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ORIGINAL ARTICLE

The prognostic significance of ALI, PLR, and Ki-67 expression in stage III–IV inoperable non-small cell lung cancer*

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Abstract

Objective The aim of the study was to investigate and compare the prognostic value of advanced inflammatory index, platelet/lymphocyte ratio (PLR), and Ki-67 expression in stage III–IV inoperable non-small cell lung cancer (NSCLC) before treatment.

Methods The clinical data of 98 inoperable patients with stage III–IV NSCLC in our hospital (Fifth Department of Oncology, Hebei General Hospital, Shijiazhuang, China) before treatment were retrospectively analyzed, and advanced lung cancer inflammation index (ALI) was calculated using body mass index (BMI) × serum albumin (ALB) ÷ neutrophil/lymphocyte ratio (NLR). he optimal cutoff values of ALI and PLR for predicting prognosis is determined. Chi-square test was used to analyze the relationship between patients and clinical characteristics. Kaplan-Meier method was used to calculate the total survival of patients, and log-rank test was used for comparison. Independent prognostic factors were assessed by univariate and multivariate analyses. Spearman correlation was used to analyze the relationship among ALI, PLR, and Ki-67.

Results In our study of the 98 cases, the survival time of the patients with ALI < 18 was significantly lower than that of patients with ALI > 18 ($P < 0.001$), with a median survival time of 10 months and 25 months, respectively. The survival time of patients with a PLR < 185 was significantly higher than that of patients with a PLR > 185 (median survival time was 27 months vs. 10 months, $P < 0.001$).The higher the Ki-67 expression, the shorter the survival time ($P < 0.005$).The combined ALI and PLR detection results indicated that the survival time of patients with high ALI and low PLR was significantly longer than that of patients with low ALI and high PLR ($P < 0.001$). Univariate analysis showed that smoking history, degree of differentiation, KPS score, Ki-67 expression, ALI value, and PLR affected the prognosis of patients. Multivariate analysis showed that KPS score, ALI value, and Ki-67 expression were independent prognostic factors.

Conclusion ALI, PLR, and Ki-67 expression are important predictors of stage III-IV inoperable NSCLC. In terms of the prognostic value, ALI seems to have the best ability to predict patient survival. In addition, the combined detection of ALI and PLR levels before treatment seems to be more helpful in improving our prediction of patient prognosis. Moreover, it is expected to play a role in future clinical applications.

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Key words: non-small cell lung cancer (NSCLC); advanced lung cancer inflammation index (ALI); expression of Ki-67; prognosis

Lung cancer is still the leading cause of cancer-related deaths in the world today, with more than 600 000 mortalities every year [1]. Lung cancer is divided according to different biological and morphological characteristics into small cell lung cancer and non-small cell lung cancer (NSCLC), with NSCLC accounting for more than 80% of all cancers. To our knowledge, more than half of all patients with NSCLC are diagnosed at an advanced stage and have a low 5-year survival rate. Therefore, early detection, timely diagnosis, and formulation of targeted

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treatment programs are of great importance for early control of the disease, arrest of its development, and improvement of patients' quality of life.

Inflammation is an important occurrence in the tumor microenvironment and is involved in the formation and development of tumors. Studies have found that the prognosis of cancer patients depends not only on the characteristics of the tumor itself but also on the inflammatory response of the patients [2]. An increasing number of reports have confirmed that tumor-related inflammation, especially host-related systemic inflammatory response, is closely related to disease development and progression and survival of cancer patients [3]. Some studies have assessed the degree of systemic inflammation by analyzing acute protein markers such as albumin (ALB) [4]. In the process of inflammation regulation, neutrophils, lymphocytes, and platelets are important mediators of tumor inflammation; they have been demonstrated to have potential prognostic predictors of inflammation [5–7]. In addition, a new inflammatory predictor called the advanced lung cancer inflammation index (ALI) that uses body mass index (BMI), ALB, and neutrophil/lymphocyte ratio (NLR) to arrive at a value. ALI has been proven to be a valuable prognostic factor for patients with lung cancer [8]. Platelet aggregation not only plays an important role in hemostasis and thrombosis but also in the immune response, and thus it has arole in the progression of tumors [9]. Ki-67 is an indicator of the ability of all cells to proliferate. It is also useful in determining the degree of malignancy as well as in assessing the prognosis of patients and in guiding the adjuvant therapy of tumors. According to previous studies, high Ki-67 is closely related to low overall survival (OS) rate in NSCLC patients [10–11]. Therefore, Ki-67 expression is a valuable biomarker for predicting the prognosis of lung cancer patients. The traditional method to detect Ki-67 expression is immunohistochemistry, which requires invasive methods such as biopsy or surgery to obtain specimens. Since we selected patients with unresectable stage III–IV NSCLC, our pathological results were all obtained from biopsy specimens. Because of this, biopsy may miss more aggressive lesions in the tumor, leading to an underestimation of the disease. However, this pathological result still has important reference value.

To the best of our knowledge, no studies have assessed all three indicators of ALI, platelet/lymphocyte ratio (PLR), and Ki-67 expression in NSCLC. Therefore, we retrospectively analyzed the prognostic value of ALI, PLR, and Ki-67 expressions in patients with stage III–IV NSCLC, and we also compared the relationship between ALI, PLR, and the clinical characteristics of tumor patients and Ki-67 expression.

Patients and methods

A retrospective descriptive study was conducted, from 2014 to 2018 at Hebei General Hospital (Shijiazhang, China), on 98 patients with stage III–IV inoperable NSCLC diagnosed by biopsy. The basic information of patients (age, sex, height, weight, smoking history, etc.), clinicopathological features, immunohistochemical results, time of death, and final follow-up were all collected and summarized. NLR, lymphocyte to monocyte ratio (LMR), PLR, and ALI (ALI = BMI × ALB/NLR) were also recorded. According to published articles [12], the critical values of ALI and PLR were set at 18 and 185.

The inclusion criteria of the patients were as follows: (1) patients with a pathological diagnosis of inoperable, stage III–IV NSCLC; (2) no signs of infection or history of infectious diseases or diseases affecting inflammatory indicators, such as leukemia. The exclusion criteria were as follows: (1) presence of other malignant tumors; (2) patients with severe diseases in organs such as heart, brain, liver, and kidney, or presence of mental diseases; (3) patients with other pathological types of NSCLC such as squamous cell carcinoma and adenocarcinoma were excluded; (4) signs of infection at the initial diagnosis, history of diseases of the blood system affecting the inflammatory indicators, or recent intake of drugs affecting the inflammatory indicators; and (5) missing clinical data.

The use of clinical data (from the medical records as well as the paraffin-embedded sections) was approved by the hospital ethical committee, and consent was received from the patients' families for use of this data. The main reagent, rabbit anti-human Ki-67 monoclonal antibody, was purchased from Bioworld, USA. In using the mouse anti-human SP detection reagent, sections were routinely dewaxed to water, followed by antigen repair, incubation at room temperature, placement in 3% H_2O_2 for 15 min, and then mixing with the primary antibody in a dropwise manner and incubation at 4 °C overnight, based on the instructions on the kit. Phosphate buffer saline (PBS) was using for washing, and then horseradish peroxidase-labeled secondary antibody was added; the samples were incubated at room temperature for 30 min. This was followed by another round of PBS washing, and then DAB was added for color development. The samples were washed again and hematocrit redyeing was done. Subsequently, samples were dehydrated, made transparent, and sealed with a neutral resin adhesive. The final samples were observed under the microscope.

For the positive control, Ki-67 was used to select human breast cancer-positive tablets, while for the negative control, PBS was used in place of the primary antibody. After staining, all sections were assessed by pathologists and researchers in a double-blind manner.

Ki-67 positivity was demonstrated as brown-yellow granules in the nucleus, and a value < 5% was (–), 5%–25% was (+), 25%–50% was (++), > 50% was (+++). The (–) and (+) are defined as low expression, and (++) and (+++) as high expression.

Quality of life assessment: the Karnofsky performance status (KPS, in percentile) functional status score was used, which has a total score of 100 points. The higher the score, the better the physical condition. We divided the patients into two groups based on KPS as: KPS ≥ 90 and < 90.

Statistical analysis

The enumeration data were expressed as mean ± standard deviation. The relationship among ALI, PLR, and Ki-67 expression was evaluated by chi-square test. Kaplan-Meier analysis was used to estimate OS expression based on ALI, PLR, and Ki-67 expression in patients with stage III–IV NSCLC. Single-factor and Cox multivariate analysis were performed on the clinical data, and Spearman correlation analysis was performed on the three indicators.

Follow-up

The main endpoint assessed in this study was OS, that is, the time from diagnosis to death or the last follow-up. The patients were followed up by telephone and by their visits to the outpatient services. The patients were followed up every 3 months within 2 years after diagnosis, and every 6 months thereafter. The follow-up period started on August 2018.

Results

Patient characteristics

The clinical characteristics of the 98 patients are shown in Table 1. Among them, 63 were male and 35 were female, and they were aged 33–86 years [mean: (63.15 ± 10.19) years]. There were 52 cases with poorly differentiated tumors and 46 cases with highly differentiated tumors. There were 58 cases aged < 65 years, and 40 cases aged 65 years and older. Regarding risk factors, 60 cases had either adenocarcinoma or squamous cell carcinomas, 50 cases had a history of smoking, and 48 cases had no history of smoking. Regarding laboratory values, 47 cases had KPS ≥ 90, while 51 cases had KPS < 90; 25 cases had ALI < 18, while ALI > 18 in 73 patients; and finally PLR < 185 in 75 patients, while PLR > 185 in 23 patients. There was low expression of Ki-67 in 30 cases and high expression of Ki-67 in 68 cases. The median follow-up time was 16.6 months (1–64 months). At the end of the follow-up period, 48 patients died and 50 survived.

Table 1 Patient characteristics

	n (%)
Gender	
Male	63 (64.3)
Female	35 (35.7)
Age (years)	
< 65	58 (59.2)
≥ 65	40 (40.8)
Smoking history	
No	48 (49.0)
Yes	50 (51.0)
Differentiation	
Poorly differentiated	52 (53.1)
Medium and high differentiation	46 (46.9)
Pathological pattern	
Adenocarcinoma	60 (61.2)
Squamous cell carcinomas	38 (38.8)
KPS	
≥ 90	47 (48.0)
< 90	51 (52.0)
ALI	
High	73 (74.5)
Low	25 (25.5)
PLR	
High	23 (23.5)
Low	75 (76.5)
Ki-67 expression	
High	68 (69.4)
Low	30 (30.6)

Relationships among the ALI, PLR, expression cof Ki-67, and clinicopathological factors

Table 2 shows the relationship between ALI and clinicopathological factors. ALI had no significant relationship with any of the clinicopathological factors, except for differentiation ($P = 0.008$), gender ($P = 0.049$), and KPS score ($P = 0.005$). PLR had no significant relationship with any of the clinicopathological factors, except for differentiation ($P = 0.006$) and KPS score ($P = 0.016$). As seen in Table 3, Ki-67 expression was increased in men ($P = 0.001$), patients with a history of smoking ($P = 0.020$), patients with poorly differentiated tumors ($P = 0.007$), and patients with pathological squamous cell carcinomas ($P = 0.037$; Tables 2 and 3).

Survival analyses according to the ALI

The OS rate in the low ALI groups was significantly lower than that in the high-ALI group ($P < 0.0001$; Fig. 1). The OS rates for the high PLR group and the high Ki-67 expression group were significantly lower than that for the high ALI group ($P < 0.0001$, $P < 0.005$; Fig. 2 and 3).

Survival analyses according to the PLR

The OS rate of patients with a low PLR was significantly better than that of those with a high PLR (Fig. 2).

Table 2 Association among ALI, PLR, and clinical characteristics [*n* (%)]

	ALI		*P*	PLR		*P*
	High	Low		High	Low	
Gender			0.049			0.374
Male	51 (81.0)	12 (19.0)		13 (20.6)	50 (79.4)	
Female	22 (62.9)	13 (37.1)		10 (28.6)	25 (71.4)	
Age (years)			0.397			0.205
< 65	45 (77.6)	13 (22.4)		11 (19.0)	47 (81.0)	
≥ 65	28 (70.0)	12 (30.0)		12 (30.0)	28 (70.0)	
Smoking history			0.082			0.408
No	32 (66.7)	16 (33.3)		13 (27.1)	35 (72.9)	
Yes	41 (82.0)	9 (18.0)		10 (20.0)	40 (80.0)	
Differentiation			0.008			0.006
Poorly	33 (63.5)	19 (36.5)		18 (34.6)	34 (65.4)	
Medium and high	40 (87.0)	6 (13.0)		5 (10.9)	41 (89.1)	
Pathological			0.884			0.309
Adenocarcinoma	45 (25.0)	15 (75.0)		12 (20.0)	48 (80.0)	
Squamous cell carcinomas	28 (73.7)	10 (26.3)		11 (28.9)	27 (71.1)	
KPS			0.005			0.016
≥ 90	41 (87.2)	6 (12.8)		6 (12.8)	41 (87.2)	
< 90	32 (62.7)	19 (37.3)		17 (33.3)	34 (66.7)	
Ki-67 expression			0.743			0.205
High	50 (73.5)	18 (26.5)		20 (29.4)	48 (70.6)	
Low	23 (76.7)	7 (23.3)		3 (10.0)	27 (90.0)	

Survival analyses according to the expression of Ki-67

The OS rate of the high Ki-67 expression group was significantly lower than that of the low Ki-67 expression group ($P < 0.005$; Fig. 3).

Survival analyses according to combined assessment

We found a significant negative correlation between ALI and PLR; so we divided the patients into three groups: Group 1 had high ALI and low PLR, Group 2 had low ALI and high PLR, and Group 3 had either high ALI and high PLR or low ALI and low PLR. Among the 84 patients, there were 65, 17, and 16 patients classified into Groups 1, 2, and 3, respectively. The results showed that the total survival time of patients in the three groups was significantly different ($P < 0.001$). The median survival time (30 months vs. 10 months vs. 20 months) is shown in Fig. 4.

Prognostic factors influencing the OS

The correlations between OS and various clinicopathological factors are shown in Table 3. Univariate analysis showed that OS was significantly associated with age ($P < 0.001$), smoking history ($P = 0.009$), differentiation ($P < 0.001$), KPS score ($P < 0.001$), ALI ($P < 0.001$), PLR ($P < 0.001$), and Ki-67 expression ($P = 0.001$). A multivariate analysis of these significant variables indicated that the KPS score ($P = 0.040$), Ki-67 expression ($P = 0.008$), and ALI ($P = 0.048$) were independently associated with OS (Table 4).

Table 3 Relationship between Ki-67 and clinical characteristics [*n* (%)]

	Ki-67		*P*
	Low	High	
Gender			0.001
Male	12 (19.0)	51 (81.0)	
Female	18 (51.4)	17 (48.6)	
Age (years)			0.913
< 65	18 (31.0)	40 (69.0)	
≥ 65	12 (30.0)	28 (70.0)	
Smoking history			0.020
No	20 (41.7)	28 (58.3)	
Yes	10 (20.0)	40 (80.0)	
Differentiation			0.007
Poorly	9 (17.3)	43 (82.7)	
Medium and high	21 (45.7)	25 (54.3)	
Pathological			0.037
Adenocarcinoma	7 (18.4)	31 (81.6)	
Squamous cell carcinomas	23 (38.3)	37 (61.7)	
KPS			0.252
≥ 90	17 (36.2)	30 (63.8)	
< 90	13 (25.5)	38 (74.5)	

Correlation between expression of Ki-67, ALI, and PLR in NSCLC

Spearman correlation analysis results showed that ALI

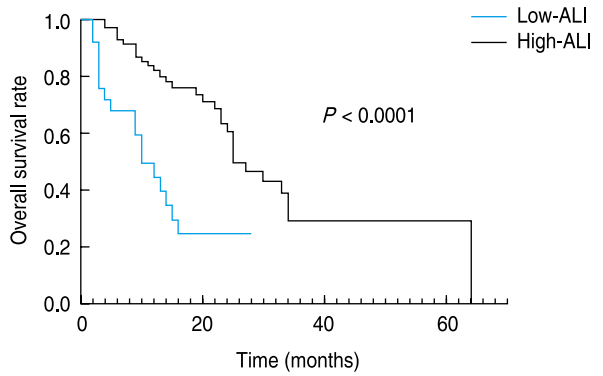

Fig. 1 Kaplan-Meier survival curves for the overall survival (OS) according to the advanced lung cancer inflammation index (ALI). A low ALI has a detrimental effect on the OS ($P < 0.0001$)

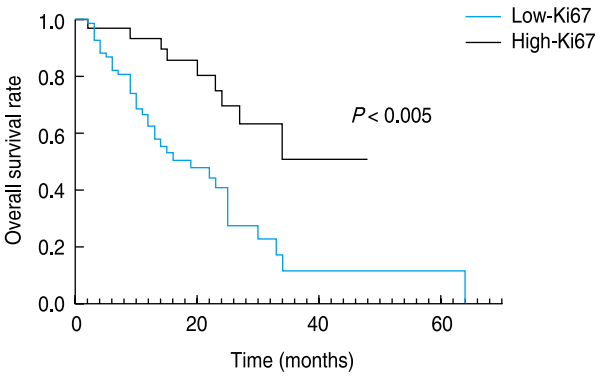

Fig. 3 Kaplan-Meier survival curves for the overall survival (OS) according to the expression of Ki-67. Low expression of Ki-67 has a detrimental effect on OS ($P < 0.005$).

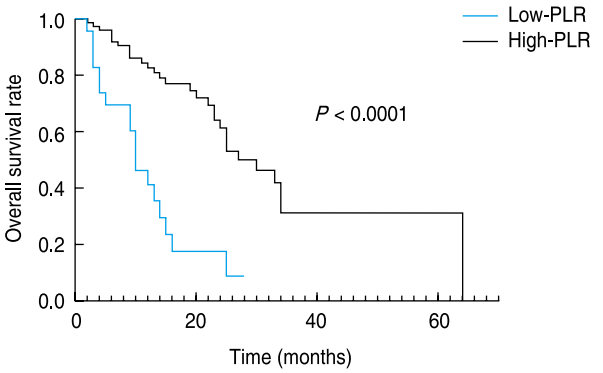

Fig. 2 Kaplan-Meier survival curves for the overall survival (OS) according to the platelet-lymphocyte ratio (PLR). The OS rate of patients with a low PLR was significantly better than that of those with a high PLR ($P < 0.0001$)

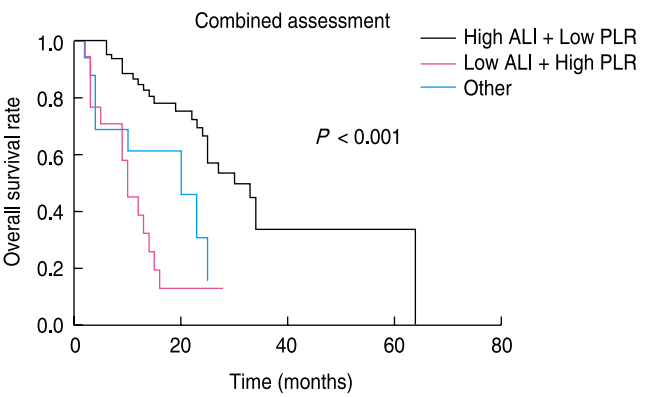

Fig. 4 Kaplan-Meier survival curves for the overall survival (OS) according to the combined assessment. A low ALI and high PLR have a significant lydetrimental effect on the OS ($P < 0.001$).

value was negatively correlated with PLR ($r_s = -0.615$, $P < 0.05$), and PLR was positively correlated with Ki-67 expression ($r_s = 0.211$, $P < 0.05$). There was no significant correlation between ALI and Ki-67 expression (Table 5).

Discussion

In recent years, the association between systemic inflammation and cancer has been extensively studied. Epidemiological observations have shown that inflammatory markers are evident in the tumor

Table 4 The correlations between the overall survival (OS) and various clinicopathological factors by univariate and multivariate analysis

	Univariate analysis		*P*	Multivariate analysis		*P*
	Hazard ratio	95% CI		Hazard ratio	95% CI	
Gender	1.388	0.761–2.530	0.285	–	–	–
Age	1.441	0.810–2.566	0.214	–	–	–
Smoking history	2.190	1.199–4.000	0.011	1.601	0.860–2.979	0.138
Differentiation	0.325	0.169–0.627	0.001	0.574	0.279–1.181	0.131
Pathological pattern	1.416	0.798–2.542	0.243	–	–	–
KPS	3.109	1.662–5.815	0.000	2.074	1.033–4.161	0.040
Ki-67 expression	3.387	1.622–7.072	0.001	3.023	1.342–6.813	0.008
ALI	0.291	0.155–0.546	0.000	0.380	0.145–0.991	0.048
PLR	4.142	2.240–7.660	0.000	1.253	0.487–3.224	0.640

Table 5 Correlation between expression of Ki-67, ALI, and PLR in NSCLC

		Ki-67	ALI	PLR
Ki-67	r_s	–	–0.033	0.211
	P	–	0.746	0.037
ALI	r_s	–0.033	–	–0.615
	P	0.746	–	0.000
PLR	r_s	0.211	–0.615	–
	P	0.037	0.000	–

microenvironment, and tumors often form at sites of chronic inflammation [13]. Recent studies have also shown a clear relationship between markers of systemic inflammatory response and poor prognosis in patients with tumors [14–16]. More specifically, our study also confirmed an independent prognostic factor – ALI – in NSCLC, but its mechanism is still unclear.

ALI is a systemic inflammatory indicator based on BMI, ALB, and NLR. In this study, the median survival time of patients in the low ALI group (10 months, 2–28 months) was significantly lower than that in the high ALI group (25 months, 1–64 months). We can hypothesize that low ALI as low BMI, low ALB, and high NLR.

BMI is a common nutritional indicator. BMI levels can vary depending on health and disease status or in obese and non-obese people and can even aid indistinguishing health status and malnutrition. Therefore, BMI is important for assessing cancer progression. Gu *et al* [17] confirmed that the survival rate of patients with high BMI before treatment or no reduction in BMI during treatment could be prolonged. ALB accounts for about half of the serum protein and is involved in scavenging free radicals, maintaining colloid osmotic pressure, and protecting nerve cells, and it is also closely related to nutritional status and systemic inflammatory response. In recent years, it has been reported that hypoalbuminemia is mainly found in tumor patients and is considered as a prognostic marker of human cancers, such as endometrial cancer, gastrointestinal tumors, and even lung cancer [18–20].

The NLR is an early indicator of systemic inflammation and has been reported to have a significant impact on the prognosis of tumors [21–22]. High NLR represents an increase in neutrophil count and/or a decrease in lymphocyte count as well as a relative decrease in lymphocytes. Lymphocytes play a crucial role in tumor defense by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration [23].

ALI is an easy assessment to evaluate systemic inflammation in patients [24]. It has been reported to be a better predictor of cancer survival than any single indicator; ALI can be seen as a simple, inexpensive, and useful biomarker in clinical practice. In a study by Mandaliya *et al* [25], ALI was regarded as a meaningful biomarker in elderly patients with stage IV NSCLC. The current study sought to find evidence of ALI as a meaningful clinical indicator. In this study, ALI was also closely related to the degree of differentiation in patients with NSCLC. That is, with poor differentiation, ALI is higher, which is similar to the results of Feng *et al* [26]. In theory, ALI could indicate both nutritional status and inflammatory response, providing guidance on how patients should be treated. In our study, ALI showed great potential as a prognostic indicator. Given the low cost of these markers and the availability of results of the same in pre-treatment evaluation, they can be easily used for routine clinical identification of high-risk patients. ALI is a reliable, objective, and inexpensive evaluation indicator for patients with NSCLC and can be considered for routine clinical use.

PLR has also received extensive attention as an inflammatory indicator, and activation of the coagulation system is often associated with tumor metastasis, invasion, and poor prognosis. Thrombus formation is a problem that tumor patients often face. There is evidence that [27] high platelet count is associated with a low survival rate in patients with lung cancer. It has been reported [28] that in addition to their role in hemostasis, platelets are increasingly recognized as regulators of inflammation. This influences the inflammatory response of cancer by affecting the activation state of endothelial cells and recruiting white blood cells to the sites of primary and metastatic tumors and to distant organs not affected by tumor growth as yet. In addition, platelets are involved in the formation of neutrophil extracellular traps, which can promote metastasis and thrombosis, and lead to organ failure. Tumor growth depends on blood vessels, and platelets contain platelet-derived cytokines that play a role in tumor angiogenesis, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Similarly, lymphocytopenia has been shown to predict poor prognosis in patients with advanced cancer [29]. This may be due to its role in mediating tumor cell destruction and inhibiting tumor growth. T cells in the tumor microenvironment may secrete cytokines such as IL-4 and IL-5 to regulate the proliferation, apoptosis, angiogenesis, and metastasis of cancer cells [30]. A cohort study with a large sample size by Ding *et al* [31] showed that PLR can be used as a representative indicator of systemic inflammation. They also showed that a PLR threshold of 150–200 is more significant than a PLR threshold of > 200. The critical value used in the current study was 185; thus, we can consider our results as being more reliable. Similarly, in our statistical analysis, we concluded that low PLR was associated with improved survival (median survival was 27 months vs. 10 months) and is an independent prognostic factor for NSCLC. This

study shows that patients with high levels of PLR have poorly differentiated tumors, which is similar to the findings of Messager *et al* [32]. In addition, recent studies have reported that low molecular weight heparin, aspirin, and other drugs have anti-tumor effects [33–35]. Therefore, in addition to considering PLR as a prognostic predictor for patients with inoperable stage III–IV NSCLC, we can also expect anticoagulation as a new antitumor therapy in the future.

Ki-67 is a widely used proliferation-related indicator related to the development, metastasis, and prognosis of a variety of tumors [36]. Except for the G0 phase of the cell cycle, Ki-67 can be detected in every mitotic phase, especially in the M phase, which can directly and sensitively reflect the proliferation activity of tumor cells and more comprehensively reflect the number of proliferating cells [37]. It has been reported that the higher the Ki-67 proliferation index, the lower the degree of tumor differentiation; this is useful since the tumor proliferation capacity often represents the malignancy of the tumor [38]. This study confirmed that in NSCLC tissues, the factors included gender, smoking status and pathological type, and there were significant differences in Ki-67 expression, and the differences were statistically significant ($P < 0.05$). Survival analysis showed that the survival time of patients with high Ki-67 expression was significantly lower than that of patients with low Ki-67 expression ($P < 0.01$). Univariate and Cox multivariate results showed that Ki-67 expression level was an independent prognostic factor in patients with stage III–IV inoperable NSCLC, and the difference was statistically significant ($P < 0.05$). The results were similar to those of Ji *et al* [39].

Pearson's correlation analysis was conducted to identify whether there was a connection between ALI, PLR, and Ki-67. Results showed that ALI was negatively correlated with PLR ($r_s = –0.615$, $P < 0.001$), while ALI and Ki-67 had no correlation ($P > 0.05$). However, Ki-67 had a weak positive correlation with PLR ($r_s = 0.211$, $P < 0.05$). Very little research has been done on the relationship between the three afore mentioned factors. Platelets involved in the formation of neutrophiltraps can be used to regulate inflammatory factors, while Ki-67 is a cell proliferation factor, and inflammation is involved in the process of cell proliferation. Given this link, perhaps ALI is associated with PLR and Ki-67. However, the mechanism behind this association is still unknown and requires further research and exploration. However, in terms of detection methods, compared with Ki-67, inflammatory markers in the peripheral blood are more easily assessed than immunohistochemical indicators.

In the study by Zhuang *et al* [40], the important role of clinicians in determining which patients will receive follow-up treatment and which will receive palliative care is emphasized. In fact, the clinician is the one who assesses the quality of life and decides on the antitumor medication regimen. Therefore, they need an appropriate prognostic indicator that will help them predict patient response and the value of antitumor therapy [41].

Our study had several limitations. First, the number of patients included was small, although the study population was histologically uniform. Second, the optimal cutoff values of ALI and PLR have not yet been determined. We determined the optimal cutoff value by reading a large number of studies; however, there are bound to be deviations in prior studies that could have affected this. Furthermore, our conclusions are limited by the retrospective nature of the study. This indicators discussed herein may be influenced by other factors, such as infection or cancer-related complications, and prospective studies with a large sample size are needed to confirm our study.

To the best of our knowledge, this is the first study to compare inflammatory markers and immunohistochemic al indicators. We conclude that ALL, PLR, and Ki-67 are some of the most important prognostic factors in stage III–IV inoperable NSCLC patients. In particular, we observed that ALI is not only an independent prognostic indicator, but, compared with PLR, seems to provide a more precise, comprehensive evaluation index in terms of its ability to predict survival in patients with NSCLC. In addition, ALI is easier to obtain than the Ki-67 values and can be easily applied in clinical practice. Statistically, ALI and PLR have a significant negative correlation. By combining ALI and PLR before treatment, we found that patients with low ALI and high PLR had a worse prognosis. In the future, we may combine these two indicators to improve the accuracy of prognosis prediction. Further prospective studies will help to confirm our findings.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin, 2020, 70: 7–30.
2. Korniluk A, Koper O, Kemona H, *et al*. From inflammation to cancer. Ir J Med Sci, 2017, 186: 57–62.
3. Rogovskii VS. The linkage between inflammation and immune tolerance: interfering with inflammation in cancer. Curr Cancer Drug Targets, 2017, 17: 325–332.
4. Hong TT, Shen D, Chen XP, *et al*. Preoperative plasma fibrinogen, but not D-dimer might represent a prognostic factor in non-metastatic colorectal cancer: A prospective cohort study. Cancer Biomarker, 2017, 19: 103–111.
5. Schwartz PB, Poultsides G, Roggin K, *et al*. PLR and NLR are poor predictors of survival outcomes in sarcomas: a new perspective from the USSC. J Surg Res, 2020, 251: 228–238.

6. Quan XY. The combined prognostic value of pretreatment neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and platelet-to-lymphocyte ratio in stage IE/IIE extranodal natural killer/T-cell lymphoma. Oncol Transl Med, 2019, 5: 137–146.
7. Yu QQ, Qiu H, Zhang MS, *et al*. Prognostic value of neutrophil-to-lymphocyte ratio in metastatic colorectal cancer. Oncol Transl Med, 2016, 2: 75–79.
8. Jafri SH, Shi RH, Mills G. Advance lung cancer inflammation index (ALI) at diagnosis is a prognostic marker in patients with metastatic non-small cell lung cancer (NSCLC): a retrospective review. BMC Cancer, 2013, 13: 158.
9. Herzog BH, Fu JX, Wilson SJ, *et al*. Podoplanin maintains high endothelial venule integrity by interacting with platelet CLEC-2. Nature, 2013, 502: 105–109.
10. Ahn HK, Jung M, Ha SY, *et al*. Clinical significance of Ki-67 and p53 expression in curatively resected non-small cell lung cancer. Tumour Biol, 2014, 35: 5735–5740.
11. Wen S, Zhou W, Li CM, *et al*. Ki-67 as a prognostic marker in early-stage non-small cell lung cancer in Asian patients: a meta-analysis of published studies involving 32 studies. BMC Cancer, 2015, 15: 520.
12. Komurcuoglu B, Evkan A, Karakurt G. Are pretreatment neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and advanced lung cancer inflamation index (ALI) levels useful in predicting the outcomes of patients with advanced non-small cell lung cancer? J Thorac Oncol, 2018, 13: 113–114.
13. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet, 2001, 357: 539–545.
14. Ozyurek BA, Ozdemirel TS, Ozden SB, *et al*. Does advanced lung inflammation index (ALI) have prognostic significance in metastatic non-small cell lung cancer? Clin Respir J, 2018, 12: 2013–2019.
15. He XB, Zhou T, Yang YP, *et al*. Advanced lung cancer inflammation index, a new prognostic score, predicts outcome in patients with small-cell lung cancer. Clin Lung Cancer, 2015, 16: e165–e171.
16. Jank BJ, Kadletz L, Schnöll J, *et al*. Prognostic value of advanced lung cancer inflammation index in head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol, 2019, 276: 1487–1492.
17. Gu WS, Fang WZ, Liu CY, *et al*. Prognostic significance of combined pretreatment body mass index (BMI) and BMI loss in patients with esophageal cancer. Cancer Manag Res, 2019, 11: 3029–3041.
18. Lei J, Wang Y, Guo XQ, *et al*. Low preoperative serum ALB level is independently associated with poor overall survival in endometrial cancer patients. Future Oncol, 2020, 16: 307–316.
19. Shibutani M, Maeda K, Nagahara H, *et al*. Prognostic significance of the preoperative ratio of C-reactive protein to albumin in patients with colorectal cancer. Anticancer Res, 2016, 36: 995–1001.
20. Ni XF, Wu J, Ji M, *et al*. Effect of C-reactive protein/albumin ratio on prognosis in advanced non–small-cell lung cancer. Asia Pac J Clin Oncol, 2018, 14: 402–409.
21. Ozyurek BA, Ozdemirel TS, Ozden SB, *et al*. Prognostic value of the neutrophil to lymphocyte ratio (NLR) in lung cancer cases. Asia Pac J Cancer Prev, 2017, 18: 1417–1421.
22. Brkic FF, Kadletz L, Jank B, *et al*. Impact of pretherapeutic neutrophil-to-lymphocyte ratio, serum albumin, body-mass index, and advanced lung cancer inflammation index on clinical outcome in sinonasal squamous cell carcinoma. J Craniomaxillofac Surg, 2020, 48: 33–37.
23. Tan TT, Coussens LM. Humoral immunity, inflammation and cancer. Curr Opin Immunol, 2007, 19: 209–216.
24. Starnes SL, Pathrose P, Wang J, *et al*. Clinical and molecular predictors of recurrence in stage I non-small cell lung cancer. Ann Thorac Surg, 2012, 93: 1606–1612.
25. Mandaliya H, Jones M, Oldmeadow C, *et al*. Prognostic biomarkers in stage IV non-small cell lung cancer (NSCLC): neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR) and advanced lung cancer inflammation index (ALI). Transl Lung Cancer Res, 2019, 8: 886–894.
26. Feng JF, Huang Y, Chen QX. A new inflammation index is useful for patients with esophageal squamous cell carcinoma. Onco Targets Ther, 2014, 7: 1811–1815.
27. Wen JH, Yang YN, Ye F, *et al*. The preoperative plasma fibrinogen level is an independent prognostic factor for overall survival of breast cancer patients who underwent surgical treatment. Breast, 2015, 24: 745–750.
28. Olsson AK, Cedervall J. The pro-inflammatory role of platelets in cancer. Platelets, 2018, 29: 569–573.
29. Lissoni P, Brivio F, Fumagalli L, *et al*. Efficacy of cancer chemotherapy in relation to the pretreatment number of lymphocytes in patients with metastatic solid tumors. Int J Biol Markers, 2004, 19: 135–140.
30. Hiraoka K, Miyamoto M, Cho Y, *et al*. Concurrent infiltration by CD8+ T cells and CD4+ T cells is a favourable prognostic factor in non-small-cell lung carcinoma. Br J Cancer, 2006, 94: 275–280.
31. Ding N, Pang ZF, Shen HC, *et al*. The prognostic value of PLR in lung cancer, a meta-analysis based on results from a large consecutive cohort. Sci Rep, 2016, 6: 34823.
32. Messager M, Neofytou K, Chaudry MA, *et al*. Prognostic impact of preoperative platelets to lymphocytes ratio (PLR) on survival for oesophageal and junctional carcinoma treated with neoadjuvant chemotherapy: A retrospective monocentric study on 153 patients. Eur J Surg Oncol, 2015, 41: 1316–1323.
33. Sheng LM, Luo M, Sun XJ, *et al*. Serum fibrinogen is an independent prognostic factor in operable nonsmall cell lung cancer. Int J Cancer, 2013, 133: 2720–2725.
34. Santilli F, Boccatonda A, Davì G. Aspirin, platelets, and cancer: The point of view of the internist. Eur J Intern Med, 2016, 34: 11–20.
35. Elaskalani O, Berndt MC, Falasca M, *et al*. Targeting platelets for the treatment of cancer. Cancers (Basel), 2017, 9: 94.
36. Sun GY, Wang SY, Wang Y. Expressions of Topo IIα and Ki-67 in breast cancer and its clinicopathologic features and prognosis. Pak J Med Sci, 2019, 35: 715–720.
37. Antonarakis ES, Keizman D, Zhang Z, *et al*. An immunohistochemical signature comprising PTEN, MYC, and Ki-67 predicts progression in prostate cancer patients receiving adjuvant docetaxel after prostatectomy. Cancer, 2012, 118: 6063–6071.
38. Zheng Y, Wang L, Zhang JP, *et al*. Expression of p53, c-erbB-2 and Ki-67 in intestinal metaplasia and gastric carcinoma. World J Gastroenterol, 2010, 16: 339–344.
39. Ji Y, Zheng MF, Ye SG, *et al*. PTEN and Ki-67 expression is associated with clinicopathologic features of non-small cell lung cancer. J Biomed Res, 2014, 28: 462–467.
40. Zhuang H, Ma Y, Wang L, *et al*. Effect of early palliative care on quality of life in patients with non-small-cell lung cancer. Curr Oncol, 2018, 25: e54–e58.
41. Zhou T, Zhao YY, Zhao S, *et al*. Comparison of the prognostic value of systemic inflammation response markers in small cell lung cancer patients. J Cancer, 2019, 10: 1685–1692.

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