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Evaluating the Prognostic Role of Pan-Immune-Inflammation Value in Patients with Advanced Non-Small Cell Lung Cancer Treated with Nivolumab

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What is already known on this topic?

- *Growing evidence indicates that composite scores derived from peripheral blood counts could serve as significant prognostic markers in cancer, indicating dysregulated inflammation within the tumor microenvironment. Pan-immune-inflammation value (PIV) is a multi-parameter index that integrates neutrophils, lymphocytes, monocytes, and platelets, and it has recently been recognized as a comprehensive prognostic tool for various cancers. The prognostic significance of PIV in patients with advanced NSCLC undergoing immunotherapy remains unclear.*

What this study adds on this topic?

- *The results of the study highlighted the prognostic impact of PIV on survival in advanced NSCLC patients receiving nivolumab. Given its simplicity and accessibility, PIV shows significant potential as a key tool for guiding personalized treatment strategies in NSCLC.*

Abstract

Objective: Non-small cell lung cancer (NSCLC) remains a leading cause of cancer-related death. Pan-immune-inflammation value (PIV), a novel biomarker that reflects systemic inflammation and immune status, has been evaluated for prognostic efficacy in various cancer types. This study aimed to investigate the efficacy of PIV on survival outcomes in patients diagnosed with advanced NSCLC who were treated with nivolumab.

Methods: The single-center, retrospective, and observational study included patients with metastatic NSCLC who received nivolumab treatment. The receiver operating characteristic (ROC) curve analysis was performed to find the optimal PIV cutoff value for predicting outcomes, and patients were divided into 2 groups: low-PIV and high-PIV.

Results: The median age was 63 years. The patient cohort comprised 68 male and 20 female patients. Adenocarcinoma histology was identified in the majority of patients (56.8%). Nivolumab was administered to 74% of patients as a second line of treatment and to 26% in the third line or later. In ROC analysis, the ideal cutoff value for PIV was established at 652 (AUC: 0.691, 95% CI: 0.568-0.814, $P = .013$). No statistically significant differences were observed in the demographic and clinicopathological features of patients between the low- and high-PIV groups. High PIV was independently associated with shorter progression-free survival (HR: 0.47, 95% CI: 0.29-0.76; $P = .002$) and overall survival (HR: 0.54, 95% CI: 0.32-0.92; $P = .023$), independent of other factors affecting outcomes.

Conclusion: The findings of the study indicate that PIV value may serve as a significant prognostic biomarker for predicting survival in metastatic NSCLC patients undergoing treatment with nivolumab.

Keywords: Biomarker, immunotherapy, lung cancer, nivolumab, pan-immune-inflammation value

Introduction

Non-small cell lung cancer (NSCLC), the most prevalent histological subtype of lung cancer, is among the leading causes of cancer-related death worldwide.[1] The therapeutic landscape of NSCLC has undergone substantial evolution, particularly within the past decade, driven by advances in molecular profiling, targeted therapies, and immunotherapeutic approaches. In the management of advanced NSCLC, the development of immune checkpoint inhibitors (ICIs) across both first- and second-line therapies has resulted in remarkable extended survival for a subset of patients.[2,3] Nivolumab is a programmed death 1 inhibitor that has shown significant improvements in survival outcomes compared to standard chemotherapy in second-line and subsequent treatment settings for advanced NSCLC.[4] However, not all patients benefit equally from nivolumab, which underscores the necessity for valuable prognostic indicators that could effectively guide treatment decisions and optimize patient outcomes.

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Systemic inflammation contributes an essential part in cancer pathogenesis, development, and immune evasion by significantly affecting the tumor microenvironment and responses to immunotherapy.[5] Inflammatory markers obtained from peripheral blood, including the systemic immune-inflammation index, the neutrophil-to-lymphocyte ratio (NLR), and the platelet-to-lymphocyte ratio, were thoroughly investigated as predictive biomarkers in NSCLC.[6-9] These indicators reflect the equilibrium between tumor-promoting inflammatory responses and immune activity against the tumor. The pan-immune-inflammation value (PIV) is a combination marker generated from the counts of neutrophils, platelets, monocytes, and lymphocytes, and has recently been recognized as a comprehensive prognostic tool in various solid tumors, including NSCLC.[10-15] The PIV integrates several components of the immune and inflammatory response, offering a more comprehensive understanding of host-tumor interactions than individual inflammatory markers.

Preliminary studies indicate that a low pretreatment PIV correlates with enhanced overall survival (OS), progression-free survival (PFS), and an increased rate of immune-related adverse events (irAEs) in patients with metastatic NSCLC treated with ICIs.[16-18] These findings suggest that PIV could serve as a valuable biomarker to predict outcomes and optimize patient management in this population. Further research is required to confirm these associations and investigate potential mechanisms underlying the relationship between PIV levels and treatment outcomes. The dynamic changes in PIV during treatment may serve as predictors of therapeutic efficacy, offering a longitudinal perspective on the immune response.[17] While numerous studies have demonstrated the prognostic significance of PIV in NSCLC, many of these analyses have focused on heterogeneous patient populations undergoing different types of ICIs, frequently in combination with other therapies. The prognostic value of pretreatment PIV in NSCLC patients treated with nivolumab has not been thoroughly investigated. This gap is clinically relevant, as nivolumab is among the ICIs commonly used in standard practice, particularly in countries where access to first-line immunotherapy is limited.

This study aims to evaluate the prognostic significance of pretreatment PIV in patients with advanced NSCLC treated with nivolumab, using real-world data to assess its association with survival outcomes.

Methods

Patients and Data Collection

This retrospective study involved patients diagnosed with advanced NSCLC between January 2018 and October 2024. Clinicopathological data were collected from patient databases and medical records. The study included patients who met the following criteria: histologically confirmed NSCLC; radiologically confirmed metastatic disease; received nivolumab in the second line or later; and measurement of serum inflammatory markers in peripheral blood samples prior to nivolumab treatment. The exclusion criteria included the absence of serum inflammatory marker measurements, the presence of other malignancies, inadequate clinical outcomes, and patients exhibiting signs of active infection during the pretreatment period.

The patient data collected from clinical records included demographic features, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status, histopathological characteristics of the primary tumor, laboratory data obtained prior to nivolumab treatment, as well as the number and locations of metastases, the response to nivolumab treatment, and the treatment-related adverse events (TRAEs). The PIV was determined using the formula (monocyte count [10^3/mL] × neutrophil count [10^3/mL] × platelet count [10^3/mL]) ÷ lymphocyte count [10^3/mL].

This research complied with the principles set forth by the Declaration of Helsinki and received approval from the Ethics Committee of İstanbul University-Cerrahpaşa. (Approval no: E-74555795-050.04-1231222; Date: January 22, 2025). Informed consent was not obtained as the requirement was waived due to the retrospective nature of the study.

Efficacy and Safety Measures

Progression-free survival was measured as the interval from the initial nivolumab dose to either disease progression or death from any cause, whichever occurred first. Patients without disease progression were censored at their most recent follow-up assessment. Overall survival was calculated as the period from the first nivolumab administration to either death from any cause or the last recorded visit. Patients still alive at the time of analysis were censored on that date. The TRAEs were evaluated using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0.[19]

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM SPSS Corp.; Armonk, NY, USA). Data were evaluated with standard descriptive statistics, encompassing mean, standard deviation, median, and range for continuous variables, and frequency and percentage for categorical variables. Continuous variables were analyzed using the Mann–Whitney *U* test and paired samples *t*-test. The chi-squared test or Fisher's exact test was employed for the comparison of categorical variables. The optimal PIV cutoff for predicting survival outcomes was established through Youden's J index, calculated from receiver operating characteristic (ROC) curve analysis.[20] Patients were divided into high-PIV and low-PIV groups based on this cutoff. Survival curves for patients were estimated through the Kaplan–Meier method, with the log-rank test used in the univariate analyses. To assess the independent impact of prognostic factors on survival, multivariable Cox proportional hazards models were applied, yielding hazard ratios (HRs) with 95% CIs. Multivariable analyses were assessed by including variables with *P*-values less than .10 from univariate analyses.

Results

Characteristics of Patients

The median age was 63 years (range: 34-83). There were 68 (77.3%) male and 20 (22.7%) female patients. The ECOG PS was 0 in 6.8% (n = 6) of the patients, score 1 in 86.4% (n = 76), and ≥2 in 6.8% (n = 6). Table 1 summarizes the initial demographic and clinicopathologic findings of the patients. Non-smokers accounted for 20.5% of the patient population, whereas smokers constituted 79.5%. Among the smokers, 67% were active smokers. The majority of patients (50 out of 88) had adenocarcinoma, and 33 (37.5%) had squamous cell carcinoma (SCC) histology. While 58% of patients presented with synchronous metastatic disease, 42% exhibited metachronous metastases. Visceral metastases were present in 53.4% of patients. The most prevalent metastatic sites were the lungs, bones, and adrenal glands (36.4%, 35.2%, and 23.9%, respectively). Nivolumab treatment was administered to 74% of patients in the second line and 26% in the third line or later. There were 18 patients who continued to receive nivolumab until the final follow-up date. All patients received platinum-based doublet chemotherapy before nivolumab. Patients received

Table 1. Baseline Demographic and Clinicopathologic Findings of Study Cohort (n = 88)

Characteristics		n (%)
Age (years)	Median	63 (34-83)
	<65	48 (54.5)
	≥65	40 (45.5)
Gender	Female	20 (22.7)
	Male	68 (77.3)
ECOG performance status	PS 0	6 (6.8)
	PS 1	76 (86.4)
	PS ≥2	6 (6.8)
Smoker	No	18 (20.5)
	Yes	70 (79.5)
Histology	Adenocarcinoma	50 (56.8)
	Squamous cell carcinoma	33 (37.5)
	NOS	5 (5.7)
PD-L1 expression	<1%	18 (20.4)
	≥1%	27 (30.7)
	Unknown	43 (48.9)
Metastatic disease	Synchronous	51 (57.9)
	Metachronous	37 (42.1)
Treatment line of nivolumab	Second line	65 (73.9)
	Third line or later	23 (26.1)
Visceral metastasis		47 (53.4)
Metastatic site	Lung	32 (36.4)
	Bone	31 (35.2)
	Adrenal gland	21 (23.9)
	Brain	14 (15.9)
	Liver	13 (14.8)
NLR, median (range)		3.79 (0.32-25.67)
PLR, median (range)		215.5 (19.0-1247.0)
SII, median (range)		1075.4 (48.1-9599.3)
IBI, median (range)		6.63 (1.50-42.28)
CAR, median (range)		4.52 (0.13-56.25)
PIV, median (range)		701.5 (29.0-8619.0)

CAR, C-reactive protein albumin ratio; ECOG, Eastern Cooperative Oncology Group; IBI, inflammatory burden index; NOS, not otherwise specified; NLR, neutrophil-to-lymphocyte ratio; PIV, pan-immune-inflammatory value; PD-L1, programmed death-ligand 1; PLR, platelet-to-lymphocyte ratio; PS, performance status; SII, systemic immune-inflammation index.

a median of 3 lines of treatment (range: 2-7). Nivolumab-related irAEs occurred in 14 patients (15.9%). The most prevalent irAE was pneumonitis, affecting 6 out of the 14 patients.

The ROC analysis was conducted to determine the optimal PIV value for predicting OS. The optimal PIV value identified was 652, with an area under the curve (AUC) of 0.691 (95% CI: 0.568-0.814, P = .013). This value demonstrated a sensitivity of 58.6% and a specificity of 77.8%. (Figure 1). Patients were categorized into low (<652) and high PIV (≥652) groups based on the optimal cutoff values for PIV that were determined. No statistically significant differences were observed between the low- and high-PIV groups in terms of demographics and baseline characteristic features. The only exception was that the rate of lung metastasis was greater in the low-PIV group than in the high-PIV group (46.5% vs. 26.7%, P = .049) (Table 2). The histology of adenocarcinoma (69% vs. 51.2%; P = .097), the presence of synchronous metastatic disease (67.4% vs. 48.9%; P = .078), and the rate of visceral metastasis (62.8% vs. 44.4%; P = .085) were numerically higher in the low-PIV group than in the high-PIV group; however, these findings did not reach statistical significance.

Survival Analyses

The median follow-up period was 11.1 months (range: 2.1-58.4). The final follow-up assessment occurred on March 1, 2025. At that time, only 18% of patients remained free of disease progression. The low-PIV group exhibited a notably longer median PFS than the high-PIV (7.5 vs. 3.8 months; P = .006) (Figure 2A). The univariate analyses showed that gender (female vs. male), the presence of liver metastases (yes vs. no), the inflammatory burden index (high vs. low), and PIV (high vs. low) were associated with poorer PFS. The multivariate analysis demonstrated that female vs. male (HR: 0.47, 95% CI: 0.27-0.83; P = .009) and high-PIV versus low-PIV (HR: 0.47, 95% CI: 0.29-0.76; P = .002) were independently associated with worse PFS. The univariate and multivariate analyses are presented in Table 3.

At the last follow-up assessment, 75% of patients had died. The median OS was also significantly higher in the low-PIV group than the high-PIV group (15.6 vs. 8.7 months; P = .003) (Figure 2B). Additionally, SCC histology (P = .020), high NLR (P = .039), high

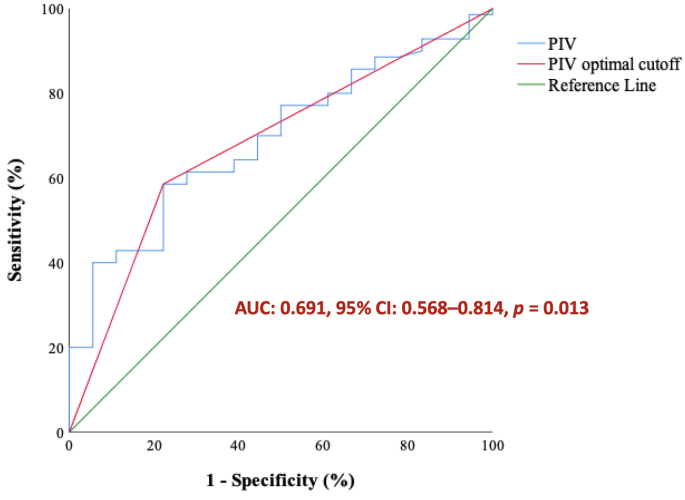

Figure 1. ROC curve for PIV in the prediction of overall survival. The area under the curve (AUC) is 0.691 with a 95% confidence interval of 0.568-0.814 (P = .013).

Table 2. Baseline Characteristics of Patients in Low-PIV and High-PIV Cohorts

Variables		Low-PIV (n = 43)	High-PIV (n = 45)	*P*
Age (years)	Median (range)	63.3 (36-83)	63.4 (34-81)	.981
	≥65, n (%)	17 (39.5)	23 (51.1)	.276
Gender, n (%)	Male	34 (79.1)	34 (75.6)	.694
	Female	9 (20.9)	11 (24.4)	
Histopathology, n (%)	Adenocarcinoma	29 (69)	21 (51.2)	.097
	Squamous carcinoma	13 (31)	20 (48.8)	
	NOS	1	4	
Smoker, n (%)	No	9 (20.9)	9 (20)	.914
	Yes	34 (79.1)	36 (80)	
PD-L1 expression	<1% ≥1% Unknown	11 (45.8) 13 (54.2) 19	7 (33.3) 14 (66.7) 24	.393
Metastatic disease, n (%)	Synchronous	29 (67.4)	22 (48.9)	.078
	Metachronous	14 (32.6)	23 (51.1)	
Treatment line of nivolumab, n (%)	Second line	33 (76.7)	32 (71.1)	.548
	Third line or later	10 (23.3)	13 (28.9)	
Visceral metastasis, n (%)		27 (62.8)	20 (44.4)	.085
Lung metastasis, n (%)		20 (46.5)	12 (26.7)	**.049**
Bone metastasis, n (%)		14 (32.6)	17 (37.8)	.608
Adrenal gland metastasis, n (%)		12 (27.9)	9 (20)	.384
Brain metastasis, n (%)		7 (16.3)	7 (15.6)	.926
Liver metastasis, n (%)		5 (11.6)	8 (17.8)	.261
TRAE, n (%)		9 (20.9)	5 (11.1)	.208

irAEs, immune-related adverse events; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; PIV, pan-immune-inflammatory value.
Bold values indicate statistical significance at $P < 0.05$.

inflammatory burden index (P = .005), high C-reactive protein albumin ratio (P = .031), and high PIV levels (P = .003) were significantly associated with shorter OS in univariate analyses. In addition, SCC histology (HR: 0.57, 95% CI: 0.34-0.96; P = .034), the presence of liver metastasis (HR: 0.50, 95% CI: 0.25-1.00; P = .050), and high-PIV levels (HR: 0.54, 95% CI: 0.32-0.92; P = .023) were significant independent prognostic factors for poorer OS in the multivariate analysis (Table 4).

Discussion

The present study evaluated the prognostic significance of the pretreatment PIV in patients with metastatic NSCLC who were treated with nivolumab. The findings indicated that a low PIV (cut-off: 652) is significantly associated with improved PFS and OS. The findings suggest that PIV may serve as a surrogate biomarker for systemic inflammation and immunosuppression levels, both of which are known to affect antitumor immunity and the effectiveness of ICIs. Multivariate Cox regression analysis confirmed that a high PIV serves as an independent prognostic marker for poorer PFS (P = .002) and OS (P = .023). Compared to other inflammatory markers, PIV's maintained statistical significance in multivariate analysis may be attributed to its inclusion of various inflammatory parameters, such as neutrophils, monocytes, lymphocytes, and platelets, which may provide a more comprehensive reflection of the tumor-host immune interaction. The findings indicated that PIV is a minimally invasive, peripheral blood-based biomarker for predicting survival outcomes in metastatic NSCLC patients receiving nivolumab.

The association between inflammation and cancer has been the subject of research since Virchow's hypothesis that tumors develop at the location of chronic inflammation.[21] Chronic inflammation can modify the extracellular matrix and enhance angiogenesis and lymphangiogenesis in the tumor microenvironment (TME), thereby promoting tumor growth and metastasis.[5] Neutrophils, lymphocytes, platelets, and monocytes are essential components of the inflammatory response and significantly impact host defense systems as well as tumor biology. Neutrophils contribute to tumor progression through their release of reactive oxygen molecules and pro-inflammatory chemokines, which promote immunosuppression, angiogenesis, and tumor invasion.[22,23] Conversely, lymphocytes play a role in preventing carcinogenesis, with CD8+ and CD4+ T cells in the TME mediating antitumoral responses.[24]

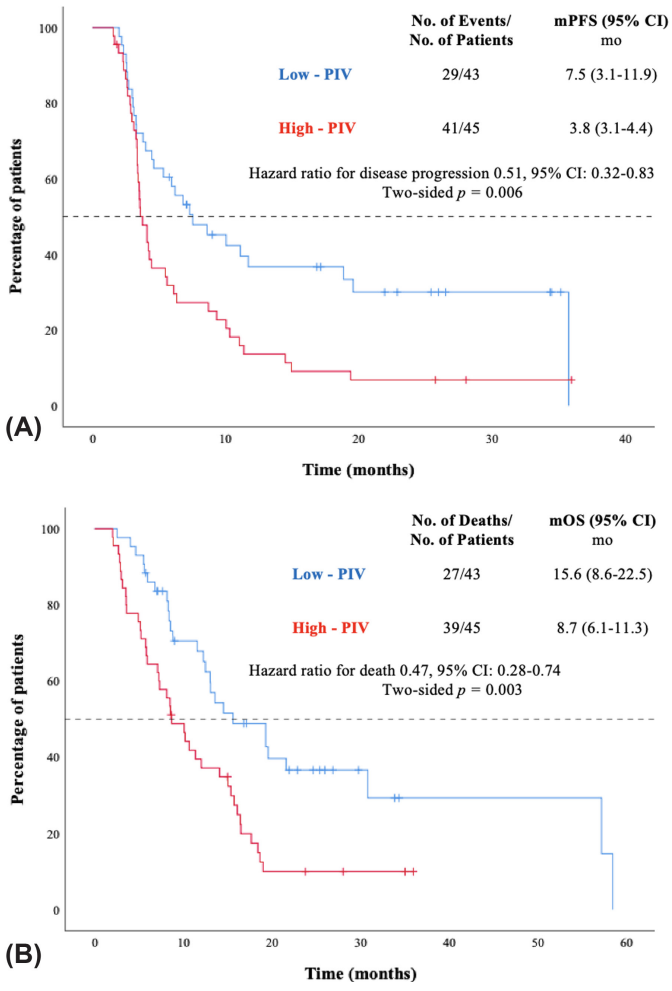

Figure 2. Kaplan–Meier curves of PFS (A) and OS (B) in patients with low PIV and high PIV. Mo, months; OS, overall survival; PFS, progression-free survival; PIV, pan-immune-inflammatory value.

Platelets facilitate the escape of immune system responses by forming a thrombus with circulating tumor cells.[25] Additionally, activated platelets can secrete various growth factors that facilitate tumor invasion.[26] Monocytes have a strong link with the formation and progression of cancer. M2-type macrophages originating from monocytes influence immunosuppression and angiogenesis through mechanisms involving tumor necrosis factor-alpha (TNF-α), interleukin (IL)-10, and vascular endothelial growth factor.[27,28]

The PIV could be used as a surrogate marker for the extent of immunosuppression, as it provides a more comprehensive assessment of the inflammatory response by incorporating both pro- and anti-tumor factors. The study results are correlated with increasing evidence that emphasizes the prognostic significance of PIV in NSCLC patients receiving ICIs. In a retrospective study conducted by Chen et al[17] that included 269 advanced NSCLC patients, a lower baseline PIV (cutoff value: 288.1) was shown to be related to a higher incidence of irAEs (OR: 0.235, 95% CI: 0.117-0.472, $P < .001$) and better PFS (10 vs. 7 months, $P = .0005$) and OS (29 vs. 21 months, $P < .0001$). Shixin Ma et al[18] demonstrated that a low PIV (cutoff: 250.51) is associated with prolonged survival in 161 NSCLC patients undergoing ICI treatment, while a high PIV serves as an independent risk factor for death (HR: 3.752, 95% CI: 2.281-6.171, $P < .001$). The researchers also reported that patients who had low PIV levels had a greater rate of irAEs ($P = .041$). Lei et al[16] investigated the prognostic significance of inflammatory and nutritional markers for the efficacy of ICIs and showed that high PIV (cutoff: 297.49) was associated with lower disease control rates (54.39% vs. 19.61%) and shorter PFS ($P < .001$) in NSCLC patients receiving ICIs. Güven et al[12] conducted a pooled analysis of 15 studies involving 4942 patients, revealing that those with lower PIV levels had a significantly decreased risk of progression or death compared to those with higher PIV levels ($P < .001$) in the various cancer types involving NSCLC.

The PIV cutoff value in the study (652) exceeds the values reported in the previously mentioned studies, which may reflect differences in patient demographics, treatment settings, or statistical methodologies used to determine optimal cutoffs. For instance, the cutoff was derived using ROC curve analysis with Youden's J index for predicting mortality risk (AUC: 0.691, $P = .013$). Despite these variations, the prognostic significance of PIV observed in the study is generally in line with previous research; however, the robustness of the identified cutoff requires further validation in larger, independent cohorts. This indicates that PIV may function as a potentially valuable prognostic indicator in selected settings.

Notably, univariate analyses identified several inflammatory markers, including NLR ($P = .039$), IBI ($P = .005$), and CAR ($P = .031$), which were significantly associated with poorer OS. However, only PIV preserved statistical significance in the multivariable Cox regression analysis. This finding emphasizes the unique value of PIV as a comprehensive biomarker and potentially captures the intricate interplay of systemic inflammation and immune response more effectively than other markers. The significant prognostic power of PIV suggests that it may serve as a useful tool for risk stratification in clinical practice. However, additional research in larger cohorts is required to clarify the reasons why PIV may outperform other inflammatory indices and to verify its clinical utility across different settings. Nonetheless, the relatively small sample size may have limited the statistical power of subgroup analyses and could have resulted in an overestimation of effect sizes in some comparisons. Furthermore, the potential for type II error should be considered, particularly in the non-significant associations observed for markers such as CAR and IBI in the multivariate analyses.

Additionally, the analysis revealed that the SCC subtype and the presence of liver metastases were independently associated with poorer survival outcomes. It is well known that squamous histology is associated with shorter survival than is nonsquamous NSCLC.[29,30] Nevertheless, pivotal ICI trials have reported patients with SCC histology show more favorable responses to ICIs compared to adenocarcinoma.[31-33] The previous studies that have highlighted reduced outcomes in patients with liver metastases treated with ICIs.[34,35] These findings further underscore the importance of accounting for both histological subtype and metastatic patterns when evaluating prognostic markers like PIV.

This study presents several limitations. Firstly, according to the retrospective design, there is a potential risk of selection bias and the influence of unmeasured confounders that may have affected both the clinical characteristics and the survival outcomes of the patients. Moreover, this was a single-center study, which may reduce the generalizability of the findings to broader patient populations and clinical settings. Secondly, certain potential cofactors influencing inflammation markers could not be controlled. In addition, ICIs are not covered by health insurance in first-line metastatic NSCLC in the country, and only nivolumab is reimbursed in second- or later-line treatment. Therefore, in the country, ICIs are often postponed to second- or later-line instead of being used in first-line settings as recommended in current guidelines. This

Table 3. Univariate and Multivariate Cox Regression Analyses for Progression-Free Survival

		Univariate Analysis		Multivariate Analysis	
Variables		**mPFS mo (95% CI)**	***P***	**HR (95% CI)**	***P***
Gender	Male	5.9 (2.5-9.4)	**.028**	0.47 (0.27-0.83)	**.009**
	Female	3.5 (2.4-4.6)			
Age (years)	<65	6.8 (1.2-12.3)	.151		
	≥65	4.2 (3.2-5.2)			
Smoker	No	5.3 (2.7-7.9)	.654		
	Yes	4.4 (2.2-6.7)			
Pathology	Adenocarcinoma	6.1 (4.6-7.6)	.267		
	SCC	3.8 (2.9-4.7)			
PD-L1 expression	<1%	4.1 (3.7-4.5)	.555		
	≥1%	5.3 (1.3-9.4)			
Metastatic disease	Synchronous	5.9 (3.7-8.1)	.962		
	Metachronous	4.2 (2.9-5.5)			
Nivolumab treatment line	2	5.6 (3.6-7.6)	.600		
	≥3	4.5 (2.4-6.5)			
Visceral metastasis	No	4.5 (2.9-6.0)	.991		
	Yes	5.9 (2.8-9.1)			
Brain metastasis	No	4.6 (2.9-6.3)	.794		
	Yes	4.1 (0-9.7)			
Lung metastasis	No	4.3 (2.9-5.6)	.989		
	Yes	6.1 (3.2-8.9)			
Liver metastasis	No	6.1 (3.8-8.4)	**.035**	0.54 (0.27-1.08)	.082
	Yes	3.4 (3.1-3.7)			
Bone metastasis	No	5.6 (2.8-8.4)	.132		
	Yes	3.8 (2.3-5.2)			
Adrenal metastasis	No	4.4 (2.9-5.9)	.161		
	Yes	7.3 (0.1-14.5)			
TRAE	No	4.4 (2.7-6.1)	.216		
	Yes	6.8 (0.4-13.1)			
NLR	Low	5.3 (2.3-8.4)	.832		
	High	4.2 (2.1-6.4)			
PLR	Low	6.1 (4.1-8.2)	.263		
	High	4.1 (3.3-4.9)			
SII	Low	5.9 (3.5-8.4)	.489		
	High	4.2 (3.3-5.1)			
IBI	Low	6.1 (3.3-8.9)	**.048**	0.68 (0.38-1.21)	.191
	High	3.8 (2.9-4.6)			
CAR	Low	5.5 (2.9-7.9)	.066	0.83 (0.32-2.12)	.691
	High	4.1 (3.1-5.2)			
PIV	Low	7.5 (3.1-11.9)	**.006**	0.47 (0.29-0.76)	**.002**
	High	3.8 (3.1-4.4)			

CAR, C-reactive protein albumin ratio; HR, hazard ratio; IBI, inflammatory burden index; Mo, months; mPFS, median progression-free survival; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed death-ligand 1; PIV, pan-immune-inflammatory value; PLR, platelet-to-lymphocyte ratio; SCC, squamous cell carcinoma; SII, systemic immune-inflammation index; TRAE, treatment-related adverse event.

Table 4. Univariate and Multivariate Cox Regression Analyses for Overall Survival

		Univariate Analysis		Multivariate Analysis	
Variables		**mOS mo (95% CI)**	***P***	**HR (95% CI)**	***P***
Gender	Male	13.6 (10.4-16.8)	.390		
	Female	8.6 (4.3-12.8)			
Age (years)	< 65	12.5 (8.2-16.8)	.575		
	≥ 65	11.6 (5.9-17.2)			
Smoker	No	13.1 (3.9-22.2)	.959		
	Yes	12.5 (8.2-16.2)			
Pathology	Adenocarcinoma	15.7 (13.9-17.5)	**.020**	0.57 (0.34-0.96)	**.034**
	SCC	8.7 (7.7-9.6)			
PD-L1 expression	<1%	10.7 (4.8-16.5)	.873		
	≥1%	13.1 (6.1-20.0)			
Metastatic disease	Synchronous	13.0 (10.4-15.7)	.884		
	Metachronous	11.4 (4.2-18.5)			
Nivolumab treatment line	2	12.5 (8.3-16.7)	.188		
	≥3	11.4 (5.2-17.6)			
Visceral metastasis	No	12.0 (7.6-16.4)	.785		
	Yes	13.0 (8.3-17.8)			
Brain metastasis	No	11.9 (7.9-16.2)	.730		
	Yes	13.1 (11.1-14.9)			
Lung metastasis	No	11.4 (7.6-15.2)	.460		
	Yes	15.6 (3.2-8.9)			
Liver metastasis	No	13.6 (10.6-16.5)	.083	0.50 (0.25-1.00)	**.050**
	Yes	8.5 (6.2-10.8)			
Bone metastasis	No	12.5 (9.6-15.3)	.441		
	Yes	10.2 (3.3-17.1)			
Adrenal metastasis	No	12.0 (7.1-17.0)	.417		
	Yes	13.6 (8.6-18.5)			
TRAE	No	12.5 (9.1-15.8)	.543		
	Yes	11.6 (0-23.2)			
NLR	Low	14.5 (11.6-17.4)	**.039**	0.89 (0.47-1.68)	.714
	High	8.1 (6.2-10.1)			
PLR	Low	13.1 (10.3-15.8)	.089	0.69 (0.35-1.36)	.286
	High	8.6 (4.6-12.6)			
SII	Low	13.0 (11.1-14.9)	.101		
	High	8.7 (1.6-15.8)			
IBI	Low	14.5 (10.4-18.7)	**.005**	0.69 (0.39-1.23)	.212
	High	8.7 (3.8-13.6)			
CAR	Low	14.1 (9.7-18.5)	**.031**	0.82 (0.34-1.97)	.661
	High	10.7 (5.8-15.5)			
PIV	Low	15.6 (8.6-22.5)	**.003**	0.54 (0.32-0.92)	**.023**
	High	8.7 (6.1-11.4)			

CAR, C-reactive protein albumin ratio; HR, hazard ratio; IBI, inflammatory burden index; Mo, months; mPFS, median progression-free survival; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed death-ligand 1; PIV, pan-immune-inflammatory value; PLR, platelet-to-lymphocyte ratio; SCC, squamous cell carcinoma; SII, systemic immune-inflammation index; TRAE, treatment-related adverse event.

difference in treatment sequence may have affected patient selection and results in the study. The assessment of the prognostic and predictive importance of PIV in advanced NSCLC patients receiving nivolumab treatment might be strengthened by the integration of these factors in additional prospective studies.

In conclusion, the significance of inflammatory biomarkers in predicting survival for patients with advanced NSCLC remains a topic of debate. This study provides compelling evidence that PIV serves as a valuable prognostic factor for advanced NSCLC patients treated with nivolumab. Given its simplicity and accessibility, PIV shows promise as a basic tool to guide personalized treatment strategies in NSCLC. Finally, there is a need for prospective studies involving larger patient cohorts to confirm these findings and more effectively illustrate the role of PIV in informing clinical decisions.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

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