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Research Article

Impact of Inflammation Markers on Survival in Patients with Metastatic Colorectal Cancer

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Abstract

Objectives: This retrospective study evaluated the prognostic significance of inflammation markers (IMs) in patients with metastatic colorectal cancer (mCRC).

Methods: A total of 101 patients—44 (43.6%) were female, and 57 (56.4%) were male—were included in the study. All medical records were reviewed retrospectively. The cut-off values for the IMs (c-reactive protein (CRP), CRP/albumin ratio (CAR), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and systemic immune-inflammatory index (neutrophils × platelets)/lymphocytes) (SIII)) were defined by receiver operating characteristic (ROC) analysis. Overall survival (OS) was plotted using the Kaplan–Meier method and compared using the log-rank test. Cox regression analysis was performed for univariate and multivariate analyses, and hazard ratios (HRs) with 95% confidence intervals (CIs) were used to quantify the indices estimating the survival.

Results: ROC analysis was performed to determine the optimal prognostic value of each parameter. Accordingly, CRP: 11 mg/dL, NLR: 2.4, PLR: 137, SIII: 798, and CAR: 2.7 were determined as cut-off values for predicting OS based on the areas under the curve (AUC) in the ROC analysis (CRP: 0.742, p<0.001 (sensitivity: 66%, specificity: 82%); NLR: 0.720, p<0.001 (sensitivity: 78%, specificity: 62%); PLR: 0.631, p=0.040 (sensitivity: 72%, specificity: 48%); SIII: 0.695, p=0.002 (sensitivity: 68%, specificity: 72%); CAR: 0.742, p<0.001 (sensitivity: 72%, specificity: 48%)). Multivariate analysis demonstrated that PLR is an independent prognostic factor for OS (p<0.001) in patients with mCRC.

Conclusion: The findings of the present study suggest that pretreatment PLR might be an independent prognostic marker for patients with mCRC and might have value compared with other established inflammation-based prognostic scores.

Keywords: C-Reactive protein to albumin ratio, metastatic colorectal cancer, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, prognostic score

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Survival in patients with metastatic colorectal cancer (mCRC) does not reach 12 months when only 5-fluorouracil is used as treatment but, currently, survival using various chemotherapies, anti-vascular endothelial growth factor (VEGF), and anti-epidermal growth factor receptor (EGFR) 3 is near to a year.[1] Although some of the predictive factors associated with the use of these treatments are important, inflammatory markers have not been adequately investigated in metastatic CRC patients.[2,3] Few studies on this subject have shown that increased inflammatory markers may affect the anti-VEGF treatment response.[4]

There is increasing data that a systemic inflammatory response is associated with poor outcomes in patients suffering from various types of cancers.[5] In cancer patients, many inflammation cells increase, such as neutrophils, lymphocytes, c-reactive protein, and many more cells, cytokines, and chemokines.[6] Increased neutrophil and c-reactive protein indicates increased inflammation. A decrease

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in the number of lymphocytes also shows that the immune system developing against the cancer cell is weakened.[7]

Systemic inflammation has also been shown to be associated with reactive thrombocytosis in many cancer types.[8] Thrombocytosis develops in 10–57% of cancer patients.[9] This is thought to be associated with IL-6 and VEGF.[10] So, thrombocytosis is associated with tumor progression, and it can induce tumor metastasis by secreting growth factors.[11] Furthermore, EGFR, one of the causes of tumor progression, is the target of treatment in mCRC patients.[12] The EGFR pathway has a role in cyclooxygenase 2 (COX^2) expression, so it is related to inflammation.[13] All this information shows us the importance of inflammation in patients with CRC.

Several standard inflammation-based prognostic scores, including the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), c-reactive protein (CRP) to albumin ratio (CAR), and systemic immune-inflammatory index (neutrophils × platelets)/lymphocytes) (SIII), have been reported to have prognostic value in patients with mCRC.[14,15]

In the present study, we investigated the prognostic value of PLR in patients with mCRC. We also evaluated CRP, NLR, CAR, and SIII in these patients and compared them with PLR.

Methods

Patients

In this cross-sectional, retrospective study, archive records between January 2014 and January 2018 for all mCRC patients in Bezmialam Vakif University Hospital were used. Patients who were not in follow-up, whose pathology report could not be obtained, or who showed other inflammatory conditions, heart failure, liver cirrhosis, or end-stage renal disease before initiation of chemotherapy were not included. Patients diagnosed with mCRC and those who received at least three-line treatment were included in the study.

We used the 2017 AJCC staging system (8^{th} Edition) for pathological TNM staging. In addition to this, gender, age, tumor location, presence of mucinous component, lymphatic invasion, perineural invasion, vascular invasion, grade, RAS and BRAF status, carcinoembryonic antigen (CEA) levels (≥5 and <5 ng/dL) at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status (PS), presence of cancer in the patient's family, number of metastases, and the history of surgical operation were collected. Follow-up schedules were applied, referring to the NCCN Clinical Practice Guidelines.

All patients were receiving a minimum of three-line treatment. The first line was anti-EGFR therapy (cetuximab or panitumumab) and bevacizumab; cetuximab was administered at a dose of 500 mg/m^2 every 14 days, panitumumab was administered at a dose of 6 mg/kg every 2 weeks and bevacizumab was administered at a dose of 7.5 mg/kg with CAPEOX (oxaliplatin 130 mg/m^2 + capecitabine 1000 mg/m^2 twice daily for 14 days) therapy and 5 mg/kg with FOLFOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, 5-fluorouracil (5-FU) 400 mg/m^2 IV bolus, 5-FU 2400 mg/m^2 IV infusion) or FOLFIRI (irinotecan 180 mg/m2, leucovorin 400 mg/m^2, 5-FU 400 mg/m^2 IV bolus, 5-FU 2400 mg/m^2 IV infusion) chemotherapies. Regorafenib 160 mg once daily for the first 21 days of each 28-day cycle was used in the third step of treatment. None of the patients had received immunotherapy or trifluridine/thymidine phosphorylase inhibitor.

Data from 151 patients were examined. Eleven patients were lost to follow-up. Thirty-nine patients who showed other inflammatory conditions were excluded. In total, 101 patients with mCRC met the requirements for inclusion and were evaluated.

Inflammation-Based Prognostic Scores and Other Variables

Values for NLR, PLR, SIII, and CAR were calculated. Blood samples were obtained before the initial treatment to measure levels of CRP (mg/dL), albumin (g/L), and hemoglobin (Hb). Also, white blood cell (WBC), neutrophil, lymphocyte, and platelet (Plt) counts were determined. NLR, PLR, and SIII were defined as absolute neutrophil count and platelet counts, respectively, divided by the total lymphocyte count.

Ethics

This study was approved by the institutional review board of the hospital and was performed in compliance with all principles of the Helsinki Declaration (Number: 07.01.2020-01/05). As the data were retrospective in nature and analyzed anonymously, informed consent was not obtained from the patients.

Statistical Analysis

Statistical analysis was carried out using SPSS for Windows, Version 24.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as the median and range or the mean±SD. The normality test was performed using Kolmogorov–Smirnov analysis. In cases where normal distribution was not available, the Mann–Whitney U test was performed to compare continuous variables between the two groups. The Pearson χ^2 test or Fisher exact test was used to compare qualitative variables. Receiver operating characteristic (ROC) curves were plotted with sensitivity (true-positive fraction) on the y-axis and 1 – specificity (false-positive fraction) on the x-axis. ROC curves were plotted for CRP, CAR, NLR, PLR, and SIII values to predict

overall survival. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. Cox regression analysis was performed for univariate and multivariate analyses, and hazard ratios (HRs) with 95% confidence intervals (CIs) were used to quantify the indices estimating survival. A two-sided p-value of <0.05 was deemed statistically significant.

Results

Patient Characteristics

The clinicopathological characteristics of the patients are shown in Table 1. A total of 101 patients with mCRC were identified on our institutional database. Fifty-seven (56.4%) patients were male, and 44 (43.6%) patients were female. The median age of the patients was 61.78±13.86 years. Eighty-three (82.2%) patients' ECOG PS was 0–1 at the time of diagnosis. The other patients' ECOG PS was 2. At the time of diagnosis, 15.8% (16/101) patients had an obstruction, and 20.8% (21/101) patients had pathological weight loss. Primary tumor location was the right colon in 23 patients (22.8%), and the left colon and rectum in 78 patients (77.2%). Sixty-nine patients underwent surgery in the early stage of diagnosis. Lymph node dissection was not available in two patients; 17.9% of patients (12/67) had insufficient lymph node dissection. Lymphatic invasion was detected in 60.9% (42/69), vascular invasion in 43.5% (30/69), and perineural invasion in 44.9% (31/69) of the patients who underwent surgery. Histologic grade was evaluated in all patients; 79.2% (80/101) were grade 2, 18.8% (19/101) were grade 3, and 2% (2/101) were grade 1. The presence of a mucinous component was found in 35.6% (35/101) of the patients. CEA and CA 19-9 elevation was 30.7% (31/101) at the time of diagnosis and was the same for both markers.

Table 1. Demographic features and tumor characteristics of the patients

Gender, %	
Female	44/101 (43.6)
Male	57/101 (56.4)
Age (Mean±SD)	61.8±13.9
ECOG-PS, %	
0-1	83/101 (82.2)
2+	18/101 (17.8)
Tumor localization, %	
Right colon	23/101 (22.8)
Left colon and rectum	78/101 (77.2)
Histology, %	
Adenocarcinoma	101/101 (100)
Lymphatic invasion, %	
Present	42/69 (60.9)
Absent	27/69 (39.1)
Vascular invasion, %	
Present	30/69 (43.5)
Absent	39/69 (56.5)
Perineural invasion, %	
Present	31/69 (44.9)
Absent	38/69 (55.1)
Grade, %	
1	2/101 (2)
2	80/101 (79.2)
3	19/101 (18.8)
Mucinous component, %	
Present	35/101 (35.6)
Absent	66/101 (64.4)
RAS, %	
Mutant	35/73 (47.9)
Wild	38/73 (52.1)

ROC Analysis

Patients' inflammation parameters (CRP, NLR, PLR, SIII, and CAR values) were recorded. ROC analysis was performed to determine the optimal prognostic value of each parameter. Accordingly, CRP: 11 mg/dL, NLR: 2.4, PLR: 137, SIII: 798, and CAR: 2.7 were determined as cut-off values for predicting overall survival based on the areas under the curve (AUC) in the ROC analysis (CRP: 0.742, p<0.001 (sensitivity: 66%, specificity: 82%); NLR: 0.720, p<0.001 (sensitivity: 78%, specificity: 62%); PLR: 0.631, p=0.040 (sensitivity: 72%, specificity: 48%); SIII: 0.695, p=0.002 (sensitivity: 68%, specificity: 72%); CAR: 0.742, p<0.001 (sensitivity: 72%, specificity: 48%)) (Table 2).

Table 2. Receiver operating characteristic parameters of positive prognostic factors for overall survival in metastatic colorectal cancer

Variable	AUC (%95 CI)	Sensitivity, %	Spesifity, %	Cut-of value	p
CRP	0.742	66	82	11 mg/dl	<0.001
CAR	0.742	65	82	2.7	<0.001
NLR	0.720	78	62	2.4	<0.001
PLR	0.631	72	48	137	<0.001
SIII	0.695	68	72	798	0.002

CRP: c-reactive protein; CAR: c-reactive protein/albumin ratio; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SIII: systemic immune inflammatory index.

Overall Survival

There were 101 patients with mCRC. The median follow-up time from metastasis was 20.4±13 months. The median overall survival (OS) was 19.9 months in all patients (95% CI: 18.2–21.7 months). The 1-year and 3-year OS rates for all patients were 70% and 25%, respectively.

The patients were divided into two groups, with CRP <11 mg/dL and CRP ≥11 mg/dL. The median overall survival was 34 months (95% CI: 22.5–45.5 months) in the first group and 16.9 months (95% CI: 7.4–26.4 months) in the second group. OS was significantly worse in patients with preoperative CRP levels above 11 mg/dL (p<0.001) (Fig. 1). The patients were divided into two groups, with NLR <2.4 and ≥2.4. Median overall survival was 33.5 months (95% CI: 24–42 months) in the first group and 18 months (95% CI: 13.3–23.9 months) in the second group. Preoperative NLR higher than 2.4 was found to be associated with worse prognosis (p<0.001) (Fig. 2). The patients were divided into two groups, PLR <137 and ≥137. Median survival was 24.7 months (95% CI: 15.8–33.7 months) in the first group and 18.8 months (95% CI: 15.7–21.9 months) in the second group. Preoperative PLR greater than 137 was associated with a significantly poorer prognosis (p=0.022) (Fig. 3). The patients were divided into two groups, with SIII <798 and ≥798. Median survival was 33.5 months (95% CI: 24.1–42.9 months) in the first group and 14.4 months (95% CI: 5.9–22.9 months) in the second group. SIII greater than 798 was associated with a significantly poorer prognosis (p<0.001) (Fig. 4). The patients were divided into two groups, with CAR <2.7 and ≥2.7. Median survival was 34 months (95% CI: 22.4–46.6 months) in the first group and 17.1 months (95% CI: 8.9–25.2 months) in the second group. At the time of diagnosis, survival was significantly worse in patients with CAR >2.7 (95% CI: 23–88 months; p<0.001) (Fig. 5).

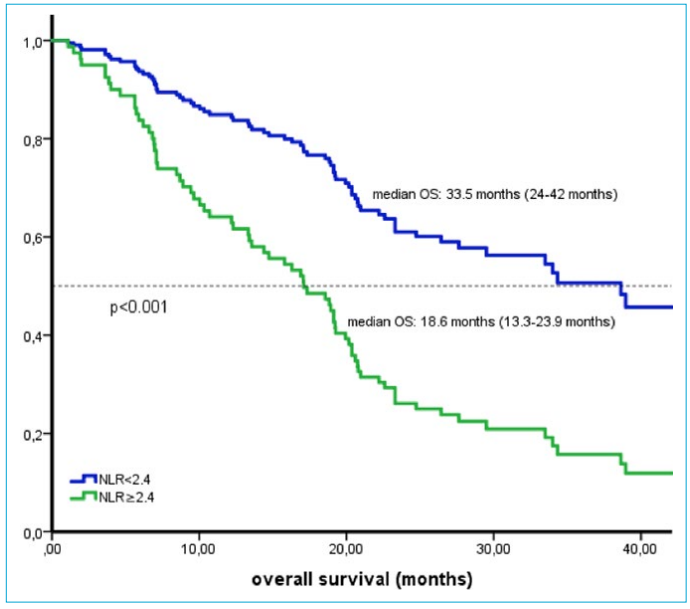

Figure 2. Kaplan-Meier curves according to N/L ratio (<2.4 and ≥2.4) of overall survival.

N: neutrophil; L: lymphocyte; OS: overall survival; CI: confidence interval.

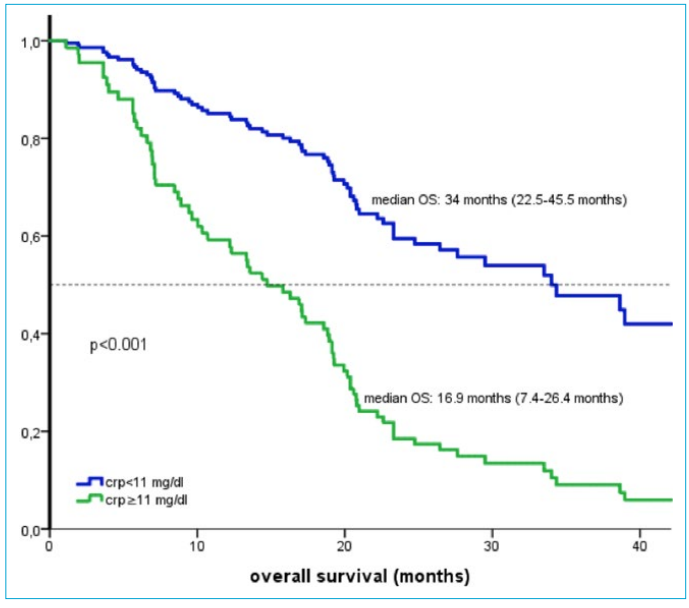

Figure 1. Kaplan-Meier curves according to CRP (<11 mg/dl and ≥11 mg/dl) of overall survival.

crp: c-reactive protein; OS: overall survival; CI: confidence interval

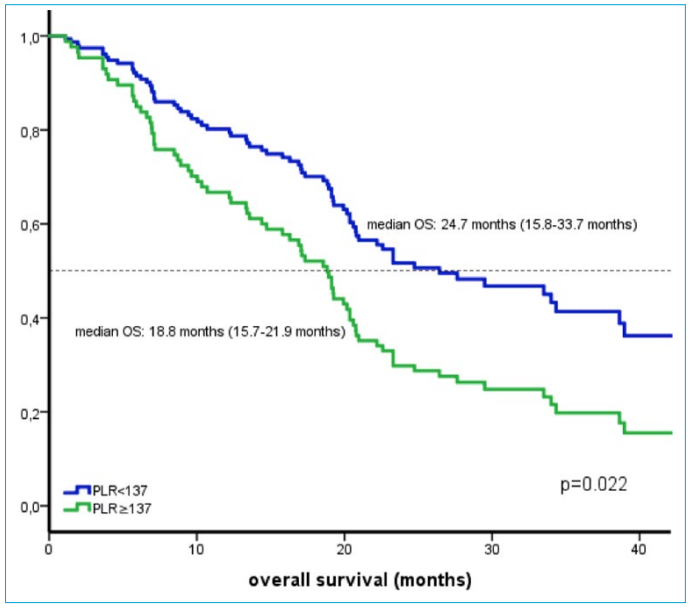

Figure 3. Kaplan-Meier curves according to Plt/L ratio (<137 and ≥137) of overall survival.

Plt: platelet, L: lymphocyte; OS: overall survival; CI: confidence interval.

Cox Regression Analysis for OS

We performed univariate and multivariate analyses to assess predictive value for OS in all patients (Table 3).

Univariant Cox Regression Analysis

Gender (HR: 0.82 (0.51–1.31), p=0.408), smoking (HR: 0.64 (0.37–1.09), p=0.097), presence of obstruction at diagnosis (HR: 0.61 (0.30–1.23), p=0.167), right or left colon localization (HR: 0.96 (0.56–1.66), p=0.881), presence of lymphatic invasion (HR: 1.42 (0.74–2.71), p=0.290), presence of perineural invasion (HR: 1.12 (0.62–2.04), p=0.702), grade (grade 2 HR: 1.29 (0.18–9.38), p=0.748; grade 3 HR: 3.03 (0.40–22.78), p=0.281), presence of mucinous component (HR: 1.29 (0.80–2.09), p=0.292), and CEA level at diagnosis (HR: 1.23 (0.74–2.05), p=0.423) were found not to significantly affect survival (Table 3). ECOG PS of ≤1 (HR: 1.91 (1.09–3.30), p=0.023), pathological weight loss in the last 6 months (HR: 2.22 (1.28–3.84), p=0.004), presence of vascular invasion (HR: 2.39 (1.31–4.37), p=0.005), RAS mutant status (HR: 1.84 (1.03–3.28), p=0.040), and a high level of Ca 19-9 at diagnosis (HR: 2.17 (1.20–3.93), p=0.011) were found to be associated with worse survival. Among the immune parameters, a CRP level ≥11 mg/dL (HR: 3.25 (1.97–5.38), p<0.001), NLR ≥2.4 (HR: 2.72 (1.56–4.78), p<0.001), PLR ≥137 (HR: 1.83 (1.09–3.09), p=0.023), SIII ≥798 (HR: 3.07 (1.86–5.09), p<0.001), and CAR ≥2.7 (HR: 3.09 (1.88–5.08), p<0.001) were significantly associated with an increased risk of death.

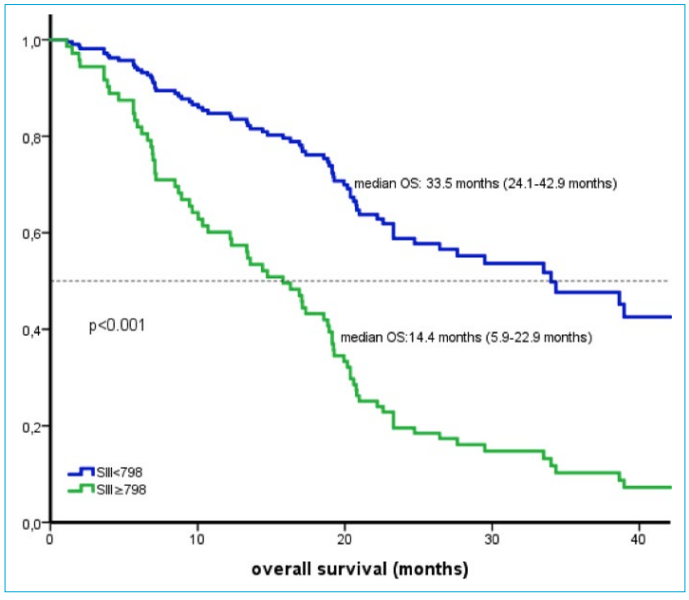

Figure 4. Kaplan-Meier curves according to SIII (<798 and ≥798) of overall survival.

SIII: systemic immune inflammation index; OS: overall survival; CI: confidence interval.

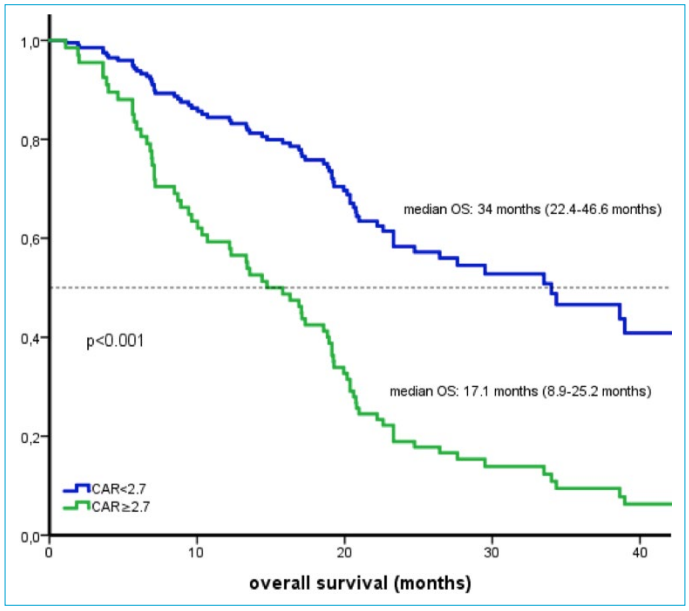

Figure 5. Kaplan-Meier curves according to CAR(<2.7 and ≥2.7) of overall survival.

crp: c-reactive protein; OS: overall survival; CI: confidence interval.

Multivariant Cox Regression Analysis

In multivariate Cox regression analysis, vascular invasion (HR: 6.31 (1.97–20.18), p=0.002) and PLR (HR: 3.9 (1.21–12.63), p=0.023) were associated with an increased risk of death. We demonstrated that elevation of all inflammatory markers was correlated with poor overall survival but only elevated PLR was found to be an independent prognostic factor compared to CRP, CAR, NLR, and SIII by multivariate analysis.

Discussion

In the present study, we assessed the prognostic value of pretreatment CRP, CAR, PLR, NLR, and SIII in patients with mCRC. We demonstrated that elevation of all inflammatory markers was correlated with poor overall survival but only elevated PLR was found to be an independent prognostic factor compared to CRP, CAR, NLR, and SIII by multivariate analysis. The results consistently showed that increased PLR is significantly associated with a shorter OS and serves as an independent prognostic factor for patients with mCRC. While PLR is an independent risk factor for OS, CRP, NLR, CAR, and SIII are not reliable prognostic factors for patients with mCRC. So, pretreatment PLR was shown to be the best prognostic index for patients with mCRC, compared with several other inflammation-based scores, including CRP, NLR, CAR, and SIII.

Many studies have shown that chronic inflammation is associated with cancer cause and progression.[16] The prognostic and predictive importance of inflammatory cells such as neutrophils, lymphocytes, and platelets in pe-

Table 3. Prognostic factors of overall mortality

	Univariate analysis HR (%95 CI)	P	Multivariate analysis HR (%95 CI)	p
Gender				
Female	Reference	0.378		
Male	0.81 (0.51-1.30)			
ECOG PS				
0-1	Reference	0.023		
2+	1.91 (1.09-3.30)			
Weight loss in the last 6 months				
Absent	Reference	0.004		
Present	2.22 (1.28-3.84)			
Smoking exposure				
Absent	Reference	0.097		
Present	0.64 (0.37-1.09)			
Obstruction				
Absent	Reference	0.167		
Present	0.61 (0.30-1.23)			
Localization				
Left	Reference	0.881		
Right	0.96 (0.56-1.66)			
Lymphatic invasion				
Absent	Reference	0.290		
Present	1.42 (0.74-2.71)			
Vascular invasion				
Absent	Reference	0.005	Reference	0.002
Present	2.39 (1.31-4.37)		6.31 (1.97-20.18)	
Perineural invasion				
Absent	Reference	0.702		
Present	1.12 (0.62-2.04)			
Grade				
1	Reference			
2	1.29 (0.18-9.38)	0.748		
3	3.03 (0.40-22.78)	0.281		
Mucinous component				
Absent	Reference	0.292		
Present	1.29 (0.80-2.09)			
RAS status				
wild	Reference	0.040		
mutant	1.84 (1.03-3.28)			
High CEA in diagnosis				
Absent	Reference	0.423		
Present	1.23 (0.74-2.05)			
High Ca 19-9 in diagnosis				
Absent	Reference	0.011		
Present	2.17 (1.20-3.93)			
CRP				
<11	Reference	<0.001		
≥11	3.25 (1.97-5.38)			
NLR				
<2.3	Reference	<0.001		
≥2.3	2.72 (1.56-4.78)			
PLR				
<137	Reference	0.023	Reference	0.023
≥137	1.83 (1.09-3.09)		3.90 (1.21-12.63)	
SIII				
<798	Reference	<0.001		
≥798	3.07 (1.86-5.09)			
CAR				
<2.7	Reference	<0.001		
≥2.7	3.09 (1.88-5.08)			

CRP: c-reactive protein; CAR: c-reactive protein/albumin ratio; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SIII: systemic immune inflammatory index.

ripheral blood has been shown in many cancers, including colon cancer.[17,18] Neutrophils have an essential role in the mechanism of metastasis via VEGF and proteases and promote metastasis.[19] Also, studies have shown that neutrophils can inhibit the immune system and eliminate the cytolytic activity of immune cells.[20] At the same time, both tumor cells and neutrophils can contribute to tumor progression by producing chemokines and cytokines.[21] Lymphocytes, on the other hand, are the most important cells of the immune mechanism against tumors, with cytotoxic, anti-proliferative, and anti-migration effects.[22] Neutrophils suppress lymphocyte activity by secreting reactive oxygen species, nitric oxide, and arginase, thus preventing antitumor immune response.[23] Also, platelets induce epithelial–mesenchymal transition in circulating tumor cells and promote their extravasation to metastatic sites.[24] Thus, modulation of the tumor inflammatory microenvironment can influence cancer progression. Furthermore, the tumor inflammatory microenvironment supports tumor progression and induces chemoresistance.[25]

NLR and PLR are associated with poor survival in many cancer types, including CRC.[14,26] The value of SIII has not been investigated as much as PLR and NLR; there are few studies on this subject, and its importance has not yet been shown.[27] Also, CRP and CAR, one of the most significant markers of inflammation are often prognostic and predictive in mCRC patients.[15] In our study, although NLR, SIII, CRP, and CAR appeared to be associated with poor survival in univariant analysis, they were not shown to be associated with survival in multivariant analysis, but PLR is an appropriate predictive and prognostic factor for mCRC patients. These results suggest that the predictive value of PLR may be superior to that of other inflammatory markers.

There are also several studies showing that inflammation in CRC patients may be related to treatment resistance. Accordingly, Dogan et al. showed that to be the case in mCRC patients who had received anti-EGFR. Also, Bilen et al. showed in patients who had received immunotherapy that progression-free survival was longer in the low PLR group than in the high PLR group.[4,28] In this study, we demonstrated the association of PLR with poor survival, independent of treatment in mCRC patients who received three series of treatments. Although previous studies have also shown that PLR is associated with poor survival in various groups of patients receiving immunotherapy, there was no patient receiving immunotherapy in our patient group.

The limitations of this study are its retrospective design and the relatively small number of patients. Multi-institutional and prospective randomized controlled trials are required to confirm our preliminary findings.

Conclusion

In summary, we demonstrated that increased pretreatment PLR is associated with shorter survival in mCRC patients and showed that it is superior to other established inflammation-based parameters in terms of its prognostic ability. Since PLR can be measured pretreatment, this system should be incorporated in routine diagnosis for risk stratification and treatment decision-making in mCRC patients.

Disclosures

Ethics Committee Approval: The Ethics Committee of Bezmialem Vakif University provided the ethics committee approval for this study (01/05-07.01.2020).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – T.D., M.B.; Design – T.D., M.B.; Supervision – T.D., M.B.; Materials – T.D., M.B.; Data collection &/or processing – T.D., M.B.; Analysis and/or interpretation – T.D., M.B.; Literature search – T.D.; Writing – T.D., M.B.; Critical review – T.D.

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