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ORIGINAL ARTICLE

Impact of neutrophil-lymphocyte and platelet-lymphocyte ratio on antiEGFR and bevacizumab efficacy in metastatic colorectal cancer

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Summary

Purpose: *The purpose of this study was to determine the influence of the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) on antiEGFR and bevacizumab efficacy in metastatic colorectal cancer patients.*

Methods: *All metastatic colorectal cancer patients who had received chemotherapy and biological agents as first-line treatment at Erciyes University Hospital were retrospectively reviewed. NLR and PLR were each divided into two groups, as high and low. The NLR high group was compared with the low group and the PLR high group was compared with the low group in patients in terms of progression-free survival (PFS) and overall survival (OS), separately. Cox regression and the Kaplan Meier method were used.*

Results: *One hundred and thirty (58%) of the patients had received bevacizumab and 94 (42%) had received antiEGFR therapy (cetuximab or panitumumab). In the bevacizumab group, PFS was 9 months in the NLR high group and 11 months in the NLR low group (p=0.013). OS was 23 months in the NLR high group and 27 months in the NLR low group (p=0.734). There was no statistically significant OS difference in patients who had received antiEGFR therapy according to NLR. There was no statistically significant PFS difference in patients who received bevacizumab according to PLR. In the antiEGFR group, PFS was 9 months (95% CI, 8.07-13.55) in the PLR high group and 18 months (95% CI, 12.02-18.68) in the PLR low group, with statistically significant difference (p=0.040). There was no statistically significant OS difference in patients who had received antiEGFR therapy according to PLR.*

Conclusions: *NLR and PLR are important inflammatory markers. In patients who had received bevacizumab, PFS was longer in the NLR low group than in the high group. In patients who had received antiEGFR, PFS was longer in the PLR low group than in the high group.*

Key words: *inflammation markers, colorectal cancer, antiEGFR, bevacizumab*

Introduction

The recent years have seen many advances in metastatic colorectal cancer treatment. The recommended first-line therapy is combined chemotherapy with targeted agents such as antiepidermal growth factor receptor (antiEGFR) and bevacizumab. Both are effective in metastatic colorectal cancer treatment [1]. Some predictive markers on antiEGFR and bevacizumab efficacy were studied in this setting [2,3] but inflammatory markers influence on antiEGFR and bevacizumab efficacy remains a question.

Inflammation is related to leukocytes, cytokines, and chemokines in cancer. The inflammation is essential for tumor microinvorement, and inflammatory cells can affect tumor proliferation, angiogenesis, metastasis, and genetic instability

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[4]. High levels of proinflammatory cytokines and signaling molecules are associated with disease activity [5]. Neutrophils secrete TGF beta and IL10, and this can cause ınflammatory response in cancer [6] The increased neutrophil level is an indicator of systemic inflammation and lymphopenia is associated with inadequate cell-mediated immune response [7]. Platelets contribute to tumor progression and inflammation and they could induce tumor metastasis by secreting growth factors [8].

In many tumors, vascular endothelial growth factor (VEGF) and EGFR are responsible for tumor proliferation [9]. VEGF regulates tumor angiogenesis and this promotes the proliferation and viability of endothelial cells and directly causes cancer cell proliferation by VEGFR1. Bevacizumab inhibits angiogenesis by binding to VEGFA [10]. EGFR is one of the targets in cancer treatment [9]. Cetuximab is the chimeric IgG1 mouse/human antibody [11] and panitumumab is the fully humanized IgG2 antibody that targets the extracellular domain of EGFR [12]. EGFR expression is important for tumor progression [13]. The EGFR pathway has a role in cyclooxygenase 2 (COX2) expression, so it is related to inflammation [14].

Neutrophil-lymphocyte and platelet-lymphocyte ratio are the simple predictors of the systemic inflammatory response [15]. Elevated levels of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are associated with poor outcomes [16].

Systemic inflammatory markers have been previously studied in colorectal cancer patients [17-19], yet the association between antiEGFR agents and bevacizumab with systemic inflammatory markers such as NLR and PLR has not been fully understood. In the present study, we aimed to determine the influence of NLR and PLR on antiEGFR and bevacizumab efficacy in metastatic colorectal cancer patients.

Methods

Study population

Between January 2010 and May 2018, all metastatic colorectal cancer patients who received chemotherapy and biological agents as first-line treatment at the Erciyes University, Department of Medical Oncology, were retrospectively reviewed. Data were collected from the hospital's patient records, including patient characteristics, tumor site, number of metastatic sites, initial CEA level, K-RAS mutation status, operation status of primary tumor, and chemotherapeutic agents.

Patients receiving antiEGFR therapy (cetuximab or panitumumab) and bevacizumab at first-line, and diagnosed with metastatic colorectal cancer were included in the study. 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 therapy and 5 mg/kg with FOLFOX or FOLFIRI chemotherapies. Patients having a history of infection, chronic disease such as heart failure, liver cirrhosis, end-stage renal disease before initiation chemotherapy were excluded.

NLR and PLR

NLR was defined the ratio of absolute neutrophil and lymphocyte count within 1 month before initiation of chemotherapy and similarly PLR was defined the ratio of platelet and lymphocyte count within 1 month before initiation of chemotherapy.

NLR was divided into two groups based on the cut-off points ≥3.44 or <3.44 as NLR high and low (area under the curve: 0.524, specificity: 0.667, sensitivity: 0.42). PLR was divided into two groups based on the cut-off points (≥ 160. 66 or <160.66) as PLR high and low (area under the curve: 0.559, specificity: 0.495, sensitivity: 0.648). ROC curve analysis was used to determine all cut off values.

Statistics

The correlations between patient characteristics and NLR and PLR were analysed with x^2 test for nonparametric variables and Mann-Whitney U test for parametric variables. Progression free survival (PFS) and overall survival (OS) related to NLR and PLR were calculated for using both Kaplan-Meier (with log-rank test) and Cox regression models. A p value <0.05 was regarded as statistically significant. SPSS 22.0 (SPSS Inc., Chicago, IL, USA) software was used in all statistical analyses.

Results

General characteristics

NLR Group

One hundred thirty (58%) patients had received bevacizumab. Age, gender, history of previous adjuvant therapy, initially metastasis status, tumor site and other clinical characteristics are shown in Table 1. There were no differences between NLR high and low group in clinical patient characteristics receiving bevacizumab in the first-line setting.

Ninety four (42%) patients had received antiEGFR treatment. All clinical general characteristics are shown in Table 2. There were no differences between NLR high and low group in clinical patient characteristics receiving antiEGFR treatment in the first-line setting.

PLR Group

In the bevacizumab group age, gender, history of previous adjuvant therapy, initially metastasis status, tumor site and other clinical characteristics

were similar between PLR high and low group. In the PLR high group 2 metastatic sites were signifiicantly more than in PLR low group (0.026; Table 1).

Ninety four (42%) patients had received antiEGFR therapy. In the PLR high group, gender was significantly different compared with the PLR low group. Other clinical general characteristics were similar in the PLR high and low group (Table 2).

There were no differences between NLR high and low group in clinical patient characteristics receiving antiEGFR in the first-line setting (Table 2).

Progression free and overall survival

Univariate and multivariate analysis

The univariate analysis revealed that high NLR level was correlated with poor PFS with a hazard ratio of 1.62 (95 % CI 1.08-2.44, p=0.019) in patients receiving bevacizumab (Table 3).

The multivariate analysis revealed that high NLR level and right site of colon were correlated with poor PFS, with a hazard ratio of 1.92 (95% CI 1.19-3.11, p=0.008) and 0.53 (95%CI 0.33-0.84, p=0.007), respectively in patients receiving bevacizumab (Table 4).

Table 1. Characteristics of patients receiving bevacizumab

Characteristics	*Overall population (n=130)*	*NLR-low (n=80), n (%)*	*NLR-high (n=50), n (%)*	*p*	*PLR-low (n=51), n (%)*	*PLR-high (n=79), n (%)*	*p*
Age (median, min-max)	61 (26-82)	62 (30-78)	60 (26-82)	0.812	61 (38-78)	61 (26-82)	0.329
Gender				0.211			0.590
Male	66	37 (46.3)	29 (58)		24 (47.1)	42 (53.2)	
Female	64	43 (53.8)	21 (42)		27 (52.9)	37 (46.8)	
Previous adjuvant or neoadjuvant therapy				0.392			0.833
Yes	30	16 (20)	14 (28)		11 (21.6)	19 (24.1)	
No	100	64 (80)	36 (72)		40 (78.4)	60 (75.9)	
Initially metastatic				0.680			0.416
Yes	97	61 (76.3)	36 (72)		36 (70.6)	61 (77.2)	
No	33	19 (23.7)	14 (28)		15 (29.4)	18 (22.8)	
Tumor site				0.226			0.155
Right	34	24 (30)	10 (20)		17 (33.3)	17 (21.5)	
Left	96	56 (70)	40 (80)		34 (66.6)	62 (78.5)	
Operated primary				0.669			0.289
Yes	100	63 (78.8)	37 (74)		42 (82.4)	58 (73.4)	
No	30	17 (21.2)	13 (26)		9 (17.6)	21 (26.6)	
KRAS mutation status				0.660			0.217
Wild	63	39 (48.8)	24 (48)		25 (49)	38 (48.1)	
Mutant	62	39 (48.8)	23 (46)		26 (51)	36 (45.6)	
Unknown	5	2 (2.5)	3 (6)		0	5 (6.3)	
Initial chemotherapy				0.189			0.356
Oxaliplatin-based	83	55 (68.8)	28 (56)		30 (58.8)	53 (67.1)	
Irinotecan-based	47	25 (31.2)	22 (44)		21 (41.2)	26 (32.9)	
Capecitabine-based	0	0	0		0	0	
Number of metastatic sites				0.261			**0.026**
1	77	51 (63.8)	26 (52)		34 (66.7)	43 (54.5)	
2	46	24 (30)	22 (44)		12 (23.5)	34 (43)	
>2	7	5 (6.2)	2 (4)		5 (9.8)	2 (2.5)	
Initial CEA				0352			0.713
<5	50	34 (42.5)	16 (32)		21 (41.2)	29 (36.7)	
≥5	79	46 (57.5)	33 (66)		30 (58.8)	49 (62)	
Unknown	1	0	1 (2)		0	1 (1.3)	

Bold number denotes statistical significance

Table 2. Characteristics of patients receiving antiEGFR

Characteristics	*Overall population (n=94)*	*NLR-low (n=57), n (%)*	*NLR-high (n=37), n (%)*	*p*	*PLR-low (n=42), n (%)*	*PLR-high (n=52), n (%)*	*p*
Age (median, min-max)	61 (24-87)	64 (31-87)	60 (24-81)	0.096	64.5 (31-87)	60 (24-81)	0.246
Gender				0.057			**0.002**
Male	48	34 (59.6)	14 (37.8)		29 (69)	19 (36.5)	
Female	46	23 (40.4)	23 (62.2)		13 (31)	33 (63.5)	
Previous adjuvant or neoajuvant therapy				0.463			0.145
Yes	22	15 (26.3)	7 (18.9)		13 (31)	9 (17.3)	
No	72	42 (73.7)	30 (81.1)		29 (69)	43 (82.7)	
Initially metastatic				0.819			0.252
Yes	67	40 (70.2)	27 (73)		27 (64.3)	40 (76.9)	
No	27	17 (29.8)	10 (27)		15 (35.7)	12 (23.1)	
Tumor site				0.404			0.590
Right	16	8 (14)	8 (21.6)		6 (14.3)	9 (17.3)	
Left	78	49 (86)	29 (78.4)		36 (85.7)	43 (82.7)	
Operated primary				0.386			0.525
Yes	59	38 (66.7)	21 (56.8)		28 (66.7)	31 (59.6)	
No	35	19 (33.3)	16 (43.2)		14 (33.7)	21 (40.4)	
KRAS mutation status				0.651			0.626
Wild	90	54 (94.7)	36 (97.3)		41 (97.6)	49 (94.2)	
Mutant	4	3 (5.3)	1 (2.7)		1 (2.4)	3 (5.8)	
Unknown				0.586			0.497
Initial chemotherapy		21 (36.8)	13 (35.1)		12 (28.6)	22 (42.3)	
Oxaliplatin-based	34	34 (59.6)	24 (64.9)		29 (69)	29 (55.8)	
Irinotecan-based	58	2 (3.5)	0		1 (2.4)	1 (1.9)	
Capecitabine-based	2			0.117			0.156
Number of metastatic sites		42 (73.7)	21 (56.8)		28 (66.7)	35 (67.3)	
1	63	13 (22.8)	11 (29.7)		13 (31)	11 (21.2)	
2	24	2 (3.5)	5 (13.5)		1 (2.4)	6 (11.5)	
>2	7			0.381			0.282
Initial CEA							
<5	34	23 (40.4)	11 (29.7)		18 (42.9)	16 (30.8)	
≥5	60	34 (59.6)	26 (70.3)		24 (57.1)	36 (69.2)	
Unknown							
Panitumumab	34	23 (40.4)	11 (29.7)	0.381	14 (33.3)	20 (38.5)	0.669
Cetuximab	60	34 (59.6)	26 (70.3)		28 (66.7)	32 (61.5)	

Bold number denotes statistical significance

Table 3. Univariate analysis for PFS and OS

Variables	*Progression-free survival*		*Overall survival*	
	Univariate analysis, HR (95%CI)	*p*	*Univariate analysis, HR (95%CI)*	*p*
EGFR Group				
NLR level(<3.44 and ≥3.44)	1.33 (0.78-2.26)	0.292	0.73 (0.37-1.43)	0.365
PLR level (<160.66 and ≥160.66)	1.72 (0.99-2.97)	0.051	1.43 (0.70-2.90)	0.322
VEGF Group				
NLR level(<3.44 and ≥3.44)	1.62 (1.08-2.44)	**0.019**	0.93 (0.60-1.42)	0.740
PLR level (<160.66 and ≥160.66)	1.10 (0.73-1.66)	0.621	0.87 (0.56-1.35)	0.555

Bold number denotes statistical significance

NLR Group

In the bevacizumab group PFS was 9 months (95% CI, 7.23-11.89) in the NLR high group and 11 months (95% CI 10.44-14.39) in NLR low group (p=0.013). OS was 23 months (95% CI, 21.99-32.57) in the NLR high group and 27 months (95% CI, 24.38-31.98) in the NLR low group (p=0.734; Figure 1).

In the antiEGFR group PFS was 10 months (95% CI, 7.94-16.07) in the NLR high group and 11 months (95% CI, 10.88-16.11) in the NLR low group (p=0.273). OS was 30 months (95% CI, 19.29-31.98) in the NLR high group and 27 months (95% CI, 31.64-55.29) in the NLR low group (p=0.358; Figure 1).

PLR Group

In the bevacizumab group PFS was 9 months (95% CI, 9.05-12.98) in the PLR high group and 11 months (95% CI 9.15-14.57) in the PLR low group (p=0.602). OS was 24 months (95% CI ,24.44-32.77) in the PLR high group and 24 months (95% CI, 22.08-31.42) in the PLR low group (p=0.545; Figure 2).

In the antiEGFR group PFS was 9 months (95% CI, 8.07-13.55) in the PLR high group and 18 months (95% CI, 12.02-18.68) in the PLR low group (p=0.040). OS was 24 months (95% CI,19.95-30.47) in the PLR high group and 27 months (95% CI, 32.55-60.42) in the PLR low group (p= 0.314; Figure 2).

Discussion

The predictive and prognostic importance of the NLR and PLR have been thoroughly studied in most tumors [20,21]. Growing evidence suggests that increased systemic inflammatory markers such as NLR and PLR are associated with poor tumor prognosis in colorectal cancer [15]. But these markers' impact on antiEGFR and bevacizumab efficacy is not well known. In our study, we report an association between NLR and PLR levels with antiEGFR and bevacizumab efficacy in metastatic colorectal cancer.

In this study, we showed that NLR low group had a longer PFS than the NLR high group in the bevacizumab-received group. OS was longer in the

Table 4. Multivariate analysis for PFS and OS

Variables	*Progression-free survival*		*Overall survival*	
	Multivariate analysis, HR (95%CI)	*p*	*Multivariate analysis, HR (95%CI)*	*p*
Patients receiving EGFR				
NLR level (<3.44 and ≥3.44)	0.89 (0.45-1.74)	0.738	1.11 (0.47-2.61)	0.798
PLR level (<160.66 and ≥160.66)	0.61 (0.28-1.30)	0.206	0.84 (0.32-2.20)	0.735
Gender (male and female)	1.20 (0.63-2.29)	0.566	1.09 (0.50-2.35)	0.818
Operated primary (No and yes)	0.81 (0.45-1.47)	0.504	1.06 (0.49-2.30)	0.869
CEA level before ChT (<5 and ≥5)	1.81 (0.94-3.50)	0.076	1.37 (0.62-3.01)	0.430
Adjuvant and neoadjuvant history (No and yes)	2.19 (0.54-8.88)	0.272	0.79 (0.17-3.70)	0.771
Tumor side (left or right)	0.83 (0.41-1.70)	0.626	0.76 (0.30-1.96)	0.579
Initially metastatic (No and yes)	2.71(0.73-10.09)	0.135	0.79 (0.20-3.07)	0.739
Number of metastases (1 and 2 and >2)	1.37 (0.87-2.16)	0.172	1.25 (0.71-2.20)	0.424
Patients receiving VEGF				
NLR level(<3.44 and ≥3.44)	**1.92 (1.19-3.11)**	**0.008**	1.18 (0.71-1.97)	0.511
PLR level (<160.66 and ≥160.66)	1.00 (0.63-1.60)	0.974	1.13 (0.67-1.91)	0.630
Gender (male and female)	1.27 (0.83-1.95)	0.258	1.30 (0.81-2.09	0.267
Operated primary (No and yes)	1.35 (0.79-2.30)	0.269	0.92 (0.52-1.63)	0.781
CEA level before ChT (<5 and ≥5)	0.72 (0.44-1.16)	0.181	1.48 (0.85-2.59)	0.161
Adjuvant and neoadjuvant history (No and yes)	0.74 (0.37-1.48)	0.403	0.88 (0.36-2.14)	0.784
Tumor side (right or left)	**0.53 (0.33-0.84)**	**0.007**	**0.44 (0.26-0.76)**	**0.003**
Initially metastatic (No and yes)	0.92 (0.48-1.75)	0.808	0.58 (0.25-1.35)	0.214
Number of metastases (1 and 2 and >2)	1.04 (0.73-1.47)	0.818	0.71 (0.48-1.06)	0.100

Bold numbers denote statistical significance

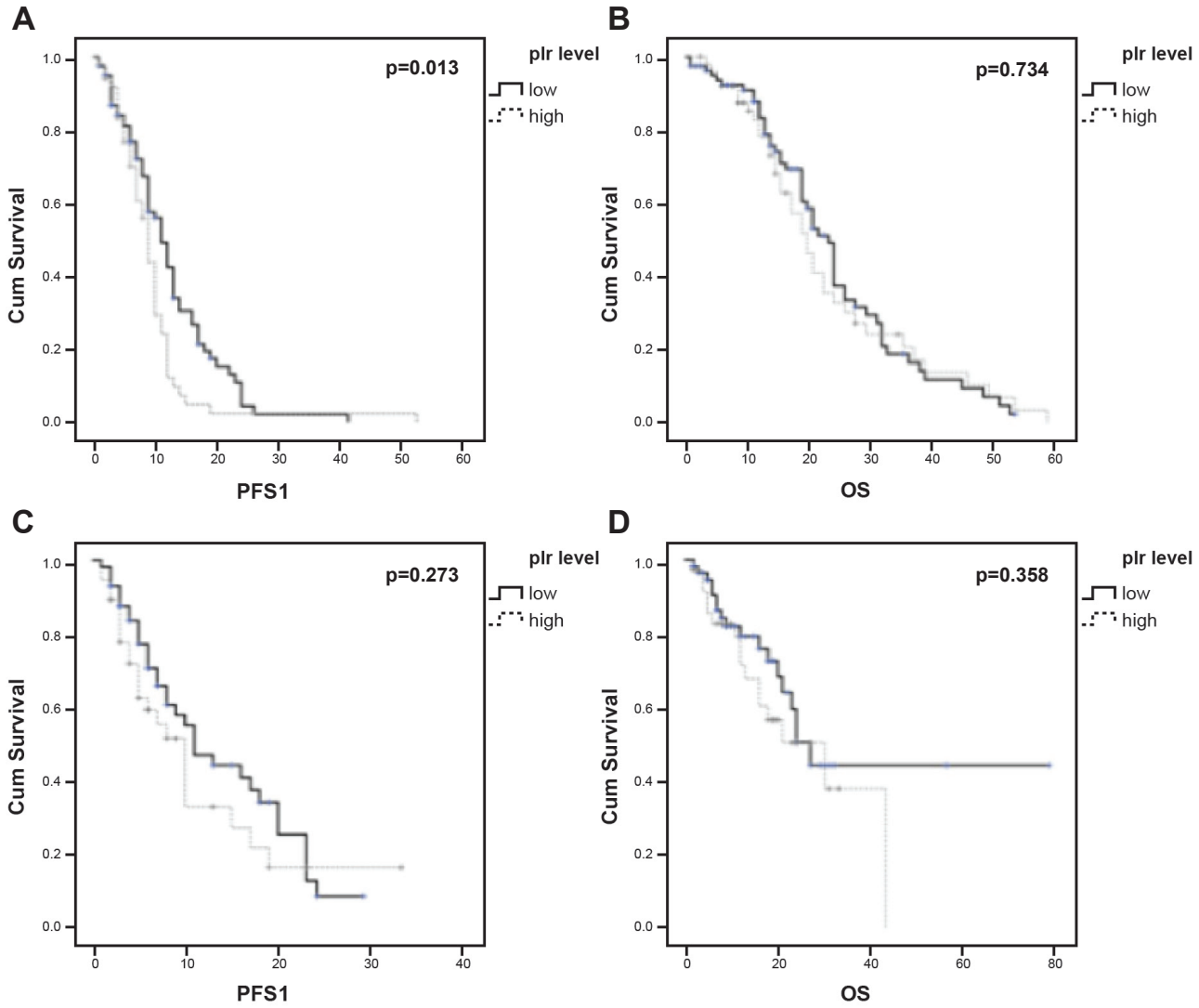

Figure 1. A: PFS in patients received bevacizumab according to NLR 9 (95% CI, 7.23-11.89) months in NLR high group and 11 (95% CI, 10.44-14.39) months in NLR low group (p=0.013). **B:** OS in patients received bevacizumab according to NLR 23 (95% CI, 21.99-32.57) months in NLR high group and 27 (95% CI, 24.38-31.98) months in NLR low group (p=0.734). **C:** PFS in patients received antiEGFR according to NLR 10 (95% CI, 7.94-16.07) moths in NLR high grooup and 11 (95% CI, 10.88-16.11) months in NLR low group (p=0.273). **D:** OS in patients received antiEGFR according to NLR 30 (95% CI, 19.29-31.98) months in NLR high group and 27 (95% CI, 31.64-55.29) month in NLR low group (p=0.358).

NLR low group than in the NLR high group, but this was not statistically significant. There is no predictive marker that shows resistance to bevacizumab. Previously Keizman et al reported that low levels of NLR are related to longer PFS and OS in metastatic renal cell carcinomas treated with the antiVEGF receptor inhibitor sunitinib [22]. Passardi et al reported that in the low NLR group adding bevacizumab to chemotherapy was related to longer PFS than chemotherapy alone, but in the high NLR group treated with bevacizumab there was shorter OS than in the chemotherapy group [17]. Botta et al showed that high NLR was associated with worse bevacizumab efficacy [23]. Preclinical studies showed that inflammatory cells derived from bone marrow such as neutrophils, play a crucial role in VEGF-independent angiogenesis [10]. This can be a responsible factor for worse survival outcomes in the NLR high group in patients treated with bevacizumab.

EGFR antibodies inhibit tumor proliferation and angiogenesis by inhibiting the MAPK pathway [24]. In our study, we found that there was no difference in the NLR high and the low group treated with antiEGFR. Yang et al reported that NLR is a negative predictive marker on PFS and OS in metastatic colorectal patients treated with cetuximab [18]. The value of 2.34 was accepted as a cut-off value of NLR in this study. In our study, the cut-off value of NLR was 3.44. Although our cut-off value was higher than in the Yang et al study, the high NLR group was not worse than the low group

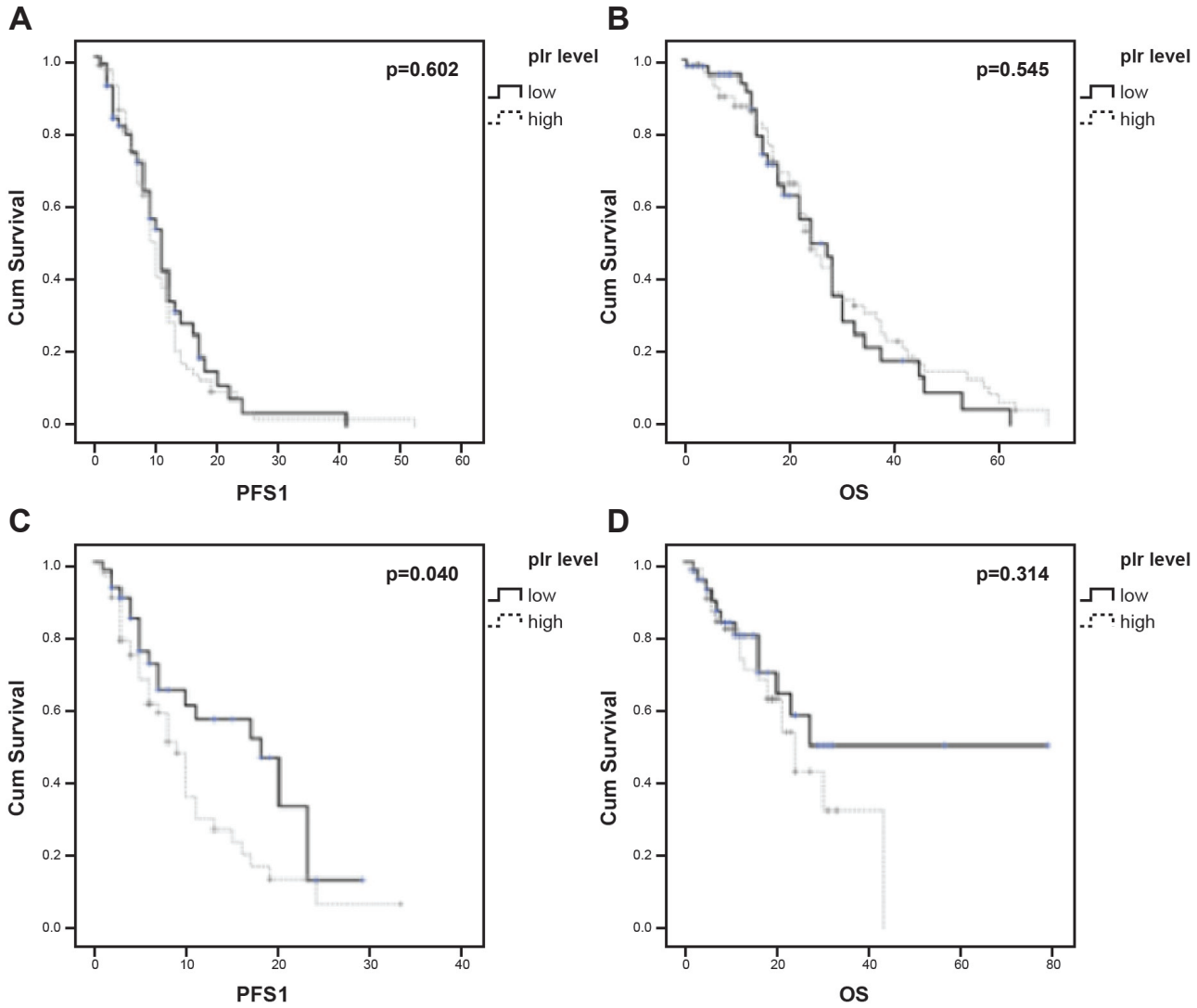

Figure 2. A: PFS in patients received bevacizumab according to PLR 9 (95% CI, 9.05-12.98) months in PLR high group and 11 (95% CI, 9.15-14.57) months in PLR low group (p=0.602). **B:** OS in patients received bevacizumab according to PLR 24 (95% CI, 24.44-32.77) months in PLR high group and 24 (95% CI, 22.08-31.42) months in PLR low group (p=0.545). **C:** PFS in patients received antiEGFR according to PLR 9 (95% CI, 8.07-13.55) moths in PLR high grooup and 18 (95% CI, 12.02-13.68) months in NLR low group (p=0.040). **D:** OS in patients received antiEGFR according to PLR 24 (95% CI, 19.95-30.47) months in PLR high group and 27 (95% CI, 32.55-60.42) month in PLR low group (p=0.314).

according to PFS and OS in the antiEGFR group. Wood et al demonstrated that adding cetuximab to chemotherapy didn't provide benefit in the high NLR group [19].

In systemic inflammation, pro-inflammatory mediators could stimulate thrombocytosis. High thrombocyte levels are associated with systemic inflammation due to cancer. Angiogenesis is associated with thrombocyte release [25]. For this reason, trombocytosis can show systemic inflammation and tumor activity.

Previous studies reported that there is an association between platelets with angiogenesis and tumor progression [26,27]. In the bevacizumab group, there was no difference between the PLR low and high groups according to PLR in our study. Platelets can affect angiogenesis by increasing VEGF [8]. In previous studies, PLR was demonstrated as a prognostic marker [18]. In one study, it was shown that adding bevacizumab to chemotherapy caused higher PFS in the low PLR group but this did not remain in the high PLR group [16].

PLR was found to be a prognostic marker in patients who received cetuximab in wild-type metastatic cancers [18]. Similarly, we showed that PFS was longer in the low PLR group but that this difference did not remain in OS. EGFR activation could be increased by trombocytosis, [28] and the high expression of EGFR can cause poor survival outcomes [29].

There are some limitations to our study: i) the study has a low number of patients ii) inflammation

markers can be affected by some situations such as the use of steroid or nonsteroid drugs – this group was not excluded, and iii) although cetuximab and panitumumab inhibit EGFR receptors, they have some different effects. Cetuximab has, for instance, some different immunological effects [30].

In conclusion, PFS was higher in the NLR and the PLR low group than in the high group, but there was no OS difference between the NLR and the PLR high group and the low group in patients who had received bevacizumab and antiEGFR treatment.

Conflict of interests

The authors declare no conflict of interests.

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