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Original Article

Pretreatment platelet-lymphocyte ratio versus neutrophil-lymphocyte ratio in the prognosis of multiple myeloma: a single center retrospective study

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Abstract: As representatives of inflammation factors, Neutrophil to lymphocyte ratio (NLR) and Platelet-lymphocyte ratio (PLR) have both showed good prognostic significance in various malignancies. In this study, we compared the usefulness of PLR with that of NLR for predicting outcomes of patients with multiple myeloma (MM). In this study, 166 MM patients (88 males and 78 females, average age: 61.6 ± 10.8 years) were retrospectively observed between January 2009 and December 2015. Their baseline platelet, lymphocyte, neutrophil counts and other clinical data were collected and the clinical characteristics were subsequently compared between different subgroups. Based on NLR and PLR, patients were divided into groups of high NLR (> 1.97) and low NLR (≤ 1.97), high PLR (> 98.45) and low PLR (≤ 98.45), respectively. Our result showed that high NLR was not always consistent with other unfavorable clinical variables though it did show a significant correlation with serum creatinine, while a decreased PLR was closely related with numerous unfavorable clinical parameters, and it was negatively related with tumor burden and renal dysfunction. More importantly, NLR was neither related with patients' overall survival (OS) nor progression free survival (PFS), while PLR showed an excellent correlation with patients' OS and PFS, thought both of them showed negative correlation with red blood cell width distribution (RDW), another readily available predictive index for MM. Furthermore, Cox univariate and multivariate regression analysis found that PLR was an independent prognostic factor for MM. In conclusion, pretreatment PLR might be superior to NLR to be predictive of survival in myeloma patients because of its better stability and reliability.

Keywords: Multiple myeloma, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), prognosis

Introduction

To date, Multiple myeloma (MM) remains an incurable hematological malignance despite the use of novel agents and even the application of latest technology chimeric antigen receptor modified T cells [1].

It is known that MM is highly heterogeneous and myeloma patients outcome is vary greatly. Till now, its prognosis depends largely on the international staging system (ISS) [2] according to β2 microglobulin and serum albumin levels, in combination with lactate dehydrogenase (LDH) levels and poor cytogenetics [3]. However, it does not take into account the complicated interaction between myeloma cells and the tumor microenvironment as well as the host immune system in sustaining myeloma cell survival and proliferation [4]. Therefore, searching for more accurate and feasible prognostic indexes is urgently needed.

Over the past decade, accumulating evidences have proved the close correlation between inflammation factors and tumorigenesis and a number of inflammation markers such as C-reactive protein [5], transforming growth factor-β as well as TNF-alpha [6] have been identified as simple and readily available prognostic factors in a wide range of malignancies. As a representative index of systemic inflamma-

tion, neutrophil to lymphocyte ratio (NLR) have showed a potent prognostic significance in kinds of solid [7-9] and hematological malignancies [10], including MM. Kelkitli et al. showed that NLR ≥ 2 was correlated to myeloma patients' poor outcomes [11].

Platelet to lymphocyte ratio, known as PLR, another systemic inflammation factor, has also showed a pleasant prognostic value in numerous solid [12, 13] and hematological malignancies. The underlying mechanism might be its potential to improve tumors angiogenesis by increasing the incidence of thrombogenicity. In fact, low platelet count had independently unfavorable significance for myeloma patients' overall survival (OS) [14], and elevated NLR and decreased PLR have been proved to predict poor clinical outcome in MM patients [15]. Nevertheless, insufficient data exists for NLR versus PLR in the prognosis of myeloma patients. The aim of this study was to elucidate the effects of preoperative PLR and NLR on OS and progression free survival (PFS) in patients with MM.

Materials and methods

Patients

A total of 166 MM patients were enrolled in this study and their medical records and laboratory results were collected from the Department of Clinical Hematology, Second Affiliated Hospital, Medical School of Xi'an Jiaotong University, from January 2009 to December 2015. This study was approved by the institutional review board of Xi'an Jiaotong University. Because the study was a retrospective analysis of patient data and followed the guidelines of the Declaration of Helsinki, the requirement for patient consent was not required.

MM diagnosis was determined by serum examination and bone marrow aspiration, according to the diagnostic guidelines of National Comprehensive Cancer Network (NCCN). Furthermore, conventional chromosome analysis with G-banding technique and inter-phase fluorescence in situ hybridization (iFISH) were also performed to detect chromosomal abnormalities so as to give patients more precise risk stratification [16]. All patients were staged according to the Durie and Salmon staging system [17].

Measurement of clinical parameters

Baseline neutrophil count, lymphocyte count, platelet count as well as other clinical parameters were obtained when the patients came to the hospital for initial diagnosis and before systematic treatment. Blood routine test related parameters were measured using Beckman Coulter LH750 (USA). Roche Cobas8000 c701 automatic biochemical analyzer was used to measure LDH and other clinical parameters.

Statistical analysis

Values of continuous variables were presented as means ± standard deviation (SD) or medians and range. Patients were categorized into different groups according to the selected parameters. As for NLR and PLR, patients will be categorized into two groups, high NLR/PLR group (> median value) and low NLR/PLR group (≤ median value), as reported previously [18]. Patient characteristics and survival outcomes were compared between the two groups. The association between each continuous variable and stratification by threshold was evaluated using the t-test. The Kaplan-Meier method with a log rank test was used for the survival analysis. The variables we entered into the univariate analysis may be associated with prognosis of MM according to previous studies. Variables that were found to be associated with survival in the univariate analysis were further tested in a multivariate model. OS was defined as the interval between the date of the first treatment and the date of death from any cause or the last follow-up. PFS was defined as the interval between the date of first treatment and the first relapse, or the last follow-up. All data were analyzed with the SPSS statistical software version 18.0 or with Graphpad Prism 5.0 (Graphpad Software, San Diego, CA, USA). $P < 0.05$ was accepted as statistically significant.

Results

Patient clinical characteristics

Among the enrolled 166 patients, 88 were male and 78 were female, with a gender ration of 1.13:1. And their median age was 62 years with the range of 34-93 years. Their median NLR was 1.97 (range: 0.38-14.24), and median PLR was 98.45 (range: 6.75-601.37). The other clinicopathological parameters that might be

Table 1. The correlation of NLR and PLR levels with clinicopathological parameters in 166 myeloma patients

Parameters		No.of patients	NLR	*P*	PLR	*P*
Age (years)	≥ 60	97	2.68 ± 2.14	0.800	109.58 ± 76.80	0.883
	< 60	69	2.60 ± 1.94		111.27 ± 67.08	
Gender	Male	88	2.83 ± 2.32	0.217	110.99 ± 81.81	0.895
	Female	78	2.44 ± 1.70		109.48 ± 61.38	
Bone lesions	Absent	52	2.84 ± 2.18	0.403	113.89 ± 59.57	0.667
	Present	114	2.56 ± 2.00		108.63 ± 78.17	
Durie and Salmon stage	I	21	2.42 ± 1.24	0.796	129.82 ± 65.13	0.212
	II	29	2.82 ± 2.59		121.62 ± 73.40	
	III	116	2.64 ± 2.03		103.91 ± 73.44	
#1Hb (g/L)	< 85	96	2.60 ± 2.13	0.709	98.05 ± 74.73	0.011
	≥ 85	70	2.72 ± 1.96		127.05 ± 66.79	
ESR (mm/H)	≤ 25	17	2.45 ± 1.17	0.675	140.83 ± 60.28	0.043
	> 25	149	2.67 ± 2.13		106.79 ± 73.37	
Albumin (g/L)	< 35	91	2.45 ± 2.16	0.180	107.12 ± 80.55	0.540
	≥ 35	75	2.88 ± 1.91		114.11 ± 62.23	
LDH (IU/L)	< 250	141	2.55 ± 1.79	0.145	115.37 ± 75.70	0.032
	≥ 250	25	3.20 ± 3.15		81.57 ± 43.75	
Scr (μmol/L)	< 176.8	126	2.31 ± 1.69	0.003	113.93 ± 76.73	0.252
	≥ 176.8	40	3.71 ± 2.69		98.77 ± 57.65	
#2Calcium (mmol/L)	< 2.75	133	2.61 ± 2.11	0.684	112.86 ± 75.47	0.360
	≥ 2.75	33	2.78 ± 1.84		99.88 ± 60.25	

#1: Hb: hemoglobin, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase, Scr: serum creatinine. #2: calcium level was corrected by the serum albumin levels measured simultaneously.

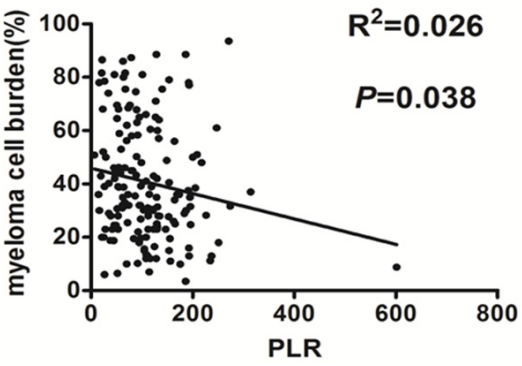

Figure 1. Correlation of PLR and myeloma cell burden.

related with patients' outcome were listed in **Table 1**. The result showed that NLR was significantly higher in patients who had a worse renal function, while a lower PLR was closely related with unfavorable hemoglobin (Hb), erythrocyte sedimentation rate (ESR) as well as lactate dehydrogenase (LDH) levels.

Correlations of NLR, PLR and myeloma cell burden

Myeloma cell burden (showed as myeloma cell percents in the patients' bone marrow) was an important index of tumor burden. To some extent, a high tumor burden means an unfavorable outcome. Our correlation analysis showed that NLR was not related with myeloma cell burden with R^2 of 0.002 and *P* value of 0.601 (data not shown), while PLR showed a significantly negative correlation with patients myeloma cell burden, its R^2 was 0.026 and *P* value was 0.038 (**Figure 1**).

Correlations of NLR, PLR and 24 hours urine protein levels

24 hours urine protein levels reflex the renal destruction in MM patients, which has a similar clinical significance with serum creatinine. However, our correlation analysis showed that NLR was not correlated with 24 hrs urine protein levels (R^2 = 0.112, and *P* = 0.111), while

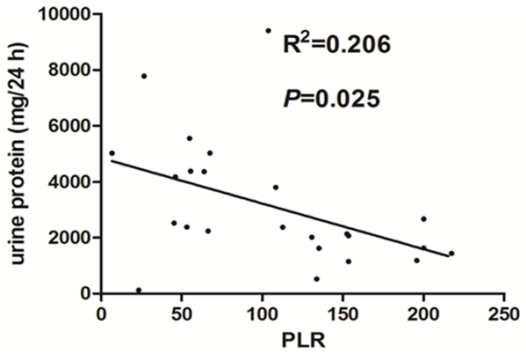

Figure 2. Correlation of PLR and 24 h urine protein levels# (#24 patients performed this examination).

PLR showed a significantly negative correlation with patients' 24 hrs urine protein levels (**Figure 2**), though there were only 24 patients underwent this examination.

Correlations of NLR, PLR and red blood cell distribution width

In our previous study, we had proved that another blood routine test related parameter, red blood cell distribution width (RDW), was also a readily available predictor of long term adverse outcome among MM patients. Here we analyzed the consistence of NLR, PLR and RDW levels to further evaluate prognostic values of NLR and PLR in these patients. The result showed that both NLR and PLR were significantly negatively related with RDW levels, the *P* value was 0.017 and 0.002, respectively (**Figure 3**).

Correlations of NLR, PLR and patients' survival time

The median follow-up duration among the 166 patients was 18.48 months (range 0.90-62.83 months). During the follow up, 38 patients relapsed after once achieving CR. All-cause mortality was observed in 40 patients.

In the NLR higher group, the median OS and PFS were 47.27 and 28.39 months, respectively, while in the NLR lower group, the median OS was 58.33 months and PFS was 33.60 months. Log-rank (Mantel-Cox) test showed that there was no significant difference in OS (*P* = 0.130, **Figure 4A**) and in PFS (*P* = 0.313, **Figure 4C**). As for PLR, the median OS and PFS were 47.95 months and 33.41 months respectively in the PLR higher group, and the median OS and PFS were 36.20 months and 25.03 months respectively in the PLR lower group. Log-rank (Mantel-Cox) test showed that both OS and PFS was much higher in PLR higher group than that in PLR lower group, as shown in **Figure 4B**, **4D**.

This result suggested that NLR was neither related with patients' overall survival nor progression free survival, while PLR showed an excellent correlation with patients' OS and PFS.

Prognostic values of the different variables including NLR and PLR

Univariate and multivariate Cox regression analysis were performed to define independent prognostic index for myeloma patients.

In the Cox univariate regression analysis, we found that albumin (HR: 0.499, 95% CI: 0.262-0.953, *P* = 0.035), LDH (HR: 3.085, 95% CI: 1.521-6.257, *P* = 0.002) and corrected calcium (HR: 1.970, 95% CI: 0.997-3.893, *P* = 0.049) levels were significantly associated with patients' OS. PLR also showed a significant correlation with OS both as a continuous variable (*P* = 0.033) and as a categorical variable (*P* = 0.046). On the other hand, neither age, gender, bone lesion, DS stage, Hb, ESR, Scr, neutrophil count, Lymphocyte count, platelet count, RDW or NLR was associated with patients' OS (*P* > 0.05). When analyzed by Cox multivariate regression analysis, LDH, corrected calcium levels and PLR (both as a continuous variable or categorical variable) remained as independent prognostic factors, as shown in **Table 2**.

As for PFS, the Cox univariate regression analysis showed that albumin (HR: 0.481, 95% CI: 0.250-0.925, *P* = 0.028), LDH (HR: 0.670, 95% CI: 1.326-5.379, *P* = 0.006), as well as RDW-CV (coefficient of variation of red blood cell volume with a normal range of 11.6-14.0%, as a continuous variable, HR: 2.049, 95% CI: 0.858-4.893, *P* = 0.016) were significantly associated with patients' PFS. PLR also showed a significant correlation with PFS both as a continuous variable (*P* = 0.031) and as a categorical variable (*P* = 0.030). When analyzed by Cox multivariate regression analysis, only LDH level and PLR as a categorical variable remained as independent prognostic factor in patients' PFS, as shown in **Table 3**.

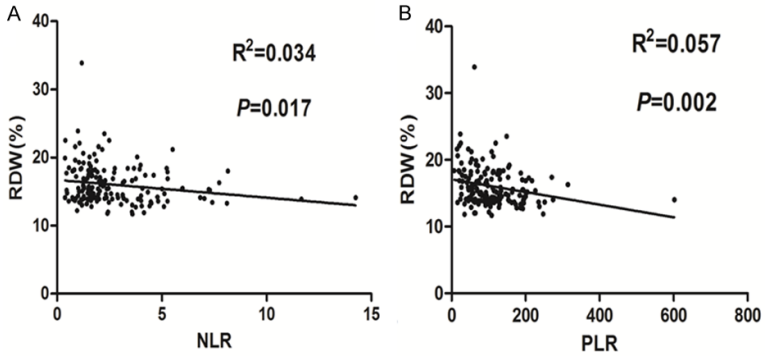

Figure 3. Correlations of NLR, PLR and RDW levels.

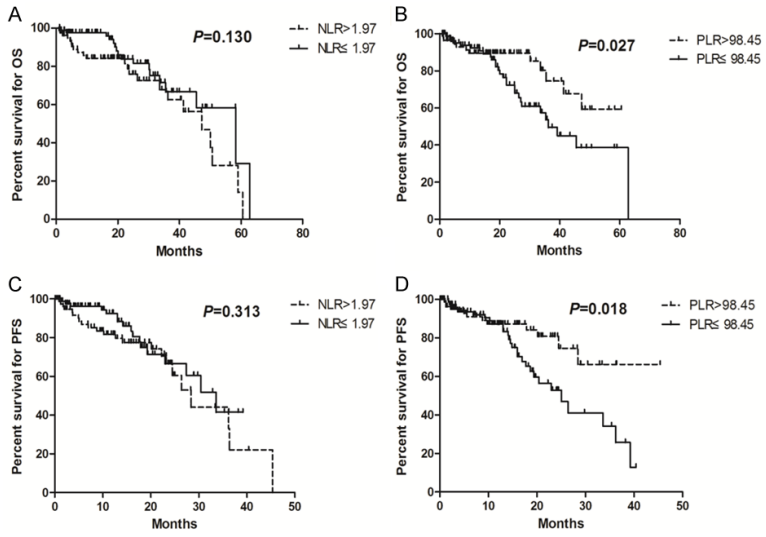

Figure 4. Correlation of NLR and PLR with patients' survival time.

Discussion

In recent years, accumulating evidences have proved the prognostic significance of systematic inflammation in numerous malignancies including MM. As a hallmark of cancer, inflammation factors lead to angiogenesis, inhibition of apoptosis, and DNA damage [19, 20], which then promote cancer and affect host immunity as well as tumor response to treatment [21, 22].

NLR was a representative factor of systematic inflammation. A high NLR means a relatively elevated neutrophil count and depletion of lymphocytes, which can change the tumor microenvironment and facilitate tumor invasion and metastasis by secreting serum vascular endothelial growth factor and various proteases [23]. On the other hand, depletion of lymphocytes means weakened antitumor immunity and therefore promote tumor proliferation. Furthermore, pretreatment lymphopenia greatly increased the incidence of severe bacterial infection for MM patients during treatment with bortezomib-based regimens, which increased the mortality at the same time [24]. In this study, we also proved the close positive correlation between NLR and serum creatinine. However, our result showed that elevated NLR were not always consistent with other unfavorable clinicopathological parameters. And moreover, we found that NLR was neither related with patients' OS nor PFS, which was controversy with other reports [15, 16]. This might be attributed to myeloma cells high heterogenecity and some other uncontrollable factors [25].

Platelet count, another inflammatory marker, also plays important role in tumor prognosis [26]. It has been reported that in MM the platelet is always over-activated [27]. Activated platelet secrets a variety of cytokines such as IL-6, VEGF, SDF-1α, and IGF-1 [28], which will cause myeloma cells microenvironments changes and provide protection of myeloma cells by inhibiting NK cells function [29]. All these result in myeloma cells survival and proliferation. On the other hand, thrombocytopenia is frequently observed in MM patients [30, 31]. Based on these findings, it can be inferred that the PLR is not only an inflammatory marker, but also a marker of tumor burden and aggressiveness in MM [16, 17]. Indeed, our result also showed that PLR was significantly negatively related with kinds of clinicopathological indexes including unfavorable Hb, ESR as well as LDH levels, as shown in **Table 1**.

In order to have a more reliable result, we performed a correlation analysis and the result showed that PLR instead of NLR was negatively

Table 2. Univariate and multivariate Cox regression analysis of OS of MM patients

Parameters	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (years) ≥ 60 vs < 60	1.177	0.625-2.216	0.615			
Gender Male vs Female	1.415	0.741-2.701	0.292			
Bone lesion Absent vs present	0.813	0.394-1.678	0.576			
Durie and Salmon stage I vs II and III	1.080	0.673-1.734	0.750			
Hb (g/L) < 85 vs ≥ 85	0.857	0.457-1.609	0.632			
ESR (mm/H) > 25 vs ≤ 25	1.206	0.428-3.397	0.723			
Albumin (g/L) ≥ 35 vs < 35	0.499	0.262-0.953	0.035			0.052
LDH (IU/L) ≥ 250 vs < 250	3.085	1.521-6.257	0.002	2.666	1.298-5.475	0.008
Scr (μmol/L) ≥ 176.8 vs < 176.8	1.184	0.561-2.500	0.658			
Calcium (mmol/L) ≥ 2.75 vs < 2.75	1.970	0.997-3.893	0.049	2.372	1.170-4.811	0.017
Neutrophil count	1.124	0.970-1.302	0.119			
Lymphocyte count	0.200	0.862-1.672	0.280			
Platelet count	0.993	0.988-1.908	0.308			
RDW-CV	0.978	0.870-1.098	0.701			
RDW-CV > 14.0% vs ≤ 14.0	1.908	0.799-4.557	0.146			
NLR	1.078	0.918-1.267	0.360			
NLR > 1.97 vs ≤ 1.97	1.014	0.857-1.200	0.872			
PLR	0.994	0.988-0.999	0.033	0.993	0.987-0.999	0.023
PLR > 98.45 vs ≤ 98.45	0.514	0.264-1.001	0.046	0.419	0.204-1.863	0.030

OS: overall survival, MM: multiple myeloma, DS stage: Durie and Salmon stage, RDW-CV: red blood cell distribution width coefficient of variation, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio.

correlated with patients' tumor burden as well as urine protein levels, both of which were unfavorable parameters for patients, as reported previously [32].

RDW level, another blood routine test derived variable, has also been proved to be a feasible prognostic index for myeloma patients [33]. In this study, we found that both NLR and PLR were significantly negatively related with RDW levels, which confused us since NLR should have be positively correlated with RDW level instead of negatively correlated with it. However, this result could be partially explained by the phenomenon we observed in **Table 1**.

On the other hand, since elevated RDW level was related with patients' OS and PFS and we have proved that RDW level was an independent prognostic factor for PFS, we hypothesized that NLR and PLR might also have correlations with patients' survival time. In fact, Romano et

Table 3. Univariate and multivariate Cox regression analysis of PFS of MM patients

Parameters	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (years) ≥ 60 vs < 60	0.709	0.370-1.359	0.301			
Gender Male vs Female	0.958	0.503-1.823	0.896			
Bone lesion Absent vs present	1.265	0.616-2.596	0.522			
DS stage I vs II and III	1.130	0.710-1.796	0.607			
Hb (g/L) < 85 vs ≥ 85	1.103	0.592-2.057	0.757			
ESR (mm/H) > 25 vs ≤ 25	1.459	0.517-4.116	0.475			
Albumin (g/L) ≥ 35 vs < 35	0.481	0.250-0.925	0.028			0.117
LDH (IU/L) ≥ 250 vs < 250	2.670	1.326-5.379	0.006	3.170	1.758-5.003	0.049
Scr (μmol/L) ≥ 176.8 vs < 176.8	1.197	0.582-2.462	0.624			
Calcium (mmol/L) ≥ 2.75 vs < 2.75	1.902	0.962-3.761	0.065			
Neutrophil count	1.122	0.978-1.288	0.101			
Lymphocyte count	1.226	0.910-1.654	0.181			
Platelet count	0.994	0.989-1.992	0.115			
RDW-CV	1.015	0.905-1.139	0.795			
RDW-CV > 14.0% vs ≤ 14.0	2.049	0.858-4.893	0.016			0.084
NLR	1.033	0.865-1.234	0.717			
NLR > 1.97 vs ≤ 1.97	1.012	0.543-1.887	0.969			
PLR	0.994	0.988-0.999	0.031			0.470
PLR > 98.45 vs ≤ 98.45	0.478	0.246-0.930	0.030	2.042	1.010-4.130	0.047

PFS: progression free survival, MM: multiple myeloma, DS stage: Durie and Salmon stage, RDW-CV: red blood cell distribution width coefficient of variation, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio.

al. had examined the NLR in a cohort of 309 newly diagnosed multiple myeloma and had proved NLR to be a predictor of PFS and OS in MM patients treated upfront with novel agents [4]. However, in our study, the Kaplan-Meier analysis result showed that NLR was neither related with patients' OS nor PFS, while PLR showed an excellent correlation with patients' OS and PFS. Moreover, univariate and multivariate Cox regression analysis proved that PLR was an independent prognostic factor for MM patients' OS and PFS, either as a continuous variable or as a categorical variable. This result was not consistent with the literature reported previously [15, 16].

Furthermore, in this study, we also proved that LDH and corrected calcium levels were also independent prognostic factors for MM patients' OS and LDH level was another independent prognostic factor for MM patients' PFS, as reported previously [34, 35].

In conclusion, this study found that pretreatment PLR might be superior to NLR to be predictive of survival in myeloma patients because

of its better stability and reliability. However, this study also has some default. First, since this was a retrospective study, the potential infection existed when the peripheral blood samples were obtained could not completely excluded. Moreover, whether the cut-off value of 1.97 for NLR and 98.45 for PLR is correct requires further investigation. Thirdly, small sample of our clinical cases may partially account for the negative outcome for the prognostic value of the NLR. Herein, Validation studies or large-scale prospective studies are warranted to verify our findings. And it will be more accurate and objective to use NLR combined with PLR to evaluate patients' outcome.

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Disclosure of conflict of interest

None.

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