Prognostic Value of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Metastatic Colorectal Cancer: A Single Institutional Experience

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Abstract:

Background: Despite advancements in the management of colorectal cancer (CRC), the prognosis of metastatic CRC remains poor. The prognostic and clinical significance of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in CRC remains uncertain, which has attracted increasing interest from researchers.

Methods: A prospective cohort study included 125 metastatic CRC patients at the Medical Oncology Department, South Egypt Cancer Institute (SECI), Assiut University, from June 2022 to June 2024. We evaluated the prognostic value of NLR and PLR in metastatic CRC patients.

Results: Among 125 patients included in our study, 62 patients (49.6%) had a high NLR ≥3 and showed shorter overall survival (OS) (13 vs 18 months (ms), P = 0.02). Furthermore, 70 patients (56%) had a high PLR ≥163 and also showed shorter OS (13 vs 18 ms, P = 0.019) after a median follow-up period of 14 months. Multivariate analysis revealed that NLR was an independent predictor factor for OS (P = 0.019), whereas PLR lost its statistical significance.

Conclusion: NLR may serve as a useful prognostic factor in metastatic CRC patients. Further studies are needed to clarify its role in CRC management.

Keywords: Colorectal cancer, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, overall survival

Background:

Worldwide, CRC is the third most common cancer, and the second leading cause of cancer-related death [1].

Metastasis is a major contributor to the high mortality rates associated with CRC [2]. Several prognostic factors influence outcomes in metastatic CRC, including tumor burden, primary tumor location, and histopathological features such as differentiation grade and lymphovascular invasion. Serum biomarkers such as carcinoembryonic antigen (CEA) and lactate dehydrogenase (LDH) levels offer further prognostic information by reflecting systemic inflammation and tumor aggressiveness. Molecular markers, including Rat Sarcoma Virus (RAS), V-Raf Murine Sarcoma Viral Oncogene Homolog (BRAF) mutations, and Microsatellite Instability (MSI) status, also play significant roles in predicting prognosis [3]. However,

identifying a cost-effective, practical, and reliable biomarker to predict the prognosis of CRC is crucial.

Recent studies have highlighted a strong correlation between inflammation and cancer, involving both intrinsic and extrinsic pathways. The intrinsic pathway is triggered by genetic alterations that drive tumor development, whereas the extrinsic pathway is associated with chronic inflammatory conditions that increase the risk of cancer development [4,5].

The NLR has been proposed as a simple indicator of systemic inflammatory response. Three synergistic mechanisms underlie NLR's prognostic significance in cancer: neutrophilia promotes tumor angiogenesis and progression; lymphopenia reflects impaired cell-mediated immunity and disease severity; and suppression of tumor-infiltrating lymphocytes enables immune evasion. This highlights NLR's dual role in both inflammatory response and immune surveillance [6–8].

Numerous studies have demonstrated that platelet-derived P-selectin promotes leukocyte-endothelial adhesion through its role as a cell adhesion molecule and significantly influences tumor development, metastasis, and prognosis [9]. As cancer progresses, PLR levels tend to rise, with higher PLR values being associated with poor prognosis [10].

NLR and PLR can be easily calculated by dividing the neutrophil count or platelet count by the lymphocyte count. Since these blood parameters are routinely measured, the assessment of NLR and PLR can be incorporated into clinical practice without additional cost [11]. Therefore, NLR and PLR have been suggested as valuable prognostic indicators in patients with CRC [12–15].

In this study, we evaluated the prognostic value of the NLR and PLR in patients with metastatic CRC.

Patients and Methods:

Study design and patients

This prospective cohort study enrolled 125 patients with synchronous stage IV CRC, as categorized by the American Joint Committee on Cancer's Staging System for colon cancer (8th Edition) [16], receiving palliative treatment at the Medical Oncology Department of SECI, Assiut University. The study included adults (≥18 years) of both sexes with histologically confirmed CRC and radiologically documented synchronous metastatic disease at diagnosis. Patients with metachronous stage IV CRC cancer, pregnant and lactating individuals, and patients with double malignancy were excluded from our study. With number IORG0006563-602, ethical permission was acquired from our institutional ethics committee, SECI-Institutional Review Board (IRB).

Assessment of NLR and PLR

Peripheral blood samples were collected from all patients at the time of diagnosis. The neutrophil, platelet, and lymphocyte counts obtained from these samples were used to compute the NLR and PLR. NLR was determined by dividing the absolute neutrophil count by the absolute lymphocyte count, and PLR was obtained by dividing the absolute platelet count by the absolute lymphocyte count.

To determine the optimal cutoff values, sensitivity, and specificity of NLR and PLR, receiver operating characteristic (ROC) curve analysis was conducted. Regarding NLR, we found the cut-off value of 3 as the best cut-off value (area under the curve (AUC): 0.627 (0.521-0.734), sensitivity: 55%, specificity: 66%). In addition, the best cut-off value for PLR was found to be 163 (AUC: 0.626 (0.519-0.734), sensitivity: 60%, specificity: 60%, Figure 1.

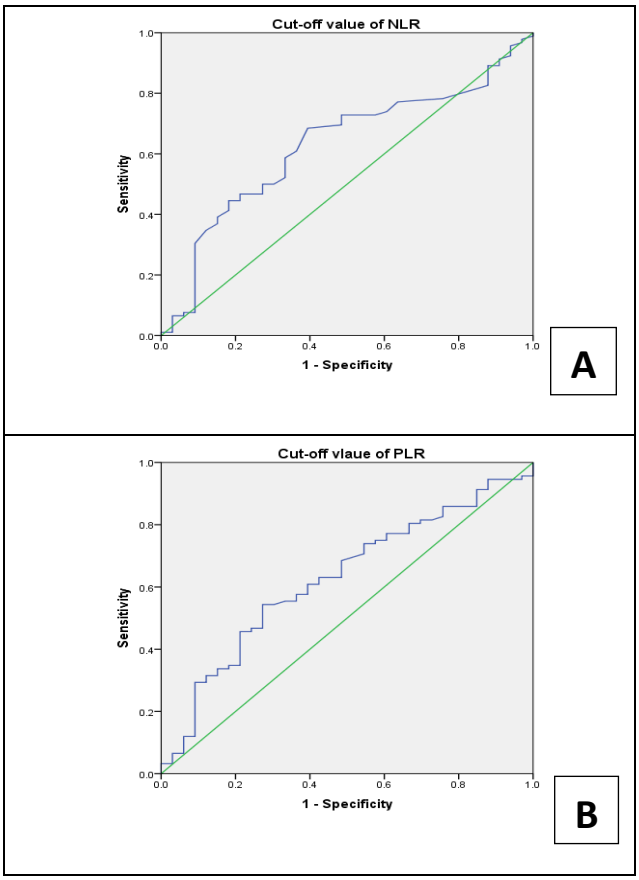

Figure 1. (A) ROC curve shows threshold value of 3 as best cut-off value of NLR (AUC: 0.62, specificity: 66%, sensitivity: 55%. (B) ROC curve shows threshold value of 163 as best cut-off value of PLR (AUC: 0.62, specificity: 60%, sensitivity: 60%).

Statistical analysis

All statistical calculations were conducted using SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) version 26. Continuous data were expressed in the form of mean ± standard deviation (SD) or median (range), while categorical data were expressed as frequency (percentage). OS was defined as the time from cancer diagnosis to either death from any cause or the last follow-up date. The associations between clinicopathological characteristics and NLR/PLR categories were assessed using the chi-

square test, with Fisher's exact test applied when expected cell counts were less than 5. Survival outcomes were evaluated through Kaplan-Meier estimation, and between-group comparisons were performed using log-rank testing. Multivariate Cox proportional hazards regression modeling was implemented to identify independent prognostic factors influencing OS. P-values less than 0.05 were considered statistically significant. ROC curves were employed to assess the predictive ability of NLR and PLR for long-term outcomes in CRC patients.

Results:

Demographics and clinicopathological criteria

The study population consisted of 125 cases of synchronous metastatic CRC, with 60(48%) males and 65 (52%) females. The median age for both genders was 45 years (range 20-80). Sixty-one cases (48.8%) were right-sided while 64 cases (51.2%) were left-sided.

Regarding histopathological criteria, thirty-six (28.8%) were with mucinous differentiation, 111(88.8%) were well or moderately differentiated (I/II), while 14(11.2%) were poorly or undifferentiated (III/IV). Thirty-six (28.8%) had RAS mutations; however, only one case had a BRAF mutation. Regarding the number of metastatic sites at presentation, 83(66.4%) had a solitary site of metastasis, 30(24%) had two sites, 9(7.2%) had three sites, and three patients (2.4%) presented with 4 sites of metastasis.

NLR and PLR

NLR was calculated for each patient, producing two groups: high NLR (NLR≥3) and low NLR (NLR<3). Sixty-two patients (49.6%) were categorized as NLR high (≥3), and 63 patients (50.4%) were categorized as NLR low (<3). Regarding PLR, 70 patients (56%) were classified as PLR high (≥163) and 55 patients (44%) were classified as PLR low (<163). Tables (2) and (3) show data analyzing the clinicopathological characteristics within the NLR and PLR groups, respectively.

Survival outcomes according to NLR and PLR

Our study demonstrated that OS was significantly shorter in patients with high NLR compared to those with low NLR (13 ms, 95% confidence interval (CI): 12.04-13.95) versus (18 ms, 95% CI: 16.44- 19.55), P = 0.02. Furthermore, patients with high PLR had shorter OS than those with low PLR (13 ms, 95% CI: 11.98-14.01),(18 ms, 95% CI: 16.69- 19.30), respectively, P = 0.019 (Figure 2).

Predictors of survival in univariate and multivariate analysis

In multivariate analysis, NLR (HR: 1.934, 95% CI: 1.112–3.365; P = 0.019), grade of differentiation (HR: 3.259, 95% CI: 1.766–6.014; P = 0.000), and mucinous differentiation (HR: 1.892, 95% CI: 1.187–3.015; P = 0.007) were the most powerful independent predictors of OS, while PLR lost its statistical significance (Table 4).

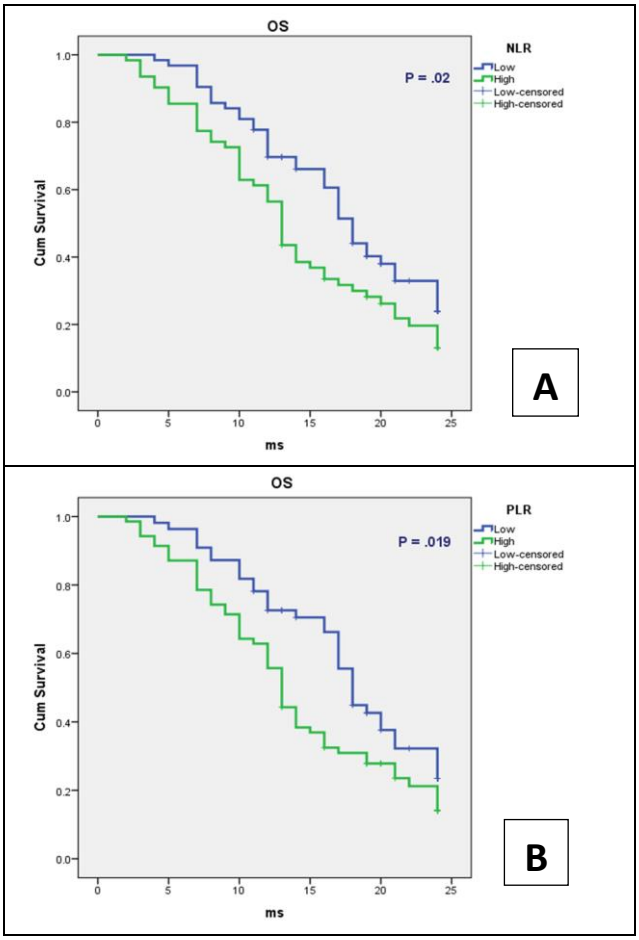

Figure 2. Kaplan-meier analysis shows OS according to NLR(A) and PLR(B).

Table 1: Demographic and clinicopathological characteristics of patients with stage IV CRC (n=125)

Age	
• **Median(range)**	45(20-80)
Gender	
• **Male**	60(48%)
• **Female**	65(52%)
Location	
• **Right-sided**	61(48.8%)
• **Left-sided**	64(51.2%)
Tumour grade	
• **Well or moderately differentiated(I/II)**	111(88.8%)
• **Poorly or undifferentiated (III/IV)**	14(11.2%)
Pathology	
• **Mucinous**	36(28.8%)
• **Non-mucinous**	89(71.2%)
BRAF status	
• **Wild type**	74(59.2%)
• **Mutant**	1(.8%)
• **Unknown**	50(40%)
RAS status	
• **Wild type**	74(59.2%)
• **Mutant**	36(28.8%)
• **Unknown**	15(12%)
Number of metastatic sites	
• **1**	83(66.4%)
• **2**	30(24%)
• **3**	9(7.2%)
• **4**	3(2.4%)
NLR	
• **Mean±SD**	5.37±8.73
• **Median(range)**	2.9(.1-80)
• **<3**	63(50.4%)
• **≥3**	62(49.6%)
PLR	
• **Mean±SD**	223.23±157.42
• **Median(range)**	166.7(68.66-936.66)
• **<163**	55(44%)
• **≥163**	70(56%)
Chemotherapy	
• **Yes**	123(98.4%)
• **No**	2 (.6%)

Quantitative data are expressed as mean ± SD or median (range), while qualitative data are presented as frequency (percentage).

Table 2: Clinicopathological characteristics according to NLR (n=125)

Variables	NLR		P-value
	Low(63)	High(62)	
Age			
• **<60**	60(95.2%)	48(77.4%)	
• **≥60**	3(4.8%)	14(22.6%)	**.004***
Location			
• **Right-sided**	29(46%)	32(51.6%)	
• **Left-sided**	34(54%)	30(48.4%)	.533
Grade of differentiation			
• **Well/moderately differentiated(I/II)**	53(84.1%)	58(93.5%)	
• **Poor/undifferentiated (III/IV)**	10(15.9%)	4(6.5%)	.155
Histopathology			
• **Mucinous**	19(30.2%)	17(27.4%)	
• **Non-mucinous**	44(69.8%)	45(72.6%)	.735
RAS status			
• **Wild**	38(70.4%)	36(64.3%)	
• **Mutated**	16(29.6%)	20(35.7%)	.497
Number of metastatic sites			
• **1**	42(66.7%)	41(66.1%)	
• **≥1**	21(33.3%)	21(33.9%)	.949

Quantitative data are expressed as median (range), while qualitative data are expressed as frequency (percentage). The Chi-square or Fisher's Exact tests were used to compare categorical data. Statistical significance was set as $p < 0.05$.

Table 3: Clinicopathological characteristics according to PLR (n=125)

Variables	PLR		P-value
	Low(55)	High(70)	
Age			
• **<60**	52(94.5%)	56(80%)	
• **≥60**	3(5.5%)	14(20%)	**.02***
Location			
• **Right-sided**	27(49.1%)	34(48.6%)	
• **Left-sided**	28(50.9%)	36(51.4%)	.954
Grade of differentiation			
• **Well/moderately differentiated(I/II)**	48(87.3%)	63(90%)	.631
• **Poor/undifferentiated (III/IV)**	7(12.7%)	7(10%)	
Histopathology			
• **Mucinous**	11(20%)	25(35.7%)	
• **Non-mucinous**	44(80%)	45(64.3%)	.054
RAS status			
• **Wild**	31(67.4%)	43(67.2%)	
• **Mutated**	15(32.6%)	21(32.8%)	.982
Number of metastatic sites			
• **1**	34(61.8%)	49(70%)	
• **≥1**	21(38.2%)	21(30%)	.336

Quantitative data are expressed as median (range), while qualitative data are expressed as frequency (percentage). The Chi-square or Fisher's Exact tests were used to compare categorical data. Statistical significance was set as $p < 0.05$.

Table 4: Univariate and multivariate analysis of factors predicting OS

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
• **< 60**	ref					
• **≥ 60**	1.271	(.691-2.336)	.440			
Gender						
• **Male**	ref					
• **Female**	.817	(.550-1.21)	.315			
Location						
• **Right-sided**	ref					
• **Left-sided**	1.244	(.825-1.876)	.297			
Histopathological type						
• **Mucinous**	1.916	(1.244-2.952)	**.003***	1.892	(1.187-3.015)	**.007***
• **Non-mucinous**	ref			ref		
Grade of differentiation						
• **Well/moderately differentiated(I/II)**	ref			ref		
• **Poor/undifferentiated (III/IV)**	2.885	(1.611-5.166)	**.000***	3.259	(1.766-6.014)	**.000***
RAS status						
• **Wild**	ref					
• **Mutated**	1.318	(.840-2.068)	.230			
BRAF status						
• **Wild**	ref					
• **Mutated**	6.358	(.821-49.251)	.077			
Number of metastatic sites						
• **1**	ref					
• **≥1**	1.147	(.749-1.758)	.528			
NLR						
• **<3**	ref			ref		
• **≥3**	1.595	(1.056-2.409)	**.026***	1.934	(1.112-3.365)	**.019***
PLR						
• **<160**	ref			ref		
• **≥160**	1.612	(1.059-2.455)	**.026***	1.025	(.589-.1.786)	.929

Cox regression analysis was used, CI: Confidence Interval, HR: Hazard Ratio, *Significance defined by P-value<.05.

Discussion:

Multiple studies have shown the correlation between host inflammatory responses and the

development of various solid tumours [17–19]. Inflammatory markers, including platelets, neutrophils, lymphocytes, C-reactive protein, LDH levels, and pretreatment fibrinogen, have been utilized to assess tumor prognosis [20].

Recently, NLR and PLR have been identified as significant inflammatory markers and potential predictors of long-term outcomes in patients with CRC. However, the underlying mechanisms through which elevated NLR or PLR contribute to poor long-term outcomes in patients with cancer remain unclear [21].

In the current study, the cut-off value of NLR was 3 (sensitivity 55%, specificity 66%), which is consistent with the Kim et al study, which included 1868 CRC patients, which set 3 as the cut-off value of NLR (sensitivity 51%, specificity 62%) [21].

Furthermore, we set the cut-off value of PLR as 163 with a specificity and sensitivity of 60% each. This is approximately the same as the cut-off value of 160 with (sensitivity 53%, specificity 55%) reported by the Kim et al. study [21].

Our study demonstrated that OS was shorter in patients with high NLR compared to those with low NLR (13 vs 18 ms, P = 0.02). Pine et al.'s study showed that OS was poorer in the high NLR group compared to

the low NLR group (P < 0.001), which aligns with our findings [22].

Additionally, our study showed that OS was shorter in patients with high PLR compared to those with low PLR (13 vs 18 ms, P = 0.019). These findings are in agreement with those of Acikgoz et al., who reported significantly worse OS in patients with high PLR tumors compared to those with low PLR (16.7 vs 38.9 months, P<0.001 [23].

On the other hand, a retrospective study of 94 metastatic CRC patients treated in Antakya reported that the median OS was similar in both the NLR-low and NLR-high groups. Furthermore, no significant difference in OS was observed between the PLR-low and PLR-high groups [24] This discrepancy may be explained by methodological and clinical variations that can prevent smaller, single center retrospective analyses from confirming the prognostic value of NLR and PLR.

In the current study, we demonstrated that NLR was one of the independent predictors of OS in stage IV CRC (HR: 1.934, 95% CI: 1.112–3.365; P = 0.019), whereas PLR lost its significance in multivariate analysis. These results agree with Kim et al.'s findings on NLR but are against their findings regarding PLR, which identified both elevated NLR and PLR as independent predictors of OS and disease-free survival (DFS) in patients with stage III and IV CRC [21]. In addition, our results align with Pine et al., who reported that NLR remained a significant prognostic factor in the multivariate model (HR 1.712, 95%CI: 1.227-2.389; P = 0.002) [22].

Furthermore, Guo et al.'s pooled analysis, which included 15 individual studies of 4001 patients, revealed a significant correlation between high PLR and reduced OS with moderate heterogeneity in the random-effect model (HR=1.40, 95% CI=1.21–1.62; P< 0.00001), which disagrees with our results [25]. However, Bulut et al.'s study revealed that neither NLR nor PLR influences OS in the multivariate analysis of metastatic CRC patients [23]. This variation likely reflects the influence of other, more powerful predictors of OS, as well as differences in patient demographics, disease characteristics, and study design.

To explore the underlying basis, both NLR and PLR reflect systemic inflammation, which plays a key role in tumor initiation and progression [26]. Of the two, NLR is preferred for clinical use because it is simple to calculate and widely available, making it a common prognostic marker in many cancers [27].

Limitations

This study has certain limitations. First, this study was conducted at a single center with a relatively small sample size. Second, NLR and PLR were assessed using a single measurement at the time of diagnosis. It would be valuable to investigate changes in NLR and PLR during the follow-up period in CRC patients to evaluate their potential role in disease monitoring.

Conclusion:

This study supports the potential of high NLR as a significant predictor of poor long-term outcomes in patients with stage IV CRC. However, discrepancies in the prognostic significance of NLR and PLR among existing studies highlight the need for further research to clarify the role of inflammatory markers in CRC prognosis and their potential application in clinical practice.

List of abbreviations

BRAF V-Raf Murine Sarcoma Viral Oncogene Homolog
CEA Carcinoembryonic antigen
CI Confidence interval
CRC Colorectal cancer
IRB Institutional Review Board
LDH lactate dehydrogenase
Ms Months
MSI Microsatellite instability
NLR Neutrophil-to-lymphocyte ratio
OS Overall survival
PLR Platelet-to-lymphocyte ratio
SECI South Egypt Cancer Institute

Conflict of interest

The authors declare no conflict of interest

Authors' contributions

Nada Mohammad Hussien analyzed and interpreted clinicopathological data, treatment responses, and patient survival outcomes. Marwa T. Hussien conducted the histopathological evaluation of the colorectal tumor samples. Rabab Mohammed Mamdouh, Ahmed Refaat, and Abeer Ibrahim were key in drafting the manuscript. All authors reviewed and approved the final version of the manuscript.

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