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Original Article

Characterization of blood inflammatory markers in patients with non-small cell lung cancer

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Abstract: Objective: To investigate the differences and correlation between blood inflammatory indexes such as monocytes (MONO), lymphocytes (LYM), haemoglobin (HGB), neutrophils (NEU), platelets (PLT), ultrasensitive C-reactive protein, albumin and platelet/lymphocyte ratio (PLR), NEU/LYM ratio (NLR), MONO/LYM ratio (MLR) and clinicopathologic characteristics of patients with non-small cell lung cancer (NSCLC). Methods: 187 patients with NSCLC who were first diagnosed in 2017-2023 and 102 with healthy check-ups during the same period (control group) were retrospectively selected as study subjects to compare the differences in inflammatory indexes between the two groups and the levels of inflammatory indexes in NSCLC patients with different clinicopathologic characteristics. Results: Correlation analysis between blood inflammatory indexes and clinicopathologic features in NSCLC group showed that C-reactive protein, CAR, and PLR values were different in different pathologic types ($P<0.05$). The values of NEU, MONO, C-reactive protein, MLR, NLR, CAR and albumin were different among various degrees of differentiation ($P<0.05$). There were differences in LYM, albumin, MLR, NLR, CAR, and C-reactive protein among M stage subgroups ($P<0.05$). Analysis of the efficacy of early diagnosis of non-small cell lung cancer has been shown, the AUC of NLR was 0.796, sensitivity of 0.679, specificity of 0.176, 95% CI=0.743-0.849 ($P<0.001$). The AUC of albumin was 0.977, the sensitivity was 0.941, the specificity was 0.941, and 95% CI was 0.959-0.994 ($P<0.001$). Conclusion: Blood inflammatory indexes are closely associated with NSCLC and vary according to pathologic features. Blood inflammatory indices can predict tumor pathologic staging and guide treatment for patients with NSCLC.

Keywords: Non-small cell lung cancer, NLR, MLR, blood inflammatory index, clinicopathological features

Introduction

Recent studies have found clear evidence that inflammation plays a critical role in the occurrence of malignant tumors [1] and that blood inflammatory markers can serve as predictors of the prevalence of malignant tumors [2]. Blood routine and ultrasensitive C-reactive protein assay are the most commonly used tests to reflect the inflammatory status of the body. Numerous studies have investigated the inflammatory markers of various malignancies and concluded that these markers are closely related to the occurrence of various human malignancies as well as different histologic types, different stages and prognosis of tumors [3]. Lung cancer is one of the common malignancies, of which about 85% is NSCLC [4]. NSCLC is often detected late, and clinical treatment for NSCLC is limited and there is a lack of effective methods for early detection. Most patients are in the middle and late stages when they are found, with a low 5-year survival rate and a high mortality rate [5]. With ongoing research into the pathogenesis of malignant tumors, it has been found that inflammatory markers can reflect the immune and nutritional status of the body. There are few studies on the correlation between clinicopathologic features of NSCLC and inflammatory indicators. In this study, we retrospectively compared the blood inflammatory markers of NSCLC patients and healthy people, and the changes in inflammatory markers in NSCLC patients based on different clini-

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copathological features. We investigated the relationship between NSCLC and blood inflammatory markers, and explored the clinical application value of inflammatory markers with regard to diagnosis and prognosis.

Materials and methods

General information

A retrospective collection of 187 patients with a first diagnosis of NSCLC from January 2017 to May 2023 from the Department of Cardiothoracic Vascular Surgery, Affiliated Hospital of Youjiang Medical University for Nationalities, and 102 patients with a healthy physical examination during the same period. The observation group included 117 males and 70 females aged 29-81 years, including 146 cases of adenocarcinoma, 29 cases of squamous cell carcinoma, and 12 cases of other histologic types; For TNM stages, 74 cases were in stage I; 50 cases were in stage II; 34 cases were in stage III; 29 cases were in stage IV. The control group included 61 males and 41 females aged 28-78 years.

Inclusion criteria were as follows: (1) Diagnosed with NSCLC through clinicopathological tissue examination at our hospital for inclusion in the NSCLC group; (2) No previous history of tumor treatment; (3) No signs of infection before treatment; (4) Complete case information. Exclusion criteria were as follows: (1) Presence of acute or chronic infectious diseases; (2) Severe organ dysfunction; (3) Prior anti-tumor treatment; (4) Recent use of hematopoietic drugs.

The study was approved by the Medical Ethics Committee of the Youjiang Medical University for Nationalities and informed consent was obtained from all subjects.

Data processing

According to patients' electronic medical records, clinical data and laboratory indicators of NSCLC group and control group were collected. The clinical data included gender, age, clinical stage, T stage, M stage, pathologic type and differentiation degree. The laboratory data included 7 inflammatory indexes of monocytes (MONO), lymphocytes (LYM), haemoglobin (HGB), neutrophils (NEU), platelets (PLT), ultrasensitive C-reactive protein, albumin and platelet/lymphocyte ratio (PLR), NEU/LYM ratio (NLR), MONO/LYM ratio (MLR), and C-reactive protein and albumin (CAR) were calculated. All laboratory data were collected from 10 ml of peripheral venous blood on an empty stomach in the early morning of the first day of admission, which was placed into an anticoagulant tube and a coagulant promoting biochemical tube, respectively, and shaken for examination. Sysmex XN-20[A1]/blood cell analyzer was used to detect the positive rate of each cell in blood samples, and the detection process was conducted in strict accordance with the instructions. Biochemical indicators in blood samples were detected by automatic biochemical instrument C702.

Statistical analysis

SPSS 27.0 statistical software was used to analyze the clinical data. The classification and counting data were tested by X^2. For normally distributed continuous quantitative data with equal variance, the independent sample t-test was used for comparisons between two groups; for continuous quantitative data that are non-normally distributed or with unequal variance, the Mann-Whitney U rank sum test was used for comparisons between two groups; the Kruskal-Wallis rank sum test was used for comparisons among multiple groups; diagnostic efficacy was analyzed using the receiver operating characteristic (ROC) curve. *p*-value <0.05 was considered statistically significant.

Results

Comparison of the general statistical results of NSCLC group and control group

The general statistical results of NSCLC group and control group are shown in **Tables 1** and **2**. A total of 187 cases were collected in the NSCLC group, of which 117 cases (62.6%) were male and 70 cases (37.4%) were female; 80 cases (42.85%) were 60 years old and above, and 107 cases (57.2%) were less than 60 years old. A total of 102 cases were collected from the control group, of which 61 (60%) were males and 41 (40%) were females; 52 (51%) were 60 years and older and 50 (49%) were younger than 60 years. There was no statistical significance in age and sex (P>0.05), and the two groups were comparable, as shown in **Table 3**.

Table 1. General data for NSCLC patients [n (%)]

Factor		n=187
Sex	Male	117 (62.6)
	Female	70 (37.4)
Age	≥60	80 (42.8)
	<60	107 (57.2)
Histologic type	Squamous cell carcinoma	29 (15.5)
	Adenocarcinoma	146 (78.1)
	Other	12 (6.4)
Degree of differentiation	Highly differentiated	40 (21.4)
	Moderately differentiated	77 (41.2)
	Poorly differentiated	67 (35.8)
	Undifferentiated	3 (1.6)
Pathologic stages	I	74 (39.6)
	II	50 (26.7)
	III	34 (18.2)
	IV	29 (15.5)
M-stage	0	157 (84.0)
	1	30 (16.0)

Table 2. General data for the control group [n (%)]

Factor		n=102
Sex	Male	61 (60)
	Female	41 (40)
Age	≥60	52 (51)
	<60	50 (49)

Table 3. Comparison of age and sex between NSCLC and control groups [n, (%)]

Factor	NSCLC group	Control group	X^2 value	*P*-value
Sex	187	102		
Male	117 (62.6)	61 (60)	0.213	0.644
Female	70 (37.4)	41 (40)		
Age	187	102		
≥60	80 (42.8)	52 (51)	1.788	0.181
<60	107 (57.2)	50 (49)		

Note: Comparison of age and sex between NSCLC and control groups, P>0.05.

Comparison of blood inflammatory markers between NSCLC and control groups

The levels of NEU, MONO, MLR, NLR and PLR were all higher in the NSCLC group than those in the control group, and the differences were statistically significant (P<0.05). HGB, albumin and LYM were all lower in the NSCLC group than in the control group, and the differences were statistically significant (P<0.05). PLT values were higher in the NSCLC group than in the control group, but the difference was not statistically significant (P>0.05). See **Table 4**.

Analysis of the correlation between blood inflammatory indexes and pathological types in patients with NSCLC

In the study on the correlation between blood inflammatory indexes and pathological types in NSCLC group, the C-reactive protein values were higher in adenocarcinoma than in squamous cell carcinoma and other groups. The CAR values in adenocarcinoma were lower than in squamous cell carcinoma and the other groups, and the PLR values in squamous cell carcinoma were significantly higher than in the other two groups, with statistically significant differences (P<0.05). See **Table 5**.

Comparison of blood inflammatory marker levels in patients with various degrees of differentiation of NSCLC

NEU, MONO, C-reactive protein, MLR, NLR and CAR values were greater in the hypofractionated group of NSCLC patients than in the other groups (P<0.05). NEU, MONO, C-reactive protein, MLR, NLR and CAR values were greater in the hypofractionated group of NSCLC patients than in the other groups (P<0.05). See **Table 6**.

Comparison of blood inflammatory marker levels in patients with different M-stages of NSCLC

LYM and albumin were lower in the NSCLC metastatic group (M1) than in the non-metastatic group (M0). MLR, NLR, CAR and C-reactive protein were all significantly different in the metastatic group compared to the non-metastatic group (P<0.05). See **Table 7**.

Comparison of inflammatory marker levels at different pathologic stages

NEU, MONO, C-reactive protein, NLR and CAR were higher in the Stage III NSCLC group than

Table 4. Comparison of blood inflammatory markers between NSCLC and control groups

Factor	NSCLC group [M(P_{25},P_{75})]	Control group [M(P_{25},P_{75})]	*P*-value
NEU	4.43 (3.44, 6.15)	3.38 (2.77, 4.28)	<0.001
LYM	1.89 (1.51, 2.39)	2.25 (1.83, 2.67)	<0.001
MONO	0.59 (0.45, 0.78)	0.52 (0.40, 0.65)	<0.001
HGB	132 (118, 141)	141 (131, 154)	<0.001
PLT	282.40	272.74	0.352
Albumin	40.1 (36.5, 42.8)	50.4 (48.5, 51.9)	<0.001
MLR	0.32 (0.24, 0.42)	0.22 (0.19, 0.28)	<0.001
NLR	2.44 (1.79, 3.45)	1.49 (1.23, 1.82)	<0.001
PLR	140.38 (103.88, 188.39)	122.22 (102.07, 153.41)	<0.001

Note: P<0.05 compared to the control group.

Table 5. Comparison of inflammatory marker levels by histologic type

Factor	Adenocarcinoma [M(P_{25},P_{75})]	Squamous cell carcinoma [M(P_{25},P_{75})]	Other [M(P_{25},P_{75})]	*P*-value
NEU	4.16 (3.34, 5.81)	5.19 (3.94, 6.62)	5.04 (4.13, 6.38)	0.073
LYM	1.91 (1.51, 2.38)	1.65 (1.44, 2.31)	2.02 (1.70, 2.59)	0.313
MONO	0.59 (0.45, 0.76)	0.59 (0.47, 0.83)	0.74 (0.54, 0.94)	0.319
HGB	133 (120.75, 141.0)	133 (115.5, 144.5)	130.5 (102.25, 136.5)	0.416
C-reactive protein	15.47 (1.29, 8.59)	5.51 (1.33, 46.25)	12.76 (4.52, 28.49)	0.009
Albumin	40.4 (37.25, 43.13)	39.3 (35.8, 41.35)	37.65 (32.98, 43.8)	0.121
MLR	0.31 (0.24, 0.41)	0.32 (0.27, 0.41)	0.372 (0.255, 0.513)	0.500
NLR	2.37 (1.71, 3.23)	2.95 (1.96, 4.42)	2.86 (2.22, 3.39)	0.069
PLR	137.98 (99.58, 178.51)	176.89 (133.12, 0.83)	140.79 (102.68, 173.96)	0.041
CAR	0.06 (0.03, 0.21)	0.15 (0.03, 1.28)	0.31 (0.12, 0.79)	0.009

Note: Comparisons among adenocarcinoma, squamous cell carcinoma, and other three groups, P<0.05.

Table 6. Comparison of blood inflammatory marker levels in patients with different degrees of differentiation of NSCLC

Factor	Highly undifferentiated [M(P_{25},P_{75})]	Moderately undifferentiated [M(P_{25},P_{75})]	Poorly undifferentiated [M(P_{25},P_{75})]	Undifferentiated [M(P_{25},P_{75})]	*P*-value
NEU	3.73 (2.93, 5.07)	4.20 (3.29, 5.57)	5.19 (3.87, 6.76)	8.36	<0.001
LYM	1.85 (1.44, 2.38)	1.93 (1.63, 2.37)	1.72 (1.44, 2.32)	2.80	0.041
MONO	0.53 (0.39, 0.77)	0.56 (0.45, 0.747)	0.64 (0.53, 0.85)	0.82	0.005
HGB	132.5 (121.25, 141.75)	133 (120, 140.5)	132 (114, 141)	124	0.915
C-reactive protein	2.04 (0.94, 7.33)	2.67 (1.14, 9.10)	4.94 (1.64, 28.78)	18.59	0.010
Albumin	41.75 (39.33, 43.98)	40.8 (38.4, 43.8)	38.7 (35.3, 41.8)	32.8	<0.001
MLR	0.27 (0.21, 0.37)	0.28 (0.22, 0.39)	0.36 (0.3, 0.49)	0.33	<0.001
NLR	2.26 (1.59, 3.37)	2.18 (1.56, 3.05)	2.75 (2.13, 4.04)	2.66	0.002
PLR	144.67 (100.29, 182.34)	135.56 (98.87, 177.15)	157.08 (113.79, 199.39)	144.08	0.300
CAR	0.05 (0.02, 0.20)	0.06 (0.3, 0.23)	0.12 (0.04, 0.79)	0.59	0.005

Note: 4-way Comparison between highly, moderately, and poorly differentiated and undifferentiated NSCLC, P<0.05.

in the other groups. MLR increased with increasing stage in the NSCLC group. Albumin decreased with increasing stage in the NSCLC group (all differences, P<0.05). See **Table 8**.

Table 7. Comparison of blood inflammatory marker levels by M-stage

Factor	0 [M(P_{25},P_{75})]	1 [M(P_{25},P_{75})]	*P*-value
NEU	4.22 (3.39, 5.94)	5.07 (3.85, 6.57)	0.136
LYM	1.91 (1.57, 2.40)	1.58 (1.27, 2.27)	0.044
MONO	0.59 (0.45, 0.78)	0.66 (0.52, 0.79)	0.301
HGB	133 (120.5, 140.5)	129.5 (113, 146)	0.667
C-reactive protein	2.54 (1.24, 10.22)	4.7 (1.83, 32.94)	0.040
Albumin	40.5 (37.45, 43.1)	37.32 (34.13, 39.83)	0.001
MLR	0.31 (0.24, 0.41)	0.37 (0.27, 0.55)	0.017
NLR	2.38 (1.76, 3.20)	3.01 (1.94, 4.48)	0.032
PLR	138.89 (103.84, 178.78)	175.69 (109.76, 216.69)	0.094
CAR	0.06 (0.03, 0.26)	0.12 (0.05, 0.98)	0.026

Note: Comparison between M0 and M1 groups, P<0.05.

Table 8. Comparison of inflammatory marker levels at different pathologic stages

Factor	I [M(P_{25},P_{75})]	II [M(P_{25},P_{75})]	III [M(P_{25},P_{75})]	IV [M(P_{25},P_{75})]	*P*-value
NEU	3.77 (3.20, 5.21)	4.28 (3.41, 5.31)	5.94 (4.16, 7.28)	5.28 (3.84, 6.87)	0.001
LYM	1.92 (1.55, 2.43)	1.83 (1.49, 2.17)	2.08 (1.60, 2.44)	1.58 (1.3, 2.40)	0.374
MONO	0.55 (0.42, 0.70)	0.57 (0.44, 0.76)	0.72 (0.52, 0.95)	0.68 (0.54, 0.81)	0.004
HGB	135 (127.25, 141.25)	132 (114.75, 140.25)	126.5 (113.75, 141)	131 (112, 144)	0.196
C-reactive protein	1.63 (0.91, 3.12)	3.16 (1.42, 10.01)	13.8 (3.09, 45.60)	6.03 (1.98, 34.88)	<0.001
Albumin	41.4 (39.25, 44.0)	39.9 (37.3, 42.4)	38.95 (34.62, 42.65)	36.4 (34.05, 39.7)	<0.001
MLR	0.27 (0.22, 0.36)	0.32 (0.24, 0.39)	0.36 (0.27, 0.48)	0.37 (0.27, 0.61)	0.001
NLR	2.11 (1.59, 2.97)	2.52 (1.76, 2.91)	3.07 (2.18, 4.14)	2.89 (1.91, 4.55)	<0.001
PLR	136.24 (101.31, 167.18)	148.34 (106.14, 174.46)	176.08 (123.68, 208.76)	174.17 (97.02, 217.90)	0.165
CAR	0.04 (0.02, 0.08)	0.08 (0.04, 0.23)	0.41 (0.07, 1.13)	0.15 (0.06, 1.09)	<0.001

Note: Comparison of stages I, II, III and IV, P<0.05.

ROC curves for the diagnosis of NSCLC by blood inflammatory markers

ROC curves were plotted and analyzed for specificity and sensitivity of blood inflammatory markers. The results showed that NLR had better diagnostic efficacy than MLR, CAR, NLR, or PLR for the diagnosis of NSCLC, with an area under the curve (AUC) of 0.796, sensitivity of 0.679, specificity of 0.176, and 95% CI=0.743-0.849 (P<0.001). Albumin had an AUC of 0.977, sensitivity of 0.941, specificity of 0.324, and 95% CI=0.959-0.994 (P<0.001). See **Figures 1**, **2**.

Discussion

In recent years, the incidence and mortality rate of lung cancer in China has been increasing. Due to its lack of distinctive early symptoms, the optimal treatment period has been missed when it is detected, which seriously affects the quality of life of patients. As research into the direct pro-tumor effects of the inflammatory microenvironment continues to intensify, inflammation and tumors have gained attention. Inflammatory factors have been found to be closely associated with tumor growth, angiogenesis, and distant metastasis in NSCLC [6], and inflammatory markers are the optimal choice for reflecting the immune function status and nutritional status of the body. As found in this study, NEU, MONO, NLR and PLR were all higher in the NSCLC group than in the control group. LYM, HGB, albumin, and MLR were all lower in the NSCLC group than in the control group (all P<0.05). This is similar to the results of other studies on the correlation between inflammation and tumor [5, 7-9], providing further evidence that NSCLC is closely related to inflammation.

In recent years, NEU, MONO, NLR and PLR in the peripheral blood have been considered as

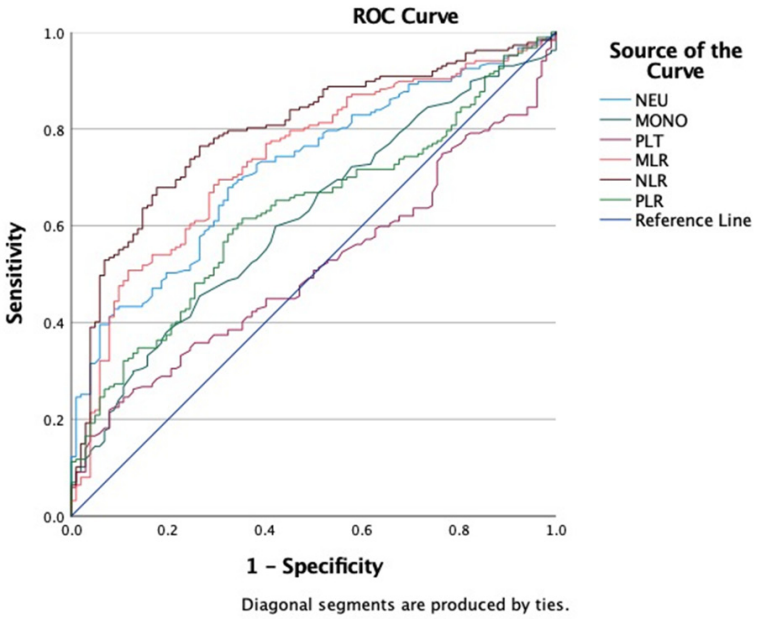

Figure 1. ROC curves for the diagnosis of NSCLC by blood inflammatory markers.

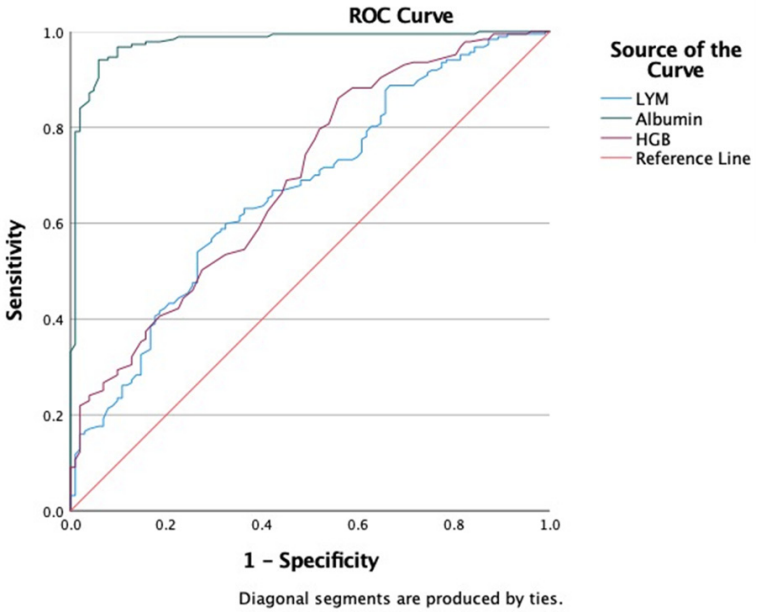

Figure 2. ROC curves for the diagnosis of NSCLC by blood inflammatory markers.

indicators to reflect the inflammatory state of the body. The correlation between NLR value and tumor has attracted recent attention. Relevant studies have shown that NEU can regulate LYM and inhibit their activity, affect the growth of malignant cells, and play a role in tumor defense [10]. Lymphocytopenia leads to a decline in the anti-tumor ability of the body, thus leading to poor prognosis. In this study, the LYM of non-small cell lung cancer (NSCLC) patients with distant metastasis was lower than that of patients with metastasis, indicating that LYM is closely related to the occurrence of distant metastasis, thus leading to poor prognosis, consistent with another study [11]. Some studies propose that an increase in NLR is caused by the necrosis of tumor tissue, which leads to an increase of inflammatory mediators. This triggers the inflammatory response and the release of inflammatory factors, thus promoting the growth of tumors and angiogenesis [4, 6, 12]. Some studies propose that NLR can reflect the balance between inhibiting and promoting tumor progression [13]. Our study found that NLR was closely related to poor differentiation and M stage, and thus, distant metastasis and poor prognosis. Therefore, NLR is correlated with patient prognosis, which is consistent with the results of Wang and Chen's study [14]. In this study, it was found that MLR was correlated with pathological stage, differentiation degree, and M stage, which means that a worse the prognosis of patients, so the results of Zhai and Chen's study are contrary to the results of our study [15]. However, the results of this study and MLR value are similar to MLR's correlation in ovarian cancer [16], colorectal cancer [17], lung cancer [18], and other cancers, so our finding needs to be further demonstrated by multi-center and big data research. The PLR value represents the change between platelets and lymphocytes, and an increase in PLR value indicates the weakening of the anti-tumor function mediated by lymphocytes,

which is conducive to the growth and metastasis of tumor [12, 19].

In the comparison of inflammatory markers of different clinicopathologic features, it was found that the hypersensitive C-reactive protein and CAR values were higher in the poorly differentiated group of NSCLC than in the other groups, and albumin was lower in the poorly differentiated group than in the other groups, with all differences being significant ($P<0.05$). LYM and albumin were lower in the M1 subgroup than in the M0 subgroup in the NSCLC group (all, $P<0.05$). The MLR values of NSCLC increased with increasing TNM stage, while the albumin value decreased with increasing stage (both, $P<0.05$). C-reactive protein is synthesized by the liver during an inflammatory response, accelerating disease progression [20]. In lung cancer patients, C-reactive protein is produced by lung epithelial cells and therefore C-reactive protein can effectively reflect prognosis [21]. Related studies have found that albumin is commonly used to reflect the nutritional status of the body and that it also has anti-oxidative stress function, improves microcirculation, and regulates the systemic inflammatory response [22]. Most patients with malignant tumors tend to have decreased albumin levels in the middle and late stages, mainly due to malnutrition and tumor consumption. Decreased albumin levels are often associated with impaired liver function and immune deficiency, resulting in tumor recurrence and metastasis, leading to poor prognosis.

In summary, inflammatory markers such as NLR, NEU, MLR and PLR are strongly associated with NSCLC and exhibit different behaviors among clinicopathological groups. Therefore, blood inflammatory markers can help predict the pathological stage of tumors and formulate treatment plans for patients with NSCLC.

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Disclosure of conflict of interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflicts of interest.

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