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Scottish Inflammatory Prognostic Score Predicts Survival in Metastatic Non-Small-Cell Lung Cancer Treated with Immune Checkpoint Inhibitors

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ABSTRACT

Objective: The Scottish Inflammatory Prognostic Score (SIPS)—based on serum albumin and neutrophil count—has prognostic value in programmed death-ligand 1 (PD-L1)-high non-small-cell lung cancer (NSCLC), but its performance in broader real-world populations is uncertain.

Material and Methods: We conducted a single-centre, retrospective study of patients with metastatic NSCLC who were treated with immune-checkpoint inhibitors between June 2016 and January 2025. SIPS was calculated pre-treatment (albumin 3.5 g/dL=1; neutrophils >7,500/μL=1). Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox regression was performed to estimate hazard ratios (HRs) and account for potential confounding.

Results: Among 178 patients, the median age was 64.9 years, 80.3% were male, and 55 (30.9%) were classified as SIPS high-risk. High-risk was associated with shorter PFS (median 3.13 months, 95% confidence interval (CI) 2.27-3.70 vs. 4.27 months, 95% CI: 3.63-6.47; p<0.001) and shorter OS (median 4.73 months, 95% CI: 3.23-7.07 vs. 15.23 months, 95% CI: 12.23-23.90; p<0.001). In multivariable analyses, SIPS high-risk predicted inferior PFS (HR: 1.72, 95% CI: 1.18-2.52; p=0.005) and OS (HR: 2.21, 95% CI: 1.48-3.31; p<0.001). Effects were consistent across PD-L1 strata, treatment regimens, and lines of therapy; no significant interactions were detected.

Conclusion: In a real-world NSCLC cohort, SIPS independently stratified PFS and OS, and may complement routine clinical variables in baseline risk discussions. Prospective multi-centre studies should validate SIPS, assess longitudinal applications, and determine whether SIPS-guided strategies improve patient-centred outcomes.

Keywords: Cancer diagnosis and treatments; immunotherapy; lung cancer; medical oncology; oncology

INTRODUCTION

Lung cancer is the leading cause of cancer mortality globally, with 2.5 million new cases and 1.8 million deaths, according to GLOBOCAN 2022 estimates.[1] Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases.[2] Over the last decade, immune checkpoint inhibitors (ICIs) have transformed the treatment of solid tumors, resulting in substantial improvements in survival outcomes.[3] Since nivolumab was approved in 2015, ICIs have become a cornerstone of NSCLC therapy, either as monotherapy or in combination with platinum-based chemotherapy.[4] In a population-based analysis using the SEER database, Wang et al.[5] reported that the 5-year cancer-specific survival rate in NSCLC improved from 9.0% in the pre-immunotherapy era (2010-2014) to 14.3% in the immunotherapy era (2015-2020), thereby confirming the real-world survival benefit of ICIs in lung cancer. Despite these advances, both primary and acquired resistance to ICIs remain common, thereby limiting the durable benefit for a significant proportion of patients.[6] Accordingly, there is a critical need for reliable biomarkers to refine patient selection for ICIs.

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Currently, programmed death-ligand 1 (PD-L1) expression and tumor mutational burden (TMB) are the most commonly used biomarkers to guide ICI therapy in NSCLC.[7] Although clinically useful, PD-L1 is an imperfect predictor: high expression does not guarantee benefit, and some patients with low expression still respond to treatment. Moreover, PD-L1 testing is affected by inter-assay variability and intratumoral heterogeneity, which reduces its predictive reliability at clinically relevant thresholds.[8] Following the phase II KEYNOTE-158 trial, pembrolizumab was approved to treat pembrolizumab to treat TMB-high tumors in previously treated patients across cancer types.[9] Nevertheless, assay and bioinformatic non-uniformity—together with variable cut-points—complicate its translation into practice.[10] Somatic genomic alterations also shape ICI response; for instance, in KRAS-mutant NSCLC, co-mutations in STK11 or KEAP1 are strongly associated with reduced benefit from PD-L1 blockade.[11] Accordingly, there is a need for complementary biomarkers that are robust, clinically practical, and amenable to serial, non-invasive assessment.

Peripheral blood biomarkers have recently attracted attention due to their accessibility, low cost, and reproducibility. Systemic inflammation can impair antitumor immunity by suppressing T-cell responses in the tumor microenvironment;[12] malnutrition has consistently been linked to poor prognosis across multiple cancer types.[13] Composite inflammatory and nutritional indices—such as the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, modified Glasgow prognostic score, and prognostic nutritional index—have demonstrated prognostic utility not only in lung cancer but also in various other malignancies.[14-16] Recently, Stares et al.[17] proposed the Scottish Inflammatory Prognostic Score (SIPS), a simple score based on serum albumin and neutrophil count, for patients with PD-L1 ≥50% NSCLC treated with first-line pembrolizumab, and showed that it effectively stratified survival outcomes. Subsequent external validations in PD-L1-high NSCLC confirmed its prognostic relevance.[18] Nevertheless, the performance of SIPS across broader patient populations—including different treatment lines and varying PD-L1 strata—remains uncertain. Therefore, we investigated the prognostic utility of SIPS in patients with metastatic NSCLC treated with ICIs and examined whether its effect was reproducible across clinical strata.

MATERIAL AND METHODS

This retrospective single-center study enrolled patients treated at the Department of Medical Oncology, Ege University, between June 1, 2016, and January 1, 2025. Eligible participants had metastatic NSCLC and were treated with ICIs. We excluded patients who lacked laboratory data or follow-up information necessary for survival analyses. The study adhered to Good Clinical Practice and to the ethical principles of the Declaration of Helsinki, and was approved by the Ege University Institutional Review Board (approval no: 25-10.1T/23, date: 16.10.2025).

Data were abstracted from electronic records and included demographics; Eastern Cooperative Oncology Group performance status (ECOG PS); histologic subtype; PD-L1 level; metastatic sites and their count; ICI treatment line; receipt of chemoimmunotherapy; and the laboratory variables required to compute the SIPS (serum albumin and absolute neutrophil count). SIPS was derived by awarding one point for albumin <3.5 g/dL and one point for neutrophils >7,500/μL. Although the original scheme defines low (0), intermediate (1), and high (2) risk, we merged the intermediate and high categories—given the small number of high-risk cases (n=9)—into a single "high-risk" group (scores 1-2), and low-risk corresponded to a score of 0. Progression-free survival (PFS) was defined as the interval from ICI initiation to documented progression or death, and overall survival (OS) was defined as the interval from ICI initiation to death from any cause.

Statistical Analysis

Categorical variables are presented as n (%), whereas continuous variables are summarized as medians and interquartile ranges (IQR). Baseline group comparisons (SIPS low vs. high) were conducted using the chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. PFS and OS were analyzed with Kaplan-Meier estimates and compared using the log-rank test. Associations with PFS and OS were explored using Cox proportional hazards models in both univariable and multivariable forms. To limit residual confounding, covariates with univariable $p<0.20$ were entered into the multivariable models. All analyses were performed in Jamovi 2.3.28 and R 4.2.2. Two-sided p-values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

In total, 178 patients were eligible. Baseline variables are detailed in Table 1. The median age was 64.9 years (IQR: 54.6-75.2), with 143 males (80.3%). Non-squamous histology was the most common subtype (67.4%). Fifteen patients (8.4%) received chemoimmunotherapy, whereas 163 (91.6%) received PD-1/PD-L1 monotherapy. ICI was given as first-line treatment to 31 patients (17.4%) and as second- or later-line treatment to 147 patients (82.6%).

SIPS was calculated from pretreatment albumin and neutrophil counts. The SIPS low-risk (0 points) and high-risk

(1-2 points) groups consisted of 123 (69.1%) and 55 (30.9%) patients, respectively. The comparison of patients' baseline characteristics by SIPS risk groups is shown in Table 1. As expected, the high-risk group had lower albumin and higher neutrophil counts (both p<0.001). ECOG PS ≥2 was more frequent in the high-risk group (30.9% vs. 7.3%; p<0.001), whereas other baseline features did not differ significantly between the risk groups (p>0.05 for each variable).

TABLE 1: Baseline clinicopathological characteristics of patients according to SIPS risk groups.

Variables	SIPS low-risk (n=123)	SIPS high-risk (n=55)	Total (n=178)	p
Age, years				
<65	63 (51.2)	27 (49.1)	90 (50.6)	0.920
≥65	60 (48.8)	28 (50.9)	88 (49.4)	
Sex				
Male	97 (78.9)	46 (83.6)	143 (80.3)	0.592
Female	26 (21.1)	9 (16.4)	35 (19.7)	
ECOG PS				
0-1	114 (92.7)	38 (69.1)	152 (85.4)	<0.001
≥2	9 (7.3)	17 (30.9)	26 (14.6)	
Histology				
Squamous	41 (33.3)	17 (30.9)	58 (32.6)	0.884
Non-squamous	82 (66.7)	38 (69.1)	120 (67.4)	
PD-L1				
Negative	42 (34.1)	12 (21.8)	54 (30.3)	0.370
1-49%	17 (13.8)	8 (14.5)	25 (14.0)	
≥50	33 (26.8)	20 (36.4)	53 (29.8)	
Unknown	31 (25.2)	15 (27.3)	46 (25.8)	
Brain metastasis				
No	94 (77.0)	44 (80.0)	138 (78.0)	0.808
Yes	28 (23.0)	11 (20.0)	39 (22.0)	
Liver metastasis				
No	110 (90.2)	45 (81.8)	155 (87.6)	0.190
Yes	12 (9.8)	10 (18.2)	22 (12.4)	
Bone metastasis				
No	78 (63.4)	32 (58.2)	110 (61.8)	0.619
Yes	45 (36.6)	23 (41.8)	68 (38.2)	
Number of metastatic sites				
<3	57 (46.3)	19 (34.5)	76 (42.7)	0.191
≥3	66 (53.7)	36 (65.5)	102 (57.3)	
Chemotherapy combination				
No	115 (93.5)	48 (87.3)	163 (91.6)	0.276
Yes	8 (6.5)	7 (12.7)	15 (8.4)	
ICI treatment line				
First	21 (17.1)	10 (18.2)	31 (17.4)	1.000
Second and later	102 (82.9)	45 (81.8)	147 (82.6)	
Albumin, g/dL	4.1 (3.9, 4.3)	3.4 (3.0, 3.8)	4.0 (3.6, 4.2)	<0.001
Neutrophil/μL	4500 (3650, 5660)	7970 (5665, 11150)	5015 (3910, 6747)	<0.001

SIPS: Scottish Inflammatory Prognostic Score; ECOG PS: Eastern Cooperative Oncology Group performance status; PD-L1: Programmed death-ligand 1; ICI: Immune checkpoint inhibitor.
Data are presented as n (%) for categorical variables and as medians (IQR) for continuous variables.

Kaplan-Meier Estimates and Cox Proportional Hazards Analyses

Kaplan-Meier estimates showed significantly worse outcomes for the SIPS high-risk group (Figure 1). Median PFS was 3.13 months [95% confidence interval (CI): 2.27-3.70] in the high-risk group versus 4.27 months (95% CI: 3.63-6.47) in the low-risk group (p<0.001). Median OS was 4.73 months (95% CI: 3.23-7.07) for the high-risk group versus 15.23 months (95% CI: 12.23-23.90) for the low-risk group (p<0.001).

Cox regression results for PFS are shown in Table 2. For PFS, univariable Cox models identified the following significant risk factors: ECOG PS ≥2 [hazard ratio (HR): 2.47 (95% CI: 1.61-3.80)], liver metastasis [HR: 2.36 95% CI: 1.47-3.77]), bone metastasis [HR: 1.42 (95% CI: 1.02-1.97)], number of metastatic sites ≥3 [HR: 2.03 (95% CI: 1.45-2.83)], and SIPS high-risk [HR: 1.85 (95% CI: 1.32-2.61)]. Variables with univariable p<0.20 were included in the multivariable analysis. SIPS high-risk status remained independently associated with shorter PFS (HR: 1.72; 95% CI: 1.18-2.52; p=0.005). ECOG PS ≥2 (HR: 1.70, 95% CI: 1.05-2.75), liver metastasis (HR: 1.66, 95% CI: 1.01-2.75), and ≥3 metastatic sites (HR: 1.98, 95% CI: 1.31-2.98) were also independent risk factors.

The Cox regression results for OS are presented in Table 3. Univariable analyses identified ECOG PS ≥2 [HR: 3.36 (95% CI: 2.14-5.26)], liver metastasis [HR: 2.44 (95% CI: 1.49-4.01)], bone metastasis [HR: 1.69 (95% CI: 1.19-2.42)], ≥3 metastatic sites [HR: 2.80 (95% CI: 1.90-4.13)], and SIPS high-risk [HR: 2.53 (95% CI: 1.74-3.67)] as significant risk factors for shorter OS. Variables with univariable p<0.20 were included in the multivariable analysis. SIPS high-risk remained an independent predictor of worse OS [HR: 2.21 (95% CI: 1.48-3.31); p<0.001], together with ≥3 metastatic sites [HR: 2.52 (95% CI: 1.57-4.03)] and ECOG PS ≥2 [HR: 2.05 (95% CI: 1.20-3.51)].

Subgroup and Interaction Analyses

To examine the consistency of effects, we fitted Cox models including an interaction term between SIPS and each prespecified subgroup (age, sex, ECOG, histological subgroups, PD-L1 level, brain, liver, or bone metastases, number of metastatic sites, receipt of chemoimmunotherapy, and treatment line). Forest plots for OS and PFS (Figure 2) showed a uniformly adverse association of high SIPS risk across all subgroups, and no significant interactions were detected (all P-interaction >0.05), indicating that the prognostic effect of SIPS was consistent across clinically relevant patient subgroups.

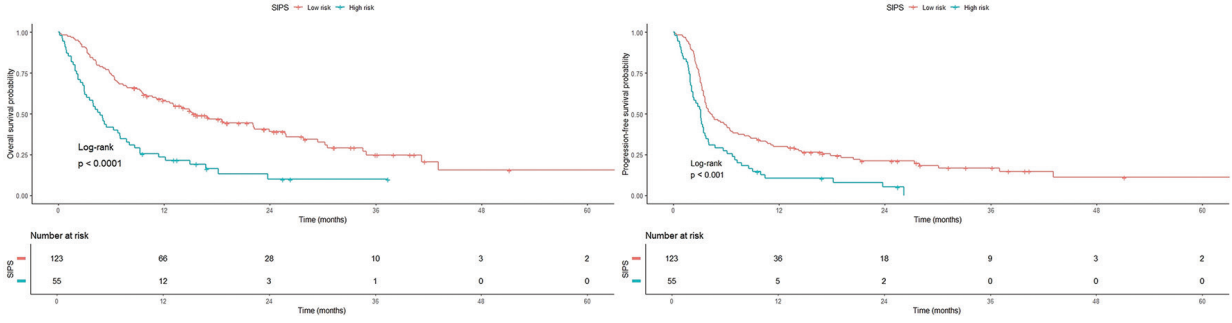

FIGURE 1: Kaplan-Meier curves for overall survival and progression-free survival and by SIPS risk groups.

SIPS: Scottish Inflammatory Prognostic Score

TABLE 2: Univariate and multivariate cox regression analyses for PFS.

Variables	Univariable analysis, HR (95% CI)	p	Multivariable analysis HR (95% CI)	p
Age, years				
<65				
≥65	1.15 (0.84-1.59)	0.382		
Sex				
Male				
Female	1.12 (0.75-1.66)	0.577		
ECOG PS				
0-1				
≥2	2.47 (1.61-3.80)	<0.001	1.70 (1.05-2.75)	0.032

TABLE 2: Continued

Variables	Univariable analysis, HR (95% CI)	p	Multivariable analysis HR (95% CI)	p
Histology				
Squamous				
Non-squamous	0.88 (0.63-1.23)	0.457		
PD-L1				
Negative				
1-49%	0.75 (0.45-1.27)	0.284	0.74 (0.44-1.27)	0.277
≥50	0.72 (0.48-1.08)	0.111	0.66 (0.43-1.01)	0.054
Unknown	1.03 (0.67-1.57)	0.902	0.99 (0.64-1.54)	0.980
Brain metastasis				
No				
Yes	1.16 (0.79-1.71)	0.453		
Liver metastasis				
No				
Yes	2.36 (1.47-3.77)	<0.001	1.66 (1.01-2.75)	0.048
Bone metastasis				
No				
Yes	1.42 (1.02-1.97)	0.035	0.84 (0.57-1.25)	0.397
Number of metastatic sites				
<3				
≥3	2.03 (1.45-2.83)	<0.001	1.98 (1.31-2.98)	0.001
Chemotherapy combination				
No				
Yes	1.12 (0.63-1.98)	0.697		
ICI treatment line				
First				
Second and later	1.18 (0.77-1.80)	0.439		
SIPS				
Low-risk				
High-risk	1.85 (1.32-2.61)	<0.001	1.72 (1.18-2.52)	0.005

SIPS: Scottish Inflammatory Prognostic Score; ECOG PS: Eastern Cooperative Oncology Group performance status; PD-L1: Programmed death-ligand 1; ICI: Immune checkpoint inhibitor; HR: Hazard ratio; CI: Confidence interval; PFS: Progression-free survival.

TABLE 3: Univariate and multivariate cox regression analyses for OS.

Variables	Univariable analysis, HR (95% CI)	p	Multivariable analysis HR (95% CI)	p
Age, years				
<65				
≥65	1.27 (0.89-1.81)	0.184	1.10 (0.75-1.62)	0.621
Sex				
Male				
Female	0.80 (0.50-1.28)	0.346		
ECOG PS				
0-1				
≥2	3.36 (2.14-5.26)	<0.001	2.05 (1.20-3.51)	0.009

TABLE 3: Continued				
Variables	**Univariable analysis, HR (95% CI)**	**p**	**Multivariable analysis HR (95% CI)**	**p**
Histology				
Squamous				
Non-squamous	0.85 (0.59-1.22)	0.369		
PD-L1				
Negative				
1-49%	0.93 (0.53-1.64)	0.812		
≥50	0.83 (0.52-1.31)	0.417		
Unknown	1.17 (0.74-1.86)	0.497		
Brain metastasis				
No				
Yes	1.36 (0.90-2.06)	0.139	1.13 (0.72-1.78)	0.594
Liver metastasis				
No				
Yes	2.44 (1.49-4.01)	<0.001	1.39 (0.80-2.39)	0.238
Bone metastasis				
No				
Yes	1.69 (1.19-2.42)	0.004	0.85 (0.54-1.34)	0.485
Number of metastatic sites				
<3				
≥3	2.80 (1.90-4.13)	<0.001	2.52 (1.57-4.03)	<0.001
Chemotherapy combination				
No				
Yes	0.86 (0.45-1.64)	0.640		
ICI treatment line				
First				
Second and later	1.47 (0.90-2.40)	0.123	1.40 (0.82-2.39)	0.215
SIPS				
Low-risk				
High-risk	2.53 (1.74-3.67)	<0.001	2.21 (1.48-3.31)	<0.001

SIPS: Scottish Inflammatory Prognostic Score; ECOG PS: Eastern Cooperative Oncology Group performance status; PD-L1: Programmed death-ligand 1; ICI: Immune checkpoint inhibitor; HR: Hazard ratio; CI: Confidence interval; OS: Overall survival.

DISCUSSION

In this study of patients with NSCLC treated with ICIs, the SIPS high-risk group was associated with shorter PFS and OS. These associations remained significant after adjustment for established covariates—including ECOG PS, metastatic burden, and PD-L1 expression—underscoring the independent prognostic value of SIPS. In addition, having ≥3 metastatic sites and an ECOG PS ≥2 were identified as adverse factors in multivariable analyses.

Our findings are consistent with, and extend, prior literature. Since SIPS was first introduced by Stares et al.[17] in 2022 as a novel prognostic score for patients with PD-L1 ≥50% NSCLC treated with pembrolizumab, Gomez-Randulfe et al.[18] externally validated SIPS in patients with PD-L1 ≥50% NSCLC, confirming robust survival stratification. In a post-progression analysis following pembrolizumab, Stares et al.[19] again showed that SIPS tracked survival and suggested its utility in identifying patients who may benefit from best supportive care and earlier referral to palliative care. Among patients with cancer of unknown primary, SIPS effectively stratified survival across favorable- and poor-risk groups defined by clinicopathologic features.[20] Evidence from other tumors further supports generalizability: in patients with

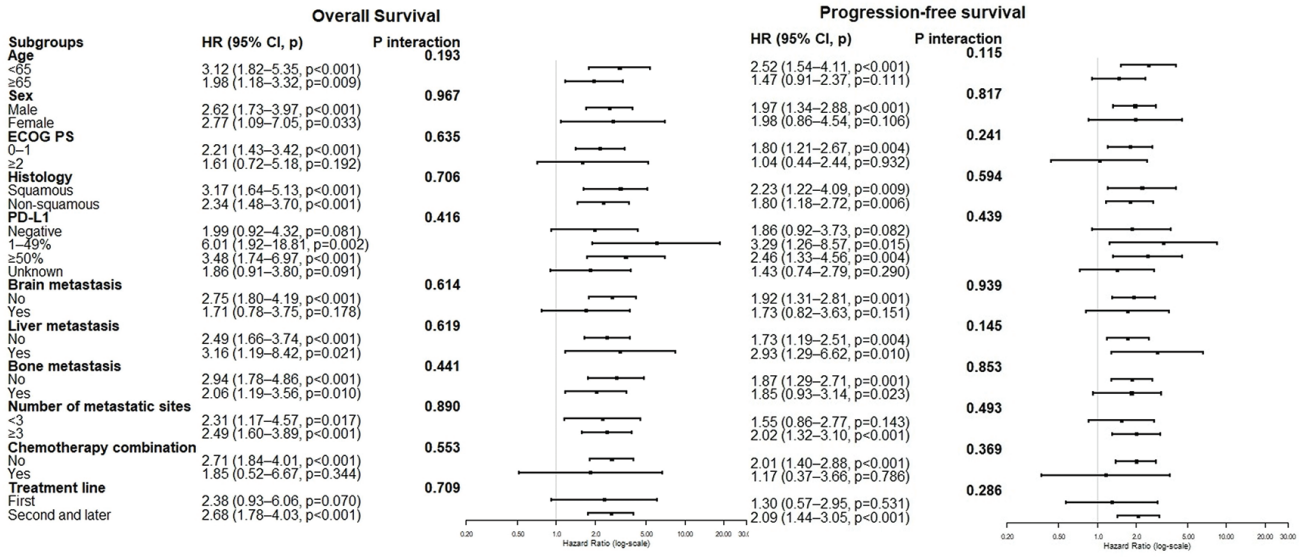

FIGURE 2: Subgroup analyses and interaction tests for SIPS high-risk with overall survival and progression-free survival.

SIPS: Scottish Inflammatory Prognostic Score

esophageal squamous cell carcinoma receiving neoadjuvant chemoimmunotherapy, pretreatment SIPS predicted 3-year disease-free survival (DFS),[21] and in patients with hepatocellular carcinoma after hepatectomy, SIPS provided meaningful DFS risk stratification.[22] Notably, Raynes et al.[23] reported higher irAE incidence in SIPS low-risk patients with lung cancer, implying that SIPS—by indexing systemic inflammation—may also identify patient subsets at increased risk of immune-related toxicity. Beyond oncology settings, Taş et al.[24] linked SIPS to in-hospital mortality among patients with acute heart failure, suggesting broader applicability of SIPS as an inflammation-based risk score. Beyond corroborating prior reports, our study adds to the generalizability by showing that in a real-world NSCLC cohort spanning all PD-L1 strata (<1%, 1-49%, ≥50%), including patients treated with chemoimmunotherapy, ICI monotherapy, and those receiving ICI beyond first-line, SIPS consistently stratified risk for both PFS and OS. Notably, efficacy associations were stable across these subgroups, and we detected no statistically significant interactions.

The biological plausibility of SIPS as a composite marker is strong. By combining neutrophilia and hypoalbuminemia, SIPS captures systemic inflammation and nutritional status in a single score. Neutrophils are the front-line defenders against pathogens; however, accumulating evidence shows they also promote tumor progression and can modulate responses to anticancer therapies. Elevated neutrophil counts—often reflective of a pro-inflammatory milieu—are associated with poorer outcomes and reduced benefit from ICI in lung cancer.[25] Mechanistically, neutrophils can reshape the tumor microenvironment, attenuating T-cell and macrophage antitumor functions,[26] fostering angiogenesis and extracellular matrix remodeling, and facilitating circulating tumor cell survival and metastatic seeding.[27] Hypoalbuminemia is an established prognostic biomarker in NSCLC.[28] As a negative acute-phase reactant largely driven by interleukin-6, serum albumin predominantly reflects chronic inflammation. Hypoalbuminemia is also frequently observed in patients with malnutrition and cancer cachexia. Prior studies indicate that poor nutritional status and persistent inflammation undermine adaptive immune responses and contribute to disease progression during ICI therapy.[26] From a pharmacokinetic perspective, low albumin may increase clearance of therapeutic monoclonal antibodies, reducing systemic exposure and the time that drug concentrations remain above efficacious level.[29]

Although our results establish SIPS as a prognostic marker in NSCLC, whether it predicts benefit from specific ICI strategies remains unresolved and warrants prospective evaluation. If validated for clinical use, SIPS could support personalized care—informing decisions about treatment escalation (e.g., combination immunotherapy or chemoimmunotherapy) or de-escalation (e.g., ICI monotherapy in suitable patients), prompting earlier supportive and palliative interventions, and guiding the intensity of follow-up and toxicity monitoring. Future work should (i) prospectively test SIPS-guided stratification as a decision aid for individualized treatment selection and supportive-care timing; (ii) assess its prognostic utility and generalizability across malignancies beyond NSCLC; (iii) evaluate longitudinal use—tracking baseline and

on-treatment changes in neutrophils and albumin—to enable dynamic risk updating for response and survival; (iv) clarify the biological and pharmacokinetic rationale in translational studies; and (v) perform head-to-head comparative studies against established indices.

Study Limitations

Several limitations should be noted. The retrospective, single-center design may introduce selection bias and leave residual confounding even after adjustment. Treatment heterogeneity (different agents, limited chemoimmunotherapy exposure, and a predominance of later-line ICI) and small subgroup sizes reduce the statistical power for interaction testing and may also limit generalizability. Importantly, ICI was administered across different treatment lines, with the majority of patients receiving ICI monotherapy as later-line treatment, which may have influenced prognostic performance and may limit extrapolation of the findings to first-line or combination settings. Because the original SIPS high-risk group was small, we merged the intermediate- and high-risk groups, precluding assessment of a three-tier gradient. Finally, SIPS was derived from a single pretreatment measurement; the absence of longitudinal assessments may reduce prognostic precision.

CONCLUSION

In this single-center cohort of metastatic NSCLC treated with ICIs, SIPS was consistently associated with shorter PFS and OS, independent of ECOG PS, metastatic burden, and PD-L1 expression. The association was stable across PD-L1 strata, treatment regimens, and lines of therapy, supporting its generalizability in real-world practice. Given its simplicity and low cost, SIPS can complement standard clinical variables to refine baseline risk discussions. Validation in multicenter cohorts is warranted to corroborate our findings and to define how SIPS should be used clinically.

Ethics

Ethics Committee Approval: The study adhered to Good Clinical Practice and to the ethical principles of the Declaration of Helsinki, and was approved by the Ege University Institutional Review Board (approval no: 25-10.1T/23, date: 16.10.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.A., H.Ç.Y., G.Ş., F.P.A., E.G., Concept: C.A., H.Ç.Y., Design: C.A., H.Ç.Y., Data Collection or Processing: C.A., G.Ş., F.P.A., Analysis or Interpretation: C.A., E.G., Literature Search: C.A., G.Ş., Writing: C.A.

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