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ORIGINAL ARTICLE

Systemic inflammatory response predicts oncological outcomes in patients undergoing elective surgery for mismatch repair-deficient colorectal cancer

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Abstract

Introduction A variety of inflammatory scoring systems and their prognostic value have been reported in many solid organ cancers. This study aimed to examine the association between the systemic and local inflammatory responses, and oncological outcomes in patients undergoing elective surgery for mismatch repair-deficient (dMMR) phenotype colorectal cancer (CRC).

Materials and methods Consecutive patients undergoing resection for dMMR CRC were identified from a prospectively maintained database and compared with a cohort of patients with proficient mismatch repair system tumours. Systemic inflammatory response was assessed by the modified Glasgow prognostic score (mGPS), neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio, lymphocyte-monocyte ratio, C-reactive protein/albumin ratio, prognostic index and prognostic nutritional index. Local inflammatory response was defined by the presence of tumour infiltrating lymphocytes, tumour infiltrating neutrophils, plasma cells or macrophages at the invasive front. The inflammatory infiltrate was assessed using the Klintrup–Mäkinen (KM) score.

Results On univariable analysis, preoperative NLR ≥ 5 (hazard ratio [HR] 2.5; 95% confidence interval [CI] 1.25–5.19; $p = 0.007$) and mGPS (HR 1.6; 95% CI 1.1–2.6; $p = 0.03$) predicted worse overall survival, but only NLR was associated with greater recurrence (HR 3.6; 95% CI 1.5–8.8; $p = 0.004$). Increased local inflammatory response, as measured by KM score (HR 0.31; 95% CI 0.1–0.7; $p = 0.009$) and the presence of macrophages in the peritumoral infiltrate (HR 0.17; 95% CI 0.07–0.3; $p < 0.001$), was associated with better outcomes. NLR was the only independent prognostic factor of overall and disease-free survival.

Conclusion Systemic inflammatory response predicts oncological outcomes in CRC patients, but only NLR has prognostic value in the dMMR group.

Keywords Colorectal cancer · Local inflammatory response · Systemic inflammatory response · Neutrophil–lymphocyte ratio · Prognostic markers · Prognostic scores

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the Western world [1, 2]. Overall survival (OS) remains poor, with 50% estimated 5-year survival [3]. TNM stage is the strongest prognostic factor, determining therapeutic options. However, outcomes and therapeutic responses vary substantially between patients with matched disease stage. Therefore, there is increasing interest in the identification of prognostic and predictive biomarkers to improve clinical outcomes [4, 5].

There is a well-documented association between inflammation and cancer, although the exact mechanisms remain incompletely understood. Increased expression of pro-

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inflammatory cytokines has been found in CRC, even when there is no clinically detectable underlying inflammatory bowel disease [6]. Systemic inflammatory scoring systems based on white cell components, such as neutrophil–lymphocyte ratio (NLR), lymphocyte–monocyte ratio (LMR) and platelet–lymphocyte ratio (PLR) have been reported in many solid organ cancers as prognostic markers [7–9]. High systemic inflammatory response measured with these and other grading systems such as modified Glasgow Prognostic Score (mGPS) has been associated with poor OS and disease-free survival (DFS) in some cancers including CRC [4, 7]. However, an increased peritumoural inflammatory infiltrate, representing the host's local immune response, appears to be associated with improved prognosis [10]. One of the most reproducible and independent prognostic scores for peritumoural inflammation is the Klintrup–Mäkinen (KM) score [11].

CRC exhibiting microsatellite instability (MSI) provokes a strong local inflammatory response with a pronounced lymphocytic infiltrate [12, 13]. These tumours evolve as a result of defects in the DNA mismatch repair (MMR) system; the function of which is to repair base–base mispairs introduced into microsatellites during DNA synthesis [14]. Deficient MMR (dMMR) results in a production of non-functional proteins or loss of a protein, which causes the MSI phenotype [2]. It occurs in the context of Lynch syndrome, due to constitutional mutations in the MMR genes (MLH1, MSH2, MSH6, PMS2 or EPCAM), [15] or more frequently, due to a biallelic epigenetic inactivation of the MLH1 gene. These tumours have been associated with a better prognosis than CRC with a proficient mismatch repair system (pMMR) [14, 16]. Some groups have reported the prognostic effect of tumour infiltrating lymphocytes (TILs) in the local tumour microenvironment as independent of MMR status [17], but to date no other inflammatory markers have been described as prognostic factors in dMMR tumours. The aim of this study was to examine the association between the systemic and local inflammatory response, and oncological outcomes in patients undergoing elective surgery for dMMR CRC.

Methods

Study population

Consecutive patients undergoing elective colorectal resection for dMMR between January 2004 and December 2015 at our institution were identified from a prospectively maintained database. A cohort of consecutive patients who underwent elective colorectal resection for pMMR CRC from January 2008 to December 2010 was selected as the control group. Exclusion criteria were neoadjuvant therapy, stage IV disease and emergency presentation of CRC. Clinical staging was determined by computed tomography of the thorax, abdomen and pelvis. For rectal cancers, pelvic magnetic resonance imaging was also required. The American Joint Committee on Cancer TNM version 7 was used to stage CRC [18]. This study was approved by St Vincent's University Hospital Research and Ethics Committee.

Preoperative laboratory measurements and other prognostic scores

Patient demographics and preoperative laboratory measurements were analysed, including White cell count (WCC) differential (total WCC, neutrophils, lymphocytes, monocytes, basophils and platelet counts), C-reactive protein (CRP), haemoglobin and albumin. Preoperative blood samples were collected 1 to 4 weeks prior to surgery. In order to study the systemic inflammatory response, NLR [7, 8], PLR [8], LMR [4], mGPS [19], prognostic index (PI) [20], prognostic nutritional index (PNI) [21] and CRP/albumin ratio [22] were calculated (Table 1). The optimal cut-off levels for the remaining preoperative laboratory measurements were determined by applying receiver operating curves (ROC).

Table 1 Systemic inflammatory markers

	Score
Neutrophil–lymphocyte ratio	
Neutrophil count: lymphocyte count < 5:1	0
Neutrophil count: lymphocyte count ≥ 5:1	1
Platelet–lymphocyte ratio	
Platelet count: lymphocyte count < 190:1	0
Platelet count: lymphocyte count ≥ 190:1	1
Lymphocyte–monocyte ratio	
Lymphocyte count: monocyte count < 1.81	0
Lymphocyte count: monocyte count ≥ 1.81	1
Modified Glasgow Prognostic Score (mGPS)	
C-reactive protein ≤ 10 mg/L and albumin ≥ 35 g/L	0
C-reactive protein > 10 mg/L	1
C-reactive protein > 10 mg/L and albumin < 35 g/L	2
Prognostic index	
C-reactive protein ≤10 mg/L and white cell count ≤ 11×10^9/L	0
C-reactive protein ≤10 mg/L and white cell count > 11×10^9/L	1
C-reactive protein >10 mg/L and white cell count ≤11×10^9/L	1
C-reactive protein >10 mg/L and white cell count >11×10^9/L	2
Prognostic nutritional index	
Albumin (g/L) + 5 × total lymphocyte count × 10^9/L < 40.2	0
Albumin (g/L) + 5 × total lymphocyte count × 10^9/L ≥ 40.2	1
C-reactive protein albumin ratio (CRPa ratio)	
C-reactive protein: albumin < 0.464	0
C-reactive protein: albumin ≥ 0.464	1

Tumour characteristics

Histopathological characteristics of tumours were recorded, including pTNM staging, tumour location, extramural vascular invasion (EMVI), lymphovascular invasion (LVI) and tumour resection margin. MMR status was assessed using immunohistochemistry for mismatch repair proteins, hMLH1 (BD Bioscience, clone G168-728), hPMS2 (BD Biosciences, clone A16-4, hMSH2 (Calbiochem, clone FE11) and hMSH6 (BD Biosciences, clone 44).

Histological grading was based on glandular differentiation, tumour budding and poorly differentiated cluster (PDC) grade were also performed on haematoxylin–eosin (H&E) stained sections. CRC grade was classified as one of the following: (i) well-differentiated (at least 95% glandular differentiation), (ii) moderately differentiated (5–95% glandular differentiation), (iii) poorly differentiated (more than 50% undifferentiated areas) or (iv) undifferentiated tumours (less than 5% glandular differentiation). PDC grade (defined as ≥ 5 cancer cells present at the invasive front of the tumour that lack full glandular formation) was assessed: grade 0 (absence of PDCs), grade 1 (1–4 PDCs), grade 2 (5–9 PDCs) and grade 3 (cases with ≥ 10 PDCs). Tumour budding was defined by the presence of individual cells and small clusters (< 5) of tumour cells at the invasive front of carcinomas [5]. Using a Nikon Eclipse 80i microscope, slides were scanned at low magnification (× 40) to assess areas with the highest density of tumour buds and rapid bud count method was used. Tumour border configuration was categorized as described by Jass et al. [23] into infiltrating (irregular advancing edge) or pushing (clear delineation of tumour at the invasive front) in a two-tier system [12].

To study the local inflammatory response in the dMMR cohort, an estimation of inflammatory cells (neutrophils and eosinophils, lymphocytes, plasma cells and macrophages) at the invasive front was made using the KM scoring system [11] (Supplementary appendix Fig. 1, panels A–D). Tumours were classified as follows: score 0 (few inflammatory cells), score 1 (mild and patchy increase but no invading cancer cell islets), score 2 (band-like infiltrate with some destruction of cancer cells) or score 3 (prominent reaction, frequent destruction of cancer cells). These scores were then classified into low (0–1) and high grade (2–3) for the statistical analysis [10]. The presence of TILs, tumour infiltrating neutrophils (TINs), eosinophils (low score < 10; high score ≥ 10 eosinophils), plasma cells (low score < 10% of 20 mm of invasive front containing > 50 plasma cells per high-power field (hpf); high score ≥ 10% of 20 mm IF containing > 50 plasma cells per hpf) and macrophages at the invasive front were also assessed.

Follow-up

All patients were reviewed in the outpatient clinic and underwent clinical examination, measurement of biochemical tumour markers, abdominal CT and colonoscopy to aid detection of tumour recurrence.

Statistical analysis

Descriptive statistics were computed for all variables. OS was calculated from the date of surgery until death from any cause, or until the date of the last follow-up in living patients. DFS was calculated from the date of surgery until the first date of confirmed local recurrence, distant metastases or death from any cause. Contingency table analysis with χ^2 test was used to determine the association between ordinal variables, and Student's t test was used for continuous variables. Kaplan–Meier curves were plotted and compared using log-rank statistics to examine the association between inflammatory response and oncological outcomes. A COX proportional hazard regression model was used to assess the effects of covariates on OS and DFS. Results were expressed as hazard ratio (HR) with 95% confidence interval (CI). Associations between the systemic and local prognostic factors were assessed using Spearman's correlation coefficients (rho). Variables with more than one category were evaluated using Kruskal–Wallis test. All tests of significance were two-tailed, with a p value of < 0.05 indicating statistical significance. Results were analysed with SPSS software package (SPSS Inc., Chicago, IL, USA) version 21.0.

Results

Clinicopathological characteristics

Eight-hundred and four patients that underwent resection for CRC were eligible for inclusion in the study. In total, 117 patients received neoadjuvant therapy; 71 had emergency surgery and 50 were diagnosed with stage IV disease (2 of those patients with stage IV disease had an emergency resection in the dMMR group; 24 underwent emergency surgery and 3 received neoadjuvant treatment in the pMMR group). Thus, 173 patients with dMMR and 393 with pMMR remained in the final analysis (Fig. 1). Rectal tumours without neoadjuvant treatment were analysed in the study as left-sided CRC. Patients with dMMR tumours were more likely to be female, slightly older than the pMMR cohort, and exhibited a high systemic inflammatory response, including thrombocytosis. Moreover, these tumours were more likely to be early-pTNM stage right-sided tumours. Although tumour differentiation was worse in the dMMR group, the EMVI rate was higher in MMR-proficient cancer (Table 2).

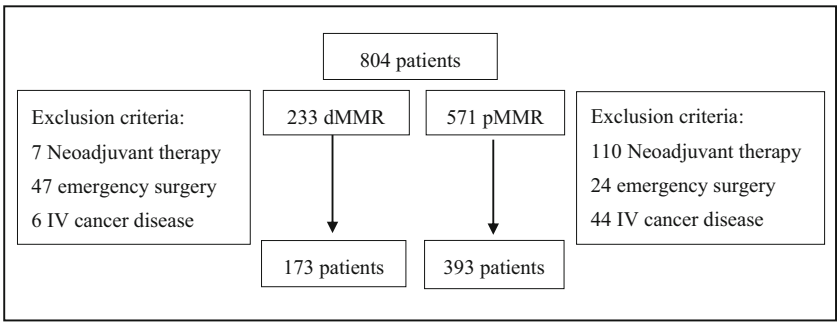

Fig. 1 Inclusion and exclusion criteria of patients with colorectal cancer

Inflammatory response and survival in CRC

A total of 62 (10.9%) patients had confirmed recurrence during a median follow-up of 60 months. There were 148 deaths (26.1%), 24 of them related to CRC (13.9%). No significant differences between the pMMR and dMMR groups were found in either recurrence (9.9% for pMMR vs 13% for dMMR; $p = 0.24$) or mortality rates (26.7% for pMMR vs 24.8% for dMMR; $p = 0.67$).

Univariable COX regression analysis of the entire cohort showed that high preoperative systemic inflammatory response measured by WCC (HR 1.06; 95% CI 1.01–1.11; $p < 0.009$), neutrophils (HR 1.66; 95% CI 1.15–2.39; $p < 0.006$) and monocytes (HR 2.15; 95% CI 1.31–3.54; $p < 0.002$) was associated with reduced OS. With regard to the prognostic score analysis, NLR, LMR, mGPS, PNI and CRP-albumin ratio predicted OS (Supplementary appendix Table 1). Those patients with the highest scores were found to have lower median survival times than those who had lower scores, with resulting HR of 2.1 for NLR ≥ 5 (95% CI 1.48–3.1; $p < 0.001$), 1.84 for CRP-albumin ratio ≥ 0.46 (95% CI 1.1–3.1; $p = 0.02$) and 1.54 for mGPS ≥ 2 (95% CI 1.1–2.1;

Table 2 Relationship between MMR status and clinicopathological features of CRC patients undergoing non-emergency resection

Characteristics	Total	dMMR	pMMR	*p
Age, mean (SD)	69.9 (12.3)	71.9 (12)	69.1 (12.3)	*0.009*
Sex, *N* (%)				
Female	306	118 (68.2)	188 (47.8)	*< 0.001*
Male	260	55 (31.8)	205 (52.2)	
Tumour location, *N* (%)				
Right	323	152 (87.9)	171 (43.5)	*< 0.001*
Left colon	243	21 (12.1)	222 (56.5)	
Total WCC (cells/mm^3), mean (SD)	7.7 (2.8)	8.1 (3.4)	7.5 (2.5)	*0.003*
Neutrophils	5.03 (2.3)	5.2 (2.4)	4.9 (2.3)	0.85
Lymphocytes	1.5 (0.6)	1.5 (0.5)	1.6 (0.6)	0.34
Monocytes	0.6 (0.2)	0.7 (0.3)	0.6 (0.2)	0.31
Basophils	0.02 (0.06)	0.2 (0.05)	0.02 (0.06)	0.18
Eosinophils	0.2 (0.5)	0.3 (0.08)	0.2 (0.1)	*0.04*
Platelet count (cells/mm^3), mean (SD)	217.1 (122.5)	316 (109.1)	286.3 (95.4)	*0.01*
pTNM stage				
I	97	32 (18.5)	65 (16.5)	*0.003*
II	265	99 (57.2)	166 (42.2)	
III	205	42 (24.3)	162 (41.2)	
Glandular differentiation grade				
Well-differentiated	76	31 (17.9)	45 (11.5)	*< 0.001*
Moderate differentiated	381	87 (50.3)	294 (74.8)	
Poorly differentiated	90	37 (21.4)	53 (13.5)	
Undifferentiated	19	18 (10.4)	1 (0.3)	
Tumour budding◊				
Presence	153	61 (43.3)	92 (41.1)	0.74
Absence	212	80 (56.7)	132 (58.9)	
EMVI	145	48 (27.7)	97 (24.7)	0.45
LVI	224	92 (53.2)	224 (57)	*< 0.001*
Tumour margin				
Pushing	284 (+2)	90 (52)	194 (49.3)	0.64
Infiltrative	282 (+3)	83 (48)	199 (50.6)	

*χ^2 test was used in determining the association between ordinal variables and t-student for continuous variables. *p* value ≤ 0.05 in italics was considered significant

◊pMMR and dMMR: 201 patients (35.5%) were not assessable for budding

$p = 0.03$). Increased monocyte count reflected in high LMR and poor nutritional status measured with PNI were associated with reduced median survival times (100.9 vs 114.2 months for LMR < 1.81 vs ≥ 1.81 $p = 0.01$; 110.5 vs 115.8 months in PNI < 40.2 vs ≥ 40.2 group $p = 0.007$). Kaplan–Meier curves were plotted to show these associations (Supplementary appendix Fig. 2).

With regard to DFS, patients with preoperative NLR ≥ 5 had a greater rate of recurrence than those with NLR < 5, on univariate analysis (median DFS in NLR < 5 group was 129.3 months vs 105.2 months in NLR ≥ 5 group, HR 1.83; 95% CI 1.03–3.2; $p = 0.03$) (Supplementary appendix Table 1).

Analysis according to MMR status

Total WCC count ($p = 0.003$), eosinophils ($p = 0.04$) and platelets ($p = 0.01$) were significantly associated with dMMR status (Table 2). NLR and mGPS were associated with worse OS on univariable analysis. Median OS in NLR < 5 group was 98.5 vs 58.1 months in NLR ≥ 5 group with HR 2.5 (95% CI 1.25–5.19; $p < 0.007$), and median OS in mGPS < 2 group was 88.2 vs 64.9 months in mGPS > 2 group with HR 1.6 (95% CI 1.1–2.6; $p < 0.03$). (Table 3; Fig. 2). However, only NLR was associated with decreased median DFS (122.9 months for NLR < 5 vs 64.2 months in NLR ≥ 5 group, HR 3.6; 95%

Table 3 Overall survival and disease-free survival of dMMR group

	N	Disease-free survival			Overall survival		
		Median (months)	HR (95%CI)	*p	Median (months)	HR (95% CI)	*p
Systemic inflammatory response							
NLR◊							
< 5	133	122.9	3.6	*0.004*	98.5	2.5	*0.007*
≥ 5	28	64.2	(1.5–8.8)		58.1	(1.25–5.19)	
PLR◊							
< 190	73	114.4	0.7	0.51	89.6	0.7	0.29
≥ 190	93	112.1	(0.3–1.7)		95.4	(0.3–1.3)	
LMR◊							
< 1.81	49	97.7	0.4	0.08	92.1	0.7	0.45
≥ 1.81	112	123.6	(0.2–1.1)		94.7	(0.4–1.5)	
mGPS◊							
0	29	113.4	1.6	0.11	88.2	1.6	*0.039*
1	22	90.3	(0.9–3.1)		74.5	(1.1–2.6)	
2	39	78.8			64.9		
Prognostic index◊							
0	27	112.9	1.8	0.13	87.2		
1	57	98.9	(0.8–4.1)		76.2	1.62	0.13
2	11	81.4			72.7	(0.8–3.1)	
Prognostic nutritional index◊							
0	77	114.2	0.7	0.43	88.1	0.6	0.12
1	86	122.4	(0.3–1.6)		100.8	(0.3–1.1)	
C-reactive protein albumin ratio◊							
0	42	119.9	1.6	0.33	106.7	1.86	0.12
1	48	81.2	(0.6–4.4)		67.6	(0.84–4.1)	
Local inflammatory response							
Klintrup–Makinen							
Low score	27	97.7	0.32	*0.008*	87.6	0.31	*0.009*
High score	146	131.9	(0.1–0.7)		104.6	(0.1–0.7)	
TILs◊							
0	37	108.2	0.46	0.08	87.7	0.48	0.106
1	128	130.8	(0.2–1.1)		103.8	(0.2–1.1)	
Eosinophils							
Low score	59	84.2	0.54	0.14	68.3	0.53	0.13
High score	114	133.4	(0.2–1.2)		113.5	(0.2–1.2)	
Plasma cells							
Low score	28	88.2	0.49	0.13	82.6	0.48	0.12
High score	145	131.7	(0.1–1.2)		103.8	(0.1–1.2)	
Macrophages							
0	39	61.8	0.18	*< 0.001*	62.1	0.17	*< 0.001*
1	134	138.2	(0.07–0.4)		109.1	(0.07–0.3)	

Hazard ratios are from univariate COX regression analysis. *p* value ≤ 0.05 in italics was considered significant

◊Missing values 53 lymphocytes, CRP 369, albumin 35TILs 8

*Median overall survival times are Kaplan–Meier estimates

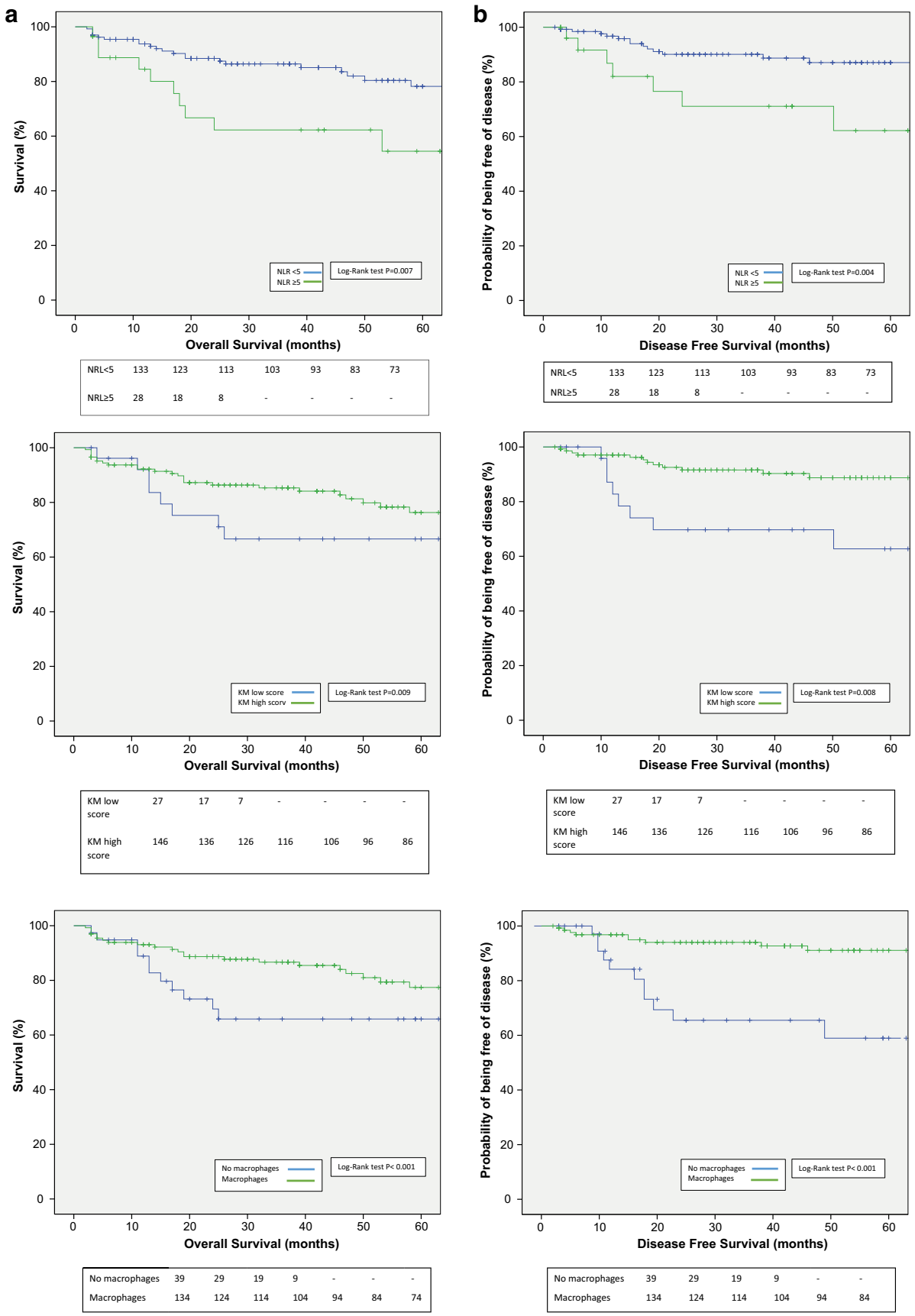

Fig. 2 Kaplan–Meier curves comparing overall survival (**a**) and disease-free survival (**b**) in patients who underwent elective surgery for dMMR CRC

Table 4 Multivariable analysis of clinicopathologic factors following elective, potentially curative surgery for CRC

Characteristics	Disease-free survival				Overall survival			
	dMMR		pMMR		dMMR		pMMR	
	HR (95% CI)	*p	HR (95%CI)	*p	HR (95% CI)	*p	HR (95% CI)	*p
Age	1.1 (1.2–1.3)	*0.01*	–	–	1.07 (1.1–1.2)	*< 0.001*	1.2 (1.1–1.3)	*0.03*
Male genre	–	–	–	–	–	–	–	–
pTNM stage	3.1 (1.5–6.5)	*0.02*	1.9 (1.1–3.3)	*0.01*	1.79 (1.1–2.9)	*0.02*	1.47 (1.1–2.1)	*0.01*
Tumour side	–	–	–	–	–	–	–	–
NLR	2.9 (1.2–7.1)	*0.01*	–	–	2.23 (1.1–4.5)	*0.02*	2.09 (1.1–3.6)	*0.01*
LMR	–	–	–	–	–	–	–	–
KM score	–	–	–	–	–	–		–

*Hazard ratios and *p* values are from multivariate Cox regression models. *p* value ≤ 0.05 in italics was considered significant

CI 1.5–8.8; $p = 0.004$) (Table 3; Fig. 2). Furthermore, NLR was also found to be an independent prognostic factor of OS and DFS when tumours were stratified according to MMR status (Table 4).

dMMR tumours with a significant local inflammatory response, evidenced by a high KM score and macrophages at the invasive front were less likely to recur. Median DFS time among those tumours with macrophages at the invasive front was more than double that of the macrophage-low group (61.8 vs 138.2 months, respectively, with HR 0.18; 95% CI 0.07–0.4; $p < 0.001$) (Table 3; Fig. 2). Moreover, these two markers of local tumour microenvironment activity were related to better OS (median OS for KM low score group was 87.6 vs 104.6 months in KM high score group, HR 0.31; 95% CI 0.1–0.7; $p = 0.009$ and median OS for the group without macrophages at the invasive front was 62.1 vs 109.1 months for the macrophages at the invasive front HR 0.17; 95% CI 0.07–0.3; $p < 0.001$) (Table 3; Fig. 2). While there was a trend towards reduced median DFS in the TIL low group compared to the high TIL infiltrate group (median DFS of 108.2 months vs 130.8, HR 0.46; 95% CI 0.2–1.1), this did not reach statistical significance.

Correlation between systemic and local inflammatory response in the dMMR cohort

Correlation between systemic and local inflammatory response was assessed, and results are reported in Supplementary appendix Table 2. There is a weak but consistent inversely proportional relationship between measured local inflammatory factors and NLR. However, LMR and PNI were found to increase with KM score, eosinophils and macrophages at the invasive tumour front, having a positive correlation.

Discussion

The main finding of the present study is that an increased systemic inflammatory response, signified by an elevated NLR, is associated with greater recurrence rates and poor survival in CRC. Moreover, we confirmed that a high inflammatory response in the tumour microenvironment is associated with better outcomes in the dMMR phenotype. Importantly, there is an inversely proportional relationship between NLR and the local inflammatory response in such tumours.

It is now widely accepted that the host immune response is partly responsible for the variation in oncological outcomes between patients. A number of studies have previously related high levels of systemic inflammatory cells in CRC patients [9, 13, 24–28], and this is confirmed in our study. Patel el al. [29] described an association between right-sided CRC and a high systemic inflammatory response, assessed using mGPS, LMR and NLR. Leitch et al. [24] reported high C-reactive protein levels and presented mGPS as an independent cancer-specific survival prognostic score in patients with either primary operable or synchronous unresectable CRC, in line with previous reports [9]. Multiple studies have suggested NLR as a prognostic systemic inflammatory marker in a range of solid tumours [7, 8, 30, 31] such as CRC [13, 32–34], although there is currently a lack of consensus, in particular regarding dMMR CRC [35, 36]. Here, we establish a raised NLR as an adverse prognostic feature in dMMR CRC.

Lymphocyte count is an important component of NLR, PLR and LMR, tending to be low if these scores are high. These immune cells secrete pro-inflammatory cytokines such as TNF-α and IL 1, 6 and 8 which induce cytotoxic cell death [13]. Therefore, lymphocytopenia downregulates the immune response against cancer and enhances tumour progression [25]. NLR is a comprehensive marker of systemic inflammation, as it reflects the activity of the adaptive immune response (lymphocytes) and the innate response (neutrophils). In our

analysis, some components of the innate immune system (WCC, neutrophils and monocytes) predict poor oncological outcomes, highlighting the role of the innate system as first barrier to control cancer progression. The exact mechanisms underpinning this have yet to be elucidated but the increased systemic inflammatory response, even in dMMR tumours, reflects underlying immune activation in patients with CRC.

The presence of inflammatory cells at the tumour invasive front is thought to be a manifestation of the immune response against cancer cells, and consequently associated with better survival [3, 10, 12, 17]. It has been postulated that some of these cells have tumour cytolytic properties, thereby controlling tumour spread [12]. Although the prognostic effect of TILs in the local tumour microenvironment, independent of MMR status, is well established [17], macrophages are one of the commonest immune cell types found at the invasive front and may predict survival [11, 17]. These cells phagocytose malignant cell targets and present them to T cells, establishing the first line of the immune response [3]. It remains unclear which other local inflammatory markers have prognostic utility in CRC, but there is a consensus regarding the use of KM system to assess tumour inflammatory infiltrate [3, 10, 11]. In our analysis, those patients whose tumours had a high KM score had better survival outcomes, which differs from results reported by Park et al. [36] in a cohort of 35 dMMR patients. The KM score includes components of both the innate and adaptive immune response, reinforcing the theory that both types of immune system cells play a crucial role in dMMR tumour progression.

Our results suggest that there is an inverse relationship between preoperative NLR and certain local peritumoural factors, such as TILs, plasma cells and eosinophils at the tumour margin and KM score system. This association has been described previously by Roxburgh et al. [37], suggesting that both peritumoural infiltrate and systemic inflammation are linked through the cell-mediated immune system. In their review of 287 patients, systemic inflammatory response was quantified by the mGPS but none of the WCC score system ratio was analysed. Other groups have hypothesised that an activated systemic response represents a loss of local response and therefore a feature of cancer progression [38]. Although the presence of high local inflammatory response may have a role in determining the benefit of adjuvant therapies [11], none of the aforementioned inflammatory markers are routinely assessed in CRC specimens. Furthermore, in addition to numerous immune and stromal cells, the local tumour microenvironment of dMMR cancers also selectively displays highly upregulated expression of multiple immune checkpoints, including programmed death-1 (PD-1) [39]. Consequently, assessment of the tumour microenvironment may be an important guide for emerging immunotherapeutic strategies [40, 41].

The present study has a number of limitations. In order to avoid confounding results, emergency cases, in which inflammatory markers could be raised, and patients who received pre-operative chemoradiotherapy were excluded from our analysis. This provides homogeneity and consistency to our results, but it is also a limitation, as this may not reflect real world practice. The majority of patients with dMMR CRC included in our analysis were early stage of disease, with relatively good prognosis, which may explain why other systemic inflammatory scores did not arise as independent prognostic markers. Although the TIL rate is higher among dMMR tumours in this series, our results do not support TILs as a prognostic marker. The H&E staining we used to count TILs is less sensitive than immunohistochemical assessment [12] and may explain this lack of association. Moreover, local inflammatory scores were only calculated for the dMMR group. Some authors have hypothesized that inflammatory factors are affected by tumour stage; an interesting direction for future research might be to perform an analysis of the local immune response in both dMMR and pMMR tumours in a group of patients with early compared to locally advanced disease.

In conclusion, preoperative measurement of systemic inflammatory response can provide useful prognostic information in patients undergoing CRC resection. Identification of systemic conditions and other molecular markers is essential to allow individualisation of CRC treatment and prediction of outcomes. An objective systemic inflammatory marker such as NLR may be easily adopted for the routine clinical assessment of patients undergoing CRC resection.

Compliance with ethical standards

This study was approved by St. Vincent's University Hospital Research and Ethics Committee.

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