# Staging the tumor and staging the host: a two centre, two country comparison of systemic inflammatory responses of patients undergoing resection of primary operable colorectal cancer

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**Tumor Markers and Signatures**

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Abstract

### Background

How systemic inflammation-based prognostic scores such as the modified Glasgow Prognostic Score (mGPS) and neutrophil:lymphocyte ratio (NLR) differ across populations of patients with colorectal cancer (CRC) remains unknown. The present study examined the mGPS and NLR in patients from United Kingdom (UK) and Japan.

### Methods

Patients undergoing resection of TNM I-III CRC in two centres in the UK and Japan were included. Differences in clinicopathological characteristics and mGPS (0-CRP≤10mg/L, 1-CRP>10mg/L, 2-CRP>10mg/L, albumin<35g/L) and NLR (≤5/>5) were examined.

### Results

Patients from UK (*n*=581) were more likely to be female, high ASA and BMI, present as an emergency (all *P*<0.01) and have higher T stage compared to those from Japan (*n*=559). After controlling for differences in tumor and host characteristics, patients from Japan were less likely to be systemically inflamed (OR: mGPS: 0.37, 95%CI 0.27-0.50, *P*<0.001; NLR: 0.53, 95%CI 0.35-0.79, *P*=0.002).

## Conclusion

Systemic inflammatory responses differ between populations with colorectal cancer. Given their prognostic value, reporting of systemic inflammation-based scores should be incorporated into future studies reporting patient outcomes.

**Summary:** Although the systemic inflammatory response is recognised as a prognostic factor in patients with colorectal cancer, it is not clear how these may differ between distinct geographical populations. The present study examines differences in the prevalence of elevated systemic inflammatory responses (modified Glasgow Prognostic Score and neutrophil:lymphocyte ratio) between two populations undergoing resection of colorectal cancer in the United Kingdom and Japan.

**Keywords:** colorectal cancer; systemic inflammation; systemic inflammatory response

## Introduction

Colorectal cancer is the third most commonly diagnosed cancer worldwide (1). Although prognosis of patients with early stage disease may be excellent, ultimately 40% of patients across all disease stages die from their disease within five years (2). Staging and additional treatment is primarily based upon assessment of pathological characteristics of the tumor, with the presence of regional lymph node metastases (TNM stage III) an indication for adjuvant chemotherapy. Similarly, other pathological characteristics, such as venous invasion, may also identify patients with high-risk, node negative disease likely to benefit from chemotherapy (3).

In addition to tumor-based characteristics, the host systemic inflammatory response is now recognised as an important determinant of disease progression (4). Assessment of the host systemic inflammatory response, utilising routinely measured circulating biomarkers, such as acute phase proteins and components of the differential white cell count (5), has prognostic value across a number of cancers, and several inflammation-based prognostic scores have been proposed to this effect.

One such score is the modified Glasgow Prognostic Score (mGPS), a cumulative score based on pre-operative serum concentrations of the routinely measured acute phase proteins C-reactive protein (CRP) and albumin (6). In patients with colorectal cancer, the mGPS has complimentary prognostic value to routine TNM-based staging of patients undergoing resection of stage I-III disease, and may potentially select for patients with stage III colon cancer less likely to derive benefit from adjuvant chemotherapy (7). Therefore, it is of interest that the mGPS has been validated internationally in patients with colorectal cancer (6, 8). Similarly, the systemic inflammation-based neutrophil: lymphocyte ratio (NLR), has been

shown to hold independent prognostic value in patients with colorectal cancer internationally (8-10). Given their routine availability, objectivity and potential role as both prognostic and predictive markers, such inflammation-based scores would be a useful adjunct to the routine staging of patients with colorectal cancer.

However, although individual studies and pooled analyses have confirmed the prognostic value of both the mGPS and NLR in patients from distinct ethnic populations (7-13), it is recognised that ethnicity itself may confound the presence of a systemic inflammatory response. For example, population studies have found individuals of Black and South Asian origin have higher CRP concentrations than those of Caucasian descent (14-16), whereas individuals of East Asian heritage have consistently been reported to having significantly lower concentrations (17-19). Although studied in healthy subjects and cardiovascular disease screening programmes, it is not clear whether the presence of a cancer-associated systemic inflammatory response similarly differs with ethnicity. Given the prognostic implications, it would be of interest to examine whether the prevalence of an elevated systemic inflammatory response was comparable or varied across different ethnic populations after controlling for clinical and pathological characteristics. Also, if different, it would suggest that routine reporting of the systemic inflammatory response would be necessary alongside TNM-based reporting to allow for comparison of both disease stage and outcomes. Indeed there is some evidence that the proportion of patients with elevated prognostic scores varies with ethnicity in patients with cancer (20). However, to our knowledge the basis of this observation is not clear since a number of potential confounding clinicopathological factors have not been examined. Many Asian research groups (in particular in Japan) have confirmed the prognostic value of systemic inflammation-based prognostic scores. As such, it is of interest to compare, in detail, patients with colorectal cancer from the UK and Japan.

Therefore, using two cohorts of patients in which the mGPS has previously been shown to hold prognostic value (7, 12), the aim of the present study was to compare systemic inflammatory profiles across two distinct populations of patients undergoing resection of stage I-III colorectal cancer in the United Kingdom (UK) and Japan.

## Methods

### UK cohort

Patients from a single surgical unit at Glasgow Royal Infirmary, UK, (GRI) were identified from a prospectively collected database of elective and emergency colorectal cancer resections. For the purposes of the present study, consecutive patients who on the basis of preoperative staging and intra-operative findings had undergone potentially curative resection of TNM stage I-III colorectal adenocarcinoma between January 1997 and May 2013 were included. Patients with inflammatory bowel disease-related cancer, or who received neoadjuvant chemoradiotherapy were excluded.

Patients undergoing elective resection had differential white cell count, serum CRP and albumin measured routinely at preoperative assessment within 30 days of surgery, whereas patients undergoing emergency resection had values on admission recorded. Body mass index (BMI) was recorded at time of admission, and categorised using World Health Organisation classification. Comorbidity was measured using American Society of Anaesthesiologists' (ASA) grade, which was recorded at time of surgery. Tumors were staged according to the fifth edition of the TNM classification as is current practice in the UK (21). Elastica staining has been used routinely in GRI since 2003, with selected retrospective staining performed on a cohort of patients before this date for a previous study (3). West of Scotland Research Ethics Committee approved the study.

**Japanese cohort**

Patients were identified from a prospectively maintained database of elective and emergency colorectal cancer resections performed by a single surgical team in the Department of Gastroenterological Surgery, Dokkyo Medical University, Japan (DMU). For the present study, patients who underwent potentially curative resection of TNM stage I-III colorectal adenocarcinoma between November 2005 to December 2015 were included. Exclusion criteria were identical to those applied to the GRI cohort, with pre-operative measurement of differential white cell count, CRP and albumin performed on day of admission. Both BMI and ASA grade were recorded at time of admission. Patients were staged according to the seventh edition of the TNM classification (22). Elastica staining was not used routinely for detection of venous invasion, and was only used at the discretion of the reporting pathologist. The local institutional review board approved the study.

**Systemic inflammatory scores**

The mGPS was calculated for both cohorts as previously described (6). Patients with CRP≤10mg/L were given a score of 0, patients with CRP>10mg/L a score of 1, and patients with CRP>10mg/L and albumin<35g/L a score of 2. On the basis of a previous literature review, a NLR>5 was considered elevated (23).

**Statistical analysis**

The relationship between study cohort, mGPS and clinicopathological characteristics was examined using the $\chi^2$ method for linear trend. In order to adjust for multiple comparisons, a $P<0.01$ was considered significant. Univariate binary logistic regression was used to examine the relationship between clinicopathological characteristics, including study cohort,

and the presence of a systemic inflammatory response (mGPS≥1 or NLR>5), calculating odds ratio (OR) and 95% confidence intervals (95% CI). Clinicopathological factors associated with the presence of a systemic inflammatory response that on univariate analysis had a $P$ <0.05 were taken into a multivariate model using a backward conditional model to identify independently significant factors, with $P$≤0.05 considered statistically significant. All analyses were performed using SPSS version 22.0 for Mac (IBM SPSS, IL, USA).

**Results**

The final study population comprised 1140 patients (581 patients from GRI and 559 patients from DMU). Data on BMI were missing for 175 patients from GRI. Data on BMI, lymph node yield, venous invasion and margin involvement were missing for 4, 2, 6 and 8 patients respectively from DMU.

A comparison of characteristics of the two cohorts is displayed in Table 1. Patients from GRI were more likely to have a high ASA grade and BMI, and present as an emergency ($P$<0.001). Patients from DMU were more likely to undergo resection for rectal cancer ($P$=0.001). N stage and lymph node yield did not differ significantly; patients from GRI were more likely to have advanced disease as evidenced by T stage, peritoneal and margin involvement and TNM stage (due to higher proportion of stage II disease). Conversely patients from DMU were more likely to have evidence of venous invasion and tumour perforation. Patients from GRI were more likely to show evidence of an elevated systemic inflammatory response as measured by both mGPS (mGPS≥1: 41% vs. 16%, $P$<0.001) and NLR (19% vs. 12%, $P$=0.001).

Binary logistic regression analysis was subsequently performed to identify host and tumor characteristics, including study cohort, associated with the presence of an elevated systemic inflammatory response (Table 2). On univariate analysis, advancing age, ASA grade, emergency presentation, T stage, margin involvement, peritoneal involvement and tumor perforation were associated with mGPS≥1 (all $P$<0.01), whereas patients with a rectal primary and from DMU were less likely to have an elevated mGPS (both $P$<0.001). On multivariate analysis, when considering only variables with $P$≤0.05 on univariate analysis, advancing age (OR 1.34, $P$=0.002), ASA grade (OR 1.25, $P$=0.046), emergency presentation

(OR 3.07, *P*<0.001), rectal primary (OR 0.57, *P*=0.001), T stage (OR 1.62, *P*<0.001), margin involvement (OR 2.24, *P*=0.011), tumor perforation (OR 2.28, *P*=0.024) and study cohort (DMU: OR 0.37, *P*<0.001) were independently associated with the presence of an elevated mGPS.

When the relationship between host and tumor characteristics associated with the presence of an elevated NLR was examined (Table 2), age (OR 1.46, *P*=0.001), BMI (OR 0.59, *P*<0.001), emergency presentation (OR 3.11, *P*<0.001), T stage (OR 1.24, *P*=0.043) and study cohort (DMU: OR 0.53, *P*=0.002) were independently associated with NLR>5.

To control for the effect of tumor location and emergency presentation on the presence of a systemic inflammatory response, binary logistic regression was performed on patients undergoing elective resection of stage I-III colon cancer only (Table 3). On multivariate analysis, age (OR 1.51, *P*<0.001), T stage (OR 1.77, *P*<0.001), tumor perforation (OR 4.91, *P*=0.005) and study cohort (DMU: OR 0.34, *P*<0.001) were independently associated with the presence of an elevated mGPS. Age (OR 1.47, *P*=0.004), T stage (OR 1.45, *P*=0.009), tumor perforation (OR 5.72, *P*=0.001) and study cohort (DMU: OR 0.57, *P*=0.013) were independently associated with the presence of an elevated NLR.

Finally, how the presence of an elevated systemic inflammatory response differed across different disease stages between the two cohorts was examined (Table 4). Patients from GRI were more likely to exhibit an elevated mGPS when stratified by T stage; although statistically significant for patients with T2-4 disease (all *P*<0.05), this failed to reach statistical significance for patients with T1 disease (*P*=0.184). When stratified by TNM stage, patients from GRI were more likely to exhibit an elevated mGPS. Although patients

from GRI were more likely to have an elevated NLR, this only reached statistical significance for patients with T3 disease ($P$=0.019).

**Discussion**

In the present study, there were significant differences in both patient and tumor-related characteristics of patients undergoing potentially curative resection of stage I-III colorectal cancer in two single institutions in the UK and Japan. Furthermore, systemic inflammatory profiles differed in these two patient cohorts, independent of other tumor and host factors. Therefore, the results of the present study suggest that the magnitude of the pre-operative systemic inflammatory response is dependent, at least in part, on racial and ethnic differences in the tumor host response. Given the adverse effect of the systemic inflammatory response on prognosis, these findings add further support to the routine reporting of systemic inflammation-based prognostic scores alongside routine TNM- based staging, particularly when comparing outcomes globally.

Patients from GRI and DMU differed with respect to tumor characteristics. Patients from GRI were more likely to undergo resection for tumors with a higher T stage, a tumor characteristic which has remained stable across different iterations of TNM staging. This preponderance towards a higher T stage would account for differences in pathological characteristics such as the increased rates of peritoneal involvement observed in patients from GRI. However, it was of interest that patients from DMU were more likely to have evidence of venous invasion; this difference persisted even when analysis was restricted to patients from GRI following the introduction of routine elastica staining ($P<0.001$). Indeed, given the routine use of elastica staining in GRI but not DMU, it would be expected that rates of venous invasion would be higher in the former, contrary to the present results. However, other differences in pathological techniques and reporting may be important; for example, sampling technique and thoroughness of pathological assessment (24), or the definition of venous invasion as either the presence of extra-mural invasion only or both extra- and intra-

mural invasion (24, 25). Nevertheless, it is worth noting that even in the GRI cohort, detection of venous invasion was still greater than the minimum audit standard of 30% recommended by the Royal College of Pathologists (21). Further work is required to understand the differences in tumor characterisation in the UK and Japan.

With reference to patient-related characteristics, GRI patients were more likely to be obese, have a higher burden of comorbidity and be more likely to present as an emergency. Such factors have previously been identified as poor prognostic factors in patients undergoing resection of colorectal cancer; for example, emergency presentation is associated with a two-fold increased risk of cancer death (26). Similarly, comorbidity and physiological status are independent determinants of survival (27). Although it would be of interest to examine more objective measures of comorbidity, the present results highlight the importance of assessment of not only tumor, but also host characteristics when comparing outcomes.

Nevertheless, even after controlling for clinicopathological characteristics, patients from the UK were more likely to exhibit elevated systemic inflammatory responses as measured by both mGPS and NLR. This is consistent with previous studies which have identified lower circulating CRP concentrations in healthy individuals of East Asian origin compared to those of European descent (17-19, 28). Similarly, the NLR has been shown to differ with race/ ethnicity (29). It was of interest that increasing T stage was associated with increasing prevalence of elevated systemic inflammatory responses in both cohorts. We have previously reported that an elevated mGPS may be observed in 50% of patients with T4 tumors compared to only 25% of those with T1 disease (30). Despite this, across all stages there remained a consistently higher proportion of patients from GRI with elevated mGPS. Although this failed to reach statistical significance for patient with T1 tumours, this likely reflects the small number of patients in this subgroup ($n$=28 and $n$=88 for GRI and DMU

respectively). As such, given the relatively small proportion of patients in this subgroup who would be expected to be systemically inflamed, the present study was likely underpowered to test for statistical significance.

Although the increased prevalence of an elevated systemic inflammatory response may be explained by differences in socioeconomic and lifestyle characteristics, markers of inflammation differ widely in individuals of different ethnicity resident in the same geographical location, thereby limiting the role of environmental factors and implicating other, intrinsic, factors (16, 28). Circulating CRP levels are partly determined by genetic polymorphisms (31). Several associated single nucleotide polymorphisms (SNPs) have been identified (32-34), with a difference in not only their prevalence, but also their subsequent effect on CRP concentrations across different ethnic populations (33). A number of these SNPs have been confirmed as potential determinants of CRP concentrations in individuals of Asian descent (34), and the differences observed presently may reflect such underlying genetic determinants. However, previous studies have generally considered mean population CRP concentrations in the region of 1-5mg/L, rather than >10mg/L as in the present study. Furthermore, in a prior study of patients with advanced cancer, no relationship between a number of candidate SNPs associated with inflammation and elevated CRP concentrations in the context of the cancer cachexia syndrome were identified (35).

A plausible mechanism that may explain the difference both systemic inflammatory responses and tumor characteristics is differing tumor biology. It is now accepted that colorectal cancers encompass varying genetic and molecular entities, and such characteristics may dictate many facets of tumor behaviour, including tumor-associated inflammation and the presence of lymphovascular invasion (36). For example, it has been reported rates of mismatch repair deficient colorectal cancer are lower in Japan compared to Western countries

countries (37). Moreover, the presence of mismatch repair deficiency has previously been associated with the presence of an elevated systemic inflammatory response in patients with stage I-III colorectal cancer (38). Therefore, in-depth studies comparing molecular characteristics, and utilising standardised pathological techniques and staging systems, is warranted.

The present study has a number of limitations. Differences in TNM staging between centres may confound the results. However, N stage was not associated with systemic inflammatory response in either cohort. Furthermore, migration from the 5$^{th}$ to 7$^{th}$ edition would be expected to account for an upstaging from node negative to node positive disease in less than 3% of cases, with little subsequent effect on prognosis (39, 40). The present study did not consider tumor molecular characteristics, such as mismatch repair deficiency, however, few molecular characteristics, except for mismatch repair status and *KRAS/BRAF* status have translated into routine practice. Due to limitations in the data collected from both centres it is not possible to analyse the data specifically by ethnicity. However, the population served by Glasgow Royal Infirmary, UK, is predominantly Caucasian (41). Similarly, the population served by Dokkyo Medical University, Japan, is predominantly east Asian (42). Therefore, although ethnicity was not specifically controlled for in each centre, it is unlikely that it was a major confounder in the present results.

The results of the present study identify several points for further consideration. Firstly, the difference in systemic inflammatory profiles between geographically distinct populations raises issue with respect to the reporting of colorectal cancer outcomes. Whereas TNM staging has been standardised internationally to aid in the recruitment to and reporting of clinical trials, similar should occur with respect to the systemic inflammatory response. Given the previously reported perceived lack of efficacy of adjuvant chemotherapy in the

systemically inflamed patient (7), such measures should be routinely reported to allow appropriate interpretation of clinical trial data. However, whether a universally standardised threshold (i.e. CRP>10mg/L), or thresholds based on ethnicity should be employed, remains to be investigated. Indeed, previous studies in East Asia and Japan have reported the prognostic value of CRP thresholds of 3, 5 and 7.5mg/L (20). Although utilising a lower threshold would accommodate for the lower proportion of patients in Japan who are systemically inflamed, it remains to be determined if prognostic value is comparable to a CRP>10mg/l in a Western population. Finally, routine reporting of the systemic inflammatory response may identify patients who could potentially benefit from novel treatment strategies targeting the systemic inflammatory response. For example, nonsteroidal anti-inflammatory drugs are associated with improved survival of patients with colorectal cancer, potentially through attenuation of tumor-associated inflammation (43).

In conclusion, using two geographically distinct populations, the results of the present study identified differences in the systemic inflammatory responses of patients undergoing potentially curative resection of stage I-III colorectal cancer. Such measures should be considered in future studies reporting outcome of patients undergoing resection of primary operable colorectal cancer.

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**Table 1.** Comparison of clinicopathological characteristics of patients from Glasgow Royal Infirmary, United Kingdom, and Dokkyo Medical University, Japan, undergoing potentially curative primary resection of stage I-III colorectal cancer

| Clinicopathological Characteristics | | GRI cohort (*n*=581) (%) | DMU cohort (*n*=559) (%) | *P* |
|---|---|---|---|---|
| **Age** | | | | 0.188 |
| | **<65** | 185 (32) | 211 (38) | |
| | **65-74** | 193 (33) | 156 (28) | |
| | **>75** | 203 (35) | 192 (34) | |
| **Sex** | | | | 0.005 |
| | **Female** | 265 (46) | 209 (37) | |
| | **Male** | 316 (54) | 350 (63) | |
| **ASA grade** | | | | <0.001 |
| | **I** | 69 (12) | 100 (18) | |
| | **II** | 245 (42) | 390 (69) | |
| | **III** | 237 (41) | 68 (12) | |
| | **IV** | 30 (5) | 1 (0) | |
| **BMI (961)** | | | | <0.001 |
| | **<18.5** | 17 (4) | 76 (14) | |
| | **18.5-24.9** | 155 (38) | 356 (64) | |
| | **25.-29.9** | 141 (35) | 106 (19) | |
| | **≥30** | 93 (23) | 17 (3) | |
| **Presentation** | | | | <0.001 |
| | **Elective** | 531 (91) | 546 (98) | |
| | **Emergency** | 50 (9) | 13 (2) | |
| **Tumor site** | | | | 0.001 |
| | **Colon** | 425 (73) | 358 (64) | |
| | **Rectum** | 156 (27) | 201 (36) | |
| **T stage** | | | | <0.001 |
| | **1** | 28 (5) | 88 (16) | |
| | **2** | 59 (10) | 70 (12) | |
| | **3** | 322 (55) | 308 (55) | |
| | **4** | 172 (30) | 93 (17) | |
| **N stage** | | | | 0.854 |
| | **0** | 358 (62) | 343 (62) | |
| | **1** | 166 (29) | 157 (28) | |
| | **2** | 57 (10) | 58 (10) | |
| **TNM stage** | | | | 0.005 |
| | **I** | 72 (12) | 140 (25) | |
| | **II** | 286 (49) | 202 (36) | |
| | **III** | 223 (38) | 217 (39) | |
| **Venous invasion (1134)** | | | | <0.001 |
| | **No** | 292 (50) | 153 (28) | |
| | **Yes** | 289 (50) | 400 (72) | |
| **Less than 12 lymph nodes retrieved (1138)** | | | | 0.835 |
| | **No** | 414 (71) | 400 (72) | |
| | **Yes** | 167 (29) | 157 (28) | |
| **Margin involvement (1132)** | | | | 0.009 |
| | **No** | 541 (93) | 532 (97) | |
| | **Yes** | 40 (7) | 19 (3) | |
| **Peritoneal involvement** | | | | <0.001 |
| | **No** | 429 (74) | 530 (95) | |
| | **Yes** | 152 (26) | 29 (5) | |
| **Tumor perforation** | | | | 0.008 |
| | **No** | 563 (97) | 523 (94) | |
| | **Yes** | 18 (3) | 36 (6) | |

| | | | | |
|---|---|---|---|---|
| **mGPS** | | | | <0.001 |
| | **0** | 345 (59) | 469 (84) | |
| | **1** | 141 (24) | 29 (5) | |
| | **2** | 95 (17) | 61 (11) | |
| **NLR** | | | | 0.001 |
| | **≤5** | 469 (81) | 493 (88) | |
| | **>5** | 112 (19) | 66 (12) | |

(*n*) given when incomplete data available. *P*-value given for $\chi^2$ method for linear trend

**Table 2.** The relationship between study cohort, host and tumor characteristics and the presence of an elevated systemic inflammatory response in patients undergoing resection of stage I-III colorectal cancer

| | Univariate OR (95% CI) | *P* | Multivariate OR (95% CI) | *P* |
|---|---|---|---|---|
| **Modified Glasgow Prognostic Score (0 vs. ≥1)** | | | | |
| **Age (<65/ 65-74/ >74)** | 1.43 (1.22-1.68) | <0.001 | 1.34 (1.12-1.61) | 0.002 |
| **Sex (female/ male)** | 0.79 (0.61-1.02) | 0.074 | - | - |
| **ASA grade (I/ II/ III/ IV)** | 1.94 (1.60-2.35) | <0.001 | 1.25 (1.00-1.57) | 0.046 |
| **BMI (<18.5/ 18.5-24.9/ 25.-29.9/ ≥30)** | 1.05 (0.88-1.25) | 0.608 | - | - |
| **Presentation (elective/ emergency)** | 7.71 (4.34-13.66) | <0.001 | 3.07 (1.64-5.75) | <0.001 |
| **Tumor site (colon/ rectum)** | 0.46 (0.34-0.62) | <0.001 | 0.57 (0.41-0.80) | 0.001 |
| **T stage (1/ 2/ 3/ 4)** | 2.17 (1.80-2.62) | <0.001 | 1.62 (1.33-1.98) | <0.001 |
| **N stage (0/ 1/ 2)** | 1.01 (0.83-1.22) | 0.944 | - | - |
| **Less than 12 nodes (no/ yes)** | 0.97 (0.73-1.29) | 0.824 | - | - |
| **Venous invasion (absent/ present)** | 0.83 (0.64-1.08) | 0.160 | - | - |
| **Margin involvement (absent/ present)** | 3.67 (2.15-6.26) | <0.001 | 2.24 (1.21-4.16) | 0.011 |
| **Peritoneal involvement (absent/ present)** | 3.68 (2.65-5.11) | <0.001 | - | 0.908 |
| **Tumor perforation (absent/ present)** | 2.43 (1.40-4.22) | 0.002 | 2.28 (1.11-4.67) | 0.024 |
| **Hospital (GRI/ DMU)** | 0.28 (0.21-0.37) | <0.001 | 0.37 (0.27-0.50) | <0.001 |
| **Neutrophil: lymphocyte ratio (≤5 vs. >5)** | | | | |
| **Age (<65/ 65-74/ >74)** | 1.56 (1.28-1.90) | <0.001 | 1.46 (1.16-1.83) | 0.001 |
| **Sex (female/ male)** | 0.97 (0.70-1.35) | 0.870 | - | - |
| **ASA grade (I/ II/ III/ IV)** | 1.58 (1.26-1.98) | <0.001 | - | 0.239 |
| **BMI (<18.5/ 18.5-24.9/ 25.-29.9/ ≥30)** | 0.66 (0.52-0.84) | 0.001 | 0.59 (0.46-0.77) | <0.001 |
| **Presentation (elective/ emergency)** | 4.94 (2.92-8.37) | <0.001 | 3.11 (1.42-6.80) | <0.001 |
| **Tumor site (colon/ rectum)** | 0.61 (0.42-0.89) | 0.010 | - | 0.414 |
| **T stage (1/ 2/ 3/ 4)** | 1.76 (1.41-2.19) | <0.001 | 1.29 (1.01-1.65) | 0.043 |
| **N stage (0/ 1/ 2)** | 1.15 (0.91-1.44) | 0.245 | - | - |
| **Less than 12 nodes (no/ yes)** | 1.31 (0.93-1.85) | 0.120 | - | - |
| **Venous invasion (absent/ present)** | 0.87 (0.63-1.21) | 0.407 | - | - |
| **Margin involvement (absent/ present)** | 2.31 (1.28-4.16) | 0.005 | - | 0.126 |
| **Peritoneal involvement (absent/ present)** | 2.39 (1.64-3.48) | <0.001 | - | 0.889 |
| **Tumor perforation (absent/ present)** | 2.89 (1.60-5.22) | <0.001 | - | 0.212 |
| **Hospital (GRI/ DMU)** | 0.56 (0.40-0.78) | 0.001 | 0.53 (0.35-0.79) | 0.002 |

**Table 3.** The relationship between study cohort, host and tumor characteristics and the presence of an elevated systemic inflammatory response in patients undergoing elective resection of stage I-III colon cancer.

| | Univariate OR (95% CI) | *P* | Multivariate OR (95% CI) | *P* |
|---|---|---|---|---|
| **Modified Glasgow Prognostic Score (0 vs. ≥1)** | | | | |
| **Age (<65/ 65-74/ >74)** | 1.44 (1.19-1.75) | <0.001 | 1.51 (1.22-1.86) | <0.001 |
| **Sex (female/ male)** | 0.88 (0.64-1.21) | 0.427 | - | - |
| **ASA grade (I/ II/ III/ IV)** | 1.77 (1.40-2.25) | <0.001 | - | 0.101 |
| **BMI (<18.5/ 18.5-24.9/ 25.-29.9/ ≥30)** | 1.00 (0.80-1.24) | 0.986 | - | - |
| **T stage (1/ 2/ 3/ 4)** | 2.03 (1.62-2.53) | <0.001 | 1.77 (1.40-2.24) | <0.001 |
| **N stage (0/ 1/ 2)** | 0.90 (0.70-1.16) | 0.427 | - | - |
| **Less than 12 nodes (no/ yes)** | 0.99 (0.69-1.40) | 0.941 | - | - |
| **Venous invasion (absent/ present)** | 0.91 (0.66-1.25) | 0.543 | - | - |
| **Margin involvement (absent/ present)** | 4.41 (1.92-10.14) | <0.001 | - | 0.121 |
| **Peritoneal involvement (absent/ present)** | 2.98 (2.00-4.46) | <0.001 | - | 0.841 |
| **Tumor perforation (absent/ present)** | 4.90 (1.82-13.24) | 0.002 | 4.91 (1.62-14.90) | 0.005 |
| **Hospital (GRI/ DMU)** | 0.31 (0.22-0.43) | <0.001 | 0.34 (0.23-0.48) | <0.001 |
| **Neutrophil: lymphocyte ratio (≤5 vs. >5)** | | | | |
| **Age (<65/ 65-74/ >74)** | 1.42 (1.11-1.83) | 0.006 | 1.47 (1.13-1.90) | 0.004 |
| **Sex (female/ male)** | 1.14 (0.76-1.71) | 0.537 | - | - |
| **ASA grade (I/ II/ III/ IV)** | 1.54 (1.15-2.07) | 0.004 | - | 0.206 |
| **BMI (<18.5/ 18.5-24.9/ 25.-29.9/ ≥30)** | 0.76 (0.57-1.02) | 0.066 | - | - |
| **T stage (1/ 2/ 3/ 4)** | 1.66 (1.27-2.18) | <0.001 | 1.45 (1.10-1.91) | 0.009 |
| **N stage (0/ 1/ 2)** | 0.96 (0.70-1.32) | 0.806 | - | - |
| **Less than 12 nodes (no/ yes)** | 1.31 (0.85-2.02) | 0.220 | - | - |
| **Venous invasion (absent/ present)** | 0.81 (0.54-1.23) | 0.324 | - | - |
| **Margin involvement (absent/ present)** | 3.31 (1.43-7.71) | 0.005 | - | 0.290 |
| **Peritoneal involvement (absent/ present)** | 2.31 (1.44-3.70) | 0.001 | - | 0.523 |
| **Tumor perforation (absent/ present)** | 5.97 (2.31-15.40) | <0.001 | 5.72 (2.08-15.73) | 0.001 |
| **Hospital (GRI/ DMU)** | 0.52 (0.34-0.80) | 0.003 | 0.57 (0.37-0.89) | 0.013 |

**Table 4.** Comparison of the prevalence of an elevated systemic inflammatory response in patients undergoing potentially curative, elective resection of colon cancer in Glasgow Royal Infirmary and Dokkyo Medical University, stratified by disease stage.

| | T stage | | | | TNM stage | | |
|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **I** | **II** | **III** |
| | **Percentage of patients with mGPS≥1** | | | | | | |
| **GRI** | 15.8% | 20.0% | 42.2% | 50.5% | 18.4% | 49.0% | 38.2% |
| **DMU** | 6.2% | 3.2% | 19.8% | 30.2% | 5.7% | 27.9% | 15.4% |
| ***P*** | 0.184 | 0.039 | <0.001 | 0.010 | 0.021 | <0.001 | <0.001 |
| | **Percentage of patients with NLR>5** | | | | | | |
| **GRI** | 10.5% | 8.6% | 18.5% | 25.2% | 8.2% | 22.4% | 18.3% |
| **DMU** | 4.6% | 12.9% | 10.2% | 19.0% | 6.9% | 14.0% | 10.8% |
| ***P*** | 0.341 | 0.571 | 0.019 | 0.353 | 0.787 | 0.057 | 0.084 |

Data displayed as percentage of patients in each group with elevated systemic inflammatory response as measured by mGPS and NLR