Pan-immune-inflammation value as a prognostic and predictive biomarker in metastatic non-small cell lung cancer treated with nivolumab: A real-world study

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Abstract. The present study aimed to assess whether the baseline pan-immune-inflammation value (PIV), a readily available blood-based marker, is linked to benefits from nivolumab treatment (response and survival) in patients with metastatic non-small cell lung cancer (mNSCLC) receiving second-line or later therapy. The data of 303 patients diagnosed with mNSCLC who received nivolumab at Kartal Dr Lütfi Kırdar City Hospital (Istanbul, Türkiye) between January 2022 and December 2023 were retrospectively reviewed. After excluding 33 ineligible cases, 270 patients were included in the final analysis. PIV was calculated from pre-treatment peripheral blood counts. The median overall survival (OS) and progression-free survival (PFS) times were assessed from the start of nivolumab treatment. Programmed death-ligand 1 expression data were unavailable in this real-world cohort, reflecting routine clinical practice. The median age was 63 years, and 84.1% of patients were male. The median OS and PFS times were 16 and 7 months, respectively. The patient responses were as follows: Progressive disease in 41.1%, partial response in 30.4%, stable disease in 22.2% and complete response in 6.3% of patients. Receiver operating characteristic analysis identified an optimal PIV cut-off of 604.5 for predicting nivolumab response. Patients with low PIV values had significantly longer median OS (25 vs. 11 months) and PFS (9 vs. 5 months) times, and a lower rate of nivolumab resistance (38.7 vs. 61.3%; P<0.001). Baseline PIV was confirmed as a significant predictor of nivolumab response (specificity, 62.9%; sensitivity, 61.3%; P<0.001). Upon multivariate logistic regression analysis, high PIV, blood group B antigen, Eastern Cooperative Oncology Group performance status 2 and lack of response to prior chemotherapy were identified as independent predictors of nivolumab resistance. In this real-world cohort, results were consistent with the known activity of nivolumab in previously treated mNSCLC. Baseline PIV was associated with treatment outcomes and may serve as a convenient, blood-based marker to inform immunotherapy decision-making. Further prospective validation is needed before routine clinical use.

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Introduction

Lung cancer remains a leading cause of cancer-related morbidity and the leading cause of cancer mortality worldwide, accounting for an estimated 2.2 million new cases and 1.8 million deaths in 2020 (1). Immune checkpoint inhibitors (ICIs), which target programmed cell death protein 1 and its ligand, programmed death-ligand 1 (PD-L1), have significantly transformed the treatment landscape for metastatic non-small cell lung cancer (mNSCLC) (2). However, only 15-20% of patients who respond to ICIs experience lasting benefits, while most exhibit resistance (3). The search for an ideal biomarker to predict NSCLC response to ICIs is ongoing; however, PD-L1 expression on tumor cells is a commonly validated and routinely used marker (4). High PD-L1 expression (>50%) is associated with better response rates and longer survival times (5). Despite this, patients with low or no PD-L1 expression can still benefit from ICIs, suggesting that PD-L1 alone is not a sufficient predictor of immunotherapy response (6).

Recently, several blood-based biomarkers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index, have exhibited prognostic relevance in NSCLC (7). A relatively new biomarker, the pan-immune-inflammation value (PIV), has been shown to have prognostic significance independent of treatment type in NSCLC (8,9), and colorectal (10), breast (11), pancreatic (12) and ovarian (13) cancer. In addition to their prognostic implications, several of these blood-based indices

have been associated with response to chemotherapy (14,15). If validated prospectively, these simple and cost-effective biomarkers could help clinicians identify patients who are more likely to benefit from ICIs, enabling a more personalized treatment approach.

Given the growing role of immunotherapy in advanced NSCLC, the present study aimed to determine whether baseline PIV could predict response to ICIs. Specifically, the study focused on the clinical outcomes, treatment-related toxicity and the predictive value of baseline PIV as assessed in patients with mNSCLC treated with nivolumab as second-line or later therapy.

Patients and methods

Patient selection. The medical records of 303 consecutive patients with mNSCLC who received nivolumab as second- or later-line therapy at the Department of Medical Oncology, Kartal Dr Lutfi Kırdar City Hospital (Istanbul, Türkiye), were retrospectively reviewed. The eligibility criteria were as follows: i) Histologically confirmed NSCLC; ii) no prior exposure to ICIs; and iii) availability of baseline laboratory data before nivolumab initiation.

Patients were eligible if nivolumab treatment had been initiated between 1 January 2022 and 31 December 2023, as predefined in the ethics committee application. The last patient inclusion date was 31 December 2023. This date refers to the final date for inclusion in the study cohort based on nivolumab treatment initiation, not the last nivolumab administration date during follow-up. Some patients had been diagnosed with early-stage disease and followed at the Outpatient Clinic for several years before developing metastatic disease. Therefore, follow-up time from initial diagnosis was reported descriptively, whereas survival endpoints [overall survival (OS) and progression-free survival (PFS)] were calculated strictly from the date of nivolumab initiation.

This retrospective study received approval from the Ethics Committee of Kartal Dr Lutfi Kırdar City Hospital (approval no: 2024/01.09.92/6; dated 27 March 2024) prior to retrospective patient screening, data collection and analysis. Patient files and electronic medical records were retrospectively accessed, reviewed and transferred to the study database between 1 April 2024 and 30 June 2024. The dataset was last updated on 30 June 2024, which served as the final data cut-off date. The latest nivolumab treatment record included in the study dataset was dated 30 June 2024. No new patients were included after 31 December 2023. Some patients may have continued nivolumab as part of routine clinical care after the final data cut-off; however, treatment or follow-up data after 30 June 2024 were not included in the analysis.

Exclusion criteria were as follows: i) Nivolumab as first-line therapy; ii) treatment in combination with chemotherapy or ipilimumab; iii) or treatment with any other ICI. A total of 22 patients who received 1-3 cycles of nivolumab and 8 patients who had received ≥4 cycles without a response assessment by the final cut-off date were excluded. Another 1 patient with mixed histology containing a small-cell component and 2 patients with concurrent hematological malignancies were also excluded, leaving 270 patients for analysis. In our healthcare setting, several treatment options were available for mNSCLC, including targeted therapies and combination immunotherapy approaches; however, nivolumab was the only reimbursed ICI for patients with mNSCLC receiving second-line or later treatment during the study period, and it was administered intravenously at a standard dose of 3 mg/kg every 14 days.

Baseline laboratory parameters and response evaluation. Baseline laboratory parameters were obtained prior to nivolumab initiation, including absolute neutrophil ($x10^3/\mu l$), monocyte ($x10^3/\mu l$), platelet ($x10^3/\mu l$) and lymphocyte ($x10^3/\mu l$) counts. PIV was calculated as a derived index using the following formula: PIV=(neutrophil count x platelet count x monocyte count)/lymphocyte count. Tumor response was assessed every 10-12 weeks as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (16). PFS was calculated from the start date of nivolumab treatment to the date of radiographic progression or death from any cause. For patients lost to follow-up, data were censored on the last date the patient was seen alive without radiographic progression. Overall survival (OS) was calculated from the start date of nivolumab treatment until death or the last follow-up. To avoid ambiguity, all time-to-event endpoints in the present study were anchored to the initiation of nivolumab.

Statistical analysis. Descriptive statistics are presented as the mean ± standard deviation, median (interquartile range), range (minimum-maximum) or n (%). The normal distribution assumption was examined using the Shapiro-Wilk test. Performance measures of the area under the curve (AUC), sensitivity and specificity were evaluated for PIV and the combined test in predicting resistance to nivolumab treatment. The Youden index was used to determine the cutoff value of 604.5 for PIV. Accordingly, patients with PIV values ≤604.5 were categorized as the low PIV group, whereas those with PIV values >604.5 were categorized as the high PIV group. The combined test score was derived through binary logistic regression predicting resistance to nivolumab, with PIV and blood type as covariates. A comparison of AUC between PIV and the combined test was conducted using DeLong's method. Binary logistic regression predicting resistance to nivolumab was performed with the enter method for univariate analysis and forward likelihood ratio for multivariate analysis. Covariates with $P<0.25$ in univariate analyses were considered for inclusion in the multivariate logistic regression model, which was performed using the forward likelihood ratio method.

Missing data were handled by complete-case analysis. For each analysis, patients with missing values in any variable required for that analysis were excluded. Therefore, the combined model that included blood type was calculated only for patients with available blood group data.

Comparisons between low and high PIV groups were examined using the Mann-Whitney U test, χ^2 test, Fisher's exact test or Yates' continuity correction. OS and progression-free survival were estimated with the Kaplan-Meier method. Survival curves for the low and high PIV groups were

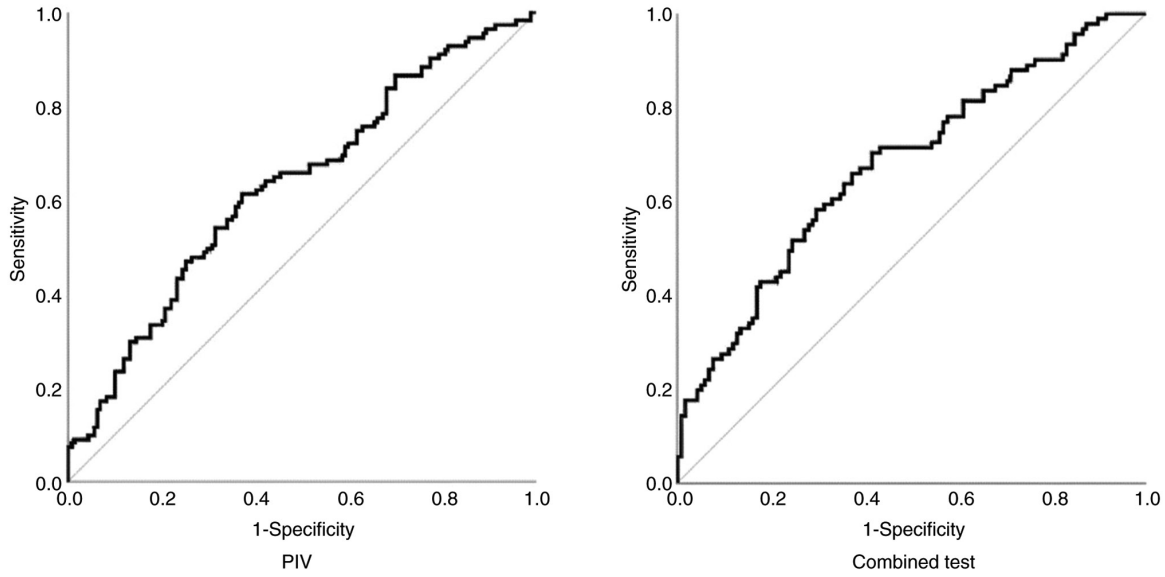

Figure 1. Receiver operating characteristic curves showing the performance of baseline PIV and the combined model (PIV + blood type) in predicting nivolumab resistance. Area under the curve, sensitivity and specificity are presented. The PIV cut-off was determined using the Youden index. PIV, pan-immune-inflammation value.

compared using the log-rank test. P<0.05 was considered to indicate a statistically significant difference. All analyses were conducted using SPSS Statistics for Windows, Version 17.0 (SPSS, Inc.) and pROC package in R (17).

Results

Patient characteristics. Baseline patient characteristics are summarized in Table I. The mean age was 62.8 years (range, 24-88 years), and 84% of the patients were male. The most common blood type was A (31.1%), followed by O (28.9%), B (10.0%) and AB (7.4%).

Comorbidities were present in 59.3% of patients, most commonly diabetes mellitus or hypertension (n=69), chronic obstructive pulmonary disease (n=45), and congestive heart failure (CHF) or coronary artery disease (CAD; n=29). The majority of patients had an ECOG performance status of 0-1 (53.3%). The median baseline PIV was 571 (IQR, 313-1031) with a range of 23 to 9,895.

Adenocarcinoma was the most common histological subtype (44.1%), followed by squamous cell carcinoma (SCC) (39.3%) and mixed histology (13.7%). At diagnosis, 41.9% of patients had early-stage disease and 57.8% had advanced-stage disease.

Regarding the prior progression pattern, 70.4% of patients had progressed during prior chemotherapy, whereas 29.6% had progressed after prior chemotherapy. Overall, the prior chemotherapy response rate among patients with available data was 41.9% (n=111/265) (Table I).

Nivolumab was administered as second-line therapy in 25.6% of patients and as third-line or later in 74.4%. The median time since the previous chemotherapy was 2 months (range, 0-76 months). Treatment responses included PD in 41.1%, PR in 30.4%, SD in 22.2% and CR in 6.3%. Treatment-related toxicity was observed in 29.3% of patients, and treatment delays occurred in 35.9%.

AUC analysis. The AUC analyses showed that both PIV (AUC, 0.63; 95% CI, 0.56-0.70) and the combined test (AUC, 0.68; 95% CI, 0.60-0.75) could distinguish nivolumab responders from non-responders (P<0.001) (Fig. 1; Table II). The specificity was 62.9% for PIV and 78.8% for the combined test, which were relatively higher than the sensitivity of both PIV (61.3%) and the combined test (42.9%) (Table II). The difference in AUC between PIV and the combined test was not statistically significant (Z=-1.191; P=0.234).

Binary logistic regression. The results of the univariate analyses and the multiple regression predicting resistance to nivolumab treatment are presented in Table III. Univariate analysis showed that high PIV (OR, 2.68; 95% CI, 1.63-4.42; P<0.001), blood type B vs. O (OR, 3.57; 95% CI, 1.42-9.00; P=0.007) and ECOG 2 vs. 0-1 (OR, 2.56; 95% CI, 1.12-5.86; P=0.027) were associated with nivolumab resistance. Variables with P<0.25 in the univariate analyses were considered for multivariate logistic regression, and Table III presents the variables retained in the final forward likelihood ratio model.

Multivariate logistic regression identified high PIV (OR, 4.46; 95% CI, 1.92-10.38; P=0.001), blood type AB (OR, 7.24; 95% CI, 1.82-28.81; P=0.005) and blood type B (OR, 4.76; 95% CI, 1.08-20.94; P=0.039) compared with O, ECOG 2 versus 0-1 (OR, 4.78; 95% CI, 1.54-14.82; P=0.007), and prior chemotherapy resistance (OR, 2.48; 95% CI, 1.07-5.76; P=0.034) as independent predictors of nivolumab resistance. The model fit was good (χ^2=32.0; P<0.001; Nagelkerke R^2=0.302), with a sensitivity of 66.1% and a specificity of 75.8% (Table III).

Low and high PIV patient groups. Among the cohort, 143 patients (53.0%) had a low PIV and 127 (47.0%) had a high PIV (Table IV). The groups were similar in terms of baseline characteristics, including age, sex, blood type, ECOG score, histology, disease stage, prior treatment history and toxicity (all P>0.05). Co-morbidity was less common in the high PIV

Table I. Baseline demographic and clinicopathological characteristics of the study population (n=270).

Variable	n (%)	Mean ± SD	Median (IQR)	Range
Age, years		62.83±8.37	63 (58-68)	24-88
Male	227 (84.07)			
Blood type				
O	78 (28.89)			
A	84 (31.1)			
B	27 (10.00)			
AB	20 (7.41)			
Missing	61 (22.59)			
CM presence				
Any CM	160 (59.26)			
COPD	45 (16.67)			
CHF or CAD	29 (10.74)			
DM or HT	69 (25.56)			
Other CM	17 (6.30)			
ECOG				
2	34 (12.59)			
0 or 1	144 (53.33)			
Missing	92 (34.07)			
PIV		876.92±998.68	571 (313-1031)	23-9895
Tumor histology				
ADC	119 (44.07)			
SCC	106 (39.26)			
Mixed	37 (13.70)			
Missing	8 (2.96)			
Stage at diagnosis				
Early	113 (41.85)			
Advanced	156 (57.78)			
Missing	1 (0.37)			
Prior progression pattern				
During prior CT	190 (70.37)			
After prior CT	80 (29.63)			
Time elapsed after CT, months		4.59±8.85	2 (1-5)	0-76
Responsive to Prior CT[a]	111 (41.89)			
Nivolumab use line				
Second-line	69 (25.56)			
Third-line or beyond	201 (74.44)			
Nivolumab resistance	111 (41.11)			
Nivolumab response				
Complete	17 (6.30)			
Partial	82 (30.37)			
Stable	60 (22.22)			
Progression	111 (41.11)			
Nivolumab delay	97 (35.93)			
Presence of toxicity	79 (29.26)			

[a]n=265. CT, chemotherapy; CM, co-morbidity; DM, diabetes mellitus; HT, hypertension; ADC, adenocarcinoma; CHF, congestive heart failure; CAD, coronary artery disease; ECOG, Eastern Cooperative Oncology Group; PIV, pan-immune-inflammation value; SCC, squamous cell carcinoma; COPD, chronic obstructive pulmonary disease.

group (41.3 vs. 58.8%; P=0.022). Treatment responses (CR, PR and SD) were significantly lower in patients with a high PIV (P=0.001), whereas nivolumab resistance was higher (61.3 vs. 38.7%; P<0.001).

Table II. Receiver operating characteristic analysis.

Test	AUC (95% CI)	Sensitivity, %	Specificity, %
PIV	0.631 (0.563-0.698)[a]	61.26[b]	62.89[b]
Combined test[c]	0.676 (0.603-0.749)[a]	42.86	78.81

[a]Null hypothesis: True area=0.50 rejected at P<0.001 level. [b]Cut-off value 604.49 estimated based on Youden Index. [c]Includes PIV and blood type (n=209). The AUCs of PIV and the combined test were compared using DeLong's method, and the difference was not statistically significant (Z=-1.191; P=0.234). AUC, area under the curve; CI, confidence interval; PIV, pan-immune-inflammation value.

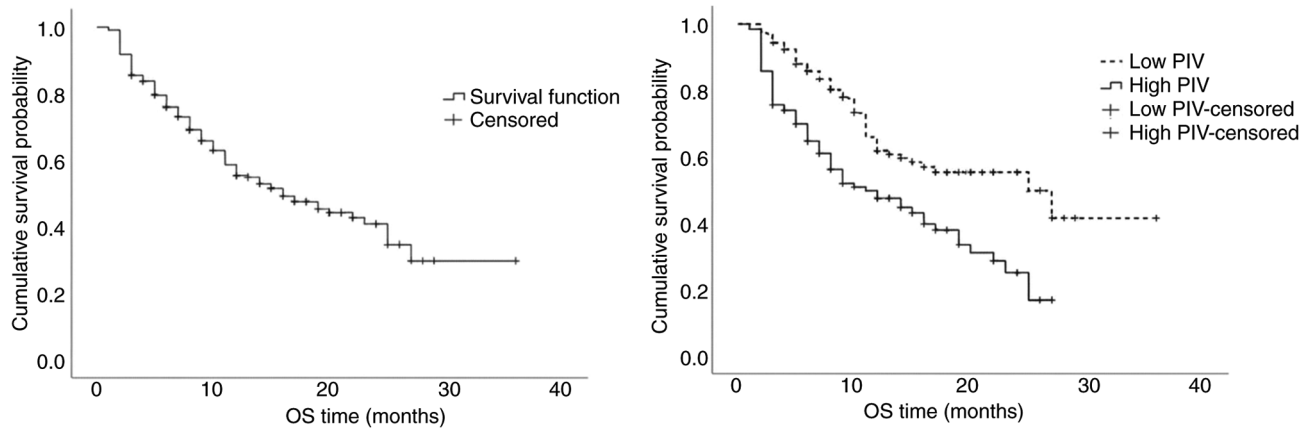

Figure 2. Kaplan-Meier curves for OS stratified by PIV groups (cut-off, 604.5). Median OS is shown. Groups were compared using the log-rank test. OS, overall survival; PIV, pan-immune-inflammation value.

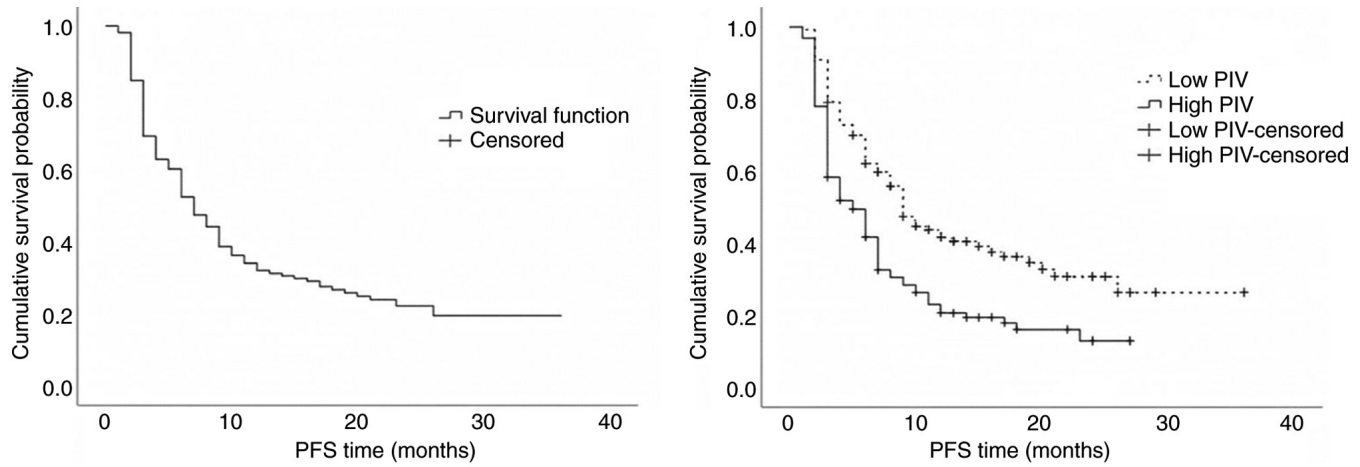

Figure 3. Kaplan-Meier curves for PFS stratified by PIV groups (cut-off, 604.5). Median PFS is shown. Groups were compared using the log-rank test. PFS, progression-free survival; PIV, pan-immune-inflammation value.

Survival analysis. Survival outcomes are presented in Table V and Figs. 2 and 3. The 12-month overall survival rate was 53.3%, and the 12-month progression-free survival rate was 32.6%. The 3-year OS and PFS rates were 29.4 and 19.4%, respectively. The median OS was 16 months (95% CI, 11.1-20.9), and the median PFS was 7 months (95% CI, 5.9-8.2). Patients with a high PIV had significantly shorter OS (11 vs. 25 months) and PFS (5 vs. 9 months) times compared with those with low PIV (both P<0.001).

Discussion

PIV, a relatively new biomarker derived from routine blood counts, has shown a prognostic value across multiple cancer types, particularly NSCLC. Emerging evidence indicates it may also predict treatment response (7,9). The present study demonstrated the effectiveness of nivolumab in mNSCLC treated with second-line and subsequent therapies, revealing both the prognostic and predictive roles of PIV in this context.

Table III. Logistic regression analysis predicting resistance to nivolumab therapy.

	Univariate regression[a]		Multivariate regression[b]	
Covariate (ref.)	OR (95% CI)	P-value	OR (95% CI)	P-value
PIV (low)				
High	2.68 (1.63-4.42)	<0.001[c]	4.46 (1.92-10.38)	0.001[c]
Blood type (O)		0.034[c]		0.035[c]
A	1.21 (0.64-2.29)	0.549	1.96 (0.76-5.03)	0.162
AB	2.18 (0.81-5.90)	0.124	7.24 (1.82-28.81)	0.005[c]
B	3.57 (1.42-9.00)	0.007[c]	4.76 (1.08-20.94)	0.039[c]
ECOG (0 or 1)				
2	2.56 (1.12-5.86)	0.027[c]	4.78 (1.54-14.82)	0.007[c]
Prior CT response (responsive)				
Resistant	1.39 (0.84-2.28)	0.200	2.48 (1.07-5.76)	0.034[c]
Age	1.01 (0.98-1.04)	0.412	-	-
Sex (male)				
Female	0.93 (0.48-1.80)	0.819	-	-
Co-morbidity (absent)				
Present	0.61 (0.37-1.00)	0.051	-	-
COPD (absent)				
Present	0.85 (0.44-1.63)	0.619	-	-
CHF or CAD (absent)				
Present	0.61 (0.27-1.40)	0.247	-	-
DM or HT (absent)				
Present	0.76 (0.43-1.34)	0.340	-	-
Other co-morbidity (absent)				
Present	1.00 (0.37-2.72)	0.995	-	-
Tumor histology (ADC)		0.155	-	-
SCC	1.40 (0.82-2.41)	0.218	-	-
Mixed type	2.01 (0.95-4.24)	0.067	-	-
Stage at diagnosis (early)				
Advanced	1.43 (0.87-2.35)	0.159	-	-
Nivolumab line (second-line)				
Third-line or beyond	1.12 (0.64-1.95)	0.698	-	-
Time elapsed after prior CT	1.00 (0.97-1.02)	0.775	-	-
Toxicity in nivolumab (absent)				
Present	1.39 (0.81-2.38)	0.230	-	-
Delay in nivolumab (absent)				
Present	1.16 (0.70-1.92)	0.572	-	-
Pattern of prior progression, (after prior CT)				
During prior CT	1.56 (0.90-2.68)	0.112	-	-

[a]Univariate logistic regression analyses were performed using the enter method. [b]Multivariate logistic regression was performed using the forward likelihood ratio method. Variables with P<0.25 in the univariate analyses were considered for inclusion, and only variables retained in the final model are shown. Final step (step 4) of the multivariate regression yielded χ^2=32.045, df=6, P<0.001; Cox & Snell R^2=0.226; Nagelkerke R^2=0.302; and Hosmer and Lemeshow χ^2 test=2.282, df=8, P=0.971. [c]P<0.05. CT, chemotherapy; CM, co-morbidity; DM, diabetes mellitus; HT, hypertension; SCC, squamous cell carcinoma; ADC, adenocarcinoma; COPD, chronic obstructive pulmonary disease; PIV, pan-immune-inflammation value; OR, odds ratio; CI, confidence interval; CHF, congestive heart failure; CAD, coronary artery disease.

In the present cohort, 84% of patients were male, which is higher than the proportions reported in the pivotal CheckMate 017 and CheckMate 057 trials (3,18). This may reflect the higher prevalence of EGFR mutations among female patients and the national reimbursement restriction in Türkiye, whereby nivolumab was not reimbursed for patients with EGFR-mutant

Table IV. Comparisons between low and high PIV groups.

Variable	Low PIV	High PIV	P-value
Median age (IQR)	63 (58-69)	62 (58-67)	0.726[a]
Sex, n (%)			
Male	119 (52.42)	108 (47.58)	0.683[b]
Female	24 (55.81)	19 (44.19)	
Blood type, n (%)			
O	35 (44.87)	43 (55.13)	0.072[b]
A	47 (55.95)	37 (44.05)	
AB	14 (70.00)	6 (30.00)	
B	10 (37.04)	17 (62.96)	
Co-morbidity presence, n (%)	94 (58.75)	66 (41.25)	0.022[b,c]
COPD presence, n (%)	25 (55.56)	20 (44.44)	0.703[b]
CHF or CAD presence, n (%)	20 (68.97)	9 (31.03)	0.078[d]
DM or HT presence, n (%)	38 (55.07)	31 (44.93)	0.684[b]
Other CM presence, n (%)	11 (64.71)	6 (35.29)	0.452[d]
ECOG, n (%)			
2	17 (50.0)	17 (50.0)	0.684[e]
0 or 1	80 (55.56)	64 (44.44)	
Tumor histology, n (%)			
ADC	69 (57.98)	50 (42.02)	0.478[d]
SCC	53 (50.0)	53 (50.0)	
Mixed	19 (51.35)	18 (48.65)	
Stage at diagnosis (early), n (%)			
Early	64 (56.64)	49 (43.36)	0.331[b]
Metastatic	79 (50.64)	77 (49.36)	
Pattern of prior progression, n (%)			
During prior CT	94 (49.47)	96 (50.53)	0.077[b]
After prior CT	49 (61.25)	31 (38.75)	
Responsive to prior CT, n (%)	65 (58.56)	46 (41.44)	0.091[b]
Nivolumab line, n (%)			
Second-line	41 (59.42)	28 (40.58)	0.213[b]
Third-line or beyond	102 (50.75)	99 (49.25)	
Median time elapsed after prior CT (IQR)	2 (1-7)	1 (0-4)	0.137[a]
Nivolumab response, n (%)			
Complete	13 (76.47)	4 (23.53)	0.001[c,d]
Partial	51 (62.20)	31 (37.80)	
Stable	36 (60.0)	24 (40.0)	
Progression	43 (38.74)	68 (61.26)	
Resistance to nivolumab, n (%)	43 (38.74)	68 (61.26)	<0.001[b,c]
Toxicity presence in nivolumab, n (%)	41 (51.90)	38 (48.10)	0.947[b]
Delay in nivolumab, n (%)	52 (53.61)	45 (46.39)	0.878[b]

Low PIV (n=143) versus high PIV (n=127) compared with [a]Mann-Whitney U test. [b]χ^2 test. [c]P<0.05. [d]Fisher's exact test. [e]Yates' continuity correction. CT, chemotherapy; CM, co-morbidity; DM, diabetes mellitus; HT, hypertension; ADC, adenocarcinoma; SCC, squamous cell carcinoma; COPD, chronic obstructive pulmonary disease; PIV, pan-immune-inflammation value; CHF, congestive heart failure; CAD, coronary artery disease; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

mNSCLC during the study period; this may have indirectly reduced the proportion of female patients eligible to receive nivolumab.

The median follow-up period from initial diagnosis was 17 months (range, 2-89 months), reflecting the inclusion of patients who had been monitored for early-stage disease before

Table V. Survival in nivolumab treatment.

A, Overall survival

Group	Total, n	Events, n (%)	Median survival time (95% CI)	Log-rank test value	P-value
All patients	270	126 (46.67)	16 (11.06-20.94)		
Low PIV	143	53 (37.06)	25 (15.24-34.76)	16.795	P<0.001[a]
High PIV	127	73 (57.48)	11 (6.15-15.85)		

B, Progression-free survival

Group	Total, n	Events, n (%)	Median survival time (95% CI)	Log-rank test value	
All patients	270	182 (67.41)	7 (5.85-8.15)		
Low PIV	143	86 (60.14)	9 (7.47-10.53)	16.869	P<0.001[a]
High PIV	127	96 (75.59)	5 (3.43-6.57)		

[a]P<0.05. Survival descriptives are estimated with the Kaplan-Meier method. PIV, pan-immune-inflammation value; CI, confidence interval.

developing metastatic progression. This relatively short median follow-up time was mainly due to the inclusion of nivolumab in the reimbursement system in Türkiye in January 2022, which led to a rapid increase in the number of patients treated.

The median OS (mOS) time was 16 months and the median PFS (mPFS) time was 7 months, both surpassing the pooled final results of CheckMate 017 and 057 (mOS, 11.1 months; mPFS, 2.5 months) (18). This difference likely reflects real-world factors, including less strict application of RECIST criteria and longer assessment intervals in routine practice (19,20). The wide variability of mOS in real-world studies, ranging from 5.9 to 18.7 months (21-24), supports this interpretation. Due to the retrospective design of the present study, detailed stratification of prior chemotherapy regimens (such as platinum-based versus non-platinum-based) was not consistently available. As a result, the potential influence of specific chemotherapy types on baseline PIV and subsequent immunotherapy outcomes could not be comprehensively assessed, which should be considered when interpreting the present findings.

Although variability in RECIST application and assessment intervals may affect median survival estimates, it is less likely to influence fixed-time-point outcomes (such as 1- or 3-year survival rates). The present 3-year OS and PFS rates were 29.4 and 19.4%, respectively, which were notably higher than those reported in the pooled CheckMate 017/057 data (17 and 10%, respectively) (25). These findings support the robustness of the present results and confirm the effectiveness of nivolumab administered in the second and subsequent lines of therapy in routine clinical practice. Notably, as 74.4% of patients received nivolumab in the third line or beyond, the observed benefit underscores its value even in later treatment settings.

Although several treatment options are currently available for mNSCLC, including targeted therapies and combination immunotherapy regimens, the treatment landscape in the present real-world setting was influenced by reimbursement policies. During the study period, nivolumab was the only reimbursed ICI in the second-line or later setting, which explains its exclusive use in this cohort. This reflects real-world clinical practice in Türkiye and should be considered when interpreting the generalizability of these findings.

The prognostic role of PIV has been reported in several cancer types, including NSCLC (7-13). The present findings confirmed its prognostic importance in mNSCLC treated with nivolumab beyond first-line therapy. Both OS and PFS times were significantly longer in the low PIV group (P<0.001; Figs. 2 and 3), despite a higher co-morbidity rate (Table IV), underscoring the prognostic value of PIV. The inverse relationship between co-morbidity and high PIV may reflect chance, selection bias or residual confounding. Unlike a prior report (26) suggesting an association with immune-related toxicities, the present data showed no significant difference in adverse events between PIV groups, indicating that baseline PIV was not predictive of nivolumab-related toxicity.

Recent studies have suggested that PIV may have both predictive and prognostic value (9,14,27). The present study supported this, showing that patients with a low PIV had higher response rates (CR, PR and SD) and fewer cases of nivolumab resistance (38.7 vs. 61.3%) than those with a high PIV (Table IV). These findings offer real-world evidence that baseline PIV can predict response to nivolumab and inform treatment decisions in routine practice. In the present study, ROC analysis demonstrated a moderate discriminative performance of baseline PIV in predicting resistance to nivolumab; however, this level of discrimination is consistent with that of most blood-based inflammatory biomarkers and does not diminish its clinical utility for risk stratification rather than absolute prediction. No universally accepted PIV threshold has been established, and previously reported cut-off values vary across studies, probably reflecting differences in tumor biology, treatment context and patient populations (8,10-14). Therefore, the optimal PIV cut-off of 604.5, determined using the Youden index in the present study, should be considered cohort-specific, and external validation is required before clinical implementation.

In multivariable logistic regression, high PIV was independently associated with 4.46-fold higher odds of nivolumab resistance than low PIV. ECOG 2 status was also associated with 4.78-fold higher odds than ECOG 0-1. Resistance was 7.24 times higher in blood group AB and 4.76 times higher in blood group B compared with group O. In addition, lack of response to prior chemotherapy was associated with a 2.48-fold increased likelihood of nivolumab resistance.

Compared with simpler inflammatory indices such as NLR and PLR, PIV provides a more integrative assessment of systemic inflammation and immune competence. By incorporating neutrophils, platelets and monocytes, key mediators of tumor-promoting inflammation, alongside lymphocytes, which reflect antitumor immune activity, PIV may more effectively capture the complex interaction between inflammation and immune response in patients with cancer. This multidimensional approach may enhance its prognostic and predictive value, particularly in the context of immunotherapy.

The association between ABO blood groups and immunotherapy outcomes remains incompletely defined and appears to be context-dependent across tumor types and treatment settings. Although some studies have suggested improved survival among patients with blood group O, the distinction between prognostic and predictive effects remains unclear and the available evidence is heterogeneous (28-30). In this context, the present findings show that patients with blood group O not only have prolonged OS and PFS times, but that they also exhibit higher objective response rates to nivolumab, suggesting that the observed survival advantage may, at least in part, reflect enhanced responsiveness to immune checkpoint blockade rather than a purely baseline prognostic effect. However, given the retrospective design, limited sample size and inconsistent findings across malignancies, ABO blood group cannot currently be considered a clinically actionable biomarker and should be regarded as a hypothesis-generating finding requiring prospective validation.

From a biological perspective, PIV reflects neutrophil-, platelet- and monocyte-driven inflammatory activity relative to lymphocytic function, potentially indicating a protumor systemic environment (31). Similarly, ABO antigens and naturally occurring anti-A/anti-B antibodies are considered to influence immune surveillance and tumor-immune interactions (32). Although mechanistic data remain limited, these frameworks may partially explain the observed associations. PIV reflects the balance between pro-tumor inflammatory processes and antitumor immune activity. Elevated neutrophil, platelet and monocyte counts are linked to tumor-promoting mechanisms, including the secretion of pro-inflammatory cytokines, facilitation of tumor growth and angiogenesis, and suppression of cytotoxic immune responses. Conversely, lymphocytes are key players in antitumor immunity through direct destruction of tumor cells and immune surveillance (31,32). Therefore, a high PIV may indicate a systemic environment with increased inflammation and reduced immune function, which could lead to resistance to ICIs. On the other hand, a low PIV might suggest a more favorable immune profile, supporting a stronger response to immunotherapy.

The present study has several limitations. First, its retrospective, single-center design may introduce selection bias and limit generalizability, although the inclusion of consecutive, unselected patients reflects real-world clinical practice. Missing data for certain clinical variables required complete-case analysis, which may have reduced statistical power. An important limitation is the lack of PD-L1 expression data. In the present study, nivolumab was used exclusively in the second-line or later setting, where treatment decisions were independent of PD-L1 status according to national reimbursement criteria; therefore, PD-L1 testing was not routinely performed. The absence of molecular and immunological biomarkers, such as tumor mutational burden, tumor-infiltrating lymphocytes and kelch-like ECH-associated protein 1/serine/threonine kinase 11 alterations, further limited comprehensive biomarker integration. In addition, established prognostic indices such as the Lung Immune Prognostic Index (33) were not available, precluding direct comparison with PIV. Systemic inflammatory markers may be influenced by confounding factors, including infections and corticosteroid use; although these could not be systematically adjusted for, patients with active infection or requiring high-dose corticosteroids are generally not considered candidates for immunotherapy, indicating a limited but non-negligible confounding effect. Finally, the lack of an independent external validation cohort further restricts generalizability. Therefore, prospective, multicenter studies are warranted before clinical implementation.

Overall, nivolumab showed positive results and manageable toxicity in second- and later-line mNSCLC, consistent with key trials. Baseline PIV had both prognostic and predictive value, whereas ABO blood groups were identified as exploratory, hypothesis-generating predictors requiring external validation. These findings emphasized the potential clinical usefulness of easily accessible baseline parameters for treatment decision-making in everyday practice.

In conclusion, the baseline pan-immune-inflammation value may serve as a simple, readily available tool for risk stratification in mNSCLC treated with nivolumab beyond first line; the observed association with ABO blood group should be considered exploratory pending prospective or external validation.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NT was responsible for study conception and design, data analysis and manuscript writing. HSY, SY, ET, UO, SO and HB performed data acquisition and interpretation. NB, HS, HB and HO were responsible for the critical review and approval of the final manuscript. NB, HS and HO contributed substantially to

the acquisition and verification of the clinical data, interpretation of the study data, critical revision of the manuscript for important intellectual content, approval of the final version to be published, and agree to be accountable for all aspects of the work. NT and HSY confirm the authenticity of all the raw data. All authors have read and approved the manuscript.

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Kartal Dr Lütfi Kırdar City Hospital (Istanbul, Türkiye; approval no. 2024/01.09.92/6; date 27 March 2024). This approval was obtained before data collection began. Retrospective data collection started on 1 April 2024, and the dataset was last updated on 30 June 2024, which served as the final data cut-off date. Due to the retrospective design and the use of anonymized patient data, the requirement for informed consent was waived by the Ethics Committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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