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Hematological markers as prognostic predictors in patients undergoing colon cancer surgery

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To determine if neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR), can predict postoperative complications (PC), 5-year survival, and 5-year disease-free survival (DFS) in stages I-III colon adenocarcinoma, analyzing outcomes generally and by tumor location (right colon vs. left colon). A retrospective multicenter cohort study analyzed patients who underwent surgery for colon adenocarcinoma with curative intent between January 2007 and December 2017. Patients were in stages I to III with at least 5 years of follow-up. Exclusion criteria included urgent surgeries, active infections, immunosuppression, rectal neoplasia, stage IV, or unresectable tumors. NLR, LMR, PLR, PC, survival, and DFS were analyzed adjusting for demographic and clinical variables. Optimal cutoff points were determined using receiver operating characteristic curves. Multivariable logistic models were performed both generally and by tumor location. The study included 805 patients with a 5-year survival rate of 75.28% and DFS of 76.27%. Multivariable analysis showed lower survival and DFS with NLR > 3.09, LMR < 2.40, and PLR > 145.16. In right-sided colon tumors, NLR and LMR were associated with 5-year survival. In left-sided colon tumors, LMR was linked to survival and DFS and NLR > 2.79 was associated with increased risk of postoperative anastomotic leaks. NLR, LMR and PLR are effective predictor of survival and DFS in colon cancer. High NLR is associated with an increased risk of anastomotic leaks. However, this associations change when analyzing by tumor location. This highlights the importance of considering tumor location in treatment planning and biomarker research for colon cancer.

Keywords Neutrophil-to-lymphocyte ratio, Lymphocyte-to-monocyte ratio, Platelet-to-lymphocyte ratio, Colon adenocarcinoma, Prognosis, Tumor location

Colorectal cancer (CRC) is the third most common cancer diagnosed worldwide, causing approximately 13,000 deaths annually in Spain[1]. The 5-year disease specific survival and overall survival (OS) rates after surgical resection are 95% and 82.7% for stage I, 84.7% and 70.3% for stage II and 68.7% and 58.3% for stage III[2].

Non-metastatic CRC treatment primarily involves surgical resection with curative intent, followed by adjuvant chemotherapy when specific criteria are met[3]. While adjuvant chemotherapy improves 5-year OS by 22–30% and reduces recurrence risk by 30% in stage III CRC, its use in stage II remains controversial. Up to 30% of stage II patients experience recurrence or metastasis despite curative surgery[2,4]. Thus, there is a critical need for accessible prognostic tools to better guide treatment decisions.

Tumor prognosis is influenced not only by tumor characteristics but also by the host's inflammatory response, which promotes tumor growth and metastasis through cytokine release[5,6]. Although various molecular markers are associated with tumor aggressiveness and survival, their high cost and limited routine use necessitate the exploration of more practical alternatives. Hematologic markers such as the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR), obtainable from preoperative blood tests, have shown promise as prognostic indicators in multiple cancers, including CRC[7].

CRC encompasses colon cancer and rectal cancer, which are often treated as the same entity, but they have different anatomy, staging and treatment, resulting in different surgical outcomes and recurrence patterns[8,9].

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Both types metastasize to the liver, but colon cancer metastasizes more to the peritoneum and rectal cancer metastasizes twice as often to the lungs[9]. The colon is divided into the right colon (RC) and the left colon (LC). The RC includes the cecum to the transverse colon, and the LC includes the splenic flexure to the rectosigmoid junction[10]. There are several differences between them: the RC originates from the midgut, with carcinogenesis more frequently via microsatellite instability and CpG island methylator phenotype pathways, and tumors have a flat morphology, making them harder to diagnose and often presenting at higher stages[10,11]. RC tumors also have higher immunogenicity and worse prognosis[12]. The LC originates from the hindgut, with carcinogenesis frequently via chromosomal instability (CIN), and tumors have a polypoid morphology[10,11]. RC tumors metastasize more frequently to the peritoneum, whereas LC tumors metastasize to the liver and lungs[8–10].

This study investigates the predictive value of NLR, LMR, and PLR for overall survival (OS), disease-free survival (DFS), and postoperative complications (PC) in stages I-III colon adenocarcinoma. Given the differences between RC and LC, we conducted analyses both generally and by tumor location (RC vs. LC).

Materials and methods

This study was designed and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to ensure transparent and standardized reporting of observational research.

Study design and population

This retrospective multicenter cohort study included patients who underwent curative surgery for stage I-III colon adenocarcinoma from January 2007 to December 2017, with a minimum follow-up of 5 years. Patients were excluded if they had urgent surgeries, active infections, immunosuppression, rectal neoplasia, stage IV, or unresectable tumors.

All patients followed their hospital's protocols for scheduled colon surgery, which included bowel preparation with cleansing solutions and oral antibiotics.

To reflect clinical differences in treatment approaches, particularly in stage II disease, we further stratified stage II into IIA and IIB/IIC. Stage III patients were retained in the analysis, as AJCC staging remains the most established and validated prognostic system in colon cancer. Including all non-metastatic stages (I–III) enabled a comprehensive evaluation of hematologic markers across a clinically relevant spectrum of disease. Multivariable models adjusted for stage to account for treatment heterogeneity and prognostic impact.

Sample size calculation

A sample of approximately 372 subjects is sufficient to detect a hazard ratio (HR) of 1.75 for the effect of the NLR with 80% power. A type I error of 5% and a dropout rate of 10% were established. It was estimated that 20% of the patients would be above the established cutoff point for NLR. Analysis by tumor location was a secondary outcome, for which we didn't calculate a sample size.

Data collection

Data on demographics, clinical variables, NLR, LMR, PLR, postoperative complications, 5-year survival, and 5-year DFS were collected. NLR, LMR, and PLR were calculated from the last preoperative blood test, which is within 30 days from the surgery. All samples were processed using the analyzer by the brand Sysmex, model XN1000.

Recurrence dates were based on colonoscopy or imaging test showing a local recurrence or distant metastases. Tumor location was classified as RC, from the caecum to transverse colon, and LC, from the splenic flexure to sigma.

Statistical analysis

Receiver operating characteristic ROC curves determined optimal cutoff points for NLR, LMR, and PLR. Descriptive statistics, univariable, and multivariable logistic regression analyses were conducted to evaluate the association between hematologic markers and outcomes, adjusting for potential confounders. Analyses were performed both generally and by tumor location (RC vs. LC) to identify any differential impacts based on the location of the tumor. Statistical analysis was carried on with R version 4.3.3.

Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of Bellvitge University Hospital in Barcelona with the reference number PR238/22 (CSAPG-38). This Committee complies with the current Spanish legislation for this type of projects as well as with the ICH guidelines and the Good Clinical Practice standards.

Results

Patient characteristics

The study included 805 patients with an average age of 68.6 years. AL was reported in 45 patients, 20 of which had a LC tumor. The 5-year survival rate was 75.28%, and the DFS was 76.27%. The mean follow-up was 91 months (standard deviation [SD] 48 months, range 61–126 months). Patient characteristics and hematologic marker distributions are detailed in Table 1.

Data exclusions

Categories Tx and Nx were not included in the analysis. There are other variables that don't add up to 805 due to information not available in the pathology results, like vascular invasion or intratumoral lymphocytes.

Variable	Category	Total ($n=805$)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value
Sex	Male Female	466 339	1.00 0.98 (0.71–1.35)	– 0.8944		
Age		68.6 (± 11.6)	1.04 (1.03–1.06)	0	1.01 (0.98–1.03)	0.5373
BMI		27.6 (± 4.8)	0.98 (0.95–1.02)	0.312		
Charlson index		4.6 (± 1.8)	1.43 (1.30–1.58)	0	1.34 (1.15–1.57)	**0.0002**
ASA	I II III IV	23 473 292 16	1.00 5.24 (1.08–94.46) 10.61(2.18–191.4) 48.40(7.13–998.8)	– 0.1074 0.0218 8e–0	1.00 4.14 (0.78–77.06) 5.42 (1.00–101.67) 11.83 (1.48–261.38)	– 0.1801 0.1139 **0.0425**
CEA	< 5 ≥ 5	596 182	1.00 1.63 (1.12–2.34)	– 0.0091	1.00 1.21 (0.79–1.84)	0.3793
Tumor size	< 5 cm ≥ 5 cm	516 246	1.00 1.03 (0.72–1.46)	– 0.8636		
Location	Right colon Left colon	382 422	1.00 0.64 (0.47–0.89)	– 0.0073	1.00 0.67(0.46–0.97)	**0.0321**
Technique	Laparoscopic Open	559 242	1.00 1.13 (0.80–1.59)	– 0.49		
PO complications	AL Ileus Sepsis SSI Others	45 (5.6%) 52 (6.5%) 20 (2.5%) 44 (5.5%) 90 (11.2%)	1.40 (0.71–2.65) 0.45 (0.18–0.96) 3.88 (1.58–9.76) 1.02 (0.48–1.99) 1.81 (1.13–2.87)	0.3084 0.0573 0.003 0.9647 0.0124	0.94 (0.40–2.09) 0.32 (0.12–0.76) 6.79 (1.99–24.53) 0.51 (0.18–1.28) 1.09 (0.61–1.92)	0.8924 **0.017** **0.0025** 0.1736 0.7678
AJCC Stage	I IIA IIB/C III	195 279 37 291	1.00 1.10 (0.69–1.77) 1.93 (0.85–4.21) 2.25 (1.46–3.53)	– 0.6997 0.1036 3e–04	1.00 0.87 (0.52–1.47) 2.12 (0.83–5.18) 1.78 (1.07–3.00)	– 0.6081 0.1066 **0.029**
T stage	T1 T2 T3 T4	92 152 486 74	1.00 0.87 (0.45–1.68) 1.27 (0.75–2.25) 2.62 (1.33–5.27)	– 0.6686 0.3843 0.0059		
N stage	N0 N1 N2	508 12 84	1.00 1.73 (1.19–2.50) 3.46 (2.13–5.60)	– 0.0036 0		
Differentiation	G1 G2 G3	591 78 130	1.00 0.80 (0.43–1.40) 1.14 (0.74–1.75)	– 0.4542 0.5413		
Vascular invasion	Yes No	138 665	1.00 0.47 (0.32–0.70)	– 1e–04	1.00 0.55 (0.33–0.90)	– **0.0169**
Perineural invasion	Yes No	110 692	1.00 0.57 (0.37–0.88)	– 0.0095	1.00 0.68 (0.40–1.17)	– 0.1584
Intratumoral lymphocytes	No Mild Moderate Severe	314 380 53 33	1.00 1.40 (0.98–2.00) 2.67 (1.44–4.89) 1.01 (0.39–2.32)	– 0.0636 0.0016 0.9794		
MSI	Yes No	195 245	1.00 0.31 (0.20–0.47)	– 0		
Adjuvant therapy	Yes No	307 494	1.00 0.95 (0.69–1.33)	– 0.7712		
NLR		3.2 (± 2.9)	1.99 (1.43–2.77)	0	1.61 (1.12–2.32)	**0.0107**
LMR		3.5 (± 1.9)	0.41 (0.29–0.58)	0	0.46 (0.31–0.67)	**0.0001**
PLR		176.2 (± 107.8)	1.78 (1.28–2.48)	6e–04	1.55 (1.07–2.24)	**0.0206**

Table 1. Association of clinicopathological characteristics of colon cancer patients with 5-year survival since surgical treatment. Significance value bold.

microsatellite instability is not a routine test and was only determined in 440 cases. Hence, it was excluded from the multivariable analysis.

Hematologic markers and outcomes

When analyzing survival and DFS, the cut-off point for NLR was 3.09, for LMR 2.40 and for PLR 145.16 (Fig. 1). When analyzing anastomotic leak (AL), it had an association with NLR, so a cut-off point was determined for this specific complication, resulting in 2.79 *ADD TABLE IN ANNEX?.

Multivariable analysis

The multivariable analysis confirmed that a high NLR and PLR, and low LMR, are independent predictors of 5-year survival ($p=0.0107$, $p=0.0206$ and $p=0.0001$ respectively, shown in Table 1) and DFS ($p=0.018$, $p=0.0252$ and $p=0.0013$ respectively, shown in Table 2). For postoperative complications, only the anastomotic

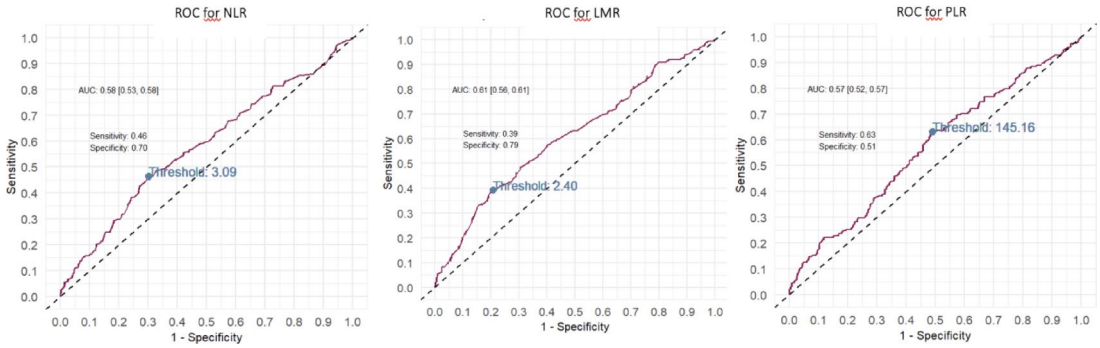

Fig. 1. ROC curves for NLR, LMR and PLR and 5-year survival.

leak (AL) had an association with NLR ($p = 0.013$, shown in Table 3). The multivariable analysis confirmed this association ($p = 0.033$, shown in Table 4).

In the analysis by tumor location, these associations change. In the RC, the NLR and LMR predicted survival ($p = 0.0164$ and $p = 0.0015$ respectively). No marker predicted DFS or AL in the RC. In the LC, LMR < 2.40 was linked to lower survival ($p = 0.0052$, shown in Table 5) and DFS ($p = 0.0045$, shown in Table 6), and NLR > 2.79 predicted AL ($p = 0.025$, shown in Table 4).

Discussion

The majority of CRC develops from de adenoma-carcinoma sequence[8,13]. An accumulation of several gene mutations must occur to promote this change and posterior tumor cells growth[14]. Moreover, several factors are responsible for these mutations, especially genetics, as well as environmental factors and chronic inflammation[8]. Chronic inflammation has been well established, specifically with inflammatory bowel disease. Immune cells, whether innate or adaptative, release pro-inflammatory cytokines that contribute to tumor growth and progression[15].

In line with the role of inflammation in CRC, our study demonstrates that the NLR, LMR and PLR are valuable prognostic markers in stages I-III colon adenocarcinoma. Specifically, higher NLR and PLR and lower LMR were associated with poorer 5-year survival and DFS, particularly in RC tumors. NLR also emerged as a predictor of anastomotic leaks in LC tumors.

NLR

The correlation between inflammation and cancer has been well established[16]. An increase in neutrophils indicates an increase in the inflammatory response, which is considered to induce tumor growth due to cytokine induced angiogenesis. On the other hand, a decrease of lymphocytes indicates a decline in the immune response to the tumor, which is cell-mediated[17–19]. The CD4 + or CD8 + T cells that should induce tumor cell apoptosis are diminished. Therefore, a high NLR should indicate a worse prognosis[20].

NLR was first described as a parameter to predict outcomes in intensive care unit patients with severe sepsis. They observed that the severity of clinical course correlated with the grade of neutrophilia and lymphocytopenia[21]. Previous studies have shown that elevated NLR is associated with worse survival and response to treatment in multiple cancers, like hepatic, biliary, pancreatic, gastric, esophageal and lung[5,20,22,23].

In CRC, NLR has been found to be significantly more elevated in higher stages[24–26]. The cut-off value varies. Nevertheless, several studies have demonstrated that a preoperative NLR ≥ 5 indicates a worse overall and cancer-specific survival and more postoperative complications[18,26]. Walsch et al.[26] first reported that CRC patients with a preoperative NLR > 5 had a significantly worse overall and a worse cancer-specific survival. Urrejola et al.[18] showed that CRC stage II with a NLR ≥ 5 had more postoperative complications and a worse overall survival and a worse disease-free survival.

Our findings align with these previous studies, highlighting the prognostic significance of NLR in CC, particularly in the RC subset. The observed correlation between elevated NLR and AL in LC tumors underscores its potential utility in preoperative risk assessment. However, further prospective studies are required to validate these findings. While the incidence of anastomotic leaks in our sample falls within the expected range for this complication, the sample size is insufficient to definitively establish the prognostic value of NLR.

LMR

Tumor-associated macrophages have been shown to promote angiogenesis and suppress adaptative immunity, promoting tumor growth, in rats and humans. This is mainly by the production of interleukin 6 (IL-6), which activates an intracellular signaling pathway that results in the induction of various target genes. These genes are involved in angiogenesis, proliferation, tumor cell survival, metastasis and more inflammation[6,15,27].

While macrophages have been shown to be tumor promoters in some cancers like breast, prostate, bladder, glioma and cervical, some studies have found them to be associated with improved prognosis, like stomach and CRC[28].

LMR reflects the balance between the inflammatory response and the adaptive immune response. It was first described as a prognostic factor in hematologic malignancies, showing a better survival when elevated[29,30].

Variable	Category	Total ($n=805$)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value
Sex	male female	466 339	1.00 0.99 (0.71–1.37)	0.942		
Age		68.6 (± 11.6)	1.01 (1.00–1.02)	0.1717		
BMI		27.6 (± 4.8)	0.96 (0.92–0.99)	0.0282	0.95 (0.91–0.99)	**0.0205**
Charlson index		4.6 (± 1.8)	1.11 (1.02–1.22)	0.019	1.18 (1.05–1.33)	**0.0067**
ASA	I II III IV	23 473 292 16	1.00 1.46 (0.53–5.10) 1.50 (0.54–5.30) 2.16(0.48–10.43)	– 0.5025 0.4760 0.4761		
CEA	< 5 ≥ 5	596 182	1.00 1.57(1.08–2.2795)	– 0.0175	1.00 1.18 (0.76–1.81)	– 0.4442
Tumor size	< 5 cm ≥ 5 cm	516 246	1.00 0.81 (0.56–1.16)	– 0.2603		
Location	Right colon Left colon	382 422	1.00 0.60 (0.43–0.84)	– 0.0026	1.00 0.59 (0.40–0.87)	– **0.0076**
Technique	Laparoscopic Open	559 242	1.00 0.92 (0.64–1.32)	– 0.6638		
PO complications	AL Ileus Sepsis SSI Others	45 (5.6%) 52 (6.5%) 20 (2.5%) 44 (5.5%) 90 (11.2%)	1.18(0.57–2.27) 0.40(0.15–0.88) 0.16(0.01–0.80) 0.49(0.18–1.10) 0.98(0.57–1.61)	0.6336 0.0385 0.0798 0.1124 0.9258	2.16(0.92–4.92) 0.26(0.07–0.70) 0.25(0.01–1.46) 0.84(0.28–2.23) 0.60(0.29–1.18)	0.0692 **0.0163** 0.2039 0.7441 0.1544
AJCC Stage	I IIA IIB/C III	195 279 37 291	1.00 1.59(0.94–2.76) 3.59(1.56–8.04) 4.22(2.61–7.08)	– 0.087 0.0021 0	1.00 1.25(0.69–2.31) 2.17(0.73–6.14) 2.89(1.49–5.76)	– 0.475 0.1507 **0.002**
T stage	T1 T2 T3 T4	92 152 486 74	1.00 1.03(0.50–2.21) 2.13(1.18–4.12) 3.92(1.88–8.51)	– 0.9409 0.0172 0.0004		
N stage	N0 N1 N2	508 12 84	1.00 2.33(1.60–3.40) 5.80(3.56–9.50)	– 0 0		
Differentiation	G1 G2 G3	591 78 130	1.00 0.96(0.53–1.66) 1.42(0.92–2.16)	– 0.8877 0.1037		
Vascular invasion	Yes No	138 665	1.00 0.51(0.35–0.77)	– 0.001	1.00 0.99 (0.60–1.66)	– 0.9804
Perineural invasion	Yes No	110 692	1.00 0.36(0.24–0.55)	– 0	1.00 0.44 (0.26–0.75)	– **0.0023**
Intratumoral lymphocytes	No Mild Moderate Severe	314 380 53 33	1.00 1.22(0.86–1.75) 2.19(1.17–4.04) 0.65(0.21–1.60)	– 0.2659 0.0126 0.3864		
MSI	Yes No	195 245	1.00 0.25(0.16–0.39)	– 0		
Adjuvant therapy	Yes No	307 494	1.00 0.49(0.36–0.69)	0	1.00 0.80(0.47–1.35)	– 0.3966
NLR		3.2 (± 2.9)	1.88(1.35–2.62)	0.0002	1.60(1.08–2.37)	**0.018**
LMR		3.5 (± 1.9)	0.49(0.34–0.69)	0.0001	0.51(0.34–0.77)	**0.0013**
PLR		176.2 (± 107.8)	1.74(1.25–2.43)	0.0012	1.56(1.06–2.32)	**0.0252**

Table 2. Association of clinicopathological characteristics of colon cancer patients with 5-year DFS since surgical treatment. OR: odds ratio, AL: anastomotic leak, SSI: surgical site infection, AJCC: American Joint Committee on Cancer, MSI: microsatellite instability, CEA: carcinoembryonic antigen, BMI: body mass index, ASA: American Society of Anesthesiologists Physical Status Classification System, PO: postoperative Significance value bold.

Since then, there has been an attempt to associate LMR with CRC, but studies disagree on its utility to predict prognosis. Some studies have found that an elevated LMR is a protective factor and indicates better survival[31–33]. Others have failed to do so[17,34]. Our study supports the association between LMR and CRC, showing that a lower LMR is associated with poorer survival in both RC and LC tumors, but it shows higher recurrence rates only in LC tumors.

MSI-high tumors are significantly more common in RC tumors, with reported rates of 20–45%, compared with approximately 5–15% in LC tumors. MSI-high tumors show strong lymphocytic infiltration, higher immunogenicity, and a distinct inflammatory profile dominated by adaptive immune activation. LMR reflects lymphocyte-mediated adaptive immunity, whereas low LMR may indicate impaired antitumor immune

Postoperative complication ($n=805$)			NLR	LMR	PLR
Anastomotic leak	Yes	45 (5.6%)	**p 0.013**	p 0.301	p 0.235
	No	760 (94.4%)			
Ileum	Yes	52 (6.5%)	p 0.814	p 0.900	0.838
	No	753 (93.5%)			
Sepsis	Yes	20 (2.5%)	p 0.063	p 0.186	p 0.510
	No	785 (97.5%)			
Surgical site infection	Yes	44 (5.5%)	p 0.423	p 0.629	p 0.243
	No	761 (94.5%)			

Table 3. Association of the biomarkers with postoperative complications. Significance value bold.

	General ($n=801$)				Right colon ($n=381$)				Left colon ($n=419$)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR 95%CI	p value	OR 95%CI	p value	OR 95%CI	p value	OR 95%CI	p value	OR 95%CI	p value	OR 95%CI	p value
NLR	1.73 0.94–3.16	0.075	1.08 1.00–1.16	**0.033**	1.16 2.49–2.62	0.72	–	–	2.71 1.09–6.88	0.031	1.11 1.01–1.21	**0.025**
LMR	0.83 0.44–1.67	0.588	–	–	0.14 0.46–3.19	0.79	–	–	0.60 0.24–1.62	0.284	–	–
PLR	1.52 0.83–2.87	0.184	–	–	2.01 0.85–5.26	0.12	–	–	1.08 0.43–2.68	0.869	–	–

Table 4. Association of the biomarkers with anastomotic leak.

	Right colon ($n=381$)				Left colon ($n=419$)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
NLR	2.38 (1.51–3.75)	0.0002	1.86 (1.12–3.08)	**0.0164**	1.56 (0.95–2.54)	0.0737	1.43 (0.85–2.4)	0.176
LMR	0.38 (0.23–0.61)	0.0001	0.41 (0.24–0.71)	**0.0015**	0.45 (0.27–0.74)	0.0017	0.45 (0.26–0.79)	**0.0052**
PLR	1.96 (1.24–3.15)	0.0048	1.58 (0.94–2.68)	0.0881	1.51 (0.94–2.44)	0.0901	1.65 (0.97–2.83)	0.0661

Table 5. Association of the biomarkers with 5-year survival according to tumor site. Significance value bold.

	Right colon ($n=381$)				Left colon ($n=419$)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
NLR	2.12(1.35–3.35)	0.0012	1.58 (0.95–2.61)	**0.074**	1.55 (0.94–2.55)	0.0843	–	–
LMR	0.49(0.30–0.79)	0.0037	0.63 (0.37–1.10)	0.1002	0.49 (0.29–0.82)	0.0066	0.44(0.25–0.78)	**0.0045**
PLR	1.99(1.25–3.21)	0.0041	1.44 (0.86–2.44)	0.1645	1.39 (0.86–2.27)	0.1789	–	–

Table 6. Association of the biomarkers with 5-year DFS according to tumor site. OR: odds ratio, AL: anastomotic leak, SSI: surgical site infection, AJCC: American Joint Committee on Cancer. MSI: microsatellite instability, CEA: carcinoembryonic antigen, BMI: body mass index, ASA: American Society of Anesthesiologists Physical Status Classification System, PO: postoperative. Significance value bold.

surveillance. Given these known differences, it is biologically plausible that in RC tumors (more frequently MSI-high), the strong pre-existing immune activation may dilute or modify the prognostic impact of LMR. And in LC tumors (typically MSS/CIN-driven)—where baseline immunogenicity is lower—variations in LMR may have a greater discriminative effect, especially for DFS.

PLR

Thrombocytosis has been associated with poor prognosis in cancer patients possibly due to a pro-angiogenic effect[35,36]. The first time platelets were shown to be involved in metastasis was in 1968, when Gasic et al. observed that thrombocytopenic mice had less tumor growth and metastasis than the control mice. These results were reversed with platelet transfusion[37].

In vitro models observe that platelet activation stimulates endothelial cell proliferation, which indicates a proangiogenic effect in vivo[35]. But the activation of platelets in the context of cancer is a complex process that involves multiple pathways and factors. Two of the main ones are the Tissue factor and the Vascular endothelial growth factor. Under pathological conditions, Tissue factor and Vascular endothelial growth factor are increased on tumor and vascular endothelial cells in different types of cancers. Interaction of platelets with tumor cells causes activation of the first ones, releasing their granule contents including Vascular endothelial growth factor that stimulates angiogenesis[35,38].

Tissue factor is expressed in adventitial cells surrounding blood vessels. It binds to factor VIIa and activates factor X, as well as fibrin and platelets. Vascular endothelial growth factor turns endothelial cells into prothrombotic by increasing TF expression on their membranes, activating the coagulation cascade, causing fibrin formation and platelet adhesion and activation[39].

Furthermore, tumor cells don't metastasize by themselves. Platelets have to adhere to these cells forming a tumor-platelet thrombi which gets trapped in microvessels and interacts with new endothelial cells[38,39].

The PLR is an indicator of systemic inflammation and its prognostic value in different types of cancers has been well documented, including ovarian, pancreas and CRC[7]. However, the cut off value differs in every study[7,40]. We propose that a PLR over 145.16 can predict increase mortality and recurrence rates within 5 years of the surgical treatment. This finding is consistent with previous research on the prognostic value of PLR in various cancers, including CRC[7,41–43]. However, when analyzing by location, the PLR lost statistical significance in RC and LC tumors. This outcome contrasts with previous studies. For instance, Guo et al.[44] identified a PLR > 145 as an independent predictor of worse survival and DFS in both RC (p 0.010) and LC ($p < 0.001$). Similarly, Yang et al.[45] found higher PLR in advance TNM stages and worse survival in LC tumors ($p = 0.002$) but not in the RC. Conversely, Barnayai et al.[46] didn't find any prognostic value in the PLR. These discrepancies may be attributed to differences in study populations, methodologies, and statistical power.

Importantly, the analysis by tumor location in our study was a secondary outcome, and the sample size was not calculated or powered to detect location-specific differences, which likely contributed to the loss of statistical significance for PLR in these subgroup analyses. Therefore, although our overall findings support the prognostic value of PLR in colon cancer, further adequately powered, prospective studies are needed—particularly those designed to evaluate right- versus left-sided tumors independently. Such research is essential to clarify the nuanced and potentially location-dependent role of PLR in clinical practice.

Tumor location

It's important to differentiate between colon cancer (CC) and rectal cancer. They're usually grouped together as CRC and analyzed as if they are the same pathology. However, they have different classification, treatment, and prognosis. Within CC, it's important to differentiate RC from LC.

Clinically, RC tumors are associated with anemia, larger tumor size, and more advanced presentation, all of which can modify neutrophil and platelet dynamics. LC tumors, on the other hand, have stronger correlations with luminal obstruction and mechanical inflammation. These patterns help explain why the predictive value of NLR, LMR, and PLR varies by location in our models.

Embryologically, RC tumors arise from midgut-derived tissue, whereas LC tumors originate from hindgut derivatives. This distinction is associated with differences in epithelial biology, lymphoid architecture, microbiome composition, and immunologic baseline activity—all factors known to influence leukocyte-based inflammatory markers.

Genetically, RC tumors show significantly higher rates of MSI-high, BRAF mutations, CIMP-high status, and immune-rich CMS1 profiles. In contrast, LC tumors are predominantly MSS/CIN-driven and enriched in CMS2/CMS3 phenotypes. MSI-high and CMS1 tumors are characterized by dense lymphocytic infiltration and heightened immunogenicity, which can directly modify circulating lymphocyte and monocyte counts, thereby altering ratios such as NLR and LMR. This differences in gene expression makes them have a different response to chemotherapy[47–49].

Regarding the tumor microenvironment, several studies have shown that right-sided cancers display a more prominent immune-activated infiltrate (TH1-type response, cytotoxic T-cell enrichment, higher PD-L1 expression), whereas left-sided cancers exhibit a more epithelial, proliferative phenotype. These differences contribute to distinct systemic inflammatory signatures, even when tumor stage is comparable.

Finally, they have a different microbiota composition, which may influence tumor behavior and response to inflammation and immune factors. It may also have an impact in postoperative AL12. This study is one of the few to have a large sample size of CC-only tumors, analyzing RC from LC separately.

Our results by location are a secondary outcome. Specific studies should be conducted to validate the differences found. Nonetheless, the differential impact of NLR, LMR, and PLR based on tumor location (RC vs. LC) highlights the need for tailored treatment approaches. This distinction should be considered in clinical practice to optimize treatment strategies.

Strengths and limitations

This study has several notable strengths. First, its large sample size and extended follow-up period provide a robust foundation for evaluating long-term survival and recurrence outcomes in stages I–III colon adenocarcinoma. The multicenter design adds further methodological strength by incorporating patients treated across different hospitals, thereby reflecting real-world clinical heterogeneity. Although variability in perioperative protocols—such as antibiotic regimens and bowel preparation—introduces heterogeneity, it also increases the external validity of the findings. These inter-center differences may influence biological factors such as the intestinal microbiota, but they simultaneously enhance the generalizability of the results.

Stage III patients are more consistently treated with adjuvant chemotherapy. However, we believe that including stage III in the analysis enhances both the generalizability and clinical relevance of our findings. The AJCC staging system is the most validated prognostic framework in colon cancer, and adjusting for stage allowed us to assess the independent prognostic value of hematologic markers such as NLR, LMR, and PLR across the full spectrum of resectable disease. This approach may also support more tailored treatment strategies for stage III patients. Additionally, we stratified stage II into IIA and IIB/IIC to reflect differences in adjuvant treatment recommendations within early-stage disease.

An important limitation is the retrospective design, which is subject to inherent biases, and prospective studies are needed to validate these findings. Additionally, the study was conducted in a single country, which may limit the generalizability of the results to other populations.

Another important limitation is the lack of biological markers. Our dataset did not systematically include MSI/MMR status for the full cohort—particularly for earlier years of the study period (2007–2017), when MSI testing was not performed routinely outside high-risk or stage II cases. As a result, MSI data were incomplete and could not be incorporated reliably into subgroup analyses without introducing selection bias. Our results should be interpreted with caution regarding mechanistic explanations involving MSI-related immunobiology.

Finally, platelet-mediated angiogenesis and VEGF/VEGFR2 signaling are biologically relevant when interpreting the prognostic role of PLR. In our cohort, VEGF or VEGFR2 expression levels were not measured, and therefore we were not able to formally assess correlations between PLR and VEGF in either right- or left-sided tumors.

Conclusion

This study suggests that NLR, LMR, and PLR may offer supportive prognostic information in colon cancer, particularly regarding survival and recurrence, and that NLR may also have a potential association with anastomotic leaks. Our findings also indicate that the prognostic performance of these markers may differ by tumor location, consistent with the known biological distinctions between right- and left-sided colon cancers.

In right-sided tumors, NLR and LMR appeared to be associated with 5-year overall survival, while in left-sided tumors LMR showed a more consistent association. These hematologic markers, although not intended to replace established clinicopathologic factors, may serve as adjunctive indicators that help refine risk stratification, given their accessibility and low cost.

Because PLR did not retain prognostic significance after stratification by tumor location, its role remains uncertain and warrants further investigation. Overall, the location-specific differences observed in our analyses should be interpreted cautiously, particularly as these subgroup assessments were secondary outcomes. Prospective studies with adequate power and mechanistic exploration are needed to validate these findings and clarify how hematologic markers may complement existing prognostic frameworks in clinical practice.

Data availability

The data generated in this study are available upon request from the corresponding author.

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Author contributions

J.P.G.S. and C.P.L. conceived the study and designed the methodology. C.P.L. curated the dataset and performed the formal statistical analyses. J.P.G.S., M.S.R.R., A.B.G., P.V.A., D.E.R., and S.L.G. contributed to data collection and investigation. J.P.G.S. prepared the original draft of the manuscript, and all authors contributed to reviewing and editing the final version. J.P.G.S. developed the visualizations. C.P.L. supervised the study. Project administration was carried out by J.P.G.S., C.P.L., and S.L.G. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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