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ORIGINAL RESEARCH

Pre-treatment inflammatory biomarkers predict early treatment response and favorable survival in patients with metastatic colorectal cancer who underwent first line cetuximab plus chemotherapy

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Objective: This study was to determine whether peripheral blood biomarkers including neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune inflammation index (SII) could predict early response to cetuximab; moreover, the prognostic ability of those biomarkers on progression free survival (PFS) and overall survival (OS) of metastatic colorectal cancer (mCRC) patients with wild-type (WT) RAS was also investigated.

Methods: mCRC patients with WT RAS treated with cetuximab plus chemotherapy were retrospectively analyzed, and early response was evaluated according to RECIST 1.1 after three or four treatment cycles. In prior to chemotherapy, hematologic data and clinic-pathological parameters were collected. The associations between pre-treatment inflammatory biomarkers and early response, and the prognostic value of those biomarkers were analyzed. A total of 102 patients were enrolled and divided into low or high NLR, PLR, and SII groups, respectively.

Results: The early response rate was significantly higher in the low NLR ($p<0.001$), low PLR ($p=0.045$), and low SII ($p=0.011$), respectively. In multivariate analyses, primary tumor resection (hazard ratio (HR) 0.411, $p<0.001$), carcino-embryonicantigen ≤5 ng/mL (HR 0.406, $p<0.001$), early treatment response (HR 0.322, $p<0.001$), and low NLR (HR 0.665, $p=0.031$) were independent factors of longer PFS. Primary tumor resection (HR 0.488, $p=0.003$) and early response (HR 0.392, $p<0.001$) were independent factors of longer OS. Further analysis showed that patients with early response, even in the high groups, can achieve better PFS and OS than non-responders.

Conclusion: Pre-treatment inflammatory biomarkers, especially NLR were predictors of benefit from cetuximab-combined therapy in mCRC patients. They were also predictors of significantly longer PFS and OS of early responders compared to non-responders.

Keywords: inflammatory biomarkers, cetuximab, early treatment response, wild-type RAS, metastatic colorectal cancer

Introduction

Recently, the prognosis of locally advanced or metastatic colorectal cancer (mCRC) with wild-type (WT) RAS had dramatically improved due to the introduction of cetuximab.[1–4] Cetuximab is a monoclonal antibody which targeting the transmembrane protein epidermal growth factor receptor (EGFR), leading to the inhibition of the MAPK pathway and therefore suppresses tumor cell differentiation, proliferation, and angiogenesis which

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contributes to tumor progression.[5] Although several mechanisms of primary or acquired resistance had been identified, the only established response predictive biomarker for the treatment of mCRC patients is the RAS mutational status.[6] Moreover, even RAS WT patients who initially responded to anti-EGFR therapy eventually would undergo tumor progression, suggesting unknown alternative mechanisms capable of influencing treatment effectiveness were still existed. In this regard, identifying more sensitive markers for predicting therapeutic efficacy to promote the development of individualized treatment is urgently needed.

It has been increasingly recognized that tumor growth and metastasis resulted from interactions between tumoral and stromal factors, including blood vessels, inflammatory cells, and immunity system which led to an inflammation status.[7,8] Markers such as C-reactive protein, hypoalbuminemia, Glasgow Prognostic Score, neutrophil count (PNC), macrophage, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), have been investigated as prognostic and predictive factors in various human cancer types, especially in radically resected or mCRC.[9–14] There is increasing evidence that inflammation markers served as an important role in the induction of chemo-resistance.[15–18] Also, certain inflammatory indexes were correlated with chemotherapeutic responses. Van Glabbeke et al,[19] demonstrated that an elevated baseline neutrophil count correlated with initial and late resistance to imatinib treatment in gastrointestinal stromal tumors. High PNC and NLR values were associated with chemo-resistance and an unfavorable prognosis in patients with stage III and IV unresectable lung cancer.[20] Elevated baseline NLR correlated with poor response treated with bevacizumab plus chemotherapy in mCRC.[21] Recently, elevated pre-treatment NLR could serve as a predictor of survival and cetuximab efficacy in mCRC patients with WT RAS.[22] However, the relationship between inflammatory biomarker, early treatment response, and cetuximab efficacy is still yet to be known.

In this single-center, retrospective study, we aimed to investigate pre-treatment parameters including NLR, PLR, and SII for their ability to predict early treatment response and survival of mCRC patients receiving first-line chemotherapy plus cetuximab.

Materials and methods

Patient and data collection

We retrospectively enrolled 102 patients who were diagnosed with primary colorectal cancer and received chemotherapy plus cetuximab as the initial treatment at Shanghai Jiaotong University School of Medicine Affiliated Ruijin Hospital between January 2010 and December 2017. This study was approved by the Medical Ethical Committee of Shanghai Ruijin Hospital and performed in accordance with relevant guidelines and regulations. Patients alive signed an informed consent for the use of their personal data for research purposes at the time of data collection. For patients who have died at the time of data collection, we had followed up the recurrence or death time by telephone, informed the related contents of the informed consent form of this study in detail, obtained the consent of patients' relatives, and archived the telephone recording, which was approved by the Medical Ethics Committee of our hospital.

The primary inclusion criteria were as follows: (a) histologically confirmed and measurable (RECIST criteria v.1.1) unresectable metastatic adenocarcinoma of the colon or rectum, (b) molecular test showing no mutation in the RAS gene of colorectal carcinoma cells, (c) patients with available and complete basic characteristics, laboratory data, and follow-up information. Patients with evidence for one mutation of the RAS gene, prior chemotherapy for metastatic disease, previous exposure to EGFR-targeting therapy, hematology, and infection diseases were excluded. Patients' demographic and clinic-pathological variables, including age, sex, tumor localization, primary tumor status, adjuvant therapy, tumor metastasis period, liver metastases, carcino-embryonicantigen (CEA), carbohydrate antigen 19-9 (CA199), lactate dehydrogenase (LDH), chemotherapy regimen, and early treatment response were collected using electronic medical records. Laboratory data were obtained within 3 days prior to the initial administration of cetuximab. Blood cell counting was detected by Sysmex hematology analyzers. NLR and PLR were defined as the absolute counts of neutrophils and platelets, respectively, divided by the absolute lymphocyte count. SII was calculated as platelet count × neutrophil count/lymphocyte count.[22]

Response assessment

Response was assessed every three or four treatment cycles using the revised Response Evaluation Criteria in Solid Tumors (version 1.1).[23] The criteria classified the responses into four categories: Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR was defined as disappearance of all target lesions, any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR was

defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for SD, taking as reference the smallest sum diameters while on study. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). Early treatment response was defined as the results of the first efficacy evaluation included CR and PR, and non-response included SD and PD. The early response rate was the ratio of early response patients to the total patients.

Statistical analysis

Progression-freesurvival (PFS) was measured as the time between treatment initiation and disease progression or death from any cause. Overall survival (OS) was defined as the time between treatment initiation and death from any cause or the date of last follow-up.

The optimal cut-off values for NLR, PLR, and SII were performed according to the early response by receiver operating characteristic curves, which were used to detect the value of each index for predicting the response to therapy. Patients' characteristics were analyzed by descriptive statistics. The χ^2 or Fisher's exact test were used to assess the association between categorical variables. PFS and OS were calculated according to the Kaplan–Meier method, and the log-rank test was used to compare survival between different patient populations. The impact of prognostic factors on PFS and OS was first assessed in univariate analysis by means of the Cox proportional hazard regression analysis, variables with statistically significant in univariate analysis were further analyzed in multivariate analysis. Hazard ratios (HRs) estimated from the Cox proportional hazard model were reported as relative risks with corresponding 95% Confidence Intervals (95% CI). All statistical analyses were performed using the SPSS version 20.0 (IBM Corporation, Armonk, NY, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics

Among 102 patients treated with cetuximab, patients were divided into high and low index groups on the basis of the specified cut-off value of NLR (3.285, AUC =0.701), PLR (171.45, AUC =0.569), and SII (660.55, AUC =0.619), respectively (Figure 1). NLR ≥3.285, PLR ≥171.45, and SII ≥660.55 were considered as high groups.

All the clinic-pathological characteristics of patients are detailed in Table 1. There are 72 (70.6%) males and 30 (29.4%) females, with 45 (44.1%) patients were >60 years and 57 patients were ≤60 (55.9%; range, 28–75 years). According to the location of the tumor, most of them (80, 78.5%) occurred in the left colon while other 22 (21.5%) were from right colon. Primary tumor resection was performed in 76 (74.5%) of all patients and 23 (37.3%) of them underwent adjuvant chemotherapy. Sixty-five (63.7%) patients suffered simultaneous metastasis while of which 37 (36.3%) were metachronism. Among the 102 patients, liver metastasis occurred in 38 (37.3%) and other 64 (62.7%) without liver metastasis. Further, 41 (40.2%) patients were with elevated CEA; 45 (44.1%) patients were with elevated CA199, respectively; 45 (44.1%) patients were with increased LDH, respectively. All the 102 patients received chemotherapy, of which 43 (42.1%) treated with FOLFOX/XELOX and 59 (57.9%) treated with FOLFIRI. Regarding early treatment response, no patients achieved CR, 53 patients achieved PR, 33 patients were SD, and 16 patients were PD. In total 102 patients, 53 (52.0%) patients were defined as responder and 49 (48.0%) patients as non-responder.

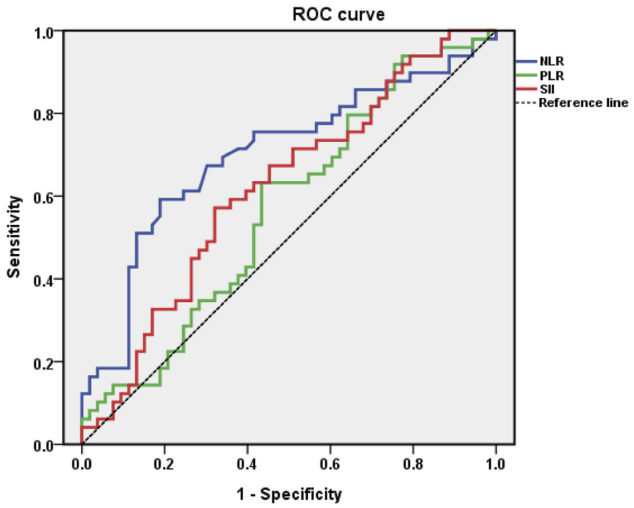

Figure 1 Diagnostic value of inflammatory biomarkers for early response according to ROC curves.

Abbreviations: ROC, receiver operating characteristic; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

Table 1 Association between inflammatory markers and clinic-pathological data

Characteristics	Total patients (N=102)	NLR		*P*-value	PLR		*P*-value	SII		*P*-value
		Low (N=63)	High (N=39)		Low (N=48)	High (N=54)		Low (N=57)	High (N=45)	
Age, years										
≤60	57 (55.9)	36 (35.3)	21 (20.6)	0.745	27 (26.5)	30 (29.4)	0.944	28 (27.5)	29 (28.4)	0.122
>60	45 (44.1)	27 (26.5)	18 (17.6)		21 (20.6)	24 (23.5)		29 (28.4)	16 (15.7)	
Sex										
Male	72 (70.6)	39 (38.2)	33 (32.4)	0.014	34 (33.3)	38 (37.3)	0.959	40 (39.3)	32 (31.3)	0.918
Female	30 (29.4)	24 (23.6)	6 (5.8)		14 (13.7)	16 (15.7)		17 (16.7)	13 (12.7)	
Site of primary tumor (%)										
Right	22 (21.5)	16 (15.7)	6 (5.8)	0.323	9 (8.8)	13 (12.7)	0.514	14 (13.7)	8 (7.8)	0.408
Left	80 (78.5)	47 (46.1)	33 (32.4)		39 (38.2)	41 (40.3)		43 (42.2)	37 (36.3)	
Resected primary tumor (%)										
Yes	76 (74.5)	50 (49.0)	26 (25.5)	0.153	40 (39.2)	36 (35.3)	0.054	46 (45.1)	30 (29.4)	0.106
No	26 (25.5)	13 (12.7)	13 (12.7)		8 (7.8)	18 (17.7)		11 (10.8)	15 (14.7)	
Previous adjuvant therapy (%)										
Yes	38 (37.3)	25 (24.6)	13 (12.7)	0.519	15 (14.7)	23 (22.6)	0.237	28 (27.5)	10 (9.8)	0.005
No	64 (62.7)	38 (37.2)	26 (25.5)		33 (32.4)	31 (30.3)		29 (28.4)	35 (34.3)	
Time to metastases (%)										
Synchronous	65 (63.7)	41 (40.2)	24 (23.5)	0.718	30 (29.4)	35 (34.3)	0.808	32 (31.3)	33 (32.4)	0.073
Metachronous	37 (36.3)	22 (21.6)	15 (14.7)		18 (17.7)	19 (18.6)		25 (24.5)	12 (11.8)	
Liver metastases (%)										
Yes	38 (37.3)	25 (24.6)	13 (12.7)	0.519	21 (20.6)	17 (16.7)	0.201	24 (23.6)	14 (13.7)	0.254
No	64 (62.7)	38 (37.2)	26 (25.5)		27 (26.4)	37 (36.3)		33 (32.4)	31 (30.3)	
CEA (ng/mL)										
≤5	17 (16.7)	10 (9.8)	7 (6.9)	0.785	6 (5.9)	11 (10.8)	0.287	11 (10.8)	6 (5.9)	0.422
>5	85 (83.3)	53 (52.0)	32 (31.3)		42 (41.2)	43 (42.1)		46 (45.1)	39 (38.2)	
CA199 (U/mL)										
≤37	41 (40.2)	29 (28.4)	12 (11.8)	0.127	22 (21.6)	19 (18.6)	0.274	27 (26.5)	14 (13.7)	0.096
>37	61 (59.8)	34 (33.3)	27 (26.5)		26 (25.5)	35 (34.3)		30 (29.4)	31 (30.4)	
LDH (IU/mL)										
≤192	45 (44.1)	32 (31.3)	13 (12.7)	0.084	23 (22.5)	22 (21.6)	0.466	30 (29.4)	15 (14.7)	0.051
>192	57 (55.9)	31 (30.3)	26 (25.5)		25 (24.6)	32 (31.3)		27 (26.5)	30 (29.4)	
CT regimen (%)										
FOLFOX/ XELOX	43 (42.1)	30 (29.4)	13 (12.7)	0.156	20 (16.6)	24 (23.5)	0.777	28 (27.5)	15 (14.7)	0.109
FOLFIRI	59 (57.9)	33 (32.4)	26 (25.5)		28 (27.5)	30 (29.4)		29 (28.4)	30 (29.4)	
Early treatment response (%)										
Response	53 (52.0)	43 (42.2)	10 (9.8)	<0.001	30 (29.4)	23 (22.6)	0.045	36 (35.3)	17 (16.7)	0.011
Non-response	49 (48.0)	20 (19.6)	29 (28.4)		18 (17.6)	31 (30.4)		21 (20.5)	28 (27.5)	

Notes: Values in the table are presented as the number of patients with the percentage in parenthesis, unless indicated otherwise, *P*-value<0.05 was considered statistically significant.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; CEA, carcino-embryonic antigen; CA199, carbohydrate antigen 19-9; LDH, lactate dehydrogenase; CT, chemotherapy.

Associations between inflammatory biomarkers and baseline characteristics

To investigate the correlation of NLR, PLR, and SII with clinic-pathologic parameters, we found that high levels of NLR were significantly associated with fewer females (p=0.014) and more non-responders (p<0.001). Only PLR was significantly associated with early treatment response (p=0.045)while SII was significantly associated with adjuvant therapy (p=0.005) and early treatment response (p=0.011). Conversely, there was no significant association between inflammatory biomarkers and other clinical parameters (Table 1; Figure 2).

Survival analyses

At a median follow-up of 33.2 months (range: 2.6–94.5), 93 (91.2%) patients progressed and of which 70 (68.6%) died. Median PFS was 13.2 months in patients with NLR^{Low} group and 7.9 months in those with NLR^{High} group (HR 0.53, 95% CI 0.31–0.91; p=0.0206). Regarding the SII, PFS prolonged with SII <660.55 as compared to SII≥660.55 (11.8 ms vs 9.5 ms, HR: 0.60, 95% CI: 0.37–0.98, p=0.0424). However, there was no significant difference in PFS between PLR^{High} and PLR^{Low} groups (HR: 0.85, 95% CI: 0.53–1.37; p=0.5137) (Figure 3).

In univariate analysis, factors associated with PFS were: right colon cancer, unresectable primary tumor, CEA >5 ng/mL, early treatment with non-response, NLR^{High}, and SII^{High} (Figure 4A). Further, those factors were integrated into multivariate analysis which showed that primary tumor resection (HR: 0.411, 95% CI: 0.264–0.641), CEA ≤5 ng/mL (HR: 0.406, 95% CI: 0.263–0.625), early treatment response (HR: 0.322, 95% CI: 0.218–0.472) and NLR^{Low} (HR: 0.665, 95% CI: 0.447–0.902) were independent predictors of PFS while other covariates were of no statistically significant (Figure 4B).

Median OS in NLR^{Low} group was significantly longer than NLR^{High} group (28.3 m vs 18.3 m, HR: 0.48, 95% CI: 0.28–0.83, p=0.0083). In contrast, there was no statistical significance difference in OS between other groups (PLR^{High} vs PLR^{Low}, HR: 0.94 and SII^{High} and SII^{Low}, HR: 0.68, respectively) (Figure 5). In univariate analysis, age (p=0.033), primary tumor resection (p=0.041), liver metastases (p=0.036), chemotherapy regimen (p=0.048), early treatment response (p<0.001), NLR (p=0.011), and SII

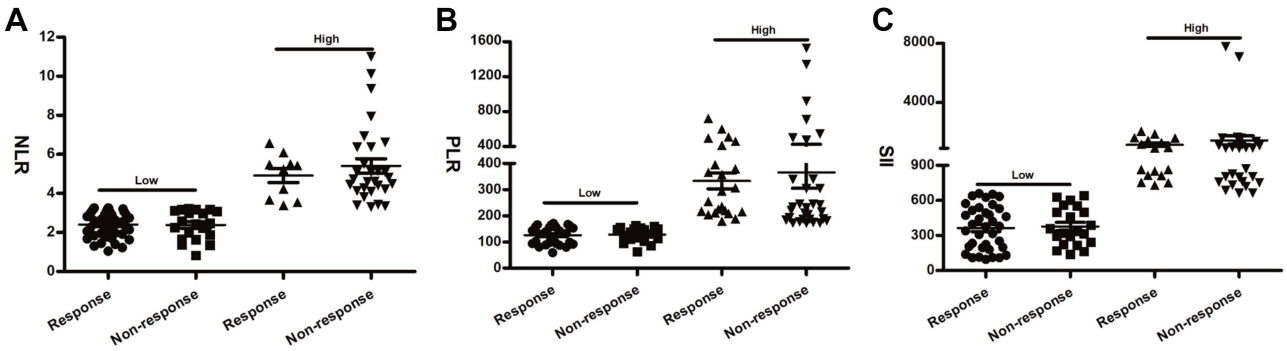

Figure 2 Distribution of NLR (**A**), PLR (**B**), and SII (**C**) according to early response.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

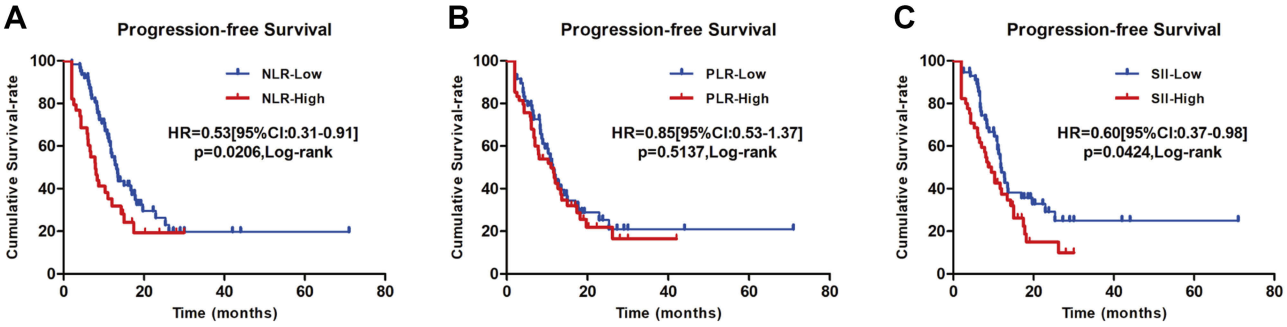

Figure 3 Kaplan–Meier curves of progression-free survival (PFS) of mCRC patients according to baseline NLR (**A**), PLR (**B**), and SII (**C**).
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; mCRC, metastatic colorectal cancer.

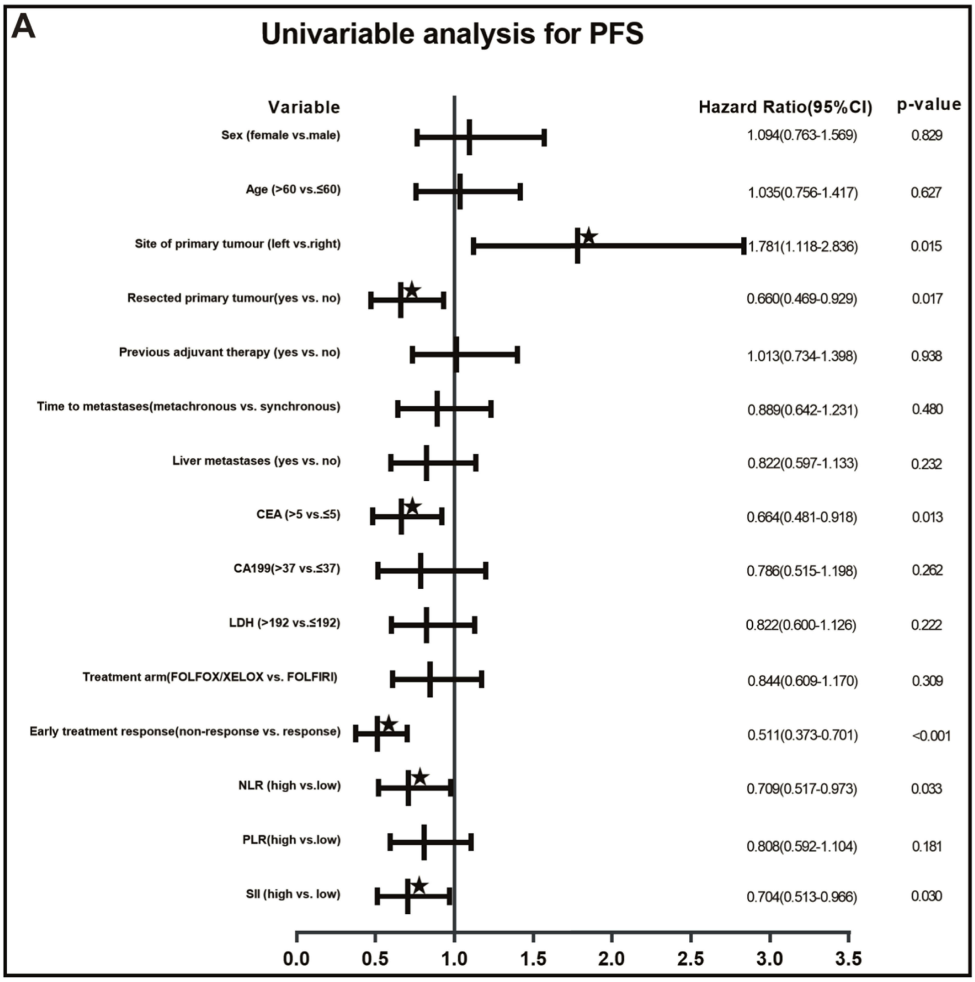

Figure 4 Forest plot illustrating the results of univariable (**A**) and multivariable (**B**) analysis of covariates associated with the risk of disease progression in mCRC. ★ means *P*<0.05.
Abbreviations: PFS, progression free survival; CEA, carcino-embryonic antigen; CA199, carbohydrate antigen 19-9; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

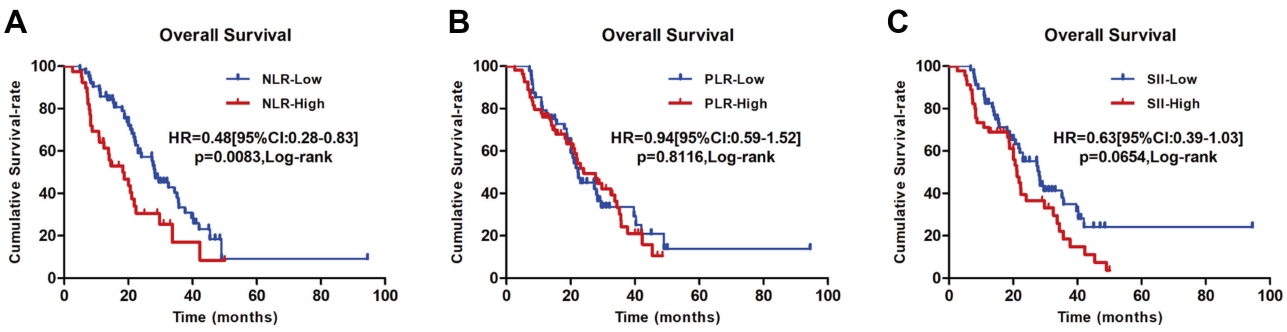

Figure 5 Kaplan–Meier curves of overall survival (OS) of mCRC patients according to baseline NLR (**A**), PLR (**B**), and SII (**C**).
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; HR, hazard ratio; mCRC, metastatic colorectal cancer.

(p=0.005) were significantly associated with OS (Figure 6A). In multivariate analysis, primary tumor resection (HR: 0.488, 95% CI: 0.302–0.788, p=0.003) and early treatment response (HR: 0.393, 95% CI: 0.252–0.613, p<0.001) were independent prognostic factors of OS (Figure 6B).

Predictive value of inflammatory biomarkers as an indicator of early treatment response

Early treatment response (response vs non-response) was associated with PFS and OS regarding inflammatory biomarkers (including NLR, PLR, and SII) (Table 2). In NLR^{Low} group, PFS was significantly improved for patients with early treatment response compared to non-response (13.5 ms vs 7.8 ms, HR: 1.61, 95% CI: 1.07–2.15, p=0.0032). However, early treatment response was not associated with OS (p=0.1180). For NLR^{High} patients, early treatment response was not associated with PFS and OS (p=0.054 and p=0.051, respectively).

Both in PLR^{Low} and PLR^{High} patients, PFS and OS were prolonged in early responders than non-responders (PLR^{Low}, p=0.0074 and p=0.0185, respectively; PLR^{High}, p=0.009 and p=0.0072, respectively). Similar results are obtained in SII groups (SII^{Low}, p=0.03 and p=0.037, respectively; SII^{High}, p=0.0070 and p=0.0411, respectively).

Discussion

Substantial evidence showed that stroma–tumor interaction which led to a chronic inflammatory state was involved in carcinogenesis and tumor progression.[24,25] Peripheral inflammatory cells including neutrophils, lymphocytes, and platelets were prognostic and predictive factors in various cancers like CRC.[20,22,26–28] Neutrophils promoted adhesion and seeding of distant organ sites through secretion of circulating growth factors such as VEGF and proteases.[29,30] Platelets induced circulating tumor cells epithelial–mesenchymal transition and promoted its extravasation to metastatic sites.[31] On the contrary, lymphocytes played a crucial role in tumor defense by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration, thereby dictating the host's immune defense to malignancy.[32] Thus, tumor inflammatory microenvironment modulation could influence cancer progression. Furthermore, tumor inflammatory microenvironment supported tumor progression and induced chemoresistance.[15,24]

In order to investigate the potential impact of surrogate markers of inflammatory reaction such as NLR, PLR, and, SII in mCRC treated with cetuximab, we showed that patients with low NLR were associated with better PFS and OS than those with high NLR. Meanwhile, elevated SII was significantly associated with poor PFS but not with OS. What is worth to mention that PLR was not significantly associated with either PFS or OS. In univariate analysis, in addition to the traditional prognostic factors (age, primary tumor resection, primary tumor location, CEA, and CT regime), NLR and SII were significantly associated with PFS and OS. In multivariate analyses, only NLR remained a prognostic factor for PFS. To date, our results are somewhat different from previous reports. Jing Yang et al,[22] indicated that NLR was an independent prognostic factor not only for PFS but also for OS. Moreover, elevated PLR was significantly associated with poor PFS but not with OS, and SII was not significantly associated with PFS and OS. The major causes of these contrasting findings can be considered as follows: Firstly, its single-center study with selection bias. Secondly, the role of PLR in the

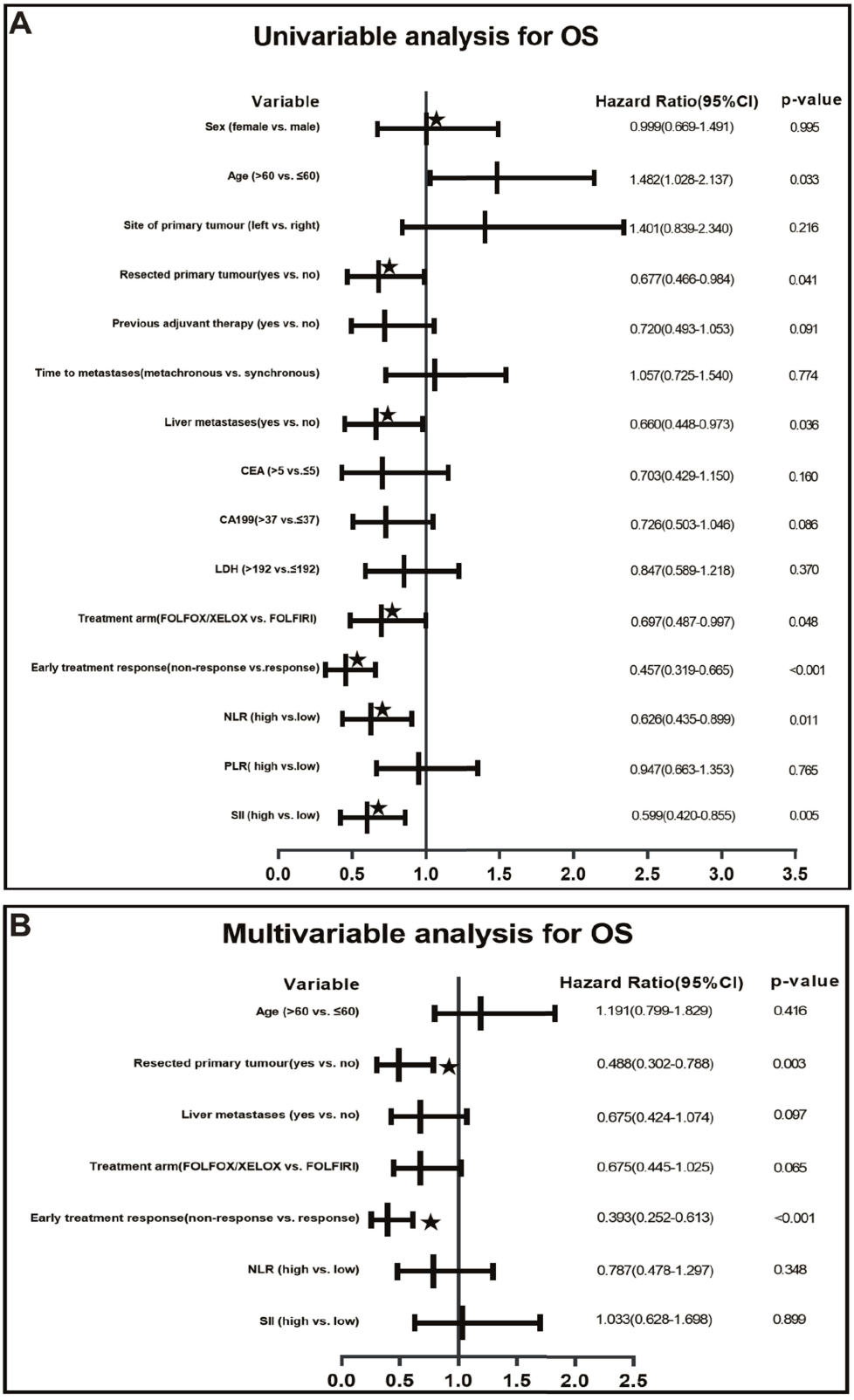

Figure 6 Forest plot illustrating the results of univariable (**A**) and multivariable (**B**) analysis of covariates associated with the overall survival in mCRC. ★ means $P<0.05$. **Abbreviations:** OA, overall survival; CEA, carcino-embryonic antigen; CA199: carbohydrate antigen 19-9, LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

Table 2 Predictive value of the inflammatory biomarkers as a function of early treatment response

	Number of event	PFS			OS		
		Median of PFS, months (95% CI)	HR (95% CI)	*p*-value	Median of PFS, months (95% CI)	HR (95% CI)	*p*-value
NLR <3.285							
Response	43	13.5 (10.6–17.9)	1.00	0.0032	29.5 (24.0–32.9)	1.00	0.1880
Non-response	20	8.4 (5.2–11.0)	1.61 (1.07–2.15)		23.2 (17.5–28.8)	1.08 (0.54–1.62)	
NLR ≥3.285							
Response	10	12.9 (10.5–16.3)	1.00	0.0540	23.3 (16.8–31.4)	1.00	0.0510
Non-response	29	7.8 (5.3–10.8)	2.18 (1.90–2.59)		15.5 (11.8–19.2)	1.62 (1.22–2.03)	
PLR <171.45							
Response	30	13.5 (6.5–19.9)	1.00	0.0074	28.1 (22.2–33.4)	1.00	0.0185
Non-response	18	8.4 (5.9–11.7)	1.61 (1.10–2.11)		18.5 (14.3–22.7)	1.80 (1.29–2.31)	
PLR ≥171.45							
Response	23	13.4 (10.3–16.9)	1.00	0.0090	27.4 (22.6–32.5)	1.00	0.0072
Non-response	31	6.0 (4.4–9.8)	2.23 (1.72–2.74)		15.6 (12.9–22.5)	1.74 (1.23–2.45)	
SII <660.55							
Response	36	12.8 (7.3–19.1)	1.00	0.0300	28.3 (23.0–34.3)	1.00	0.0320
Non-response	21	8.9 (6.4–12.1)	1.44 (0.93–1.95)		19.6 (15.6–24.4)	1.51 (0.99–2.02)	
SII ≥660.55							
Response	17	13.5 (11.3–15.8)	1.00	0.0070	24.0 (19.8–29.9)	1.00	0.0411
Non-response	28	7.7 (5.2–10.7)	2.37 (1.99–2.87)		15.4 (12.3–21.8)	1.56 (1.07–2.05)	

Notes: *P*-value<0.05 was considered statistically significant.
Abbreviations: PFS, progression-free survival; OS, overall survival; CI, confidence interval; HR, hazard ratio; nLR, Neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

prognosis of CRC patients is still controversial. Several studies supported that pre-treatment PLR as a favorable marker for CRC patients while several studies with contrast conclusion.[12,13,33–38] Thirdly, SII was only recently investigated as a prognostic factor in several types of tumors, and its prognostic value in CRC patients had been far from well defined.[39–41] For those reasons, further studies should be performed to investigate the prognostic value of PLR and SII for the efficacy of cetuximab in mCRC patients.

The mechanism underlying the association between the chronic inflammation and malignant tumor is complex, but it could be due to the association of NLR with inflammation. Increasing evidence suggests that neutrophilia can inhibit the immune system, abolishing the cytolytic activity of immune cells.[42,43] At the same time, both tumor cells and host cell, including neutrophils, can produce chemokines and cytokines, thus contributing to tumor progression.[7] On the other hand, lymphocytic response is the main component of controlling cancer progression by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration, thereby dictating the host's immune response to malignancy. Additionally, neutrophilia suppresses lymphocyte activity by releasing reactive oxygen species, nitric oxide, and arginase, therefore hindering the antitumor immune response.[44] In this way, high NLR which indicates high neutrophils counts and low lymphocyte counts are related to adverse prognosis in various solid tumors, including CRC.[9–11,13] This is consistent with our results. Meanwhile, elevated SII indicates high neutrophils, high platelets and low lymphocytes which reflects both progression of cancer and weak immune status of the host. In our study, results of multivariate analysis suggested a tendency of improved OS in patients with high SII which showed no statistical significance. Therefore, further studies are expected to confirm the prognostic value of SII. However, it should be noted that whether neutrophils, lymphocytes or platelets, they

are non-specific parameters because they are susceptible to comorbid diseases such as inflammation or infection.[45] In our study, we specifically excluded patients with infectious diseases from the study in our exclusion criteria.

In the present study, the associations between inflammatory markers, the early treatment response, and clinic-pathological parameters, in addition, the outcome of patients with mCRC was retrospectively investigated. Our data suggested that in NLR, PLR, and SII low groups, more patients achieved early response than high groups. This study also confirmed that early treatment response was significantly associated with PFS and OS in univariate and multivariate analyses. Additionally, PFS and OS according to early response were also analyzed in different inflammatory marker groups. These results revealed that the significant differences on PFS and OS were universal in PLR and SII, despite the differences between the low and high groups. However, PFS showed that a significant difference was only existed in the low NLR group, but not in the high NLR group; meanwhile, there was no difference regarding OS. This may be due to the insufficient sample size (only 10 patients) in high NLR group with early response.

The present study has a number of limitations, including its retrospective nature, which may lead to bias in the data analysis, and the relatively small sample of patients received cetuximab. Thus, prospective, multi-center, and larger population studies are needed to validate these results.

In summary, our results showed a positive correlation between per-treatment inflammatory biomarkers (especially NLR) and PFS and OS in patients with mCRC treated with cetuximab in first line. Furthermore, per-treatment inflammatory biomarkers were indicators of early treatment response. This study provides a highly reproducible, easily obtainable, inexpensive, reliable, and practical index for predicting cetuximab efficacy, and to facilitate the administration of therapy in patients with a low NLR and early treatment response in order to achieve an improved response which would enhance the long-term outcomes for patients with mCRC. However, the potential underlying mechanisms and the performance of those inflammatory biomarkers in clinical practice should be validated in further prospective studies.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Van Cutsem E, Kohne CH, Lang I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol*. 2011;29:2011–2019. doi:10.1200/JCO.2010.33.5091
2. Stintzing S, Modest DP, Rossius L, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. *Lancet Oncol*. 2016;17:1426–1434. doi:10.1016/S1470-2045(16)30269-8
3. Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. *JAMA*. 2017;317:2392–2401. doi:10.1001/jama.2017.7105
4. Qin S, Li J, Wang L, et al. Efficacy and tolerability of first-line cetuximab plus leucovorin, fluorouracil, and oxaliplatin (FOLFOX-4) versus FOLFOX-4 in patients with RAS wild-type metastatic colorectal cancer: the open-label, randomized, Phase III TAILOR trial. *J Clin Oncol*. 2018;36(30):3031–3039. doi:10.1200/JCO.2018.78.3183.
5. Oda K, Matsuoka Y, Funahashi A, Kitano H. A comprehensive pathway map of epidermal growth factor receptor signaling. *Mol Syst Biol*. 2005;1:2005 0010. doi:10.1038/msb4100014
6. Yonesaka K, Zejnullahu K, Okamoto I, et al. Activation of ERBB2 signaling causes resistance to the EGFR-directed therapeutic antibody cetuximab. *Sci Transl Med*. 2011;3:99ra86. doi:10.1126/scitranslmed.3002442
7. Balkwill F, Mantovani A. Cancer and inflammation: implications for pharmacology and therapeutics. *Clin Pharmacol Ther*. 2010;87:401–406. doi:10.1038/clpt.2009.312
8. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol*. 2014;15:e493–e503. doi:10.1016/S1470-2045(14)70263-3
9. Chua W, Charles KA, Baracos VE, Clarke SJ, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. *Br J Cancer*. 2011;104:1288–1295. doi:10.1038/bjc.2011.100
10. Absenger G, Szkandera J, Pichler M, et al. A derived neutrophil to lymphocyte ratio predicts clinical outcome in stage II and III colon cancer patients. *Br J Cancer*. 2013;109:395–400. doi:10.1038/bjc.2013.346
11. Clarke S, Burge M, Cordwell C, Gibbs P, Reece W, Tebbutt N. An Australian translational study to evaluate the prognostic role of inflammatory markers in patients with metastatic ColorEctal caNcer Treated with bevacizumab (Avastin) [ASCENT]. *BMC Cancer*. 2013;13:120. doi:10.1186/1471-2407-13-120
12. Li Y, Jia H, Yu W, et al. Nomograms for predicting prognostic value of inflammatory biomarkers in colorectal cancer patients after radical resection. *Int J Cancer*. 2016;139:220–231. doi:10.1002/ijc.30071
13. Wu Y, Li C, Zhao J, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict chemotherapy outcomes and prognosis in patients with colorectal cancer and synchronous liver metastasis. *World J Surg Oncol*. 2016;14:289. doi:10.1186/s12957-016-1044-9

14. Kim IH, Lee JE, Yang JH, Jeong JW, Ro S, Lee MA. Clinical significance of changes in systemic inflammatory markers and carcinoembryonic antigen levels in predicting metastatic colorectal cancer prognosis and chemotherapy response. *Asia Pac J Clin Oncol*. 2018;14:239–246. doi:10.1111/ajco.12784
15. de Visser KE, Jonkers J. Towards understanding the role of cancer-associated inflammation in chemoresistance. *Curr Pharm Des*. 2009;15:1844–1853. doi:10.2174/138161209788453239
16. Jinushi M, Komohara Y. Tumor-associated macrophages as an emerging target against tumors: creating a new path from bench to bedside. *Biochim Biophys Acta*. 2015;1855:123–130. doi:10.1016/j.bbcan.2015.01.002
17. Olive KP. Fanning the flames of cancer chemoresistance: inflammation and anticancer therapy. *J Oncol Pract*. 2017;13:181–183. doi:10.1200/JOP.2017.021154
18. Sanderson RD, Elkin M, Rapraeger AC, Ilan N, Vlodavsky I. Heparanase regulation of cancer, autophagy and inflammation: new mechanisms and targets for therapy. *FEBS J*. 2017;284:42–55. doi:10.1111/febs.13932
19. Van Glabbeke M, Verweij J, Casali PG, et al. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: a European Organisation for Research and Treatment of Cancer-Italian Sarcoma Group-Australasian Gastrointestinal Trials Group study. *J Clin Oncol*. 2005;23:5795–5804. doi:10.1200/JCO.2005.11.601
20. Sun H, Hu P, Du J, Wang X. Predictive value of inflammatory indexes on the chemotherapeutic response in patients with unresectable lung cancer: a retrospective study. *Oncol Lett*. 2018;15:4017–4025. doi:10.3892/ol.2018.7781
21. Dell'Aquila E, Cremolini C, Zeppola T, et al. Prognostic and predictive role of neutrophil/lymphocytes ratio in metastatic colorectal cancer: a retrospective analysis of the TRIBE study by GONO. *Ann Oncol*. 2018;29:924–930. doi:10.1093/annonc/mdy004
22. Yang J, Guo X, Wang M, Ma X, Ye X, Lin P. Pre-treatment inflammatory indexes as predictors of survival and cetuximab efficacy in metastatic colorectal cancer patients with wild-type RAS. *Sci Rep*. 2017;7:17166. doi:10.1038/s41598-017-17130-6
23. Watanabe H, Okada M, Kaji Y, et al. [New response evaluation criteria in solid tumours-revised RECIST guideline (version 1.1)]. *Gan To Kagaku Ryoho*. 2009;36:2495–2501.
24. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420:860–867. doi:10.1038/nature01322
25. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. *Future Oncol*. 2010;6:149–163. doi:10.2217/fon.09.136
26. Goto W, Kashiwagi S, Asano Y, et al. Predictive value of lymphocyte-to-monocyte ratio in the preoperative setting for progression of patients with breast cancer. *BMC Cancer*. 2018;18:1137. doi:10.1186/s12885-018-4242-8
27. Yang J, Xu H, Guo X, et al. Pretreatment inflammatory indexes as prognostic predictors for survival in colorectal cancer patients receiving neoadjuvant chemoradiotherapy. *Sci Rep*. 2018;8:3044. doi:10.1038/s41598-018-21093-7
28. Deng Q, He B, Liu X, et al. Prognostic value of pre-operative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model. *J Transl Med*. 2015;13:66. doi:10.1186/s12967-015-0541-x
29. Cools-Lartigue J, Spicer J, McDonald B, et al. Neutrophil extracellular traps sequester circulating tumor cells and promote metastasis. *J Clin Invest*. 2013. doi:10.1172/JCI67484
30. Rossi L, Santoni M, Crabb SJ, et al. High neutrophil-to-lymphocyte ratio persistent during first-line chemotherapy predicts poor clinical outcome in patients with advanced urothelial cancer. *Ann Surg Oncol*. 2015;22:1377–1384. doi:10.1245/s10434-014-4097-4
31. Labelle M, Begum S, Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. *Cancer Cell*. 2011;20:576–590. doi:10.1016/j.ccr.2011.09.009
32. De Giorgi U, Mego M, Scarpi E, et al. Relationship between lymphocytopenia and circulating tumor cells as prognostic factors for overall survival in metastatic breast cancer. *Clin Breast Cancer*. 2012;12:264–269. doi:10.1016/j.clbc.2012.04.004
33. Szkandera J, Pichler M, Absenger G, et al. The elevated preoperative platelet to lymphocyte ratio predicts decreased time to recurrence in colon cancer patients. *Am J Surg*. 2014;208:210–214. doi:10.1016/j.amjsurg.2013.10.030
34. Passardi A, Scarpi E, Cavanna L, et al. Inflammatory indexes as predictors of prognosis and bevacizumab efficacy in patients with metastatic colorectal cancer. *Oncotarget*. 2016;7:33210–33219. doi:10.18632/oncotarget.8901
35. Azab B, Shah N, Radbel J, et al. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. *Med Oncol*. 2013;30:432. doi:10.1007/s12032-012-0432-4
36. Zou ZY, Liu HL, Ning N, Li SY, Du XH, Li R. Clinical significance of pre-operative neutrophil lymphocyte ratio and platelet lymphocyte ratio as prognostic factors for patients with colorectal cancer. *Oncol Lett*. 2016;11:2241–2248. doi:10.3892/ol.2016.4216
37. Ozawa T, Ishihara S, Kawai K, et al. Impact of a lymphocyte to monocyte ratio in stage IV colorectal cancer. *J Surg Res*. 2015;199:386–392. doi:10.1016/j.jss.2015.06.014
38. Ying HQ, Deng QW, He BS, et al. The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. *Med Oncol*. 2014;31:305. doi:10.1007/s12032-014-0374-0
39. Feng JF, Chen S, Yang X. Systemic immune-inflammation index (SII) is a useful prognostic indicator for patients with squamous cell carcinoma of the esophagus. *Medicine*. 2017;96:e5886. doi:10.1097/MD.0000000000005886
40. Hong X, Cui B, Wang M, Yang Z, Wang L, Xu Q. Systemic immune-inflammation index, based on platelet counts and neutrophil-lymphocyte ratio, is useful for predicting prognosis in small cell lung cancer. *Tohoku J Exp Med*. 2015;236:297–304. doi:10.1620/tjem.236.297
41. Huang L, Liu S, Lei Y, et al. Systemic immune-inflammation index, thymidine phosphorylase and survival of localized gastric cancer patients after curative resection. *Oncotarget*. 2016;7:44185–44193. doi:10.18632/oncotarget.9923
42. Petrie HT, Klassen LW, Kay HD. Inhibition of human cytotoxic T lymphocyte activity in vitro by autologous peripheral blood granulocytes. *J Immunol*. 1985;134(1):230–234.
43. el-Hag A, Clark RA. Immunosuppression by activated human neutrophils. Dependence on the myeloperoxidase system. *J Immunol*. 1987;139(7):2406–2413.
44. Lee S, Oh SY, Kim SH, et al. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. *BMC Cancer*. 2013;13:350. doi:10.1186/1471-2407-13-350
45. Azab B, Jaglall N, Atallah JP, et al. Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. *Pancreatology*. 2011;11(4):445–452. doi:10.1159/000331494