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Original Research

The Pan-Immune-Inflammation Value predicts the survival of patients with anaplastic lymphoma kinase-positive non-small cell lung cancer treated with first-line ALK inhibitor

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ABSTRACT

Background: Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) have significantly improved the clinical outcomes of patients with ALK-positive non-small cell lung cancer (NSCLC). However, reliable biomarkers to predict the prognostic role of this treatment are lacking. The Pan-Immune-Inflammation Value (PIV) has recently been demonstrated as a novel comprehensive biomarker to predict survival of patients with solid tumors. Our study aimed to evaluate the prognostic power of PIV in this group of patients.

Patients and methods: 94 patients with advanced ALK-positive NSCLC who received first-line ALK inhibitors were enrolled in this study. PIV was calculated as the product of peripheral blood neutrophil, monocyte, and platelet counts divided by lymphocyte count. Kaplan-Meier method and Cox hazard regression models were used for survival analyses.

Results: The 1-year progression-free survival (PFS) was 63.5%, and the 5-year overall survival (OS) rate was 55.1%. Patients with higher PIV, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index (SII) had worse PFS in univariate analysis, but only the PIV (hazard ratio [HR] = 2.90, 95% confidence interval [CI]: 1.79–4.70, $p < 0.001$) was an independent prognostic factor in multivariate analysis. Similarly, patients with higher PIV, NLR, PLR, and SII had a worse OS in the univariate analysis, but only the PIV (HR = 4.70, 95% CI: 2.00–11.02, $p < 0.001$) was significantly associated with worse OS in multivariate analysis.

Conclusion: PIV is a comprehensive and convenient predictor of both PFS and OS in patients with ALK-positive advanced NSCLC who received first-line ALK TKIs. Prospective clinical trials are required to validate the value of this new parameter.

Introduction

Lung cancer is the leading cause of cancer-related mortality and the most commonly diagnosed cancer [1]. Approximately 3% to 5% of patients with non-small-cell lung cancer (NSCLC) have anaplastic lymphoma kinase (ALK) rearrangement [2,3].

The first approved ALK tyrosine kinase inhibitor (TKI), crizotinib, demonstrated improved efficacy compared to platinum-based chemotherapy in the PROFILE 1014 trial as indicated by a prolonged median progression-free survival (PFS) of 10.9 months and an objective response rate of 74% in patients with TKI-naive advanced ALK-positive NSCLC [4]. Recently, next-generation ALK inhibitors, including

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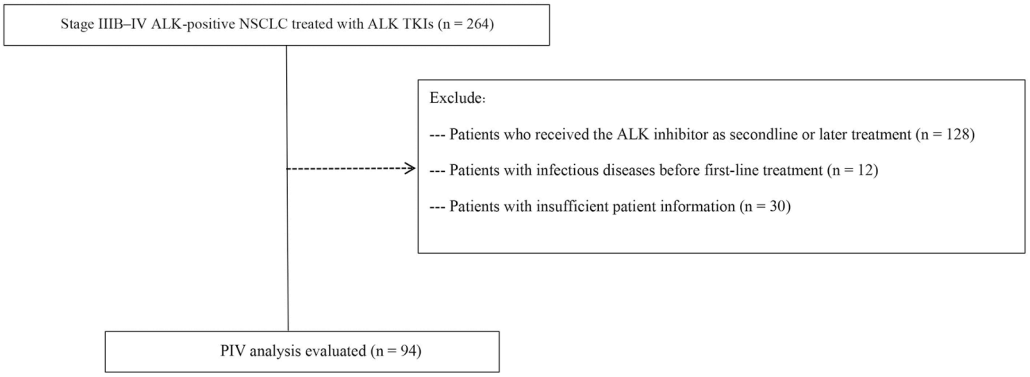

Fig. 1. Patient flowchart illustrating selection of the study population. Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, Non-small cell lung cancer; PIV, Pan-Immune -Inflammation Value.

Table 1
Baseline Patient Characteristics ($n = 94$).

Characteristic	No. (%)
Age, years	
Median (range)	48 (18–76)
<50	42 (44.7)
≥50	52 (55.3)
Gender	
Female	39 (38.3)
Male	55 (58.5)
Smoking status	
Never	61 (64.9)
Former/current	33 (35.1)
Pretreatment KPS	
>70	91 (96.8)
≤70	3 (3.2)
Histology	
Adenocarcinoma	91 (96.8)
Non-adenocarcinoma	3 (3.2)
Stage	
IIIB	1 (1.0)
IIIC	1 (1.0)
IV	92 (98.0)
Number of metastatic sites	
0	3 (3.2)
1	49 (52.1)
2	19 (20.2)
3	14 (14.9)
>3	9 (9.6)
Brain metastases	
No	63 (67.0)
Yes	31 (33.0)
Liver metastases	
No	75 (80.0)
Yes	19 (20.0)
First-line ALK TKI	
Crizotinib	84 (89.4)
Alectinib	10 (10.6)
Ceritinib	1 (1.0)
PIV	
Median (range)	364 (55.2–6840)
NLR	
Median (range)	3 (0.8–10.8)
PLR	
Median (range)	158 (22.8–652.5)
SII	
Median (range)	842 (158–4997)

Abbreviation: ALK, anaplastic lymphoma kinase; KPS, Karnofsky performance status; NLR, neutrophil-to-lymphocyte ratio; PIV, Pan-Immune-Inflammatory Value; PLR, platelet-to lymphocyte ratio; SII, systemic immuneinflammation index; TKI, tyrosine kinase inhibitor.

alectinib, ceritinib, ensartinib, brigatinib, and lorlatinib, have shown excellent clinical efficacy and have even better central nervous system penetration [5–9]. Although patients with ALK-positive NSCLC respond dramatically to ALK TKIs, a small number of these patients who receive ALK TKIs as first-line therapy undergo early disease progression and have poor survival outcomes [10]. Therefore, identifying new and easily accessible treatment-predicting biomarkers, such as peripheral blood parameters, to predict prognosis is of great importance.

It is well known that inflammation impacts every step of tumorigenesis from initiation and tumor promotion all the way to metastatic progression [11–13]. Recent studies have highlighted the important role of systemic inflammation markers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index (SII) that can predict the prognosis of a variety of malignancies [14,15]. Moreover, several studies have shown that these inflammation markers might have the ability to predict the prognosis of patients with lung cancer including their PFS and overall survival (OS), especially in patients with epidermal growth factor receptor (EGFR) mutations [16–19]. However, the prognostic value of these markers for patients with ALK-positive advanced NSCLC remains unclear.

More recently, a new comprehensive marker called the Pan-Immune-Inflammatory Value (PIV), which incorporates the counts of neutrophils, platelets, monocytes, and lymphocytes, showed a strong association with OS in patients with advanced colorectal cancer who received first-line biochemotherapy and patients with human epidermal growth factor receptor 2 (HER2+) positive advanced breast cancer who were treated with first-line trastuzumab-pertuzumab biochemotherapy [20,21]. Both studies both demonstrated that PIV outperform other well-established immune biomarkers, such as NLR and PLR, in predicting patient outcomes. Therefore, our study aimed to assess the predictive value of PIV and other inflammatory markers, including NLR, PLR, and SI, in patients with ALK-rearranged advanced NSCLC receiving ALK TKIs as first-line therapy.

Material and methods

Patients

This was a retrospective, monocentric study of patients with ALK-positive NSCLC patients who initially received ALK TKIs between January 2014 and January 2019 at the Sun Yat-Sen University Cancer Center (SYSUCC). This study was reviewed and approved by the Guangdong Association Study of Thoracic Oncology (No. A2017–002) and the institutional review board/ethics committee of the participating hospitals, and an exception to the requirement of informed consent was approved. The inclusion criteria were as follows: (1) histologically or cytologically confirmed unresectable, locally advanced or metastatic NSCLC; (2) ALK rearrangement was detected by fluorescence *in situ* hybridization (FISH) or Ventana immunohistochemistry (IHC); (3) patients who received oral ALK TKIs as first-line therapy; (4) available pretreatment absolute counts of peripheral blood neutrophils,

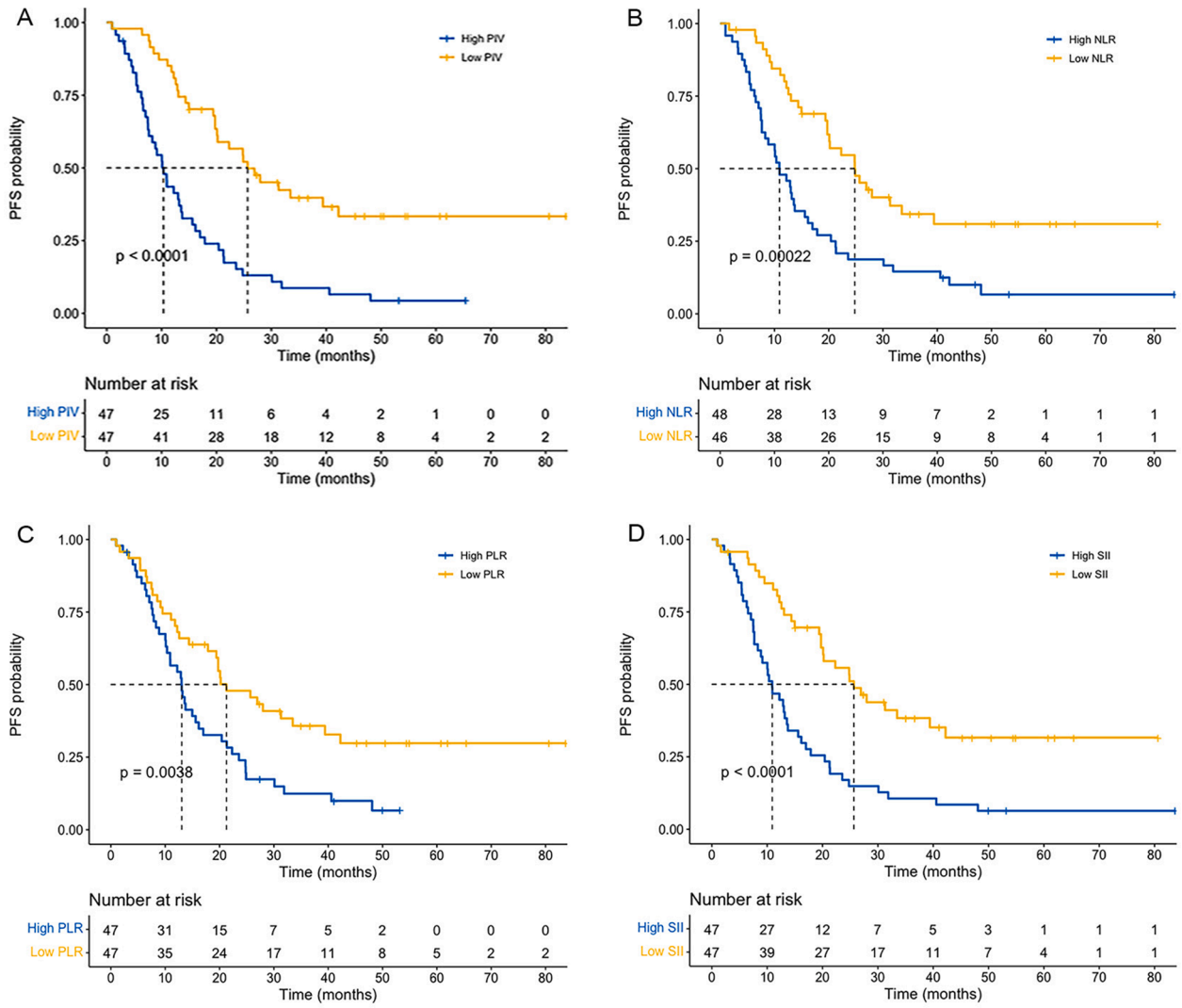

Fig. 2. Kaplan-Meier curves for progression-free survival (PFS) in patients with advanced ALK-positive NSCLC according to baseline (A) PIV, (B) NLR, (C) PLR, (D) SII. The median value of each parameter was used as a cut-off point to definite the parameter categories (high vs. low). Abbreviations: PIV: Pan-Immune -Inflammation Value; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index.

monocytes, platelets, and lymphocytes; and (5) available clinical data and follow-up information at SYSUCC. Patients with acute infectious diseases within 4 weeks of treatment, autoimmune diseases, or chronic inflammatory diseases were excluded from the study. Patient follow-up was April 30, 2021, thereby ensuring a minimum follow-up time of over 2 years for each patient.

Data collection

The absolute counts of peripheral blood neutrophils, platelets, monocytes, and lymphocytes were obtained within 3 weeks before starting TKI treatment. PIV was calculated as neutrophil count (10^9/L) x platelet count (10^9/L) x monocyte count (10^9/L)/lymphocyte count (10^9/L); NLR was calculated as neutrophil count (10^9/L)/lymphocyte count (10^9/L); PLR was calculated as platelet count (10^9/L)/lymphocyte count (10^9/L); SII was calculated as neutrophil count (10^9/L) x platelet count (10^9/L)/lymphocyte count (10^9/L). The median values of PIV, NLR, PLR, and SII were used to define the cut-off points to stratify patients into a high group or a low group.

Patients characteristics, including age, gender, smoking history, Karnofsky performance status (KPS) at diagnosis, histology, cancer stage, number of metastatic sites, brain metastases, and liver metastases were also collected.

Statistical analysis

PFS was calculated from the date of treatment initiation to the date of disease progression or patient death from any cause. OS was calculated from the date of treatment initiation to the date of death from any cause. Statistical differences in patient characteristics based on low PIV and high PIV were analyzed using chi-square tests or Fisher's exact test for categorical measures.

PFS and OS were estimated using the Kaplan-Meier method and were compared using the log-rank test. The relationships among these peripheral blood parameters were analyzed using Pearson correlation. Covariables with $p < 0.1$ in the univariate model were entered into a forward multivariable Cox proportional hazard model to identify independent predictors of survival. The Cox proportional hazards model was used to calculate the hazard ratio (HR) and corresponding 95% confidence interval (CI). Statistical significance was defined as a two-sided p-value < 0.05. Statistical analyses were performed using R (version 4.0.5) and R Studio (version 1.4.1106).

Table 2
Cox proportional hazards regression models for PFS.

Variable	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p-value	HR	95% CI	p - value
Age (years) < 50 vs. ≥ 50	1.14	0.72–1.80	0.588			
Gender Male vs. Female	1.47	0.92–2.35	0.110			
Smoking status Former/current vs. Never	1.24	0.76–2.01	0.389			
Pretreatment KPS ≤ 70 vs. > 70	3.86	1.19–12.50	0.024			
Histology Non-adenocarcinoma vs. Adenocarcinoma	1.42	0.44–4.54	0.556			
Stage IV vs. III	1.23	0.39–3.92	0.725			
Number of metastatic sites ≥ 2 vs. < 2	3.22	1.90–5.48	< 0.001			
Brain metastases Yes vs. No	1.53	0.93–2.52	0.093	1.68	1.01–2.78	0.045
Liver metastases Yes vs. No	3.82	2.17–6.70	< 0.001	3.60	2.01–6.44	< 0.001
PIV High vs. Low	3.07	1.90–4.94	< 0.001	2.90	1.79–4.70	< 0.001
NLR High vs. Low	2.38	1.48–3.81	< 0.001			
PLR High vs. Low	1.98	1.24–3.17	0.004			
SII High vs. Low	2.38	1.48–3.81	< 0.001			

Abbreviation: ALK, anaplastic lymphoma kinase; KPS, Karnofsky performance status; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PIV, Pan-Immune-Inflammatory Value; PLR, platelet-to lymphocyte ratio; SII, systemic immuneinflammation index; TKI, tyrosine kinase inhibitor.

Results

Patients characteristics according to PIV

A flow diagram of the study is presented in Fig. 1. Out of 264 extracted patients, a total of 94 were enrolled in our study. The characteristics of evaluated patients are described in Table 1. The majority (89.4%, $n = 84$) of patients received first-line treatment with crizotinib, followed by 10.6% ($n = 9$) of patients who were treated with alectinib and 1.0% ($n = 1$) of patient received ceritinib. The median baseline PIV was 364 (ranging from 55.2 to 6840.4), the median baseline NLR was 3 (ranging from 0.8 to 10.8), the median baseline PLR was 158 (ranging from 22.8 to 652.5), and the median baseline SII was 842 (ranging from 158.0 to 4997.0). Compared to patients with low PIV, a higher proportion of patients with high PIV had more than one site of metastasis ($p = 0.038$), while no significant differences were observed between patients with low or high PIV in terms of age, sex, smoking status, KPS, histology, cancer stage, brain metastases, liver metastases, and first-line ALK TKI regimens (*Supplementary Table S1*). In addition, a moderate, positive correlation was found between NLR and PIV ($R = 0.68$), and between PLR and PIV ($R = 0.51$), while PIV and SII ($R = 0.84$) were strongly correlated (*Supplementary Table S2 and Fig. S1*).

Impact of peripheral blood parameters on PFS

The median follow-up time was 47.0 months (interquartile range, 38.5 to 55.5). A total of 73 tumor progression events were evaluated, and the median PFS was 16.2 months (95% CI, 16.6 to 25.0). The one- and three-year PFS rates were 63.5% and 24.1%, respectively. The median PFS was significantly longer in patients with low PIV (25.7 months, 95% CI, 16.4 to 34.9) as those with high PIV (10.3 months, 95% CI, 8.0 to 12.6, $p < 0.001$, Fig. 2A). Similar results were observed for NLR, PLR, and SII. Patients with a low NLR had a longer PFS (24.8 months, 95% CI, 17.8 to 31.8) than those with a high NLR (10.9 months, 95% CI, 7.7 to 14.1, $p < 0.001$, Fig. 2B). Regarding PLR, patients with lower PLR had a median PFS of 21.3 months (95% CI, 14.4 to 28.1), while those with high PLR had a median PFS of 13.0 months (95% CI, 10.1 to 15.9, $p = 0.004$, Fig. 2C). As for SII, the median PFS was 25.7 months (95% CI, 18.6 to 32.7) in patients with low SII when compared with 10.9 months (95% CI, 8.0 to 13.8, $p < 0.001$, Fig. 2D) in patients with high SII. Specific variables identified as significant ($p < 0.1$) by univariate analysis included pretreatment KPS, number of metastatic sites, brain metastases, liver metastases, PIV, NLR, PLR, and SII. These variables were then entered into the multivariate model. Finally, only a higher PIV (HR = 2.9, 95% Cl: 1.79–4.70, $p < 0.001$), liver metastases (HR = 3.60, 95% Cl: 2.01–6.44, $p < 0.001$) and brain metastases (HR = 1.68, 95% Cl: 1.01–2.78, $p = 0.045$) were independent prognostic factors for poor median PFS (Table 2).

Impact of peripheral blood parameters on OS

A total of 32 deaths events occurred during the follow-up period, and the median OS was not reached. The three- and five-year OS rates were 70.4% and 55.1%, respectively. The median OS for patients with low PIV was not reached compared with 38.7 months (95% CI, 28.2 to 49.2, $p < 0.001$, Fig. 3A) in patients with high PIV. In addition, lower NLR, PLR, and SII were also associated with longer median OS ($p = 0.006$, $p = 0.008$, and $p = 0.001$, respectively; Fig. 3B, C, and D). Univariate analysis showed that pretreatment KPS, number of metastatic sites, liver metastases, PIV, NLR, PLR, and SII were associated with poor median OS. When performed multivariate analysis, only the higher PIV (HR = 4.70, 95% Cl: 2.00–11.02, $p < 0.001$) and liver metastases (HR = 5.16, 95% Cl: 2.42–11.01, $p < 0.001$) were independently associated with poor survival outcomes (Table 3).

Discussion

Our study firstly demonstrated that PIV, a new inflammation-based biomarker that incorporates neutrophils, platelets, monocytes, and lymphocyte counts, was the only parameter that retained an independent prognostic role for PFS and OS in the multivariable analysis of patients with ALK-positive advanced NSCLC patients who received first-

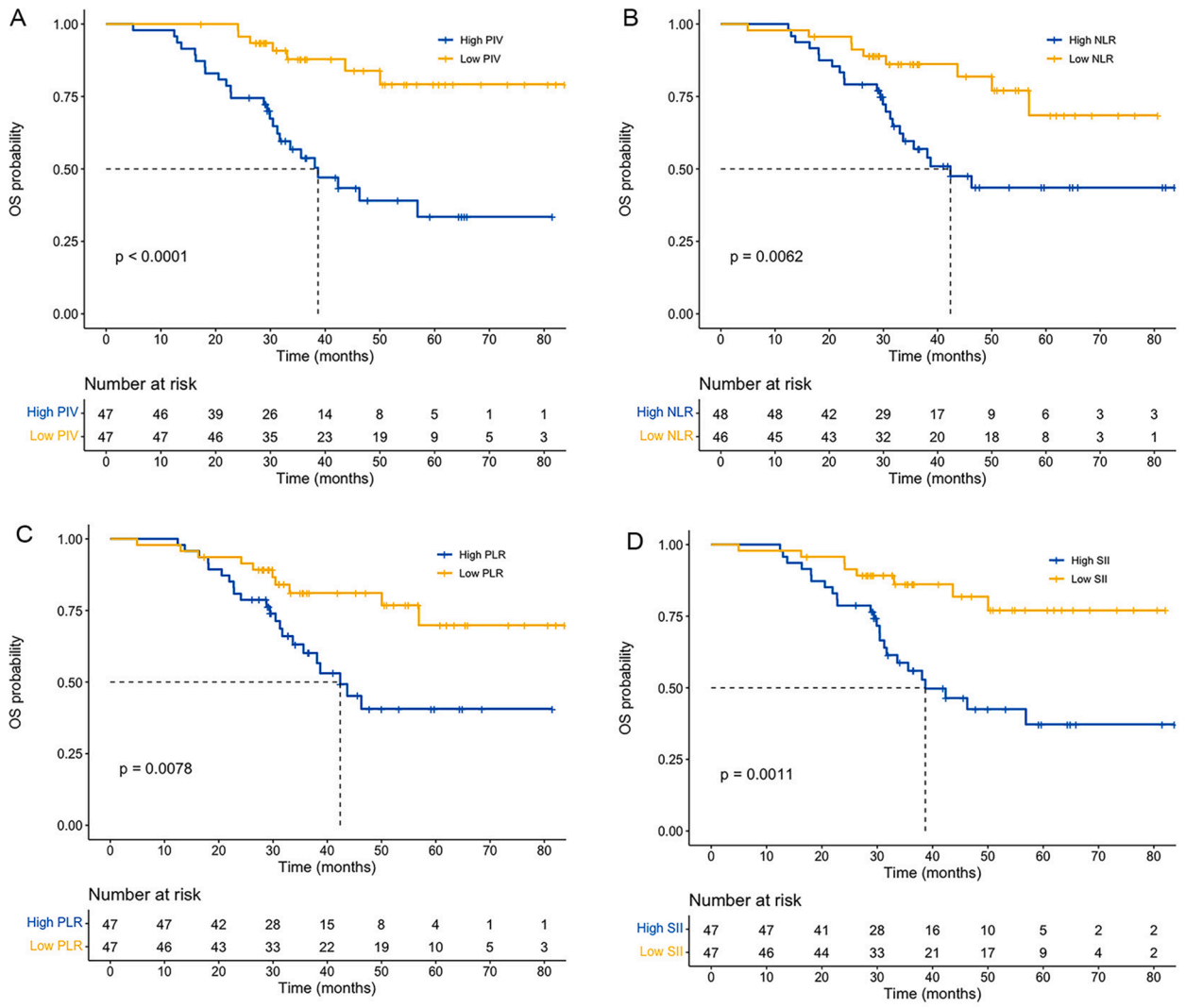

Fig. 3. Kaplan-Meier curves for overall survival (OS) in patients with advanced ALK-positive NSCLC according to baseline (A) PIV, (B) NLR, (C) PLR, (D) SII. The median value of each parameter was used as a cut-off point to definite the parameter categories (high vs. low). Abbreviations: PIV: Pan-Immune -Inflammation Value; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index.

line ALK TKI.

Inflammation plays an important role in cancer progression and it can be triggered by a variety of blood immune cells, including neutrophils, macrophages, lymphocyts, and dendritic cells.[22] Each type of cell performs its function but they all work together to reflect systemic and intratumor immune system status. Neutrophils in the tumor microenviroment usually play a pro-tumor role through the release of reactive oxygen species, the secretion of pro-tumor cytokines and chemokines, and the promotion of immunosuppression [23]. On the other hand, tumor-associated macrophages (TAMs) derived from circulating monocytes have two phenotypes: the M1 phenotype has antitumor activity, whereas the M2 phenotype promotes cancer progression [24]. It has been reported that the peripheral monocyte count was associated with the density of the TAMs, which is correlated with a poor prognosis [25]. Moreover, platelets interact with circulating tumor cells to form thrombus, which helps tumor cells escape immune system attack. Activated platelets can also release various of biologically active factors to promote the invasion and growth of tumor [26,27]. By contrast, lymphocytes usually play a role in antitumor immunity and are widely used as a measure of immunocompetence, especially for tumor antigen-specific CD8+ cytotoxic T lymphocyte (CTL)-mediated killing of tumor cells that plays a crucial role in cancer immune rejection [28]. Over the past decades, a large number of studies have examined the effect of the combined indicators, such as NLR [29–31], PLR [32–34], and SII [35–37] in lung cancer patients, and have been reported to be predictive of cancer prognosis.

PIV is a new immune-inflammatory biomarker that integrates neutrophil, monocyte, lymphocyte, and platelet counts and was firstly reported by Giovanni Fucà et al. in metastatic colorectal cancer lately [20]. The results showed that PIV is a strong predictor of survival outcomes with better performance than other well-known immune-inflammatory biomarkers in patients with colorectal cancer who were treated with first-line therapy. Then, results from another study reported by Francesca Ligorio found that high PIV did not show a statistically significant and independent association with worse PFS but was independently associated with worse OS in patients with HER2+ advanced breast cancer patients who received first-line taxane--trastuzumab-pertuzumab [21]. Indeed, PIV, unlike other indicators that use two or three types of blood cells, allows us to “comprehensively quantify” the cellular components of systemic inflammation and strongly reflects different aspects of antitumor immunity.

The prognostic value of different systemic inflammation markers has been reported in NSCLC patients, especially in the EGFR-mutated population. However, few studies have analyzed the prognostic value of the peripheral inflammatory blood markers in ALK-positive NSCLC patients receiving ALK TKIs as first-line treatment and it deserves investigation.

Table 3
Cox proportional hazards regression models for OS.

Variable	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p-value	HR	95% CI	p - value
Age (years)	1.14	0.60–2.28	0.714			
< 50 vs. ≥ 50						
Gender	1.61	0.78–3.35	0.200			
Female vs. male						
Smoking status	1.52	0.75–3.08	0.247			
Never vs. former/current						
Pretreatment KPS	7.04	2.11–23.54	0.002			
> 70 vs. ≤ 70						
Histology	2.45	0.58–10.29	0.222			
Adenocarcinoma vs. non-adenocarcinoma						
Stage	1.50	0.20–11.0	0.690			
III vs. IV						
Number of metastatic sites	3.73	1.83–7.59	< 0.001			
< 2 vs. ≥ 2						
Brain metastases	1.48	0.72–3.04	0.284			
No vs. Yes						
Liver metastases	5.14	2.48–10.68	< 0.001	5.16	2.42–11.01	< 0.001
No vs. yes						
PIV	4.74	2.05–11.0	< 0.001	4.70	2.00–11.02	< 0.001
Low vs. High						
NLR	2.82	1.30–6.10	0.009			
Low vs. High						
PLR	2.66	1.25–5.64	0.011			
Low vs. High						
SII	3.48	1.56–7.75	0.002			
Low vs. High						

Abbreviation: ALK, anaplastic lymphoma kinase; KPS, Karnofsky performance status; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PIV, Pan-Immune-Inflammatory Value; PLR, platelet-to lymphocyte ratio; SII, systemic immuneinflammation index; TKI, tyrosine kinase inhibitor.

In a retrospective study, Han et al. reported that PLR was an independent prognostic factor in ALK-positive NSCLC [38]. In this study, only the parameters of NLR and PLR were included, and most of the patients (75.7%) had stage I-III cancer with 17.3% of patients received TKI therapy. Besides, Yang et al. evaluated the role of NLR, PLR, and WBC in ALK-positive advanced NSCLC patients receiving crizotinib, and found that high pretreatment NLR and PLR are strongly related to poor survival in univariate analysis but not multivariable analysis [39]. Our study is the first to comprehensively analyze the prognostic value of these four parameters: PIV, NLR, PLR, and SII in ALK-positive advanced NSCLC, and the results were similar to those previously published data in advanced colorectal cancer and advanced HER2+ breast cancer. We found that only the high PIV was independently correlated with worse PFS and OS.

On these bases, PIV should be a more objective marker that reflects the balance between host inflammatory and immune response status than all the other systemic inflammation index such as the NLR and SII. However, molecular mechanisms underlying relationship between PIV and poor ALK-positive advanced NSCLC are still unclear. A plausible explanation is that the levels of cytokines are increased and the phenotypes of immune cells are changed when cancer generates an inflammatory response, which lead to a rapid increase of tumor growth and drug therapy resistance [40,41].

The present study had several limitations. First, similar to all retrospective analyses, it cannot be denied that various biases may have influenced the results. Second, the study had a monocentric design with a comparatively small sample size, and no validation group was used to confirm the results. Future prospective, large sample size studies are needed to verify the prognostic value of PIV in patients with ALK-positive advanced NSCLC. Finally, approximately 90% of patients were treated with crizotinib as first-line therapy in our study and only 10 patients received second-generation TKIs, including alectinib or ceritinib, which have been so far successfully and routinely used as first-line therapy for advanced ALK-positive NSCLC patients. In the future, further studies are needed to extend this finding to include more patients treated with the next-generation ALK-TKIs.

Conclusions

In summary, the present study showed that PIV, which is non-invasive, low-cost, and easily obtained in clinical practice, was an independent predictor of PFS and OS in patients with ALK-positive advanced NSCLC patients who received first-line ALK TKIs. Further prospective studies are needed to evaluate the role of PIV as a predictive biomarker in patients with advanced ALK-positive NSCLC patients.

Financial disclosure

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Ethical statement

This study was approved by the Guangdong Association Study of Thoracic Oncology (No. A2017–002) and the institutional review board/ethics committee of the participating hospitals, and exception to the requirement of informed consent was approved.

CRediT authorship contribution statement

Xinru Chen: Conceptualization, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition, Data curation, Formal analysis. **Xiangchan Hong:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition, Data curation, Formal analysis. **Gang Chen:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing, Formal analysis, Data curation. **Jinhui Xue:** Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Jie Huang:** Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Fan Wang:** Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Wael Ab dullah Sultan Ali:** Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Jing Li:** Conceptualization, Visualization, Writing – original

draft, Writing – review & editing. **Li Zhang:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All authors declare no conflicts of interest.

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None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2021.101338.

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