, 3.31]	2015
Zhou 2015	1.654	0.406	180	359	1.0%	5.23 [2.36, 11.59]	2015
Kasuga 2015	1.888	0.409	61	61	1.0%	6.61 [2.96, 14.73]	2015
Tan 2015	0.519	0.251	0	114	2.0%	1.68 [1.03, 2.75]	2015
Namikawa 2016	0.26	0.342	223	224	1.3%	1.30 [0.66, 2.54]	2016
Arigami 2016	0.959	0.589	68	68	0.5%	2.61 [0.82, 8.28]	2016
Hsieh 2016	1.023	0.282	248	256	1.7%	2.78 [1.60, 4.83]	2016
Subtotal (95% CI)			10022	11441	80.1%	2.06 [1.86, 2.28]	
Heterogeneity: Tau² = 0.04; Chi² = 86.40, df = 38 (P < 0.0001); I² = 56%							
Test for overall effect: Z = 13.74 (P < 0.00001)							
1.8.2 CSS							
Crumley 2006	0.412	0.108	211	258	4.1%	1.51 [1.22, 1.87]	2006
Al Murri 2006	0.815	0.374	51	96	1.2%	2.26 [1.09, 4.70]	2006
Leitch 2007	0.365	0.182	71	84	2.9%	1.44 [1.01, 2.06]	2007
Ramsey 2007	0.854	0.227	102	119	2.3%	2.35 [1.51, 3.67]	2007
Crumley 2008	0.525	0.268	59	65	1.9%	1.69 [1.00, 2.86]	2008
Ishizuka 2010	1.804	0.672	44	112	0.4%	6.07 [1.63, 22.67]	2010
Inoue 2012	0.62	0.218	0	164	2.4%	1.86 [1.21, 2.85]	2012
Leung 2012	0.513	0.137	47	101	3.6%	1.67 [1.28, 2.18]	2012
Jiang 2015(i)	0.51	0.354	138	138	1.3%	1.67 [0.83, 3.33]	2015
Subtotal (95% CI)			723	1137	19.9%	1.69 [1.48, 1.92]	
Heterogeneity: Tau² = 0.00; Chi² = 8.37, df = 8 (P = 0.40); I² = 4%							
Test for overall effect: Z = 7.74 (P < 0.00001)							
Total (95% CI)			10745	12578	100.0%	1.99 [1.82, 2.17]	
Heterogeneity: Tau² = 0.04; Chi² = 99.21, df = 47 (P < 0.0001); I² = 53%							
Test for overall effect: Z = 15.13 (P < 0.00001)							
Test for subgroup differences: Chi² = 5.40, df = 1 (P = 0.02), I² = 81.5%							




Study or Subgroup
log[Hazard Ratio]
SE
Experimental Total
Control Total
Weight
Hazard Ratio IV, Random, 95% CI
Year
Hazard Ratio IV, Random, 95% CI
1.9.1 OS
Yamanaka 2008 0.419 0.072 984 1220 2.7% 1.52 [1.32, 1.75] 2008
Teramukai 2009 0.445 0.184 276 388 1.9% 1.56 [1.09, 2.24] 2009
Kao 2010 0.993 0.197 131 173 1.8% 2.70 [1.83, 3.97] 2010
An 2010 1.502 0.605 95 95 0.4% 4.49 [1.37, 14.70] 2010
Wang 2011 0.299 0.122 464 497 2.3% 1.35 [1.06, 1.71] 2011
Chua 2011(i) 0.693 0.258 68 68 1.4% 2.00 [1.21, 3.32] 2011
An 2011 0 0 0 0 Not estimable 2011
Chua 2011 0.531 0.187 315 349 1.9% 1.70 [1.18, 2.45] 2011
Kaneko 2012 1.479 0.452 27 50 0.7% 4.39 [1.81, 10.64] 2012
Lee 2012 0.122 0.034 0 199 2.8% 1.13 [1.06, 1.21] 2012
Pinato 2012 0.723 0.293 81 112 1.2% 2.06 [1.16, 3.66] 2012
He 2012 0.389 0.178 199 243 1.9% 1.48 [1.04, 2.09] 2012
Jeong 2012 0.501 0.24 94 104 1.5% 1.65 [1.03, 2.64] 2012
Cetin 2013 0.878 0.304 54 100 1.2% 2.41 [1.33, 4.37] 2013
Unal 2013 0.593 0.226 81 94 1.6% 1.81 [1.16, 2.82] 2013
Linton 2013(A) -0.02 0.216 0 0 1.7% 0.98 [0.64, 1.50] 2013
Jafri 2013 0.562 0.167 173 173 2.0% 1.75 [1.26, 2.43] 2013
Linton 2013 0.077 0.135 84 112 2.2% 1.08 [0.83, 1.41] 2013
Yao 2013 0.566 0.242 91 182 1.5% 1.76 [1.10, 2.83] 2013
Fox 2013 0.351 0.131 357 362 2.3% 1.42 [1.10, 1.84] 2013
Kim 2014 0.673 0.265 141 141 1.4% 1.96 [1.17, 3.29] 2014
Sonpavde 2014 0.438 0.083 516 784 2.6% 1.55 [1.32, 1.82] 2014
Kacan 2014 0.531 0.253 204 299 1.4% 1.70 [1.04, 2.79] 2014
Lin 2014 1.191 0.363 56 81 0.9% 3.29 [1.62, 6.70] 2014
Keizmann 2014 1.082 0.198 203 244 1.8% 2.95 [2.00, 4.35] 2014
Cho 2014 0.45 0.126 268 268 2.3% 1.57 [1.23, 2.01] 2014
Li 2014(i) 0.099 0.028 132 205 2.8% 1.10 [1.05, 1.17] 2014
Nuhn 2014 0.633 0.21 237 238 1.7% 1.88 [1.25, 2.84] 2014
Kang 2014(i) 0.382 0.189 187 187 1.8% 1.47 [1.01, 2.12] 2014
Troppan 2014 0.708 0.28 92 290 1.3% 2.03 [1.17, 3.51] 2014
Templeton 2014 0.637 0.204 345 357 1.7% 1.89 [1.27, 2.82] 2014
Formica 2014 0.589 0.442 60 106 0.7% 1.80 [0.76, 4.29] 2014
Yoo 2014 0.749 0.292 112 138 1.2% 2.11 [1.19, 3.75] 2014
Kim 2015 0.356 0.175 343 343 1.9% 1.43 [1.01, 2.01] 2015
Santoni 2015 0.793 0.308 53 151 1.2% 2.21 [1.21, 4.04] 2015
Luo 2015(i) 0.35 0.106 394 403 2.5% 1.42 [1.15, 1.75] 2015
Ho 2015 0.485 0.344 41 148 1.0% 1.62 [0.83, 3.19] 2015
Langsenlehner 2015 0.77 0.313 60 415 1.1% 2.16 [1.17, 3.99] 2015
Mitsunaga 2015 0.262 0.258 141 141 1.4% 1.30 [0.78, 2.15] 2015
Chen 2015(i) 0.548 0.263 0 166 1.4% 1.73 [1.03, 2.90] 2015
Mitchell 2015 0.211 0.104 1239 1239 2.5% 1.23 [1.01, 1.51] 2015
Yao 2015 1.004 0.487 55 57 0.6% 2.73 [1.05, 7.09] 2015
Lorente 2015 0.438 0.089 0 755 2.6% 1.55 [1.30, 1.84] 2015
Jiang 2015(i) 0.907 0.283 80 154 1.3% 2.48 [1.42, 4.31] 2015
Wu 2015 0.576 0.219 366 366 1.6% 1.78 [1.16, 2.73] 2015
Martin 2015 0.47 0.206 114 124 1.7% 1.60 [1.07, 2.40] 2015
Hong 2015 0.096 0.118 892 919 2.4% 1.10 [0.87, 1.39] 2015
Kou 2016 0.932 0.19 249 306 1.8% 2.54 [1.75, 3.69] 2016
Zhang 2016 0.33 0.157 373 373 2.1% 1.39 [1.02, 1.89] 2016
Wang 2016 1.317 0.631 23 60 0.4% 3.73 [1.08, 12.86] 2016
Choi 2016 1.074 0.15 396 396 2.1% 2.93 [2.18, 3.93] 2016
Hsieh 2016 0.713 0.262 248 256 1.4% 2.04 [1.22, 3.41] 2016
Ferrucci 2016 0.829 0.106 662 720 2.5% 2.29 [1.86, 2.82] 2016
Zaragoza 2016 0.789 0.397 22 58 0.8% 2.20 [1.01, 4.79] 2016
Beltran 2016 1.554 0.499 59 83 0.6% 4.73 [1.78, 12.58] 2016
Moon 2016 1.169 0.412 27 153 0.8% 3.22 [1.44, 7.22] 2016
Namikawa 2016 0.501 0.168 223 224 2.0% 1.65 [1.19, 2.29] 2016
Lee 2016 0.626 0.173 197 221 2.0% 1.87 [1.33, 2.62] 2016
Li 2016 0.01 0.332 86 110 1.1% 1.01 [0.53, 1.94] 2016
Ahn 2016 0.432 0.152 205 205 2.1% 1.54 [1.14, 2.07] 2016
Subtotal (95% CI) 12675 16405 97.6% 1.71 [1.57, 1.86]
Heterogeneity: Tau² = 0.06; Chi² = 272.64, df = 58 (P < 0.00001); I² = 79%
Test for overall effect: Z = 12.40 (P < 0.00001)
1.9.2 CSS
An 2011 0.554 0.21 102 363 1.7% 1.74 [1.15, 2.63] 2011
Moon 2016 1.418 0.451 24 153 0.7% 4.13 [1.71, 9.99] 2016
Subtotal (95% CI) 126 516 2.4% 2.44 [1.07, 5.59]
Heterogeneity: Tau² = 0.25; Chi² = 3.02, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 2.12 (P = 0.03)
Total (95% CI) 12801 16921 100.0% 1.72 [1.58, 1.87]
Heterogeneity: Tau² = 0.06; Chi² = 280.49, df = 60 (P < 0.00001); I² = 79%
Test for overall effect: Z = 12.64 (P < 0.00001)
Test for subgroup differences: Chi² = 0.72, df = 1 (P = 0.40), I² = 0%
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
1.10.1 OS							
Lin 2014(ii)	0.868	0.172	255	281	9.4%	2.38 [1.70, 3.34]	
Rambaldi 2013	0.631	0.183	392	700	8.5%	1.88 [1.31, 2.69]	2013
Li 2013	0.583	0.149	1465	1547	11.7%	1.79 [1.34, 2.40]	2013
Go 2014	0.387	0.183	152	188	8.5%	1.47 [1.03, 2.11]	2014
Lin 2014(i)	0.635	0.49	370	370	1.4%	1.89 [0.72, 4.93]	2014
Song 2015	0.506	0.213	177	177	6.6%	1.66 [1.09, 2.52]	2015
Koh 2015	1.302	0.66	48	351	0.8%	3.68 [1.01, 13.40]	2015
Ho 2015	0.424	0.363	41	148	2.5%	1.53 [0.75, 3.11]	2015
Jiang 2015	0.693	0.097	458	672	20.6%	2.00 [1.65, 2.42]	2015
Simon 2016	1.717	0.659	13	121	0.8%	5.57 [1.53, 20.26]	2016
Lin 2016	0.413	0.142	479	488	12.6%	1.51 [1.14, 2.00]	2016
Subtotal (95% CI)			3850	5043	83.2%	1.84 [1.64, 2.07]	
Heterogeneity: Tau² = 0.00; Chi² = 10.86, df = 10 (P = 0.37); I² = 8%							
Test for overall effect: Z = 10.29 (P < 0.00001)							
1.10.2 CSS							
Li 2013	0.402	0.115	1457	1547	16.8%	1.49 [1.19, 1.87]	2013
Subtotal (95% CI)			1457	1547	16.8%	1.49 [1.19, 1.87]	
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.50 (P = 0.0005)							
Total (95% CI)			5307	6590	100.0%	1.78 [1.58, 1.99]	
Heterogeneity: Tau² = 0.01; Chi² = 13.61, df = 11 (P = 0.26); I² = 19%							
Test for overall effect: Z = 9.74 (P < 0.00001)							
Test for subgroup differences: Chi² = 2.60, df = 1 (P = 0.11), I² = 61.5%							




Experimental
Control
Hazard Ratio
Hazard Ratio
Study or Subgroup
log[Hazard Ratio]
SE
Total
Total
Weight
IV, Random, 95% CI
Year
IV, Random, 95% CI
1.15.1 OS
Liu 2013 0.706 0.187 210 210 8.4% 2.03 [1.40, 2.92] 2013
Unal 2013 0.626 0.226 81 94 7.6% 1.87 [1.20, 2.91] 2013
Li 2015(i) 0.0029 0.0005 208 243 11.3% 1.00 [1.00, 1.00] 2015
Cannon 2015 1.386 0.508 28 59 3.2% 4.00 [1.48, 10.82] 2015
Wu 2015 0.076 0.2 366 366 8.1% 1.08 [0.73, 1.60] 2015
Martin 2015 0.457 0.198 114 124 8.2% 1.58 [1.07, 2.33] 2015
Nakamura 2015(i) 1.436 0.658 32 32 2.2% 4.20 [1.16, 15.27] 2015
Langsenlehner 2015(i) 0.626 0.309 65 374 5.9% 1.87 [1.02, 3.43] 2015
Hong 2015 -0.025 0.112 892 919 10.1% 0.98 [0.78, 1.21] 2015
Jiang 2015(iii) 0.604 0.182 137 1261 8.6% 1.83 [1.28, 2.61] 2015
Kou 2016 -0.041 0.147 249 306 9.4% 0.96 [0.72, 1.28] 2016
Li 2016 0.82 0.285 86 110 6.3% 2.27 [1.30, 3.97] 2016
Subtotal (95% CI) 2468 4098 89.3% 1.49 [1.20, 1.84]
Heterogeneity: Tau² = 0.09; Chi² = 62.63, df = 11 (P < 0.00001); I² = 82%
Test for overall effect: Z = 3.63 (P = 0.0003)
1.15.2 CSS
Jiang 2015(iii) 0.61 0.192 125 1261 8.3% 1.84 [1.26, 2.68] 2015
Langsenlehner 2015(i) 1.384 0.618 18 374 2.4% 3.99 [1.19, 13.40] 2015
Subtotal (95% CI) 143 1635 10.7% 2.17 [1.17, 4.03]
Heterogeneity: Tau² = 0.09; Chi² = 1.43, df = 1 (P = 0.23); I² = 30%
Test for overall effect: Z = 2.45 (P = 0.01)
Total (95% CI) 2611 5733 100.0% 1.56 [1.26, 1.93]
Heterogeneity: Tau² = 0.10; Chi² = 77.62, df = 13 (P < 0.00001); I² = 83%
Test for overall effect: Z = 4.12 (P < 0.0001)
Test for subgroup differences: Chi² = 1.27, df = 1 (P = 0.26), I² = 21.5%
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]