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Evaluation of the prognostic value of systemic inflammation and socioeconomic deprivation in patients with resectable colorectal liver metastases

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ABSTRACT

Background: There is increasing evidence that the presence of a pre-operative systemic inflammatory response (SIR) independently predicts poor long-term outcome in patients with colorectal cancer (CRC). Socioeconomic deprivation was reported to correlate with the presence of the SIR and to independently predict poor outcome following primary CRC resection. The aim of this study was to determine the prognostic value of pre-operative systemic inflammatory biomarkers and socioeconomic deprivation in patients undergoing resection of colorectal liver metastases (CLM) and to examine correlations between these variables in this context.

Patients and methods: Clinicopathological data, including the Memorial Sloan-Kettering Cancer Centre Clinical Risk Score (CRS), were obtained from a prospectively maintained database for 174 patients who underwent hepatectomy for CLM between January 2000 and December 2005 at a single United Kingdom (UK) tertiary referral hepatobiliary centre. Inflammatory biomarkers (total and differential leucocyte counts, neutrophil–lymphocyte ratio, platelet count, haemoglobin, and serum albumin) were measured from routine pre-operative blood tests. Socioeconomic deprivation was measured using the Carstairs deprivation score.

Results: On multivariable analysis, poor CRS (3–5), high neutrophil count (>6.0 × 10^9/l) and low serum albumin (<40 g/dl) were the only independent predictors of shortened overall survival following metastasectomy, with neutrophil count representing the greatest relative risk of death. These factors were also the only independent predictors of shortened disease-free survival following hepatectomy. Socioeconomic deprivation was associated with neither systemic inflammation nor long-term outcome in this context.

Conclusions: The presence of a pre-operative systemic inflammatory response, but not socioeconomic deprivation, independently predicts shortened survival following resection of CLM.

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1. Introduction

Hepatectomy offers the only hope of cure for patients with colorectal liver metastases (CLM), resulting in 5-year survival rates of 30–50%.[1–3] Recurrence in the liver that is remnant and/or extrahepatic sites is common, however, affecting up to two-thirds of patients despite optimal metastasectomy.[3] The ability to predict individual patient prognosis prior to hepatectomy is desirable in order to guide surgical and chemotherapeutic treatment according to individual recurrence risk. This is particularly pertinent given the increasing rates of hepatic resection for CLM. Clinicopathological factors have been shown to predict recurrence risk following metastasectomy,[1,4] but lack the sensitivity for accurate individual prognostication. The role of molecular tumour biomarkers in determining disease recurrence is also under investigation, but requires further validation.[5]

In addition to intrinsic tumour factors, patient prognosis is also influenced by the host inflammatory response to malignancy, with data supporting a direct role for inflammatory cells and mediators in the promotion of both primary tumour growth and disease dissemination.[6,7] At the local level, the immune response involves infiltration of the tumour environment by both lymphocytes and cells of myeloid lineages.[7,8] This local inflammatory cell infiltration has been shown to have prognostic significance in numerous malignancies, including primary colorectal cancer (CRC).[7,9,10]

A systemic inflammatory response (SIR), more easily assessable pre-operatively, accompanies the local immune response, driven by the production of pro-inflammatory cytokines, including interleukin-1β, interleukin-6 and tumour necrosis factor-α, by both tumour cells and recruited immune cells.[11] These cytokines stimulate the release of acute phase proteins, most notably C-reactive protein (CRP).[11] Elevated CRP has been shown to predict shortened long-term survival in a range of solid and haematological malignancies[12–14] and in CRC, independently predicted decreased survival following both primary tumour and CLM resection.[2,15,16]

Cellular components of the SIR have also been shown to have prognostic significance in malignancy, though published data are scarce compared to that relating to CRP. Elevated neutrophil, monocyte and/or total leucocyte counts have been reported to predict adverse outcome in patients with a variety of solid tumours,[17–19] including primary CRC.[20] In resectable CLM, examination of cellular indices of the SIR has been limited to the assessment of the neutrophil–lymphocyte ratio (NLR), an index derived as a marker of the systemic inflammation associated with cardiovascular disease and critical illness.[21,22] The NLR was recently reported to independently predict poor outcome following hepatectomy for CLM and to do so as well as CRP.[2] Available data suggest, however, that the NLR is not the optimal prognostic cellular index of the SIR in malignancy,[20] due to the frequent lack of association between circulating lymphocyte count and survival in this context.[20,23,24] Indeed, in a recent study of resectable primary CRC, whilst neutrophil count predicted cancer-specific survival, neither lymphocyte count nor the NLR showed any association with the outcome.[20] These results indicate that examination of the prognostic role of individual leucocyte subtypes is also required in the context of resectable CLM.

A further biomarker of systemic inflammation is the 'negative' acute phase protein serum albumin. Hypoalbuminaemia correlates with poor outcome in patients with advanced malignancy,[25] an association presumed to be due to nutritional depletion secondary to the tumour. Recently, however, it has been postulated that hypoalbuminaemia develops secondary to the SIR.[26,27] Hypoalbuminaemia predicts poor outcome in several cancer types,[28] and has been combined with CRP to form inflammatory prognostic scores in a number of malignancies.[20,28,29] The prognostic value of serum albumin and its relationship to other systemic inflammatory biomarkers have yet to be examined in the context of resectable CLM.

Factors influencing malignancy-associated inflammation are poorly understood. Recent data have demonstrated that socioeconomic deprivation is associated with shortened overall and cancer-specific survival in patients with primary CRC.[30,31] Neither clinicopathological factors nor treatment modality explained this correlation, but a significant association was noted between deprivation and the SIR,[30,31] suggesting that the tumour-host response may be altered in deprived patients. The basis for this association is unclear, but it is postulated to relate to the increased rates of smoking and obesity in deprived patients.[32] The association of socioeconomic deprivation with systemic inflammation and prognosis in the context of CLM has yet to be explored.

The primary aim of the current study was, therefore, to validate the prognostic value of systemic inflammatory biomarkers in resectable CLM, including determination of the cellular index with optimum prognostic value. In addition we sought to explore possible correlations between socioeconomic deprivation, systemic inflammation and patient outcome in this context.

2. Patients and methods

All patients who underwent hepatectomy for CLM between January 2000 and December 2005 at a single hepatobiliary tertiary referral centre (Leicester General Hospital, UK) were identified from a hepatobiliary database. During the study period, clinical data had been recorded prospectively in the database. These data were analysed retrospectively, with any additional information gathered from medical records. Radiology reports, pathology results, inpatient records and clinic notes from all follow-up appointments, as well as from any other clinical encounter, were also scrutinised.

Variables constituting the Clinical Risk Score (CRS), devised by the Memorial Sloan-Kettering Cancer Centre,[1] were recorded for each patient. The score is derived from five independent prognostic variables, with each scoring one point: positive nodal status of the primary tumour, disease-free interval from the diagnosis of primary lesion to the discovery of liver metastases of 12 months or less, number of hepatic metastases greater than one, diameter of the largest hepatic tumour greater than 5 cm and pre-operative carcinoembryonic antigen (CEA) level greater than 200 ng/ml. As reported

previously,[33] the number and size of liver metastases were calculated from pre-operative imaging in order to allow pre-operative derivation of the CRS. Other clinicopathological variables recorded, previously shown to have prognostic significance,[3] included age, gender, primary tumour site and the use of adjuvant or neoadjuvant chemotherapy. Haematological variables and serum albumin were obtained from blood tests routinely performed within the 24-h period prior to surgery. At the time of sampling, no patient had clinical evidence of infection or other inflammatory conditions. The Carstairs deprivation score,[34] a UK-based composite score based on four variables (overcrowding, social class, male unemployment and car ownership), was used to stratify cases for the level of socioeconomic deprivation, using 2001 Census data for the UK (Office of National Statistics). A Carstairs score was allocated to each of the individuals based on their enumeration district of residence, which was found by linking with their postcode. Scores can be either positive (more deprived) or negative (less deprived).

Staging protocol prior to hepatectomy included contrast-enhanced multi-slice spiral computerised tomography of the chest, abdomen and pelvis using an iodinated contrast agent, gadolinium-enhanced magnetic resonance imaging of the liver, and staging laparoscopy and intra-operative ultrasound. Standard follow-up surveillance protocol included a post operative clinical review at 6 weeks post surgery, followed by clinical evaluation, routine serum investigations including liver function tests, serum CEA level, and abdominal ultrasound scan performed by a Specialist Consultant Radiologist, all were performed every 3 months for the first year, every 6 months for the second year, and then annually to 5 years post hepatectomy. Abnormal results during routine post operative surveillance triggered further investigation. Development of symptoms prompted review earlier than scheduled. The cause of death was determined from case notes, computerised records and death certificates.

The primary outcome measure was overall survival (as of June 2007). Disease-free survival was considered as the secondary end-point. Patients who died in the hospital following hepatectomy were excluded from the analysis. For staged procedures, variables were recorded prior to the first stage procedure and patients who were inoperable at the attempted second stage were excluded from the analysis. In the case of patients who underwent a repeat liver resection following the diagnosis of operable recurrence, only the initial resection was included in the analysis.

3. Statistics

As reported previously,[20,23] grouping of the variables CRS, leucocyte count, neutrophil count, lymphocyte count, monocyte count, haemoglobin, platelet count, albumin and the NLR was carried out using standard thresholds.[2,12,17,20,23,28,35] For simplicity, high numbers of cells indicate cell numbers higher than the cut-off levels and low numbers of cells indicate cell numbers lower than the cut-off levels. Carstairs deprivation scores were analysed following allocation into established UK-based score quintiles.[34] Continuous variables without predefined cut-offs (eosinophil and basophil counts) were analysed following division into tertiles.

The Chi-squared and Fisher's exact tests were used to analyse for significant associations and differences between subgroups within the cohort. Where variables did not follow a normal distribution, the Mann–Whitney *U* test was applied. Univariate prognostic significance of variables was determined by means of univariate Cox regression analysis, Kaplan–Meier analysis and application of the log-rank test. Multivariable analysis was performed, using all variables with $P < 0.10$ on univariate analysis, through their entry into Cox proportional hazard regression analysis using a stepwise backward procedure. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using Statistical Package for the Social Sciences 14.0® (SPSS, Chicago, IL, USA).

4. Results

A total of 181 patients underwent hepatectomy for CLM over the study period. All resections were performed with curative intent. In-hospital mortality rate following hepatectomy was 2.2% ($n = 4$). Three patients were deemed inoperable at the second stage of an attempted two-stage procedure. One hundred and seventy-four patients were, therefore, eligible for inclusion in the study. Of these patients, 108 (62.1%) had a 'major' resection (resection of more than three Couinaud segments). Neither ablative techniques nor hepatic lymphadenectomy was performed in any case. No patient with synchronous liver metastases had simultaneous resection of primary and metastatic tumours. There were 106 (60.9%) men and 68 (39.1%) women. The mean age at the time of the surgery was 61 years (mean age 60.7 years; range 32–79 years). The median number of tumours on pre-operative imaging was 2 (range 2–12). Tumour size ranged from 5 to 140 mm, with a median size of 40 mm. A poor pre-operative CRS (score 3–5) was recorded in 46.6% of patients ($n = 81$). Seventy-three patients (42.0%) had systemic chemotherapy in the 6 months prior to their liver resection and 67 patients (38.5%) received systemic chemotherapy following metastasectomy.

There was no significant difference in demographic or clinicopathological factors between patients stratified according to any individual haematological parameter or the deprivation score, though high neutrophil count was associated with a trend towards increasing metastasis size ($P = 0.078$) and low albumin was associated with a trend towards increasing number of metastases ($P = 0.093$). Neither deprivation score nor pre-operative chemotherapy correlated with any haematological parameter. Serum albumin showed no significant correlation with any other haematological parameter.

4.1. *Outcome*

The overall median follow-up period was 36 months (range 6–69 months). No patient was lost to follow-up. The 3-year and 5-year overall survival rates for patients undergoing hepatectomy were 48.5% and 36.6%, respectively (median 34 months, 95% confidence interval (CI), 27.3–40.7 months). Similarly, the 3-year and 5-year disease-free survival rates were 31.4% and 25.3%, respectively (median 15 months, 95% CI, 11.5–18.5 months).

The results of univariate and multivariable analyses for overall and disease-free survival are shown in Tables 1 and 2, respectively. On univariate analysis, the following variables were associated with poor overall survival following metastasectomy: number of metastases > 1, poor CRS (Fig. 1), high leucocyte count, high neutrophil count (Fig. 2), high monocyte count, high NLR, high platelet count and low serum albumin (Fig. 3). These same variables, save monocyte count and platelet count, were also associated with shortened disease-free survival following metastasectomy. Neutrophil count was the most significant predictor of both overall and disease-free survival on univariate analysis. Five-year overall survival for patients with a normal neutrophil count was 47.6% compared to 0% in patients with a high neutrophil count ($P < 0.001$, Fig. 2). Other haematological variables, including lymphocyte count, showed no significant correlation with either outcome. No association between Carstairs deprivation score and outcome was demonstrated.

On multivariable analysis (Table 2), poor CRS, high neutrophil count and low serum albumin were all independently associated with the decreased overall survival following metastasectomy, with neutrophil count associated with a greater relative risk of death than the other two factors. These three variables were also the only factors independently associated with disease recurrence following metastasectomy, with all factors presenting a similar relative risk of recurrence.

4.2. *Prognostic score*

As reported previously,[17,19,23,36] a simple prognostic score for overall survival was derived from variables maintaining significance on multivariable analysis. Based on the ratios for regression coefficients (log hazard ratios in the final Cox model) of variables (Table 3), weights of prognostic factors were defined as follows: poor CRS and low albumin were assigned weight 1 (minor variables) and high neutrophil count was assigned weight 2 (major variable). A prognostic score of the sum of the weights of these three variables was used to assign patients to low risk (no variable, score = 0), intermediate-risk (one/two minor or one major variable, score = 1–2) and high-risk (one major plus one/two minor variables, score = 3–4) groups for overall survival (Fig. 4). The mean overall survival of low risk ($n = 70$), intermediate-risk ($n = 84$) and high-risk ($n = 20$) patients was 48.3 months (95% CI, 41.6–54.9 months), 38.1 months (95% CI, 32.4–43.8 months) and 20.4 months (95% CI, 13.9–26.6 months) respectively (Fig. 4, $P < 0.001$). The 3-year overall survival rates for these groups were 65.7%, 43.8% and 12.0%, respectively. Five-year overall survival rates were 54.9%, 40.9% and 0%, respectively.

5. Discussion

Increasing evidence has demonstrated an independent correlation between pre-operative systemic inflammation and

Table 1 – Clinicopathological characteristics of patients who underwent metastasectomy: Univariate Cox regression analysis

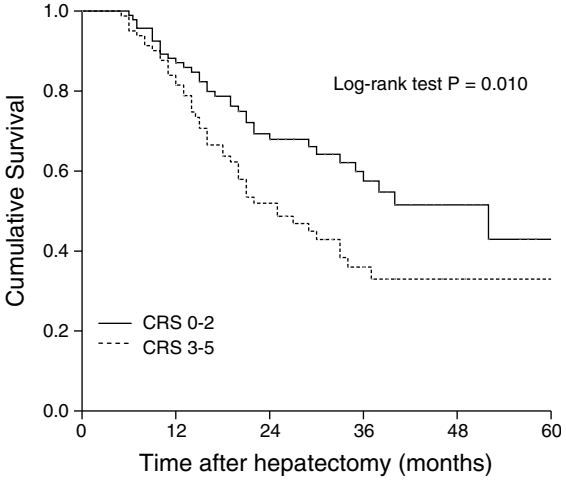
Variable	Patients ($n = 174$)	Overall survival		Disease-free survival	
		Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
(A) Clinicopathological variables					
Age: <65/⩾65 years	112/62	1.15 (0.74–1.80)	0.53	1.06 (0.72–1.54)	0.78
Gender: male/female	106/68	0.70 (0.44–1.13)	0.15	0.71 (0.48–1.05)	0.09
Site of primary tumour: rectum/colon	94/80	1.08 (0.69–1.67)	0.74	0.96 (0.66–1.38)	0.82
Stage of primary tumour: node positive/node negative	54/120	1.45 (0.88–2.42)	0.15	1.36 (0.90–1.04)	0.15
Number of liver metastases: 1–3/>3	130/44	1.30 (0.80–2.12)	0.29	1.13 (0.74–1.72)	0.59
1/>1	68/106	1.86 (1.15–3.03)	0.012	1.71 (1.16–2.53)	0.007
Diameter of liver metastases: ⩽50/>50 mm	118/56	1.43 (0.91–2.25)	0.12	1.20 (0.82–1.77)	0.35
Temporal presentation of metastases: DFI ⩽12/>12 months	115/59	0.94 (0.59–1.49)	0.78	1.09 (0.74–1.60)	0.68
Pre-operative CEA: ⩽200/>200 ng/ml	163/11	1.69 (0.78–3.69)	0.19	1.82 (0.92–3.61)	0.086
Clinical risk score: 0–2/3–5	93/81	1.76 (1.13–2.75)	0.012	1.72 (1.19–2.49)	0.004
Chemotherapy within 6 months prior to liver resection: yes/no	73/101	0.93 (0.60–1.45)	0.75	0.93 (0.64–1.35)	0.69
Adjuvant chemotherapy: yes/no	67/107	1.11 (0.71–1.74)	0.63	1.41 (0.97–2.05)	0.070
Carstairs deprivation index: UK quintiles	56/46/33/21/18	1.0 (0.85–1.18)	1.0	1.04 (0.91–1.19)	0.53
(B) Haematological variables					
Leucocyte count: <8.5/8.5–11.0/>11.0 × 10^9/l	144/23/7	1.81 (1.27–2.56)	0.001	1.56 (1.11–2.19)	0.01
Neutrophil count: ⩽6.0/>6.0 × 10^9/l	146/28	2.59 (1.57–4.28)	< 0.001	2.03 (1.28–3.22)	0.003
Lymphocyte count: <1.5/⩾1.5 × 10^9/l	77/97	0.89 (0.57–1.38)	0.60	1.08 (0.74–1.56)	0.69
Neutrophil–lymphocyte ratio: <5/⩾5	153/21	2.35 (1.37–4.01)	0.002	1.95 (1.19–3.19)	0.008
Monocyte count: ⩽0.7/>0.7 × 10^9/l	128/46	1.75 (1.10–2.78)	0.017	1.42 (0.95–2.12)	0.084
Eosinophil count: <0.1/0.1–0.2/>0.2 × 10^9/l (tertiles)	75/46/53	1.09 (0.84–1.41)	0.51	1.05 (0.85–1.31)	0.63
Basophil count: <0.01/0.01–0.04/>0.04 × 10^9/l (tertiles)	70/49/55	1.07 (0.83–1.37)	0.60	0.98 (0.79–1.22)	0.88
Haemoglobin: <12.0/⩾12.0 g/dl	31/143	0.95 (0.54–1.70)	0.87	0.91 (0.57–1.46)	0.69
Platelet count: <400/⩾400 × 10^9/l	168/6	3.55 (1.42–8.83)	0.007	2.25 (0.91–5.53)	0.078
Serum albumin: <40/⩾40 g/dl	36/138	1.98 (1.21–3.25)	0.007	1.83 (1.19–2.81)	0.006

CI: confidence interval; DFI: disease-free interval; and CEA: carcinoembryonic antigen. Results where $P > 0.1$ are rounded to 2 dp.

Table 2 – Multivariable Cox regression analysis for overall and disease-free survival

Risk factor	Overall survival				Disease-free survival			
	Hazard ratio	95% CI	*P*-value	Regression coefficient	Hazard ratio	95% CI	*P*-value	Regression coefficient
Clinical risk score: 0–2/3–5	1.64	1.05–2.57	0.031	0.49	1.63	1.13–2.36	0.010	0.49
Neutrophils: $\leqslant 6.0/>6.0 \times 10^9$/l	2.25	1.35–3.77	0.002	0.82	1.82	1.14–2.90	0.012	0.60
Serum albumin: <40/$\geqslant$40 g/dl	1.68	1.01–2.79	0.045	0.52	1.66	1.08–2.56	0.022	0.51
Weight (contribution to cumulative risk score)								
0 *versus* 1								
0 *versus* 2								
0 *versus* 1								

CI: confidence interval.



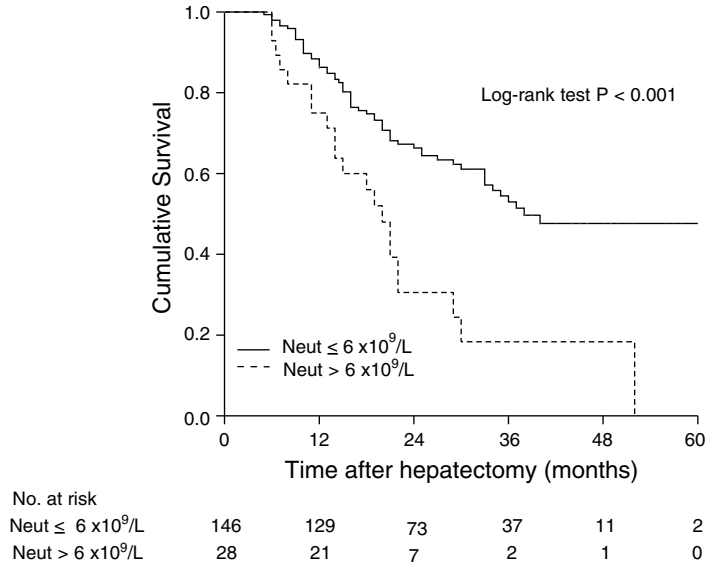
No. at risk						
CRS 0-2	93	82	48	25	9	1
CRS 3-5	81	68	32	14	3	1

Fig. 1 – The relationship between Memorial Sloan-Kettering Cancer Centre Clinical Risk Score (CRS) and overall survival following resection of colorectal liver metastases.

poor outcome in patients undergoing resection of varied malignancies, including primary CRC.[12–14,17–20] Little information is available regarding the prognostic role of the SIR in patients undergoing resection of CLM. Elevated CRP was recently demonstrated to independently predict outcome following metastasectomy.[2,16] Evidence for cellular markers of the SIR in this context has been limited to the demonstration of the prognostic significance of the NLR,[2,37] a cellular index devised and validated as a marker of inflammation in patients with cardiovascular disease and critical illness.[21,22]

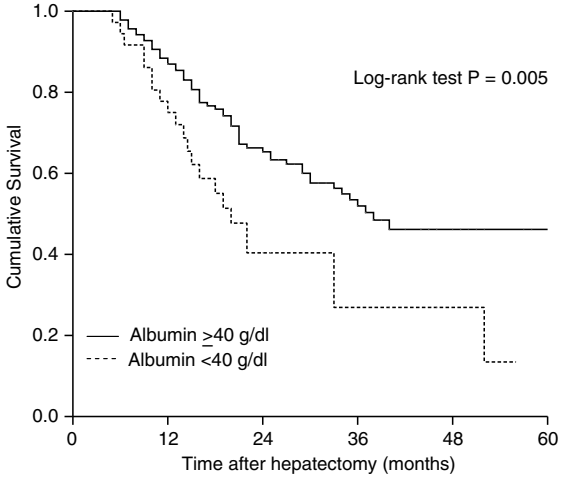
The current study demonstrates that both cellular and acute phase reactant biomarkers of the SIR, routinely available pre-operatively, predict outcome following metastasectomy and do so independently of established clinicopathological factors. These results suggest that the magnitude of the SIR is not simply a marker of increased tumour burden, but reflects an inherently more aggressive tumour phenotype. Whilst confirming the prognostic value of the NLR in this context, analysis of individual leucocyte subsets demonstrated that the prognostic value of this index is derived entirely from the neutrophil count, with the circulating lymphocyte count showing no correlation with patient outcome. Consequently, the NLR was subordinate to the neutrophil count in multivariable analyses for both overall and disease-free survival, with neutrophil count being the single most significant independent predictor of outcome following metastasectomy.

The prognostic value of the circulating neutrophil count has been reported previously in numerous malignancies,[18,19,23,36] including primary CRC.[20,35] Whilst it is possible that the increasing neutrophil count is simply an epiphenomenon of the inflammatory response in the vicinity of the tumour, the emerging theory of 'immune enhancement' suggests that cells of the myeloid lineage, particularly neutrophils, are recruited from the circulation and play a direct role in promoting aggressive tumour phenotypes.[7,8] Neutrophils are the major producers of a number of ligands that may



No. at risk						
Neut ≤ 6 x10^9/L	146	129	73	37	11	2
Neut > 6 x10^9/L	28	21	7	2	1	0

Fig. 2 – The relationship between pre-operative neutrophil count and overall survival following resection of colorectal liver metastases.

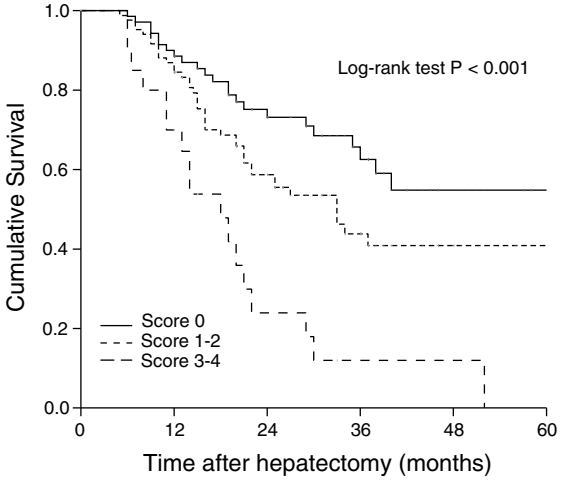


No. at risk						
Albumin ≥40 g/dl	138	122	69	35	10	2
Albumin <40 g/dl	36	28	11	4	2	0

Fig. 3 – The relationship between pre-operative serum albumin and overall survival following resection of colorectal liver metastases.

induce tumour cell proliferation and invasion, including transforming growth factor-β.[38] Furthermore, granulocytes, particularly neutrophils, contain over two-thirds of circulating vascular endothelial growth factor, liberation of which may promote tumour vascularisation.[39] Neutrophils may further promote invasion and metastasis through the production and release of matrix metalloproteinases[40] and through the promotion of cancer cell intra- and extravasation.[41,42] Though subordinate to neutrophil count in multivariable analyses, an association between monocyte count and adverse outcome was also demonstrated in this study. A similar association was noted previously in hepatocellular carcinoma[24] and renal cell carcinoma.[23] This phagocyte class exerts a number of biological actions in common with neutrophils that may explain this prognostic value.[7]

In this study no association was found between the peripheral lymphocyte count and outcome following CLM resection, even when further analyses were conducted to evaluate multiple cut-off points (data not shown). In CRC, the concept of lymphocytic 'immune surveillance' has undergone a recent resurgence, with higher tumour lymphocytic infiltration shown to correlate with lower tumour stage and to be a better predictor of patient survival than current histopathological staging systems.[9] Similarly, tumour lymphocytic



No. at risk						
Score 0	70	63	38	21	7	1
Score 1-2	84	73	38	17	4	1
Score 3-4	20	14	4	1	0	0

Fig. 4 – The relationship between pre-operative prognostic score and overall survival following resection of colorectal liver metastases.

infiltration was shown to independently predict patient outcome in patients with CLM.[43] The prognostic value of lymphocytes does not appear to be reflected at the systemic level, however, as whilst the number of tumour-infiltrating CD8+ T-lymphocytes was found to correlate with patient outcome in primary CRC, the number of these cells in the systemic circulation showed no correlation with prognosis.[44] Similarly, a recent study found no correlation between total circulating lymphocyte count and outcome in patients with either operable primary CRC or unresectable CLM.[20] The findings of the current study are in line with these data.

The results of the current report agree with those of the only other study which compares the prognostic value of the NLR in malignancy with that of individual leucocyte subsets. In primary CRC, Leitch et al. recently reported circulating neutrophil count to be associated with adverse outcome following primary CRC resection, but found that neither lymphocyte count nor NLR correlated with survival.[20] Together, these data have implications for the design and application of therapeutic agents targeting the SIR in both primary and metastatic CRC. Whilst authors have previously discussed the possibility of targeting the adaptive immune response,[37] these results suggest that, at the systemic level, the innate immune system may be a more viable target.

Systemic inflammation is also known to be associated with a decrease in serum albumin concentration,[26,27] attributed to the raised levels of circulating pro-inflammatory cytokines, particularly IL-6.[45] Albumin was previously found to predict poor outcome both following resection of primary CRC[46] and in patients with metastatic disease.[47,48] The current study is the first to confirm that serum albumin is also an independent risk factor for poor outcome following CLM resection, though this prognostic value was inferior to that of the neutrophil count. Serum albumin was previously demonstrated to predict poor long-term outcome following cancer resection independently of CRP and has subsequently been combined with CRP to produce prognostic inflammatory scores validated in varied malignancies.[20,28,29] The current study confirmed that serum albumin and cellular markers of the SIR may also exhibit independent prognostic significance in malignancy, and along with the CRS, the other independent predictor of outcome, could be combined to produce a novel score with high prognostic value. Of note, these data are all routinely available pre-operatively.

CRP, the other major biomarker of the SIR, is not routinely measured prior to hepatectomy and was not, therefore, available for inclusion in the current study. A recent study, however, reported equally poor prognosis in two separate patient groups with either elevated CRP or an elevated NLR prior to CLM resection.[2] Of note, it has previously been shown that CRP and neutrophil count may also exhibit simultaneous independent prognostic significance in malignancy.[17] Further studies are required, therefore, to determine whether CRP, cellular indices and serum albumin exert independent prognostic significance in patients undergoing metastasectomy, thereby potentially enabling even greater refinement of prognosis in this patient group.

Socioeconomic deprivation was previously found to be associated with the SIR in primary CRC and to itself independently predict shortened long-term survival following tumour resection.[30,31] In the current study deprivation showed no association with either. Of note, the association between deprivation and survival in patients with primary CRC was previously found to be confined to patients undergoing curative resection, with no difference in survival in patients undergoing palliative surgery.[30] Similarly, deprivation was recently found to have no correlation with outcome in patients with synchronous unresectable liver metastases.[20] Together with the current series, these data suggest that deprivation is not associated with outcome in patients with disseminated colorectal malignancy.

In summary, the results of this study confirm that systemic inflammatory biomarkers, routinely available pre-operatively, independently predict long-term survival following resection of CLM. As demonstrated here and elsewhere,[27–29,47,48] merging of inflammatory indices with the existing prognostic scoring systems may enable further refinement of patient prognosis, so guiding the allocation of the existing therapeutic modalities. Inflammatory biomarkers may also represent novel therapeutic targets. A myriad of agents targeting varied facets of the innate immune system, including chemokine, interleukin-6 and tumour necrosis factor antagonists, are already in clinical trial.[6] Furthermore, it is now established that CRP plays a direct role in malignant progression[49] and is itself a valid therapeutic target,[50] with several small molecule inhibitors in development. Future studies must define the interplay between the varied facets of the inflammatory response, including the role of particular leucocyte subtypes and cellular products, to enable the rational design and allocation of anti-inflammatory strategies in this context.

Conflict of interest statement

None declared.

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