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The Lymphocyte-to-Monocyte Ratio is a Superior Predictor of Overall Survival in Comparison to Established Biomarkers of Resectable Colorectal Cancer

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Objective: The study aims to investigate the prognostic value of the lymphocyte-to-monocyte ratio (LMR) in patients with colorectal cancer (CRC) undergoing curative resection and to compare it to established biomarkers including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), modified Glasgow prognostic score (mGPS), and combined BRAF-mismatch repair (MMR) status.

Background: The prognostic significance of systemic inflammatory markers in CRC such as the NLR, PLR, and mGPS has been well defined. Commonly used genetic markers such as combined BRAF-MMR status have also been found to be prognostic. Recent evidence, although limited, suggests that the preoperative LMR may be prognostic in CRC.

Methods: Data from the Northern Sydney Local Health District from January 1998 to December 2012 were retrospectively collected. Of 3281 consecutive patients identified, 1623 patients who underwent curative resection were deemed eligible for inclusion. The relation between the LMR, clinicopathologic variables, and other biomarkers were analyzed in Kaplan-Meier log-rank survival analysis and then multivariate Cox regression models looking for association with overall survival (OS).

Results: In multivariate analysis of all patients, elevated LMR was associated with better OS (hazard ratio 0.569, 95% confidence interval: 0.478–0.677, $P < 0.001$) independent of age ($P < 0.001$), T stage ($P < 0.001$), N stage ($P < 0.001$), and grade ($P = 0.049$). The NLR, PLR, and combined BRAF-MMR status were not independently significant. In multivariate subgroup analysis of 389 patients with mGPS, LMR remained the only independently significant biomarker (hazard ratio 0.620, 95% confidence interval: 0.437–0.880, $P = 0.007$).

Conclusions: The LMR is an independent predictor of OS in patients with CRC undergoing curative resection and appears to be superior to pre-existing biomarkers.

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Disclosure: The authors have no conflicts of interest to declare.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

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ISSN: 0003-4932/16/26503-0539
DOI: 10.1097/SLA.0000000000001743

Keywords: BRAF mutation, colorectal cancer, lymphocyte-monocyte ratio, mismatch repair, modified Glasgow prognostic score, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, prognosis, systemic inflammation

(*Ann Surg* 2017;265:539–546)

Worldwide, colorectal cancer (CRC) remains one of the leading causes of cancer death, with more than 1.4 million cases diagnosed each year.[1] Despite advances in preceding decades, CRC survival in late stages remains poor, which makes it critically important to optimize treatment of early stage disease, including use of adjuvant therapies, by identifying patients at greatest risk of worse outcomes. Recently there has been increasing interest in improving CRC prognostication using clinical, inflammatory, and molecular biomarkers; however, there remains a lack of reliable, reproducible, and low-cost biomarkers that can be readily incorporated into routine practice to optimally predict prognosis and guide treatment.

There is growing consensus that inflammation is involved in the development of malignancy and that evidence of an ongoing systemic inflammatory response is associated with worse prognosis in numerous cancers.[2] This idea has led to the study of markers of systemic inflammation in the hope of developing cost-effective prognostic biomarkers in cancer patients. One widely studied group of inflammatory markers is derived from elements of the ubiquitously available and inexpensive full blood count (FBC). Specifically, the neutrophil-to-lymphocyte ratio (NLR) and the platelet- to-lymphocyte ratio (PLR) have both been demonstrated to be independent prognostic markers of CRC in advanced disease patients receiving chemotherapy and in operable patients.[3–5] Of these, the NLR has been the more widely studied and has been adopted as a predictor of mortality and morbidity in other diseases.[6]

Interestingly, monocyte levels have not been widely investigated as a biomarker in CRC despite evidence implicating them in carcinogenesis. In particular, tumor-associated macrophages (TAMs), which are derived from circulating monocyte populations, have been reported to be a key player in the tumor microenvironment, encouraging metastasis and tumor progression.[7] Only recently has the lymphocyte-to-monocyte ratio (LMR) been proposed and investigated as a prognostic marker in patients with solid tumors. There is recent evidence that the preoperative LMR is prognostic in patients with stage 3 and 4 resectable CRC.[8] The clinical utility of the LMR across earlier stages of colon and rectal cancer, however, remains poorly defined.

The modified Glasgow prognostic score (mGPS), a composite score of C-reactive protein (CRP) and albumin concentrations, has also been reported to be prognostic in CRC. There is some suggestion from previous investigations that the mGPS is superior to other established markers such as NLR; however, direct comparisons of the mGPS to the NLR in CRC have been limited to small cohort studies.[9] More importantly, CRP is, however, not performed routinely in

clinical treatment of CRC, limiting its widespread adoption and clinical utility.

In light of these recent findings, the present study aimed to investigate the prognostic value of the preoperative LMR in each stage of resectable CRC. In addition, we aimed to compare the relative prognostic value of existing routinely available biomarkers in patients with CRC. The study investigated these aims in a large cohort of stage I to III patients undergoing resection of primary tumors in an attempt to clarify the optimal use of these markers.

METHODS

Patient Cohort

We performed a retrospective analysis of a clinicopathological database at Northern Sydney Local Health District (NSLHD) (Sydney, NSW, Australia). Consecutive patients who had undergone resection of their CRC between January 1998 to December 2012 were eligible for inclusion. Patients without preoperative blood counts (within 30 days of surgery), without *BRAFV600E* or mismatch repair (MMR) immunohistochemistry (IHC), those treated endoluminally only, with histologies other than adenocarcinoma, those with partial synoptic reporting, and those with metastatic disease were excluded. The patients examined in the database encompassed patients from 2 major quaternary centers and 4 community hospitals with general surgical units. Prospective data collected perioperatively included sex, age, and histological grading. All cases were reviewed and restaged according to the *AJCC* 7th edition 2009 staging system.

Patient management was routinely discussed at multidisciplinary team meetings. Patients with high-risk stage II and III colon cancer disease were generally offered standard adjuvant chemotherapy, whereas those with stage II or III rectal cancers were usually treated with neoadjuvant chemoradiotherapy. Patients were treated at multiple public and private medical oncology and radiation units throughout NSLHD and consequently data for the use of chemotherapy and radiotherapy, both in the adjuvant and advanced disease setting in this cohort are incomplete and were not incorporated into the current analyses.

In the majority of patients follow-up consisted of 3 to 6 monthly clinical history and physical examination; 3 to 6 monthly biochemistry, FBC, and CEA; and 1 computed tomography of chest, abdomen, and pelvis 12 to 18 months postoperatively.[10]

Immunohistochemistry

Using previously described methods, which we have demonstrated to be highly accurate,[11,12] IHC was routinely performed to determine the MMR and *BRAFV600E* mutation status of this cohort. These findings have been previously reported.[11–14] The combined MMR-BRAF status was constructed as a composite of MMR proficient (MMRp)/deficient (MMRd) and BRAF mutant (BRAFV600E)/wild type (BRAFwt). Specifically, group 1 was MMRp/BRAFV600E, group 2 was MMRd/BRAFwt, group 3 was MMRd/BRAFV600E, and group 4 was MMRp/BRAFwt.

Survival Data

The primary endpoint for analysis was overall survival (OS), measured from the date of surgery until date of last follow-up or date of death from any cause. Follow-up data for patients were computed from electronic medical records, hospital pathology database, private offices, central death registries, and publically available obituary notices up to July 2015.

Serum Markers of Systemic Inflammation

Patients routinely received blood tests in the 30 days before surgery. All blood tests performed in the 30 days before surgery were obtained from local pathology databases. This included the FBC, albumin, and CRP (where available).

Statistics

The R package MaxStat was used to dichotomize the LMR, NLR, and PLR as previously described.[15,16] This package iteratively tests all possible cutpoints to find the cutpoint in which the maximum log-rank statistic is achieved. Patients are then dichotomized into ''low'' and ''high'' groups, in which ''low'' is less than or equal to the cutpoint and ''high'' is greater than the cutpoint. Associations between variables were analyzed using the χ^2 test. The relation between serum inflammatory markers and OS was examined using Kaplan-Meier log-rank test and univariate Cox proportional hazards regression. Variables found to be statistically significant ($P < 0.05$) in univariate analysis were entered into a Cox regression multivariate model using a forward conditional method. A P value of <0.05 was considered to be significant. Analyses were performed using SPSS software version 20 (SPSS Inc., Chicago, IL) and R (Version 3.2.1).

The present study was approved by the NSLHD Human Research Ethics Committee under protocol 1201–035M and RESP/14/97.

RESULTS

Of 3281 consecutive patients who underwent surgical resection of their CRC from January 1998 to December 2012 inclusive, 954 were missing preoperative FBCs, 385 were missing BRAF or MMR IHC, 211 had incomplete synoptic reporting, and 108 had metastatic disease. After exclusion, the final cohort consisted of 1623 patients (Fig. 1). We compared the baseline characteristics of patients who were included and those excluded. Although there were some statistically significant differences in age and T stage, these differences were small in absolute terms. Other baseline characteristics including N stage, sex, and site were not significantly different (supplementary Table 1, http://links.lww.com/SLA/B6).

MaxStat analysis was performed to find the optimal cutpoint for the LMR, NLR, and PLR. In analysis of all patients, a cutpoint of 2.38 for the LMR was found to have the highest log-rank statistic of any cutpoint. In pooled analysis we subsequently dichotomized patients into low LMR ($\leq$2.38) and high LMR ($>$2.38) groups. Similarly in pooled analysis, cutpoints of 3.19 and 258 were identified for the NLR and PLR, respectively. High and low groups were created using the same method as for the LMR. We also identified cutpoints for LMR in each stage of CRC, with values of 2.13, 1.59, and 2.38 for stages 1, 2, and 3, respectively. The individual cutpoints per stage for NLR and PLR can be found in supplementary Tables 2–4, http://links.lww.com/SLA/B6. In terms of the LMR, 826 (50.9%) patients had a low LMR and 797 (49.1%) had a high LMR. For the NLR, 721 patients (44.4%) were in the low group, whereas 902 (55.6%) were in the high group. For the PLR, 1075 (66.2%) patients were in the low group, whereas 548 (33.8%) were in the high group.

The complete baseline characteristics of all the patients and separately in the low and high LMR groups can be seen in Table 1. Patients were frequently older than 70 years of age (59.8%), had tumors of T stage 3/4 (54.3%/23.9%), N stage 0 (54.5%), and of low grade (43.8%). Sex was well balanced (women 50.6%). Most patients had left-sided colon tumors (46.8%) compared to 28% with right-sided colon and 25.2% with rectal tumors. In terms of MMR-BRAF status, the majority of patients were in the MMR proficient/BRAF wild-type group (73.9%). Median follow-up was 52 months (interquartile range 27–92 mo) with 560 deaths from any cause. The 5- and 10-year OS for CRC patients were 63.2% and 42.0%, respectively (Table 2).

We found that a low LMR was associated with both age ($P < 0.001$) and sex ($P = 0.002$). In particular, those with a low LMR were

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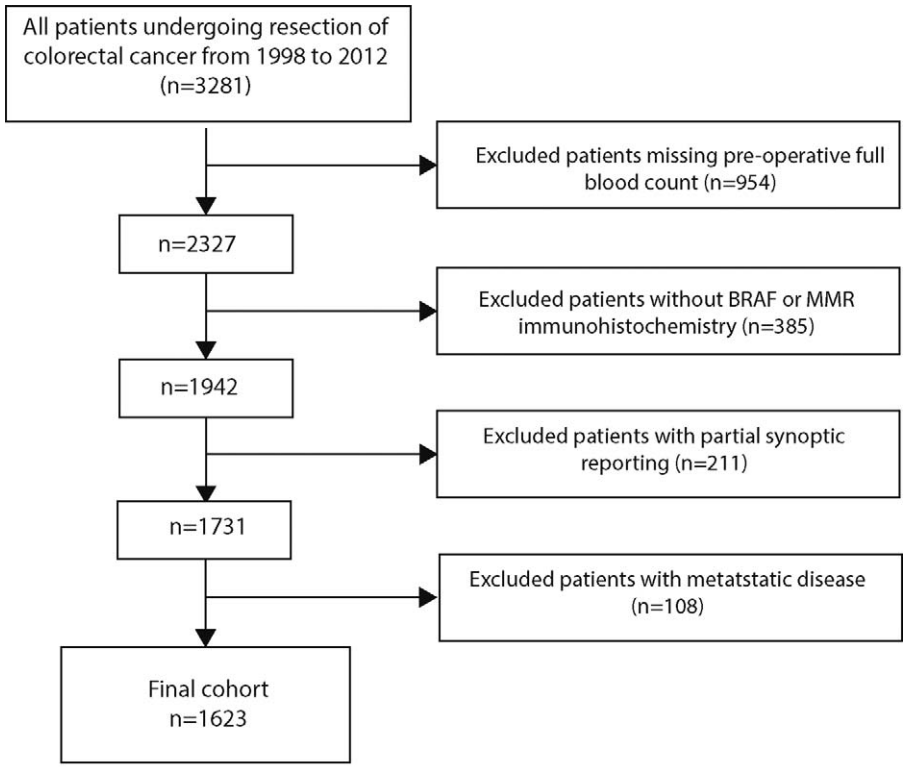

FIGURE 1. Flow chart of the patient cohort based on inclusion and exclusion criteria.

more likely to be older than 70 years (68.8%) compared to both the overall cohort (59.8%) and those with high LMR (51.3%). The patients were also more likely to be men (53.2%), whereas those in the high LMR group were more likely to be women (54.6%). The LMR was associated with T stage ($P < 0.001$) and grade ($P < 0.001$) but not N stage ($P = 0.103$). In patients with a low LMR we found that they were more likely to be stage 3 (56.0%) and 4 (30.1%) compared to stage 1 (3.9%) and 2 (11.0%). In contrast, in patients with a high LMR, there was a shift toward stages 1 (8.5%) and 2 (20.5%) and away from stage 3 (52.4%) or stage 4 (18.6%). There was also a higher likelihood that those with a low LMR possessed high-grade tumors (22.6%) compared to those in the high LMR group (14.9%). In terms of tumor site, the LMR was significantly associated with tumor site ($P < 0.001$). Patients with a low LMR were more likely to have left-sided colon tumors (51.5%) than right-sided (27.7%) or rectal (20.8%). In comparison, those with a high LMR had lower rates of left-sided colon tumors (42.0%) and higher rates of right-sided (28.2%) and rectal (29.8%). There was also an association between LMR and BRAF-MMR status ($P = 0.017$). We noted that patients with a low LMR were less likely to be in the MMR-proficient/BRAF wild-type group (70.6%) compared to those with a high LMR (77.4%). The LMR was also strongly associated with both NLR ($P < 0.001$) and PLR ($P < 0.001$). Specifically, high NLR was more likely in the low LMR group (84.4%) than in the high LMR group (25.7%). Similarly, a high PLR was more common in patients with a low LMR (54.1%) than those with a high LMR (12.7%).

Inflammatory Markers and Outcomes

Univariate analyses were performed on age, sex, LMR, NLR, PLR, and clinicopathologic factors to determine their association with OS. Those that were significant were evaluated in multivariate analyses (see Table 3). Older age ($P < 0.001$), higher T stage ($P < 0.001$), higher N stage ($P < 0.001$), higher grade ($P < 0.001$), combined BRAF-MMR status ($P = 0.002$), high NLR ($P < 0.001$), low LMR ($P < 0.001$), and high PLR ($P < 0.001$) were significantly associated with reduced OS in univariate analysis. In multivariate analyses, elevated LMR was associated with better OS (hazard ratio 0.565, 95% confidence interval: 0.475–0.672, $P < 0.001$), independent of age ($P < 0.001$), T stage ($P < 0.001$), N stage ($P < 0.001$), or grade ($P = 0.049$). Other biomarkers such as NLR, PLR, and combined BRAF-MMR status did not retain independent significance.

Considering outcomes by site, the overall 5- and 10-year survival for the cohort was similar whether the primary was located in the colon or rectum. In addition, the prognostic value of the LMR was similar in both groups (Table 2, Fig. 2).

In separate analysis of individual stages, LMR was shown to be significantly prognostic across all tumor stages in univariate analysis (Fig. 3). In multivariate analysis by separate stages, LMR was independently prognostic in stage 2 ($P < 0.001$) and stage 3 ($P < 0.001$) CRC but not in stage 1 CRC (full data supplementary Tables 2–4, http://links.lww.com/SLA/B6). The prognostic value of the LMR was consistent when considering subgroups by age, sex, stage, or site (Fig. 2). Of the 1623 patients in our cohort with full data sets, 386 also had mGPS values available for analysis. In multivariate analysis we found LMR to be independently significant (hazard ratio 0.620, 95% confidence interval: 0.437–0.880, $P = 0.007$) of age ($P < 0.001$, T stage <0.001, grade $P = 0.031$). NLR ($P = 0.585$), PLR ($P = 0.493$), and mGPS ($P = 0.066$), however, did not achieve independent significance on prognosis (full results in supplementary Table 5, http://links.lww.com/SLA/B6).

DISCUSSION

Our findings demonstrate that the preoperative LMR is an independent predictor of OS for patients with CRC undergoing

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TABLE 1. Baseline Patient Clinicopathologic Characteristics

Clinicopathologic Characteristics	Total LMR (n = 1623), No (%)	Low LMR (n = 826, 50.9%), No (%)	High LMR (n = 797, 49.1%), No (%)	*P*
Age				
≤70	652 (40.2)	264 (31.2)	388 (48.7)	<0.001
>70	971 (59.8)	562 (68.8)	409 (51.3)	—
Sex				
Female	882 (50.6)	387 (46.8)	435 (54.6)	0.002
Male	801 (49.4)	439 (53.2)	362 (45.4)	—
T Stage				
1	100 (6.2)	32 (3.9)	68 (8.5)	<0.001
2	254 (15.7)	91 (11.0)	163 (20.5)	—
3	881 (54.3)	463 (56.0)	418 (52.4)	—
4	388 (23.9)	249 (30.1)	148 (18.6)	—
N stage				
0	885 (54.5)	431 (52.2)	454 (57.0)	0.103
1	478 (29.5)	250 (30.2)	228 (28.6)	—
2	260 (16.0)	145 (17.6)	115 (14.4)	—
Grade				
Low	711 (43.8)	331 (40.0)	380 (47.7)	<0.001
Mod	606 (37.3)	308 (37.3)	298 (37.4)	—
High	306 (18.9)	187 (22.6)	119 (14.9)	—
Site				
Left-sided colon	760 (46.8)	425 (51.5)	335 (42.0)	<0.001
Right-sided colon	454 (28.0)	229 (27.7)	225 (28.2)	—
Rectum	409 (25.2)	172 (20.8)	237 (29.8)	—
MMR-BRAF status				
MMRp/BRAFV600E	161 (9.9)	90 (10.9)	71 (8.9)	0.017
MMRd/BRAFwt	76 (4.7)	43 (5.2)	33 (4.1)	—
MMRd/BRAFV600E	186 (11.5)	110 (13.3)	76 (9.5)	—
MMRp/BRAFwt	1200 (73.9)	583 (70.6)	617 (77.4)	—
NLR				
Low (≤3.19)	721 (44.4)	129 (15.6)	592 (74.3)	<0.001
High (>3.19)	902 (55.6)	697 (84.4)	205 (25.7)	—
PLR				
Low (≤258)	1075 (66.2)	379 (45.9)	696 (87.3)	<0.001
High (>258)	548 (33.8)	447 (54.1)	101 (12.7)	—

The values in this table are expressed as No. (%).

curative surgical resection. We have also established that the LMR is superior to NLR and PLR as a predictor of OS in this cohort of patients. Furthermore, in the subgroup of patients for whom mGPS values were available, we found that the LMR was superior to mGPS. Finally, we demonstrate that these results are independently predictive of OS regardless of *BRAFV600E* mutation or MMR status. Together, the present study represents the single largest consecutive CRC cohort to investigate and compare the prognostic value of these established markers of inflammation.

The first part of the study was successful in defining the utility of the LMR as a prognostic marker in CRC. Previous studies examining the LMR in CRC, had been limited both in size and scope to select populations within stage III and IV diseases.[8,17,18] In this present study, we show for the first time that the LMR is an independent prognostic marker in pooled analysis of stages I to III disease and also individually in stage II and stage III CRC. Furthermore, we have defined optimal cutpoints for the first time in stage I and II CRC, with values of 2.13 and 1.59, respectively. We have also calculated optimal

TABLE 2. Relation Between the LMR and 5- and 10-Year OS in Patients With Stage I to III CRC

	Low LMR (≤2.38)		High LMR (>2.38)		Total	
Stage I–III	**n**	**5-Year OS**	**n**	**5-Year OS**	**n**	**5-Year OS**
Colon	654	52.2 (2.4)	560	74.8 (2.2)	1214	63.1 (1.7)
Rectal	172	53.5 (4.5)	237	70.7 (3.7)	409	63.4 (2.9)
Total colorectal	826	52.5 (2.1)	797	73.6 (1.9)	1623	63.2 (1.5)
	n	**10-Year OS**	**n**	**10-Year OS**	**n**	**10-Year OS**
Colon	654	33.6 (3.1)	560	50.7 (3.8)	1214	41.8 (2.5)
Rectal	172	38.5 (5.8)	237	52.7 (5.5)	409	42.5 (4.1)
Total colorectal	826	32.5 (2.8)	797	51.4 (3.1)	1623	42.0 (2.1)

The values in this table are expressed as % (standard error). The percentage of patients surviving is shown individually and together for colon and rectal cancers.

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TABLE 3. Univariate and Multivariate Analysis of Clinicopathologic Variables in Relation to Overall Survival in Patients With CRC Undergoing Curative Resection

Clinicopathologic Characteristics	Univariate Analysis, HR (95% CI)	*P*	Multivariate Analysis, HR (95% CI)	*P*
Age				
≤70	1 (Referent)	<0.001	1 (Referent)	<0.001
>70	2.057 (1.713–2.470)	—	1.981 (1.642–2.388)	—
Sex				
Female	1 (Referent)	0.162	—	—
Male	1.125 (0.953–1.328)	—	—	—
T Stage				
1	1 (Referent)	<0.001	1 (Referent)	<0.001
2	0.985 (0.592–1.640)	—	0.900 (0.540–1.498)	—
3	1.805 (1.147–2.840)	—	1.380 (0.873–2.182)	—
4	4.834 (3.044–7.677)	—	3.282 (2.039–5.282)	—
N stage				
0	1 (Referent)	<0.001	1 (Referent)	<0.001
1	1.518 (1.254–1.837)	—	1.246 (1.023–1.517)	—
2	3.041 (2.444–3.785)	—	2.299 (1.809–2.922)	—
Grade				
Low	1 (Referent)	<0.001	1 (Referent)	0.049
Mod	1.309 (1.066–1.606)	—	1.293 (1.053–1.589)	—
High	1.654 (1.303–2.100)	—	1.148 (0.898–1.467)	—
Site				
Left-sided colon	1 (Referent)	0.618	—	—
Right-sided colon	1.062 (0.873–1.293)	—	—	—
Rectum	0.949 (0.772–1.166)	—	—	—
MMR-BRAF status				
MMRp/BRAFV600E	1 (Referent)	0.002	—	0.146
MMRd/BRAFwt	0.644 (0.406–1.024)	—	—	—
MMRd/BRAFV600E	0.533 (0.378–0.753)	—	—	—
MMRp/BRAFwt	0.650 (0.506–0.836)	—	—	—
NLR				
Low (≤3.19)	1 (Referent)	<0.001	—	0.124
High (>3.19)	1.830 (1.539–2.176)	—	—	—
LMR				
Low (≤2.38)	1 (Referent)	<0.001	1 (Referent)	<0.001
High (>2.38)	0.486 (0.409–0.576)	—	0.569 (0.478–0.677)	—
PLR				
Low (≤258)	1 (Referent)	<0.001	—	0.592
High (>258)	1.592 (1.343–1.886)	—	—	—

CI indicates confidence interval; HR, hazard ratio.

outpoints for both stage III CRC and also pooled stages I to III CRC of 2.38, values which are similar to cutpoints previously defined for stage III colon and stage IV CRC of 2.83 and 3.0, respectively.[8,17,18]

The study revealed some interesting associations between the LMR and clinicopathologic factors. Firstly, the study demonstrated that a low LMR was associated with more advanced T stage and higher grade tumors but not N stage. This finding suggests that the

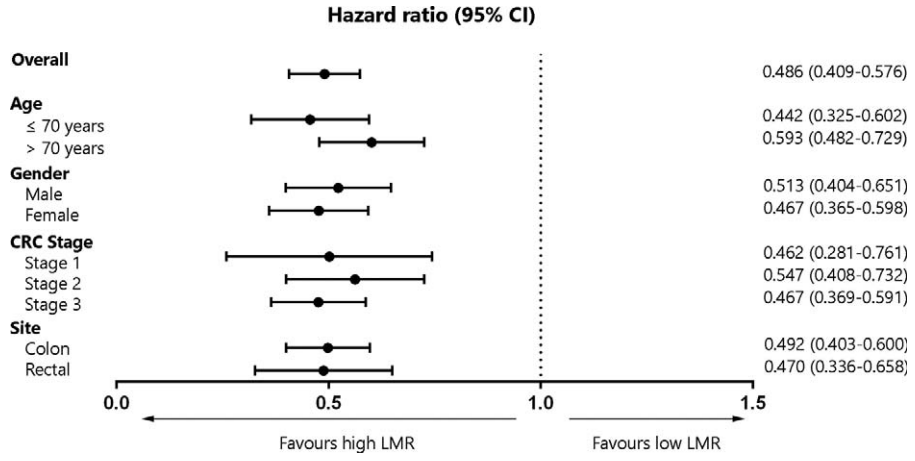

FIGURE 2. Hazard ratios for overall survival according to subgroups (age, sex, stage, and site). Hazard ratios were derived from a Cox proportional hazards model.

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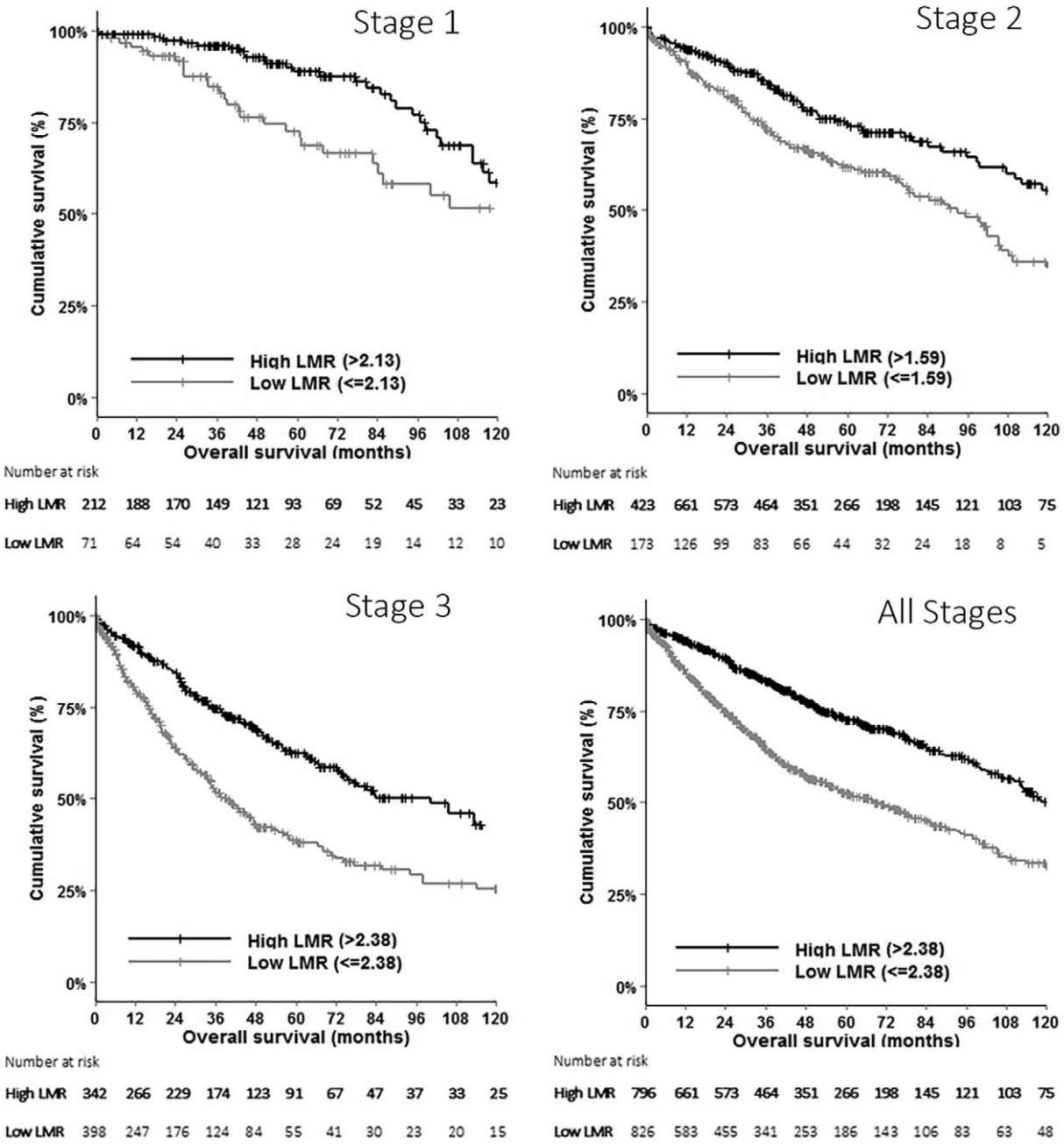

FIGURE 3. Relation between OS and LMR by stage. Top left: relation between OS and stage 1 CRC ($P < 0.001$). Top right: relation between OS and stage 2 CRC ($P < 0.001$). Bottom left: relation between OS and stage 3 CRC ($P < 0.001$). Bottom right: relation between OS and pooled stage 1 to stage 3 patients with CRC ($P < 0.001$).

LMR may be a more potent driver of tumor proliferation than metastatic potential. Secondly, we found that the site of tumors was significantly more likely to be left sided and less likely to be rectal in patients with low LMR. The significance of this finding is not clear, but it could suggest that the colon is more susceptible to mediators of inflammation than the rectum. Finally and perhaps most interesting of all the associations, there was a tendency in patients with low LMR to have MMR deficiency or BRAF mutation. If such an association between inflammation and DNA damage could be validated, then inflammatory biomarkers such as the LMR may hold value as surrogates to existing genomic markers. Interestingly, however, a recent study that attempted to find a correlation between the NLR and MMR status was negative.[19] Certainly, the present study provides a foundation for a future examination of the association between genomic mutation and inflammation.

The present study did not aim to provide a mechanistic understanding of why the LMR is prognostic. On a general level, markers derived from the FBC are, however, a reflection of

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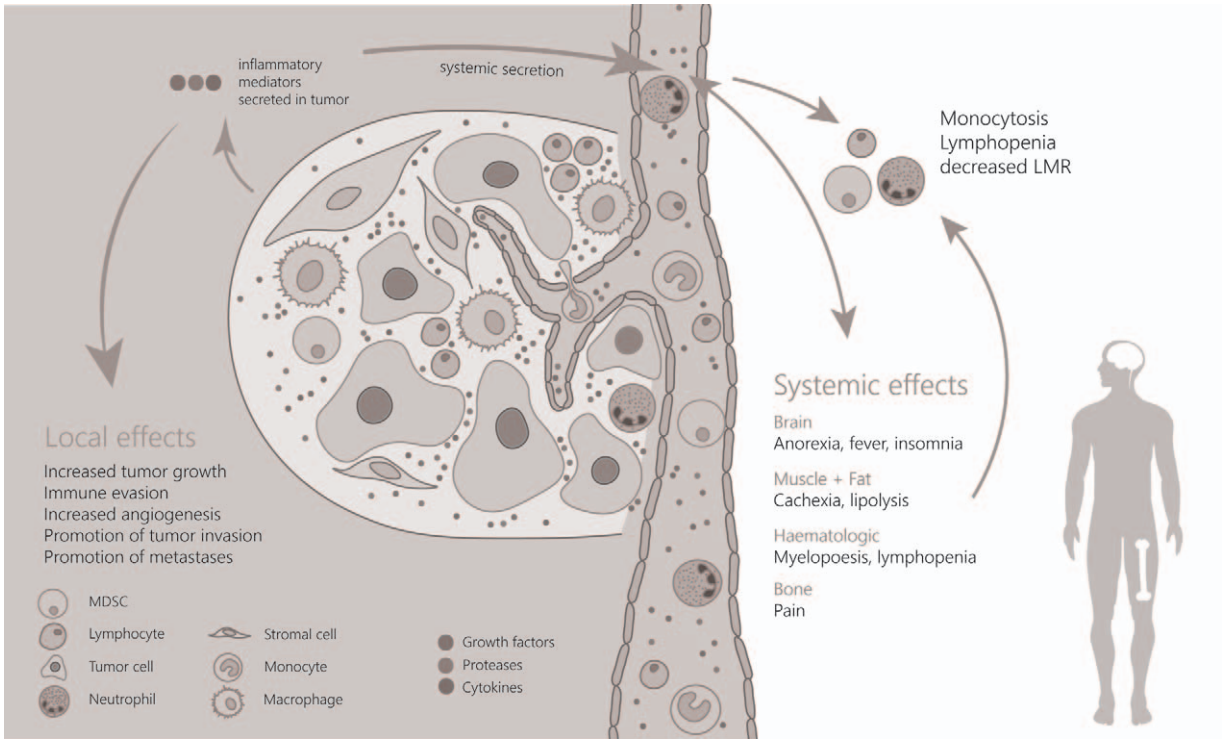

FIGURE 4. Overview of the interactions of the tumor microenvironment. Cytokines, growth factors, proteases, and other mediators are secreted both in the tumor and into systemic circulation where they exert local and systemic inflammatory effects. One particular effect is changes to the hematologic system. The LMR therefore reflect inflammatory processes not only at the tumor level but also systemically.

inflammation that occurs both at a local and systemic level during cancer (Fig. 4). The lymphocyte component of these markers has been well documented in studies as early as the 1970s in which lymphocyte counts were observed to be decreased in patients with more advanced colon cancer.[20] This has been part of the basis of other established markers such as the NLR and the PLR. The association that monocytes may be useful has, however, only recently been evaluated and found to be prognostic. To date, there have only been preliminary hypotheses put forward to explain why monocytes may confer prognostic information. Here we propose several additional mechanisms. First, it may be important to consider that the immature neutrophils (common in an excessive ''blast-like'' acute inflammatory reaction) may in fact be gated as monocytes on automated Coulter counters used in routine clinical practice. Given our findings that the LMR is, however, more significant than the NLR, we suggest that this is not the predominant reason for the current findings. Instead, circulating monocytes may contribute to both tumor growth and reduced immunosurveillance, which is supported by previous literature.[21] Second, serum monocytes differentiate into macrophages within the tumor after infiltration. There is mounting evidence that TAMs exert activity that is primarily protumoral including promotion of metastasis, immunosuppression, and tumor angiogenesis.[7] Therefore, elevated circulating serum levels of monocytes may reflect increased levels of TAMs and poorer prognosis. Finally, myeloid-derived suppressor cells are a subset of circulating leucocytes known to have immunosuppressive activity. An elevated monocytic myeloid-derived suppressor cell count may also be reflected by increased monocyte count. Facilitating immunosuppression may lead to reduced tumor immunity and confer a worse prognosis.

In addition to defining the LMR, the present study also expanded on comparisons of established markers in CRC. To our knowledge, this is the first time that the LMR has been demonstrated to be superior to the NLR and PLR, both established independent predictors of OS. Before this finding, studies had generally reported the NLR to be superior to the PLR[5,22,23]; however, we found neither the NLR nor the PLR to be independently prognostic when studied together with the LMR. Importantly, the cutpoints used in these findings for NLR and PLR of 3.19 and 258, respectively were in concordance with previous literature.[3,11,13] This not only reaffirms the reproducibility of hematologic markers across differing populations, but also strengthens the argument that the LMR is a superior predictor.

The study also attempted to clarify the utility of the mGPS in comparison to ratios derived from the FBC. As CRP and albumin are not routinely performed preoperatively in our cohort, we set out to perform a preplanned subgroup analysis of patients for whom the mGPS was available. This selected cohort was significantly older and more advanced in tumor stage than the general cohort. Analysis demonstrated that the only independently significant biomarker in multivariate analysis was LMR; however, the mGPS did trend closer to significance than the NLR, suggesting concordance with some previous reports.[9] Finally, the study demonstrated the LMR to be independently prognostic of a 4-tiered combination of the commonly used genomic markers of *BRAFV600E* mutation and MMR status. Previously these markers had been shown to be an independent prognostic marker of OS in CRC.[12,14] The finding that the LMR is a superior prognostic marker is of great interest as the LMR can be routinely done at a much lower cost than genomic markers.

The present study has several limitations that require discussion. First, the study was uncontrolled and retrospective in nature;

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however, the cohort represents one of the largest consecutive cohorts ever to be used in the study of systemic markers of inflammation. Second, as some patients were subsequently treated with chemotherapy and radiotherapy in a number of different public and private treatment centers, we do not have complete data on these aspects of management and thus we have not included information on the types of radiotherapy or chemotherapeutic treatment received by patients. A previous study by us, supported by other published data, however, showed that the NLR, although prognostic, was not predictive of cancer-specific survival or benefit from adjuvant therapy in stage III patients and thus, we do not believe that this limitation significantly detracts from the current results.[8,24] Furthermore, our aim was not to address specific therapeutic implications but rather to better characterize the LMR and provide an overview as to its role in prognostication compared to other markers of systemic inflammation in the context of operable patients with CRC.

The findings of our study suggest numerous avenues for follow-up studies. Importantly, there needs to be a re-evaluation of the optimal use of systemic markers of inflammation. Before the study, there was much debate regarding the value of markers derived from the FBC when compared to the mGPS. There was evidence to suggest that the mGPS was superior to the NLR; however, the routine nature of the FBC gave weight in favor of the NLR over the mGPS. The present study adds the LMR to the discussion, with evidence that the LMR is the superior marker to both hematologic and some simple genomic biomarkers. Certainly there needs to be further independent validation of the findings of the present study (ideally in a prospective fashion) especially with regards to the predictive value of LMR across all stages of CRC.

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