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Platelet to lymphocyte ratio is associated with tumor localization and outcomes in metastatic colorectal cancer

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Abstract

The aim of this study was to investigate the predictive and prognostic value of PLR, and the relationship between PLR and tumor localization.

A total of 229 patients with de-novo metastatic CRC were retrospectively analyzed. The cutoff value for PLR was defined by the receiver operating characteristic (ROC) curve analysis and threshold value of 196.5 as best cut-off value was found.

The higher rate of *BRAF* mutation was significantly detected for patients with PLR^{high} (> 196.5) compared to those with PLR^{low} (≤196.5) ($P = .001$). PLR was significantly higher in tumors located on the right colon ($P = .012$). PLR, tumor localization, the presence of surgery for primary tumor, the presence of curative surgery, the presence of metastasectomy for progression-free survival (PFS) and PLR, gender, *BRAF* mutation, tumor localization, the presence of surgery for primary tumor, the presence of metastasectomy for overall survival (OS) were found to be prognostic factors by univariate analysis. Multivariate analysis showed that PLR, the presence of curative surgery and the presence of metastasectomy for both PFS and OS were found to be independent prognostic factors. Moreover, a logistic regression analysis indicated that PLR and tumor localization were found to be an independent factors for predicting response to systemic treatment ($P < .001$ and $P = .023$ respectively).

Our results showed that pretreatment PLR was readily feasible and simple biomarker predicting response to treatment and survival, in addition it was significantly associated with tumor localization.

Abbreviations: BRAF = serine/threonine-protein kinase B-raf, CR = complet response, CRC = colorectal cancer, LCC = left-sided colon cancer, mCRC = metastatic colorectal cancer, PD = progressive disease, PLR = platelet-to-lymphocyte ratio, PR = partial response, RCC = right-sided colon cancer, SD = stable disease, SIR = systemic inflammatory response.

Keywords: metastatic colorectal cancer, platelet-to-lymphocyte ratio, prognostic factor, survival, treatment response

1. Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in males and the second in female.[1] Association with high mortality and frequency rates led to maintain its importance for decades. It is vital to seek appropriate prognostic factors in order to choose patients for systematic treatment. Many prognostic factors such as clinical and pathological TNM stage, tumor localization and tumor grade have been investigated to predict treatment response in CRC.[2,3] However, there is a lack of precise biomarkers for predicting prognosis in CRC that can be used for individualized treatment. Thus, it is clinically important to find reliable prognostic markers for treatment.[4]

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The Local Ethics Committee of Istanbul Medipol University approved the study.

The datasets generated during and/or analyzed during the present study are not publicly available, but are available from the corresponding author on reasonable request.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Previous studies showed clinical differences between the right-sided colon cancer (RCC) and left-sided colon cancer (LCC).[5–7] In addition, recently, there are growing data about tumor location, particularly its predictive and prognostic significance on survival.[8–10] The majority of publications revealed that RCCs have associated with shorter progression-free survival (PFS) and overall survival (OS). On the other hand, some other clinico-pathological features have been investigated as a prognostic factor and to predict to response to treatment.[8–11]

It has been previously documented that tumor growth and metastasis resulted from interactions between tumoral and stromal factors, including blood vessels, inflammatory cells, and immunity system.[12–15] The inflammatory indexes, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and systemic immune-inflammation index (SII) have been investigated as prognostic and predictive factors in various human cancer types, especially in radically resected CRC or mCRC.[16–19] Moreover, elevated baseline NLR correlated with poor response to bevacizumab in combination with chemotherapy in mCRC.[20] Yang et al[21] showed that elevated pre-treatment NLR was potential biomarker to predict the survival of patients and the efficacy of cetuximab treatment in patients with metastatic WT RAS CRC. However, the relationship between inflammatory parameters, treatment response, and tumor localization has not yet been clearly demonstrated in mCRC. The majority of studies on PLR in CRC have been done in early stage disease.[22,23] Recently, Jia et al[24] analyzed the prognostic value of pretreatment PLR and NLR for patients with CRC who received neoadjuvant chemotherapy. They showed that a high PLR might be prognostic factor. Among the parameter, PLR is regarded as an easily reproducible, cost-effective and widely used marker of both inflammation and coagulation response in patients with malignancy.[25,26]

In this current study, we aimed to evaluate the predictive and prognostic value of PLR, and the relationship between PLR and tumor localization, and treatment response in patients with mCRC.

2. Patients and methods

Between 2013 and 2018, a total of 229 mCRC patients who had not received systemic treatment were included in the study. Patient data were retrospectively obtained from patients' charts with respect to age, gender, histopathological type, tumor localization, RAS (K-RAS and N-RAS) and BRAF mutations status, pretreatment complete blood cell counts, systemic treatments in metastatic settings, the presence of metastatectomy and other local treatments and responses to treatment and survival after written informed consent had been obtained from patients or their relatives.

The eligibility criteria consisted of patients aged ≥18 years with diagnosed a histologically confirmed newly diagnosed and de novo metastatic CRC and survival expectancy longer than 3 months. Patients who had insufficient disease information, unknown K-RAS and N-RAS mutation status and had early stage disease at diagnosis were excluded from data analysis. The Local Ethics Committee of Istanbul Medipol University approved the study.

The response to treatment was assessed by chest CT scan and abdomino-pelvic CT scan or MRI findings using responses to treatment were evaluated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A complete response (CR) was defined as the disappearance of all measurable disease, a partial response (PR) represented a decrease of at least 30% of the tumor volume and stable disease (SD) defined small changes that do not meet above criteria without actual progression of disease. Progressive disease (PD) was defined as more than 20% increase in tumor volume or any new sites of disease.

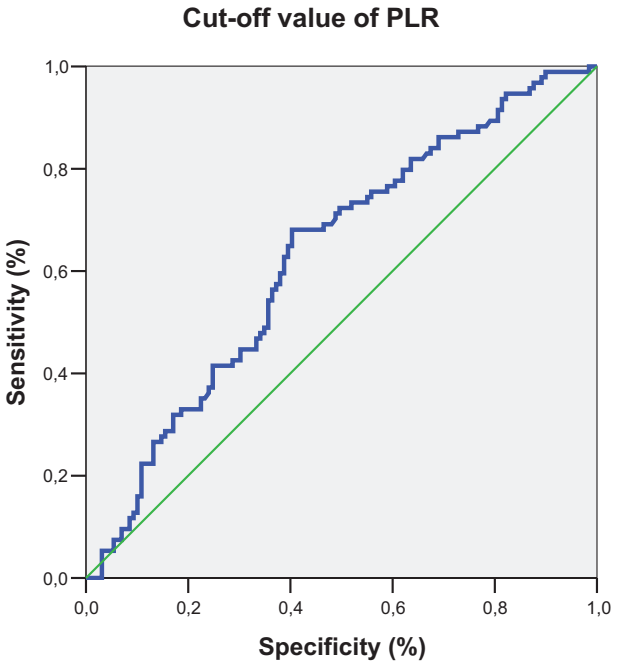

Figure 1. ROC curve shows threshold value of 196.5 as best cut-off value of PLR (AUC: 0.69 specificity: 0.85 sensitivity: 0.65).

The cutoff value for PLR was defined by the receiver operating characteristic (ROC) curve analysis and threshold value of 196.5 as best cut-off value was found (area under the curve: 0.69 specificity: 0.85 sensitivity: 0.65, Fig. 1).

2.1. Statistical analysis

All data were analyzed with SPSS 22.0 (SPSS Inc., Chicago, IL, USA) software. The relationship clinicopathological factors and PLR groups were compared by means of the chi-squared test and Fisher's exact test. The survival analyses and curves were established with the Kaplan–Meier method and compared with the log-rank test. PFS was defined as from the initiation of treatment until disease first progression or to the date of death or loss of follow-up. OS was described as the time from diagnosis to the date of the patient's death or loss of follow-up. Univariate and multivariate analyses were performed with the Cox proportional hazards model to evaluate the importance of the tumor localization and other clinicopathological features. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. The optimal cut-off values as well as sensitivity and specificity were determined according to the receiver operator characteristic (ROC) analysis. The best cut-off values were expressed using the Youden index. The area under the ROC (AUROC) curve also was calculated. To identify predictive factors related with response to systemic treatment, logistic regression analysis was

used. All *P* values were two-sided in tests and *P* values less than .05 were considered statistically significant.

3. Results

Ninety-five patients (41.4%) were female and 134 (58.6%) were male, with a median age of 59 years (range; 28–84 years). Based on the tumor localization, in 166 (72.4%) patient's tumors were classified as left-sided and 63 (27.6%) as right-sided. One hundred and fifteen patients (50.2%) had RAS mutated tumor, while 114 patients (49.8%) had RAS wild-type tumor. In the majority of patients (75.9%) BRAF mutation status was found to be wild-type. The presence of surgery for primary tumor in 97 (42.3%), while 132 (57.7%) patients have not undergone surgery. One hundred and fourty three (62.4%) patients out of 229 were administered anti-VEGF containing regimen, and 86 (37.6%) anti-EGFR in the first-line setting. The cutoff value for PLR was defined by ROC curve analysis and threshold value of 196.5 as best cut-off value was found (Fig. 1). According to this analysis, 113 patients (49.3%) were classified as PLR^{high} (>196.5) and 116 patients (50.7%) were classified as PLR^{low} (≤196.5).

Significant relationship was detected between PLR and BRAF mutation, tumor localization and the presence of disease progression. The higher rate of BRAF mutation was significantly detected for patients with PLR^{high} (>196.5) compared to those with PLR^{low} (≤196.5) (*P*=.001). In addition, PLR was significantly higher in tumors located on the right colon than those with tumor on the left colon (*P*=.012). The correlation between PLR and clinicopathological factors is listed in Table 1.

At the median follow-up of 17.5 months (range; 4.5–140.4 months), the median PFS time was 12.5 months and the median OS time was also 24.3 months for all patients. Univariate analysis was performed for PFS and OS in all mCRC cohort. It showed that the presence of primary surgery, tumor localization, the presence of metastasectomy and/or local treatment, type of surgery and PLR were found to be important factors for PFS. However, gender, presence of primary surgery, tumor localization, the presence of metastasectomy and/or local treatment, type of surgery, BRAF mutations status and PLR and tumor were significant prognostic indicators for OS. In other words, median PFS and OS intervals for patients with left-sided tumors, was significantly better compare to patients with right-sided tumors. (PFS: 20.6 vs 12.6 months, *P*=.031, and OS: 30.9 vs 22.8 months, *P*=.038, respectively).

A multivariate analysis with the Cox proportional hazards model was performed in order to further evaluate all of the significant prognostic factors that were detected in the univariate analysis for all mCRC patients. This showed that type of surgery (HR: 2,47, *P*=.007), the presence of metastasectomy and/or local treatment (HR: 0.44, p=0.026) and PLR^{low} (≤196.5) (HR:3.01, *P*=.006) were found to be independent prognostic factors for PFS. Afterthat, the multivariate analysis was carried out for OS, and it demonstrated that type of surgery (HR: 3.77, *P*=.016), the presence of metastasectomy and/or local treatment (HR: 0.23, *P*=.009) and PLR^{low} (≤196.5) (HR:3.82, *P*=.027) were found as independent prognostic indicators. The results of univariate and multivariate analysis for both PFS and OS in all patients with mCRC are shown in Tables 2 and 3.

When this PLR^{low} (≤196.5) patient group was analyzed separately, the median age of the patients were 59 (range; 28–84), while 66 (56.9%) were male and 50 (43.1%) were female. According to tumor localization, 23 patients (19.8%) were localized in the right colon and 93 (90.2%) in the left colon. According to RAS status, 56 (48.3) patients wild-type and 60 (51.7) RAS mutated. Most patients had BRAF wild-type (81.8%). Seventy one (61.2%) of the patients received bevacizumab containing regimen and the remaining 45 (38.8%) were treated with anti-EGFR containing regimen. Fifty two (44.8%) of the patients had surgery for primary tumor. The median PFS time of patients with PLR^{low} (≤196.5) tumors was better than that of patients with PLR^{high} (> 196.5) tumors (25.8 vs 10.6 months, *P*<.001, Fig. 2). Furthermore, the median OS of patients with PLR^{high} (> 196.5) tumors was significantly worse than that of patients with PLR^{low} (≤196.5) tumors (16.7 vs 38.9 months, *P*<.001 Fig. 3).

A logistic regression analysis was performed in order to further evaluate all of the significant prognostic factors that might be predicted response to systemic treatment. It showed that PLR and tumor localization were found to be an independent factors for predicting response to systemic treatment (*P*<.001, OR:3.97, 95%CI 2.00–7.88 and *P*=.023, OR: 1.15, 95%CI 0.56–2.35, respectively). Table 4 shows the results of logistic regression analysis of the predictive factors for response to systemic treatment.

Table 1

The correlation between PLR and clinicopathological factors.

Factors	PLR ≤ 196.5 n (%)	PLR > 196.5 n (%)	*P*
Gender			.68
Female	50 (43.1)	45 (39.8)	
Male	66 (56.9)	68 (60.2)	
Age (year)			.11
<60	70 (60.3)	56 (49.6)	
≥60	46 (39.7)	57 (50.4)	
Tumor localization			**.012**
Right	23 (19.8)	40 (35.4)	
Left	93 (80.2)	73 (64.6)	
Surgery for primary tumor			.50
Absent	64 (55.2)	68 (60.2)	
Present	52 (44.8)	45 (39.8)	
RAS status (K&N-RAS)			.69
Wild-type	56 (48.3)	58 (51.3)	
Mutated	60 (51.7)	55 (48.7)	
B-RAF status			**.001**
Wild-type	95 (81.8)	79 (69.9)	
Mutated	1 (0.4)	7 (6.3)	
Unknown	20 (17.2)	27 (23.8)	
Targeted-treatment			.78
Anti-VEGF	71 (61.2)	72 (63.7)	
Anti-EGFR	45 (38.8)	41 (36.3)	
Progression			**<.001**
Absent	70 (60.3)	45 (39.8)	
Present	46 (39.7)	68 (47.9)	

4. Discussion

In the present study, significant relationship was found between PLR and BRAF mutation, tumor localization, and the presence of disease progression. The higher rate of *BRAF* mutation was significantly detected for patients with PLR^{high} (> 196.5) compared to those with PLR^{low} (≤196.5). In addition, PLR was significantly higher in tumors located on the right colon than those with tumor on the left colon. PLR, tumor localization, the

Table 2

Univariate and multivariate analysis for progression-free survival (PFS).

Variant	Median PFS (month)	Univariate *P* value	Multivariate *P* value	HR 95% CI
Age		.67		
<60	17.8			
≥60	25.8			
Gender		.52		
Male	16.3			
Female	20.6			
Surgery for primary tumor		**<.001**	.21	
Absent	12.5			0.44
Present	35.0			0.12–1.60
Type of surgery		**.019**	**.007**	
Curative	42.5			2.47
Palliative	21.7			1.27–3.79
Tumor Localization		**.031**	.15	
Right	12.6			0.61
Left	20.6			0.30–1.21
RAS status (K&N-RAS)		.80		
Wild-type	17.4			
Mutated	15.6			
B-RAF mutation status		.17		
WT	25.0			
Mutant	12.6			
Unknown	12.5			
Targeted treatment		.36		
Anti-VEGF	15.8			
Anti-EGFR	20.6			
Metastasectomy		**<.001**	**.026**	
Absent	12.5			0.44
Present	35.7			0.21–0.90
PRL		**<.001**	**.006**	
≤196.5	25.8			3.01
>196.5	10.6			1.37–4.56

*CI = confidence interval, EGFR = Epidermal growth factor receptor, NA = not available, NR = could not be reached, PFS = progression-free survival, VEGF = Vascular endothelial growth factor.

presence of surgery for primary tumor, the presence of curative surgery, the presence of metastasectomy for PFS and PLR, gender, *BRAF* mutation, tumor localization, the presence of surgery for primary tumor, the presence of metastasectomy for OS were determined to be prognostic factors. Moreover, PLR, the presence of curative surgery and the presence of metastasectomy for both PFS and OS were found to be independent prognostic factors by multivariate analysis. A logistic regression analysis indicated that PLR and tumor localization were found to be an independent factor for predicting response to systemic treatment.

Inflammation plays a very important role in cancer development. The immune system is also a host response mechanism to tumor aggression; the role of both platelets and lymphocytes as independent regulators of various processes in cancer has been known for a long time.[27] In addition, pro-inflammatory mediators could also stimulate thrombocytosis. Thrombocytosis is related with systemic inflammation due to cancer, and several studies revealed that angiogenesis and tumor invasion were also associated with thrombocyte release through increasing production of vascular epidermal growth factor in tumor microenviroment. Therefore, thrombocytosis can show systemic inflammation and tumor activity.[28]

The PLR has been demonstrated as a prognostic factor in several cancers.[29–33] On the other hand, prognostic role of PLR in patients with CRC is still controversial. Tumor cells have the ability to alter platelet activity to best manage tumor growth, proliferation, survival and metastasis.[28–34] Several studies have identified the relationship between poor prognosis and high PLR in solid tumors, while the others have not proved the positive role of high PLR as a prognostic factor.[30,35,36] In our study, high PLR levels were found to be worse prognostic factor. In other words, OS and PFS were significantly better for patients with PLR^{low} compared with patients with PLR^{high}. Our results were thus compatible with the literature.[20,21,25] Moreover, PLR was significantly higher in tumors located on the right colon than those with tumor on the left colon. Although there are few studies on the association of treatment response with systemic inflammatory markers in the literature,[21,36] to the best of our knowledge, the relationship between PLR and tumor localization has not been previously reported in patients with mCRC. Therefore, we believe that our study will contribute to the literature.

A study performed by Yang et al[21] showed that PLR was significantly correlated with PFS but not with OS in univariate analysis. In addition, they found that no statistical relationship between PLR and survival in mCRC patients with wild-type RAS treated with chemotherapy plus cetuximab by multivariate analysis. In contrast to their findings, we found to be PLR as an independent prognostic factor by both univariate and multivariate analysis. In other words, PLR^{low} was significantly independent prognostic indicator for both PFS and OS in mCRC patients in our study. Passardi et al[36] investigated the role of pretreatment systemic inflammatory markers as predictors of prognosis and treatment efficacy in patients with mCRC from

Table 3

Univariate and multivariate analysis for overall survival (OS).

Variant	Median OS (month)	Univariate *P* value	Multivariate *P* value	HR 95% CI
Age		.53		
<60	26.1			
≥60	31.7			
Gender		**.033**	.09	
Male	24.7			0.40
Female	32.4			0.14–1.17
Surgery for primary tumor		**<.001**	.11	
Absent	22.1			0.14
Present	45.3			0.10–1.71
Type of surgery		**.002**	**.016**	
Curative	61.0			3.77
Palliative	28.7			1.47–8.12
Tumor Localization		**.038**	.17	
Right	22.8			0.45
Left	30.9			0.14–1.42
RAS status (K&N-RAS)		.44		
Wild-type	26.9			
Mutated	25.0			
B-RAF mutation status		**.01**	.23	
WT	32.4			1.40
Mutant	18.9			0.80–2.45
Unknown	28.0			
Targeted treatment		.77		
Anti-VEGF	26.0			
Anti-EGFR	25.7			
Metastasectomy		**<.001**	**.009**	
Absent	21.7			0.23
Present	73.9			0.07–0.69
PRL		**<.001**	**.027**	
≤196.5	38.9			3.82
>196.5	16.7			1.16–9.66

*CI = confidence interval, EGFR = Epidermal growth factor receptor, NA = not available, NR = could not be reached, OS = overall survival, VEGF = Vascular endothelial growth factor.

the prospective multicenter randomized ITACa trial. They found that PFS and OS were higher in patients with low NLR and low PLR. In addition, while low NLR was shown to predict treatment response who were candidates for chemotherapy plus Bevacizumab, PLR could not.[36] In an updated systematic review and meta-analysis of 24 studies, Chen et al[25] demonstrated that elevated PLR was predicted shorter OS, poorer disease-free survival (DFS) and worse recurrence-free survival in both metastatic and nonmetastatic CRC patients. Thus, our results were compatible with their results.[25]

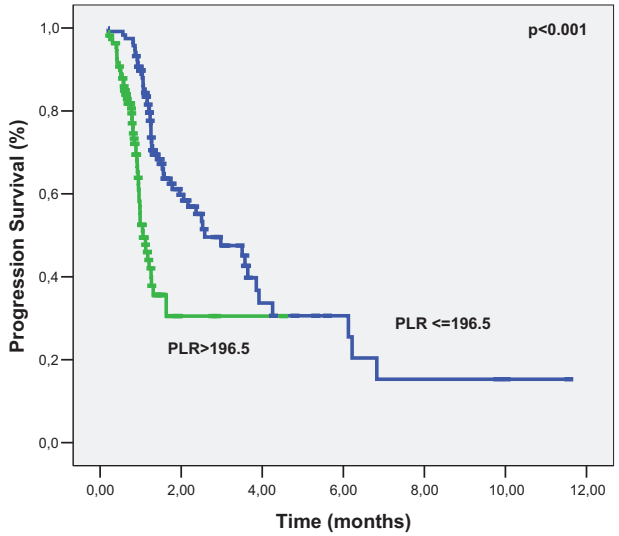

Figure 2. Progression-free survival curves according to the PLR.

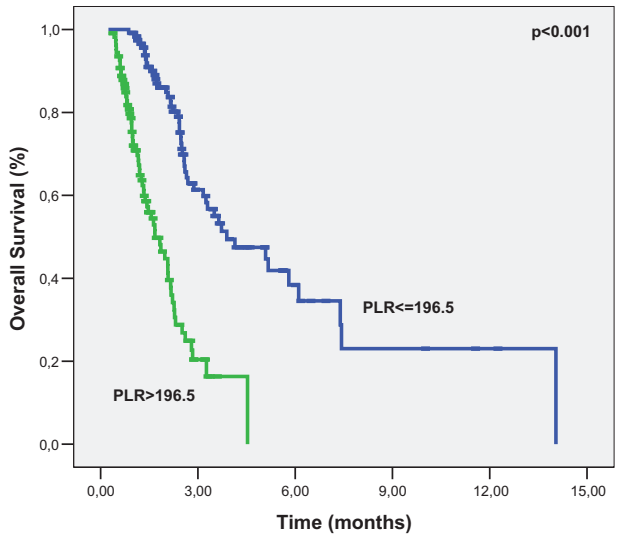

Figure 3. Overall survival in PLR groups.

Table 4

Logistic regression analysis of the predictive factors for response to treatment.

Factors	*P*	OR	95% CI
PRL (≤196.5 vs >196.5)	<.001	3.97	2.00–7.88
Tumor Localization (Right vs Left)	.023	1.15	0.56–2.35
RAS mutation (WT vs Mutant)	.29	0.59	0.22–1.57
B-RAF mutation (WT vs Mutant)	.90	1.02	0.71–1.46
Targeted treatment (Anti-VEGF vs Anti-EGFR)	.76	0.85	0.30–2.36

*CI = confidence interval, EGFR = Epidermal growth factor receptor, OR = Odds ratio, VEGF = Vascular endothelial growth factor, WT = wild-type.

In the present study, univariate analysis showed that the presence of primary surgery, tumor localization, the presence of metastasectomy and/or local treatment, type of surgery for PFS, and gender, presence of primary surgery, tumor localization, the presence of metastasectomy and/or local treatment, type of surgery, BRAF mutations status for OS, as was PLR were prognostic factors. Similar to the literature, metastasectomy and surgery of the primary tumor at the time of diagnosis were associated with better OS and PFS in the patient with PLR^{low}.[37] Neofytou et al[37] in their study, revealed that preoperative both PLR and NLR were associated with decreased DFS and OS by univariate analysis in patients with liver-only mCRC after hepatectomy. However, they found to be only PLR independent prognostic factor in multivariate analysis. Thus, they concluded that preoperative PLR was superior to preoperative NLR as an adverse prognostic factor in patients who had undergone liver metastasectomy for liver-only mCRC patients.[37] Yang et al[21] have firstly investigated the role of pretreatment both NLR and PLR as predictors for treatment efficacy of cetuximab in 95 mCRC patients with wild-type RAS. Nevertheless, they have not analyzed between treatment response and pretreatment inflammatory indexes. Moreover, in a study carried out by Jiang et al.,[38] 102 mCRC patients with wild-type RAS treated with cetuximab plus chemotherapy were retrospectively analyzed and early response to treatment was evaluated. They showed that only NLR was predictor of benefit from cetuximab-combined therapy in mCRC patients.[38] In our study, a logistic regression analysis was performed in order to further evaluate all of the significant prognostic factors that might be predicted response to systemic treatment in 239 patients with mCRC with both RAS mutated and wild-type. It showed that both PLR and tumor localization were found to be an independent factors for predicting response to systemic treatment ($P < .001$, OR:3.97, 95%CI 2.00–7.88 and $P = .023$, OR: 1.15, 95%CI 0.56–2.35, respectively). In other words, the efficacy of chemotherapy plus targeted treatment was significantly better in patients with PLR^{low} and left-sided tumor with both RAS status.

The major limitations of our study were the retrospective nature and relative small sample size, which might have influenced the results. The other limitation of this study was short follow-up interval. Although our findings should be confirmed by prospective studies and separately analyzed in patients with both all and only RAS wild-type with respect to the tumor localization, as well as both anti-VEGF and anti-EGFR treatments, we believe that they contribute to the literature because our study were included all RAS population and analyzed between PLR and tumor localization, as was treatment response for patients with mCRC, unlike previous studies which evaluated the relationship between survival and PLR only.[35,36]

5. Conclusion

Our findings demonstrate that high PLR levels were significantly correlated with both poorer survivals and treatment response in patients with mCRC. Furthermore, PLR was also significantly higher in tumors located on the right colon than those with tumor on the left colon. To the best of our knowledge, this study is the first one in the literature to show that PRL levels are associated with tumor localization in patients with RAS wild-type mCRC. In addition, low PLR levels can predict going response to systemic treatment in mCRC patients. PLR test may be useful for evaluating treatment effects and survival, and it may be widely applied in daily clinical practice as routinely available and less expensive, but their importance should be tested after multiple chemotherapy sessions in larger prospective studies with long follow-up time.

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