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Research Article

Pretreatment CALLY Index and Survival Outcomes in Metastatic Non-Small Cell Lung Cancer Treated with Nivolumab: A Multicenter Retrospective Study

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Abstract

Objectives: The C-reactive protein–albumin–lymphocyte (CALLY) index reflects systemic inflammation, nutritional status, and immune competence. We evaluated its prognostic value in patients with metastatic non-small cell lung cancer (NSCLC) treated with nivolumab in the second-line or later setting.

Methods: This multicenter retrospective study included 181 patients receiving nivolumab monotherapy. The CALLY index was calculated from pretreatment albumin, absolute lymphocyte count, and C-reactive protein levels. Patients were divided into low and high CALLY groups using the cohort median. Progression-free survival (PFS) and overall survival (OS) were analyzed with Kaplan–Meier method, and independent prognostic factors were evaluated using Cox proportional hazards regression analyses.

Results: Median follow-up was 27.6 months. Median PFS was shorter in the low CALLY group than in the high CALLY group (5.2 vs. 10.9 months; p=0.002), as was median OS (10.3 vs. 19.3 months; p<0.001). In multivariable analyses, a high CALLY index remained independently associated with longer PFS (HR 0.62, 95% CI 0.42–0.90; p=0.012) and OS (HR 0.47, 95% CI 0.31–0.72; p<0.001).

Conclusion: The pretreatment CALLY index was independently associated with survival outcomes in patients with metastatic NSCLC treated with nivolumab and may be useful for prognostic risk stratification in this population.

Keywords: CALLY Index, Non-Small Cell Lung Cancer, Nivolumab

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Although there have been significant improvements in systemic therapies, advanced non-small cell lung cancer (NSCLC) still exhibits considerable clinical heterogeneity and variable survival outcomes.[1,2] As molecular profiling has become a standard part of clinical practice, the management of metastatic NSCLC has become increasingly individualized, and immune checkpoint inhibitors (ICIs) have become a central component of systemic therapy for patients without actionable driver alterations.[3–5] However, the clinical benefit derived from immunotherapy varies considerably among patients; while some achieve durable disease control, others experience early progression.[6,7] Although programmed death-ligand 1 (PD-L1) expression may contribute to patient selection, it does not provide a sufficiently practical and reliable predictive tool for all patients because of tissue requirements, tumor heterogeneity, and a lack of standardization.[8–10] Therefore, there remains a need for easily applicable, low-cost, blood-based biomarkers that can help estimate prognosis in patients with metastatic NSCLC receiving immunotherapy.[11,12]

Cancer-related systemic inflammation is one of the key biological processes involved in tumor progression, immune escape, and treatment response.[13,14] As a result, there has been growing interest in using inflammatory and nutritional indicators derived from peripheral blood to predict outcomes in patients with NSCLC undergoing immunotherapy.[15,16] Routine blood tests can be used to generate composite measures that reflect inflammation, nutritional status, and immune competence. Such measures have been associated with survival outcomes and may offer a practical way to estimate prognosis in patients with NSCLC receiving immunotherapy.[17–21]

The C-reactive protein–albumin–lymphocyte (CALLY) index is calculated from routine laboratory values and provides a composite representation of inflammatory burden, nutritional status, and immune status.[22] Its components, C-reactive protein, albumin, and lymphocyte count, provide information on inflammatory burden, nutritional and inflammatory status, and immune competence, respectively.[22–24] In numerous solid tumors, particularly those affecting the gastrointestinal tract, the CALLY index has demonstrated prognostic significance.[22,25] Recently, its prognostic value has also been demonstrated in patients with metastatic melanoma undergoing anti-PD-1 treatment, supporting its potential role in immunotherapy.[26] Research in NSCLC has investigated the association between the CALLY index and survival outcomes; however, the available data have mainly been derived from heterogeneous NSCLC cohorts, surgically resected patients with early- to locally advanced-stage disease, or locally advanced populations treated with thoracic radiotherapy.[27–29] The available evidence does not appear to include a dedicated evaluation of the CALLY index in patients with metastatic NSCLC receiving ICIs. Moreover, the cutoff values used in previous studies have varied according to tumor type, treatment setting, and statistical method, indicating the need to evaluate the CALLY index separately across different clinical contexts.[25,26,30]

This multicenter, real-world analysis examined whether baseline CALLY levels could stratify survival among patients with metastatic NSCLC receiving nivolumab beyond the first-line setting.

Methods

Study Design and Patient Population

Between May 2016 and October 2024, this retrospective cohort study was conducted at two oncology centers and included patients with metastatic NSCLC treated with nivolumab beyond the first-line setting. Eligible patients were required to be at least 18 years old, have histologically or cytologically confirmed NSCLC, have radiological evidence of metastatic disease, and have received nivolumab monotherapy after at least one prior systemic treatment. Inclusion was limited to patients for whom the baseline laboratory parameters required to calculate the CALLY index were available. Laboratory values were recorded within two weeks before the initiation of nivolumab therapy.

Patients were excluded if they had insufficient clinical or survival data, missing pretreatment CRP, albumin, or lymphocyte values, a concomitant active malignancy, or clinical evidence of active infection during the pretreatment period.

Clinical Data and CALLY Index

Data on demographics, clinicopathological characteristics, and laboratory findings were collected retrospectively from the participating institutions. The clinical variables documented included patient demographics, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking history, timing of metastatic disease (synchronous or metachronous), histological subtype, PD-L1 status, metastatic sites, and nivolumab treatment line.

The pretreatment CALLY index was calculated by dividing the product of the serum albumin level (g/dL) and absolute lymphocyte count (10^3/μL) by the CRP level (mg/L).

Since a validated cutoff value for the CALLY index in patients with metastatic NSCLC receiving nivolumab has not been established, the cohort was divided into low- and high-CALLY groups using the cohort median as an outcome-independent threshold, thereby avoiding the derivation and testing of a survival-optimized cutoff within the same dataset.

For comparison, NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, while PNI was calculated as 10×albumin (g/dL)+0.005×absolute lymphocyte count (/mm^3). NLR and PNI were also dichotomized at their cohort medians. GPS was categorized as 0 or 1–2 according to CRP and albumin levels, with a score of 0 for CRP≤10 mg/L and albumin≥3.5 g/dL, 1 when either parameter was abnormal, and 2 when both were abnormal.

Outcome Definitions

Progression-free survival (PFS) was calculated from the first nivolumab dose to radiological progression or death, whichever occurred first. Patients without either event were censored on the date of their last clinical assessment. Overall survival (OS) was calculated from nivolumab initiation to death from any cause, with survivors censored at their most recent follow-up.

Statistical Analysis

Analyses were performed using IBM SPSS Statistics 27.0. Continuous variables were summarized according to the results of the Shapiro–Wilk test, and categorical variables were presented as numbers and percentages. Between-group comparisons were performed using parametric or nonparametric tests for continuous data and chi-square or Fisher's exact tests for categorical data.

Kaplan–Meier curves and log-rank tests were used for PFS and OS. Cox models were fitted for univariate and adjusted analyses; variables with p<0.10 or clear clinical relevance were considered for multivariable modeling. Hazard ratios are reported with 95% confidence intervals, and two-sided p<0.05 indicated statistical significance. A sensitivity analysis was additionally performed in patients with available PD-L1 data to evaluate whether the association between the CALLY index and survival outcomes was maintained after accounting for PD-L1 status.

Separate multivariable Cox models were used for CALLY, NLR, PNI, and GPS. Each index was assessed with the same clinical covariates used in the corresponding primary PFS or OS model rather than entering the inflammation-based indices together because their components overlap.

Ethical Considerations

Approval for this retrospective study was granted by the Ethics Committee of İstanbul University-Cerrahpaşa (Date: January 22, 2025, Decision no: E-74555795-050.04-1231222) in accordance with the principles of the Declaration of Helsinki. Owing to the retrospective design, informed consent was waived by the Ethics Committee.

Results

Baseline Patient Characteristics

This research included 181 patients diagnosed with metastatic NSCLC who received nivolumab treatment. The median age of the participants was 64 years (IQR, 59–70). Among these patients, 141 (77.9%) were male. A substantial proportion, 82.3%, had an ECOG performance status of 0–1, and 85.6% had a history of smoking. Synchronous metastatic disease was observed in 95 patients, accounting for 52.5% of the cohort. Adenocarcinoma was the most prevalent histological subtype, accounting for 56.4% of cases.

The median CALLY index was 0.32 (IQR, 0.11–0.99). According to this value, 91 patients were assigned to the low-CALLY group, while 90 were assigned to the high-CALLY group. The proportion of male patients was higher in the low-CALLY group than in the high-CALLY group (84.6% vs. 71.1%, p=0.029). Additionally, a greater proportion of patients in the low-CALLY group had an ECOG PS≥2 (26.4% vs. 8.9%, p=0.002). Bone metastasis was also more prevalent in the low-CALLY group (42.9% vs. 28.9%, p=0.050). No significant differences were observed between the groups in the other baseline characteristics. Baseline characteristics according to the CALLY index group are shown in Table 1.

Survival Outcomes

The median follow-up duration was 27.6 months (95% CI, 22.3–32.9), and 136 patients (75.1%) experienced progression or death. Median PFS for the entire cohort was 6.9 months (95% CI, 5.4–8.4). According to the CALLY category, median PFS was 5.2 months (95% CI, 3.5–6.9) in the low-CALLY group and 10.9 months (95% CI, 5.4–16.5) in the high-CALLY group (p=0.002) (Figure 1).

Univariate Cox regression identified ECOG PS≥2, metastatic presentation, and liver and bone involvement as factors associated with PFS. Patients with a high CALLY index had a lower risk of progression or death than those with a low CALLY index (HR, 0.58; 95% CI, 0.41–0.82; p=0.002). This association remained significant after adjustment for other variables (HR, 0.62; 95% CI, 0.42–0.90; p=0.012). In the multivariable model, age≥65 years, ECOG PS≥2, and liver metastasis were also associated with poorer PFS (Table 2).

During follow-up, 119 patients (65.7%) died. Median OS was 13.9 months for the entire cohort (95% CI, 11.7–16.1). The corresponding values were 10.3 months in the low-CALLY group (95% CI, 7.3–13.3) and 19.3 months in the high-CALLY group (95% CI, 10.6–28.0; p<0.001) (Figure 2).

For OS, univariate Cox regression showed significant associations with ECOG PS≥2, liver and bone metastases, ele-

Table 1. Baseline characteristics of the study population according to CALLY index group.

	All patients n=181	Low CALLY group n=91	High CALLY group n=90	p
Age (years), median (IQR)	64 (59–70)	64 (59–70)	64.5 (58.75–72)	0.324
Age category, n (%)				
<65 years	94 (51.9)	49 (53.8)	45 (50.0)	0.605
≥65 years	87 (48.1)	42 (46.2)	45 (50.0)	
Gender, n (%)				
Female	40 (22.1)	14 (15.4)	26 (28.9)	**0.029**
Male	141 (77.9)	77 (84.6)	64 (71.1)	
ECOG PS, n (%)				
0–1	149 (82.3)	67 (73.6)	82 (91.1)	**0.002**
≥2	32 (17.7)	24 (26.4)	8 (8.9)	
Smoking status, n (%)				
Yes	155 (85.6)	81 (89.0)	74 (82.2)	0.193
No	26 (14.4)	10 (11.0)	16 (17.8)	
Timing of metastatic disease, n (%)				0.411
Synchronous	95 (52.5)	45 (49.5)	50 (55.6)	
Metachronous	86 (47.5)	46 (50.5)	40 (44.4)	
Histology, n (%)				
Adenocarcinoma	102 (56.4)	47 (51.6)	55 (61.1)	
Squamous cell carcinoma	64 (35.4)	35 (38.5)	29 (32.2)	0.410
NOS	15 (8.3)	9 (9.9)	6 (6.7)	
PD-L1 status, n (%)				
<1%	36 (19.9)	17 (18.7)	19 (21.1)	
≥1%	55 (30.4)	30 (33.0)	25 (27.8)	0.739
Unknown	90 (49.7)	44 (48.4)	46 (51.1)	
Metastatic pattern, n (%)				
Visceral	78 (43.1)	40 (44.0)	38 (42.2)	0.814
Non-visceral	103 (56.9)	51 (56.0)	52 (57.8)	
Metastatic sites, n (%)				
Lung metastasis	128 (70.7)	61 (67.0)	67 (74.4)	0.273
Liver metastasis	28 (15.5)	14 (15.4)	14 (15.6)	0.975
Bone metastasis	65 (35.9)	39 (42.9)	26 (28.9)	**0.050**
Adrenal metastasis	42 (23.2)	22 (24.2)	20 (22.2)	0.756
Brain metastasis	31 (17.1)	18 (19.8)	13 (14.4)	0.341
Nivolumab treatment line, n (%)				
Second line	156 (86.2)	81 (89.0)	75 (83.3)	0.268
Third line or later	25 (13.8)	10 (11.0)	15 (16.7)	
LDH, U/L, median (IQR)	192 (162–230)	192 (159–261)	192 (168–219)	0.715
CALLY index, median (IQR)	0.32 (0.11–0.99)	0.11 (0.05–0.17)	0.99 (0.55–2.44)	**<0.001**

CALLY: C-reactive protein–albumin–lymphocyte index; ECOG PS: Eastern Cooperative Oncology Group performance status; IQR: interquartile range; LDH: lactate dehydrogenase; NOS: not otherwise specified; PD-L1: programmed death-ligand 1.

vated LDH, and CALLY category. A high CALLY index was associated with a reduced risk of death in both the univariate analysis (HR, 0.45; 95% CI, 0.31–0.66; p<0.001) and the adjusted model (HR, 0.47; 95% CI, 0.31–0.72; p<0.001). Age≥65 years and liver metastasis were independently associated with worse OS (Table 3).

In a sensitivity analysis restricted to patients with available PD-L1 data (n=91), a high CALLY index remained associated with longer PFS (median, 14.7 vs. 4.7 months; p=0.013) and OS (median, 21.6 vs. 10.5 months; p=0.005). After adjustment for PD-L1 status, a high CALLY index remained significantly associated with improved PFS (HR, 0.53; 95% CI, 0.32–0.88; p=0.014) and OS (HR, 0.46; 95% CI, 0.27–0.79; p=0.005).

In the comparative analysis, the cohort medians were 3.44 for NLR and 46.75 for PNI. NLR, PNI, and GPS were all associated with PFS and OS in univariate analyses. After adjustment using the same clinical covariates as in the primary models, NLR and GPS remained significantly associated with both PFS and OS, whereas PNI did not retain statistical significance. CALLY remained independently associated with both outcomes. Detailed results are provided in Supplementary Tables 1 and 2.

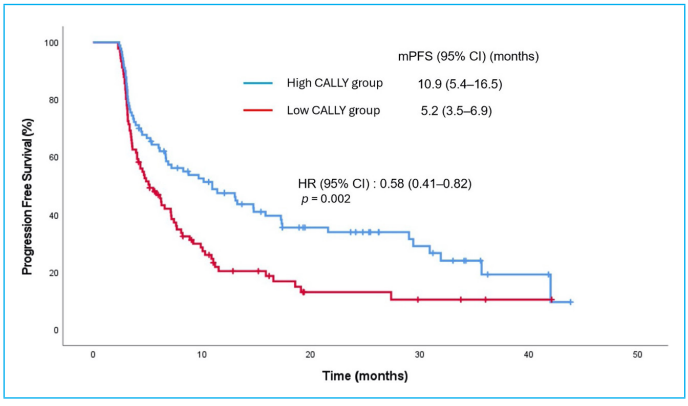

Figure 1. Kaplan–Meier curves for progression-free survival according to CALLY index group.

CALLY: C-reactive protein–albumin–lymphocyte index; CI: confidence interval; PFS: progression-free survival.

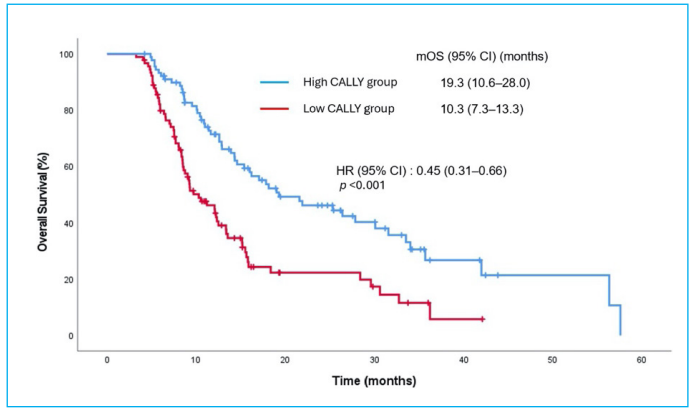

Figure 2. Kaplan–Meier curves for overall survival according to CALLY index group.

CALLY: C-reactive protein–albumin–lymphocyte index; CI: confidence interval; OS: overall survival.

Table 2. Univariate and multivariate Cox regression analyses for progression-free survival.

Variable		Univariate analyses HR (95% CI)	p	Multivariate analyses HR (95% CI)	p
Age	<65	1		1	
	≥65	1.31 (0.93–1.83)	0.119	1.56 (1.09–2.22)	0.015
Gender	Female	1		1	
	Male	1.46 (0.98–2.18)	0.064	1.51 (0.99–2.31)	0.058
ECOG PS	0–1	1		1	
	≥2	2.39 (1.58–3.61)	< 0.001	1.92 (1.19–3.10)	0.007
Smoking status	No	1			
	Yes	0.89 (0.56–1.44)	0.642		
Timing of metastatic disease	Synchronous	1		1	
	Metachronous	0.71 (0.50–1.00)	0.049	0.79 (0.55–1.14)	0.215
Histology	Adenocarcinoma	1			
	Squamous cell carcinoma	1.08 (0.76–1.55)	0.669		
PD-L1 status	<1%	1			
	≥1%	0.79 (0.49–1.29)	0.353		
Metastatic pattern	Non-visceral	1			
	Visceral	1.18 (0.84–1.65)	0.341		
Lung metastasis	No	1			
	Yes	1.01 (0.70–1.46)	0.967		
Liver metastasis	No	1		1	
	Yes	2.19 (1.42–3.38)	<0.001	2.10 (1.29–3.43)	0.003
Bone metastasis	No	1		1	
	Yes	1.45 (1.02–2.04)	0.037	1.34 (0.93–1.95)	0.120
Adrenal metastasis	No	1			
	Yes	1.03 (0.69–1.52)	0.899		
Brain metastasis	No	1			
	Yes	0.91 (0.57–1.43)	0.671		
Nivolumab treatment line	Second line	1		1	
	Third line or later	1.58 (1.00–2.50)	0.052	1.57 (0.96–2.56)	0.072
LDH level	Normal	1		1	
	Elevated	1.38 (0.93–2.05)	0.109	1.22 (0.77–1.91)	0.401
CALLY index group	Low CALLY	1		1	
	High CALLY	0.58 (0.41–0.82)	0.002	0.62 (0.42–0.90)	0.012

CALLY: C-reactive protein–albumin–lymphocyte index; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hazard ratio; LDH: lactate dehydrogenase; PD-L1: programmed death-ligand 1.

Table 3. Univariate and multivariate Cox regression analyses for overall survival.

Variable		Univariate analyses HR (95% CI)	p	Multivariate analyses HR (95% CI)	p
Age	<65	1		1	
	≥65	1.34 (0.93–1.93)	0.112	1.63 (1.11–2.39)	0.012
Gender	Female	1			
	Male	1.11 (0.72–1.71)	0.627		
ECOG PS	0–1	1		1	
	≥2	1.77 (1.13–2.77)	0.012	1.23 (0.75–2.00)	0.413
Smoking status	No	1			
	Yes	0.95 (0.57–1.57)	0.831		
Timing of metastatic disease	Synchronous	1			
	Metachronous	0.88 (0.61–1.26)	0.479		
Histology	Adenocarcinoma	1			
	Squamous cell carcinoma	1.10 (0.75–1.61)	0.640		
PD-L1 status	<1%	1			
	≥1%	0.91 (0.53–1.54)	0.716		
Metastatic pattern	Non-visceral	1			
	Visceral	1.10 (0.76–1.57)	0.618		
Lung metastasis	No	1			
	Yes	1.08 (0.73–1.61)	0.705		
Liver metastasis	No	1		1	
	Yes	1.99 (1.27–3.12)	0.003	1.93 (1.19–3.12)	0.008
Bone metastasis	No	1		1	
	Yes	1.64 (1.13–2.38)	0.009	1.26 (0.86–1.85)	0.241
Adrenal metastasis	No	1			
	Yes	1.10 (0.72–1.68)	0.674		
Brain metastasis	No	1			
	Yes	1.01 (0.62–1.64)	0.964		
Nivolumab treatment line	Second line	1			
	Third line or later	1.30 (0.79–2.13)	0.300		
LDH level	Normal	1		1	
	Elevated	1.64 (1.09–2.46)	0.018	1.28 (0.82–1.98)	0.279
CALLY index group	Low CALLY	1		1	
	High CALLY	0.45 (0.31–0.66)	<0.001	0.47 (0.31–0.72)	<0.001

CALLY: C-reactive protein–albumin–lymphocyte index; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hazard ratio; LDH: lactate dehydrogenase; PD-L1: programmed death-ligand 1.

Discussion

In this multicenter, real-world study, the pretreatment CALLY index demonstrated significant prognostic value for both PFS and OS in patients with metastatic NSCLC receiving nivolumab in the second-line or later setting. Even after adjustment for relevant clinical and disease-related factors, a high CALLY index remained independently associated with longer PFS and OS. No prior study appears to have assessed the prognostic significance of the pretreatment CALLY index in patients with metastatic NSCLC receiving nivolumab monotherapy. Given that it can be easily derived from standard laboratory parameters, the CALLY index may serve as a practical and accessible tool for initial risk stratification in this patient population.

The prognostic value of the CALLY index has been investigated in various solid tumors, particularly gastrointestinal malignancies, in which a low CALLY index has generally been associated with poorer survival outcomes, as supported by a recent systematic review and meta-analysis.[25] In colorectal cancer, the CALLY index was independently associated with OS, further supporting its prognostic relevance across different clinical settings.[22] In recent studies, a low pretreatment CALLY index has been associated with shorter PFS and OS in patients with metastatic melanoma receiving anti-PD-1 therapy. This finding suggests that the

index may also have prognostic relevance in immunotherapy-treated populations.[26]

Data on the CALLY index in NSCLC remain limited and have been derived from different disease stages and treatment settings. In a large and heterogeneous NSCLC cohort, a low CALLY index was associated with shorter OS, and a prognostic model incorporating the CALLY index was found to provide additional prognostic information beyond clinical variables.[27] Likewise, among patients with early-stage or locally advanced NSCLC who underwent surgical resection, a low CALLY index was associated with shorter recurrence-free survival and OS.[28] Among patients with locally advanced NSCLC who received thoracic radiotherapy, post-treatment CALLY values were associated with survival outcomes.[29] However, these studies do not directly represent patients with metastatic disease receiving nivolumab monotherapy, leaving a clear knowledge gap regarding the prognostic value of the pretreatment CALLY index in this specific clinical setting.

Evidence from immunotherapy-treated NSCLC cohorts suggests that combined markers of host inflammation, nutrition, and immunity may provide prognostic information. In advanced disease, the Glasgow Prognostic Score, based on CRP and albumin, has been associated with both PFS and OS.[21] Albumin- and lymphocyte-based measures, including the prognostic nutritional index, have also shown associations with survival.[24,31] In addition, the C-PLAN index, which combines CRP, albumin, ECOG performance status, LDH, and dNLR, has demonstrated prognostic value in patients treated with first-line chemoimmunotherapy and other ICI-containing regimens.[32,33] Taken together, these observations support the prognostic relevance of inflammation- and nutrition-based indices in immunotherapy-treated NSCLC. In our cohort, CALLY, NLR, and GPS remained associated with both PFS and OS after adjustment for the same clinical covariates, whereas PNI did not retain statistical significance. Thus, pretreatment CALLY appears to provide prognostic information alongside established indices, although our analysis does not establish superior or incremental discriminatory performance.

A validated, universally applicable cutoff for the CALLY index has not yet been established across different tumor types and treatment settings. Previous studies have used varying threshold values and different methods for determining cutoffs.[22,25,26,28] The median CALLY value of 0.32 was used to divide the cohort into two similarly sized groups without reference to survival outcomes. Although ROC analysis can generate thresholds tailored to a specific endpoint, a cutoff developed and tested within the same dataset may reflect cohort-specific characteristics. Therefore, although the median-based threshold applied in our analysis is methodologically sound, the value of 0.32 should be regarded as a cohort-derived research threshold rather than a clinically validated cutoff and should not currently be considered suitable for routine clinical application. Independent external validation, ideally in prospective cohorts, is required before its clinical use.

The primary strengths of our study include its multicenter, real-world design, its focus on a relatively homogeneous cohort of patients with metastatic NSCLC receiving nivolumab monotherapy, and its evaluation of the associations between the CALLY index and both PFS and OS using multivariable analyses. Moreover, because the CALLY index can be derived from standard laboratory parameters without additional costs or specialized tests, it may serve as a practical tool for prognostic evaluation before treatment. Nonetheless, although our findings support the prognostic significance of the CALLY index, they should not be interpreted as evidence that it is a predictive biomarker specific to nivolumab therapy.

This study has several limitations. Due to its retrospective design, there is a risk of selection bias and residual confounding from clinical variables that were either not measured or incompletely recorded. The CALLY index was determined at a single pretreatment time point without assessing changes during therapy. The cohort represents real-world practice in Türkiye during a period when reimbursement policies limited the use of nivolumab to the second-line or later setting. Consequently, these results may not be fully applicable to patients receiving first-line immunotherapy-based treatment. Furthermore, the lack of PD-L1 data for a substantial proportion of patients and the absence of external validation for the median-based cutoff limit the interpretation of the findings. Larger prospective studies with external validation are needed to confirm these results.

Conclusion

Pretreatment CALLY levels independently stratified both progression-free and overall survival among patients with metastatic NSCLC receiving nivolumab beyond the first-line setting. The CALLY index may offer a simple and clinically accessible method for prognostic assessment in this population. Further prospective validation is required, particularly in cohorts treated with first-line immunotherapy-based regimens.

Disclosures

Ethics Committee Approval: This study was approved by the Ethics Committee of İstanbul University-Cerrahpaşa (Date: January 22, 2025, Decision no: E-74555795-050.04-1231222).

Informed Consent: The requirement for informed consent was waived by the Ethics Committee because of the retrospective design of the study.

Conflict of Interest: None declared.

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References

1. Padinharayil H, Varghese J, John MC, Rajanikant GK, Wilson CM, Al-Yozbaki M, et al. Non-small cell lung carcinoma (NSCLC): Implications on molecular pathology and advances in early diagnostics and therapeutics. Genes Dis 2022;10(3):960–89. [CrossRef]
2. Ganti AK, Klein AB, Cotarla I, Seal B, Chou E. Update of incidence, prevalence, survival, and initial treatment in patients with non-small cell lung cancer in the US. JAMA Oncol 2021;7(12):1824–32. [CrossRef]
3. Mosele MF, Westphalen CB, Stenzinger A, Barlesi F, Bayle A, Bièche I, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group Ann Oncol 2024;35(7):588–606. [CrossRef]
4. Meyer ML, Fitzgerald BG, Paz-Ares L, Cappuzzo F, Jänne PA, Peters S, et al. New promises and challenges in the treatment of advanced non-small-cell lung cancer. Lancet 2024;404(10454):803–22. [CrossRef]
5. Liu T, Wu S, Fang W, Li H, Su L, Qi G, et al. Identifying optimal first-line immune checkpoint inhibitors based regiments for advanced non-small cell lung cancer without oncogenic driver mutations: A systematic review and network meta-analysis. PLoS One 2023;18(4):e0283719. [CrossRef]
6. Grant MJ, Herbst RS, Goldberg SB. Selecting the optimal immunotherapy regimen in driver-negative metastatic NSCLC. Nat Rev Clin Oncol 2021;18:625–44. [CrossRef]
7. De Giglio A, Zullo L, Di Federico A, Cani M, Aldea M, Soldato D, et al. Immunotherapy beyond progression combined with platinum-based chemotherapy after primary resistance to first-line immunotherapy in patients with advanced NSCLC and PD-L1 ≥50. ESMO Open 2025;10(12):105897. [CrossRef]
8. Mino-Kenudson M, Schalper K, Cooper W, Dacic S, Hirsch FR, Jain D, et al. Predictive biomarkers for immunotherapy in lung cancer: perspective from the international association for the study of lung cancer pathology committee. J Thorac Oncol 2022;17(12):1335–54. [CrossRef]
9. Goh KY, Cheng TY, Tham SC, Lim DW. Circulating biomarkers for prediction of immunotherapy response in NSCLC. Biomedicines 2023;11(2):508. [CrossRef]
10. Li S, Zhang C, Pang G, Wang P. Emerging blood-based biomarkers for predicting response to checkpoint immunotherapy in non-small-cell lung cancer. Front Immunol 2020;11:603157. [CrossRef]
11. Tsai YT, Schlom J, Donahue RN. Blood-based biomarkers in patients with non-small cell lung cancer treated with immune checkpoint blockade. J Exp Clin Cancer Res 2024;43(1):82. [CrossRef]
12. Kaczmarek F, Marcinkowska-Gapińska A, Bartkowiak-Wieczorek J, Nowak M, Kmiecik M, Brzezińska K, et al. Blood-based biomarkers as predictive and prognostic factors in immunotherapy-treated patients with solid tumors-currents and perspectives. Cancers (Basel) 2025;17(12):2001. [CrossRef]
13. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol 2014;15(11):e493–503. [CrossRef]
14. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, et al. Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther 2021;6(1):263. [CrossRef]
15. Fang Q, Yu J, Li W, Luo J, Deng Q, Chen B, et al. Prognostic value of inflammatory and nutritional indexes among advanced NSCLC patients receiving PD-1 inhibitor therapy. Clin Exp Pharmacol Physiol 2023;50(2):178–90. [CrossRef]
16. Lei W, Wang W, Qin S, Yao W. Predictive value of inflammation and nutritional index in immunotherapy for stage IV non-small cell lung cancer and model construction. Sci Rep 2024;14(1):17511. [CrossRef]
17. Liu J, Li S, Zhang S, Liu Y, Ma L, Zhu J, et al. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab. J Clin Lab Anal 2019;33(8):e22964. [CrossRef]
18. Mountzios G, Samantas E, Senghas K, Zervas E, Krisam J, Samitas K, et al. Association of the advanced lung cancer inflammation index (ALI) with immune checkpoint inhibitor efficacy in patients with advanced non-small-cell lung cancer. ESMO Open 2021;6(5):100254. [CrossRef]
19. Guliyev M, Alan Ö, Fidan MC, Abbasov H, Cebeci S, Aliyev V, et al. Evaluating the prognostic role of pan-immune-inflammation value in patients with advanced non-small cell lung cancer treated with nivolumab. Cerrahpaşa Medical Journal 2025;49:1–9. [CrossRef]

20. Nuransoy Cengiz A, Bozkurt O, Cengiz M, Ozkan M, Inanc M, Kefeli U, et al. Prognostic significance of C-PLAN Index in patients treated with immunotherapy for non-small-cell lung cancer. J Clin Med 2026;15(2):642. [CrossRef]
21. Takamori S, Takada K, Shimokawa M, Matsubara T, Fujishita T, Ito K, et al. Clinical utility of pretreatment Glasgow prognostic score in non-small-cell lung cancer patients treated with immune checkpoint inhibitors. Lung Cancer 2021;152:27–33. [CrossRef]
22. Yang M, Lin SQ, Liu XY, Tang M, Hu CL, Wang ZW, et al. Association between C-reactive protein-albumin-lymphocyte (CALLY) index and overall survival in patients with colorectal cancer: From the investigation on nutrition status and clinical outcome of common cancers study. Front Immunol 2023;14:1131496. [CrossRef]
23. Xie H, Ruan G, Ge Y, Zhang Q, Zhang H, Lin S, et al. Inflammatory burden as a prognostic biomarker for cancer. Clin Nutr 2022;41(6):1236–43. [CrossRef]
24. Yildirim S, Dogan A, Akdag G, Cavdar E, Kinikoglu O, Oksuz S, et al. A Novel Prognostic Indicator for Immunotherapy Response: Lymphocyte-to-Albumin (LA) Ratio Predicts Survival in Metastatic NSCLC Patients. Cancers (Basel) 2024;16(14):2512. [CrossRef]
25. Wu B, Liu J, Shao C, Yu D, Liao J. Integrating inflammation, nutrition, and immunity: the CALLY index as a prognostic tool in digestive system cancers - a systematic review and meta-analysis. BMC Cancer 2025;25(1):672. [CrossRef]
26. Acar C, Yüksel HÇ, Şahin G, Açar FP, Gunenc D, Karaca B. Prognostic utility of the CALLY index in metastatic melanoma: building a nomogram for Patients on Anti-PD-1 therapy. Clin Transl Oncol 2025;27(9):3770–80. [CrossRef]
27. Liu XY, Zhang X, Zhang Q, Ruan GT, Liu T, Xie HL, et al. The value of CRP-albumin-lymphocyte index (CALLY index) as a prognostic biomarker in patients with non-small cell lung cancer. Support Care Cancer 2023;31(9):533. [CrossRef]
28. Mizota K, Kinoshita F, Giacomo B, Tokunaga T, Hashinokuchi A, Matsudo K, et al. The prognostic impact of c-reactive protein-albumin-lymphocyte index (cally index) in patients with surgically resected non-small-cell lung cancer. Ann Surg Oncol 2026;33:987–95. [CrossRef]
29. Yin X, He X, Guo W, Lu H, Chen H, Huang R, et al. Prognostic value of CALLY index in patients with locally advanced non-small cell lung cancer treated with thoracic radiotherapy. BMC Cancer 2026;26(1):722. [CrossRef]
30. Kim KW, Lee HY, Lee JI, Lee EC. Prognostic value of the C-reactive protein-albumin-lymphocyte (CALLY) index in surgically treated non-small cell lung cancer. Front Nutr 2026;13:1784875. [CrossRef]
31. Peng L, Wang Y, Liu F, Qiu X, Zhang X, Fang C, et al. Peripheral blood markers predictive of outcome and immune-related adverse events in advanced non-small cell lung cancer treated with PD-1 inhibitors. Cancer Immunol Immunother 2020;69(9):1813–22. [CrossRef]
32. Sonehara K, Ozawa R, Hama M, Nozawa S, Agatsuma T, Nishie K, et al. C-PLAN index as a prognostic factor for patients with previously untreated advanced non-small cell lung cancer who received combination immunotherapy: A multicenter retrospective study. Thorac Cancer 2023;14(6):636–42. [CrossRef]
33. Wang J, Guo H, Yang J, Mao J, Wang Y, Yan X, et al. Identification of C-PLAN index as a novel prognostic predictor for advanced lung cancer patients receiving immune checkpoint inhibitors. Front Oncol 2024;14:1339729. [CrossRef]

Supplementary Table 1. Comparative univariate and multivariable Cox regression analyses of inflammation-based prognostic indices for progression-free survival

Prognostic index		Univariate analyses HR (95% CI)	p	Multivariate analyses HR (95% CI)	p
CALLY index	Low	1		1	
	High	0.58 (0.41–0.82)	0.002	0.62 (0.42–0.90)	0.012
NLR	Low	1		1	
	High	1.46 (1.04–2.05)	0.029	1.46 (1.02–2.07)	0.037
PNI	Low	1		1	
	High	0.69 (0.49–0.96)	0.030	0.76 (0.53–1.08)	0.120
GPS	0	1		1	
	1-2	1.97 (1.36–2.86)	<0.001	1.81 (1.22–2.67)	0.003

CALLY: C-reactive protein–albumin–lymphocyte index; CI: confidence interval; GPS: Glasgow Prognostic Score; HR, hazard ratio; NLR: neutrophil-to-lymphocyte ratio; PNI: Prognostic Nutritional Index.

Supplementary Table 2. Comparative univariate and multivariable Cox regression analyses of inflammation-based prognostic indices for overall survival

Prognostic index		Univariate analyses HR (95% CI)	p	Multivariate analyses HR (95% CI)	p
CALLY index	Low	1		1	
	High	0.45 (0.31–0.66)	<0.001	0.47 (0.31–0.72)	<0.001
NLR	Low	1		1	
	High	1.68 (1.16–2.43)	0.006	1.68 (1.14–2.49)	0.009
PNI	Low	1		1	
	High	0.60 (0.42–0.87)	0.007	0.69 (0.47–1.01)	0.055
GPS	0	1		1	
	1-2	2.83 (1.87–4.29)	<0.001	2.59 (1.68–3.97)	<0.001

CALLY: C-reactive protein–albumin–lymphocyte index; CI: confidence interval; GPS: Glasgow Prognostic Score; HR, hazard ratio; NLR: neutrophil-to-lymphocyte ratio; PNI: Prognostic Nutritional Index.