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The prognostic impact of the pan-immune-inflammation value (PIV) on the efficacy of treatment and clinical outcomes in patients with extensive-stage small cell lung cancer (ES-SCLC)

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ABSTRACT

Aims: This study aimed to assess the prognostic and predictive implications of pre-treatment pan-immune-inflammation value (PIV) on treatment efficacy and clinical outcomes in patients with extensive-stage small-cell lung cancer (ES-SCLC), comparing it with established indices such as the systemic immune-inflammation index (SII) and neutrophil to lymphocyte ratio (NLR).

Methods: A retrospective cohort study included 70 patients diagnosed with ES-SCLC treated with standard chemotherapy with or without immune checkpoint inhibitors. PIV was calculated as PIV=(neutrophils×platelets×monocytes)÷lymphocytes. Patients were categorized into low PIV (<825) and high PIV (≥825) groups. The primary endpoint was overall survival (OS).

Results: Patients with low PIV exhibited significantly longer OS compared to those with high PIV (p=0.047). Although progression-free survival in the low-PIV group was longer than the high-PIV group, the difference was not statistically significant (p=0.081). The highest area under the receiver operating characteristic (ROC) curve AUC values were found for PIV at 0.83 (95% CI: 0.65-1.0), SII at 0.90 (95% CI: 0.81-0.99), and NLR at 0.81 (95% CI: 0.67-0.95). Univariate and multivariate analyses revealed that PIV's impact on clinical outcomes in ES-SCLC was less pronounced compared to SII. Elevated values of the SII (≥829.5) and the NLR (≥5.5) demonstrated superior predictive performance for adverse PFS and OS outcomes, albeit the study's limited sample size might have influenced these findings. Moreover, independent predictors of poorer prognosis included liver metastasis and elevated SII, underscoring the importance of systemic inflammation and disease burden in treatment decisions.

Conclusion: This study provides valuable insights into the value of PIV as a prognostic biomarker for survival outcomes in ES-SCLC patients. It suggests potential for PIV to aid in personalized treatment strategies for this aggressive lung cancer subtype. Despite limitations, such as the study's retrospective nature and relatively small sample size, future research with larger cohorts is essential to validate these findings and support the routine clinical integration of PIV in ES-SCLC management.

Keywords: Extensive-stage small-cell lung cancer, survival, prognosis, pan-immune-inflammation, biomarker

INTRODUCTION

Lung cancer, the second most common cause of cancer-related mortality,[1] encompasses various subtypes, including small-cell lung cancer (SCLC), constituting approximately 15 percent of all cases. SCLC, predominantly occurring in smokers, is characterized by its neuroendocrine nature and aggressive behavior, quick doubling time, and early metastatic dissemination, setting it apart clinically from most non-small cell lung cancers (NSCLC).[2,3]

Chronic inflammation promotes cancer pathogenesis by causing DNA damage, genetic mutations, and dysregulated cell proliferation due to sustained cell renewal and prolonged presence of immune cells.[4] Platelets, neutrophils, monocytes, and lymphocytes, which play critical roles in the inflammatory response, possess distinct characteristics that affect the immune system. These cells constitute the main components of peripheral blood elements in this process. There is a growing interest in identifying prognostic indices formulated from these different components, which can aid in the treatment decision-making process and improve patient outcomes. Peripheral blood-derived inflammatory indices have been extensively studied in lung cancer prognosis and found to be associated.[5-8] They are easily and quickly calculable biomarkers that facilitate clinicians' treatment approaches owing to their ease of use and low cost. One such biomarker is the pan-immune inflammation value (PIV), which integrates various immune and inflammatory cell counts derived from routine blood tests. The prognostic utility of PIV has been extensively investigated across various cancer types including colon cancer (CC),[9] esophageal cancer,[10] melanoma,[11] kidney cancer,[12] breast cancer,[13] Merkel cell carcinoma,[14] prostate

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cancer,[15] and nasopharyngeal carcinoma.[16] Studies have demonstrated that PIV is linked to clinical outcomes and prognosis in these cancer types, and it may serve as a valuable biomarker for predicting survival and treatment efficacy. PIV has also been compared with other inflammatory markers and shown to be independently associated with disease recurrence and survival outcomes.[17] These findings suggest that PIV could be a promising tool for guiding personalized treatment strategies and improving the prognosis of patients with cancer.[18]

This study aimed to comprehensively investigate the relationships between clinical-pathological features and PIV, as well as its associations with other established prognostic indices such as SII and NLR. Furthermore, a detailed comparative power analysis was conducted between PIV and the others. Understanding the role of PIV and other inflammatory markers in extensive-stage small-cell lung cancer (ES-SCLC) could enhance risk stratification and treatment decisions, ultimately improving care and prognosis for these patients. In light of the existing literature to date, this study stands out as the first to investigate the sole prognostic significance of PIV in ES-SCLC treated with conventional chemotherapy.

METHODS

Study Design & Patient Selection & Collection of the Data

The present study followed the principles set forth in the Declaration of Helsinki, and approved by the University of Health Sciences Antalya Training and Research Hospital Clinical Researches Ethics Committee (Date: 14.12.2023, Decision No: 17/4).

This retrospective study includes patients followed at the Oncology Department of University of Health Sciences Antalya Training and Research Hospital (HSUAERH) between January 2013 and June 2023. The data were collected from 91 patients with pathologically confirmed ES-SCLC. 7-10 days before treatment, comprehensive biochemical tests including complete blood count, uric acid, lactate dehydrogenase (LDH), albumin, and C-reactive protein (CRP) were conducted. Patients with chronic immune or inflammatory diseases, active acute infections, documented within the past month, a history of medications (such as steroids or antibiotics) that could affect immune and inflammatory responses, or those who underwent blood transfusion in the last three months were excluded from the study. The final analysis included 70 patients with complete clinical and laboratory data.

After reviewing the clinical, laboratory, and radiological records of the patients, the following data were collected: age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), body-mass index (BMI), smoking habits, presence of comorbidities, presence of brain metastases at diagnosis, disease stage at diagnosis, tumor localization, treatment history, treatment response, progression-free survival (PFS), second-line treatments administered upon progression, and overall survival (OS).

PIV was calculated using the formula proposed by Fuca et al.,[19] defined as follows: PIV = (neutrophils × platelets × monocytes) ÷ lymphocytes. Additionally, NLR was calculated as neutrophils ÷ lymphocytes,[6] SII as NLR × platelets.[20]

Treatment Details and Response Evaluation

Diagnostic imaging, which includes computed tomography (CT), 18F-fluorodeoxyglucose positron emission CT (PET-CT), and brain magnetic resonance imaging (MRI) scans, were conducted for disease staging. The disease was classified as ES-SCLC (Stage IV: T any, N any, M 1a/b/c), or T3-4, due to either extensive multiple lung nodules or tumor/nodal volume exceeding the capacity of a tolerable radiation plan according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, eighth edition. Following the initial clinical evaluation, all patients received the standard treatment protocol including platinum and etoposide with or without immune checkpoint inhibitors (ICIs) in accordance with the National Comprehensive Cancer Network (NCCN) recommendations. Clinical responses were assessed and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). PFS was defined as the time elapsed from the date of pathological diagnosis to the date of progression or death from any cause. OS was calculated as the time elapsed from the date of pathological diagnosis to the date of death from any cause or last visit. The primary endpoint of the study was OS.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows 27 (IBM SPSS Inc., Chicago, IL). Normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. For numerical variables exhibiting normal distribution, mean ± standard deviation was presented, while for those not exhibiting normal distribution, the median (min-max) was presented. The diagnostic performance of PIV, SII, and NLR for mortality was assessed using ROC Curve analysis. The cutoff values for PIV, SII, and NLR ratios were determined using the Youden index method. The relationship between PIV and clinical/laboratory markers was determined using the chi-square, Mann-Whitney U, and Kruskal-Wallis tests. PFS and OS were estimated using the Kaplan-Meier method and compared using the log-rank test. The association between variables and survival was further analyzed in detail using univariate and multivariate Cox regression models. Differences were considered statistically significant at $p<0.05$.

RESULTS

In this retrospectively designed study, out of the initial 91 patients diagnosed with ES-SCLC who were screened, 3 patients who underwent cranial radiotherapy along with steroid treatment, 10 patients using chronic immunosuppressive drugs or antibiotics, and 8 patients with incomplete clinical and laboratory data during follow-up were excluded from the study. Therefore, a total of 70 patients who fulfilled all criteria were included in the final analysis. The standard treatment regimen for all patients included chemotherapy with platinum

and etoposide. Among these patients, 10 received an ICI in conjunction with chemotherapy: 8 patients were treated with atezolizumab, while 2 patients received durvalumab.

The median age of the cohort was 63 years, ranging from 42 to 80. Of the patients included in the study, 59 (84.3%) were male, and 44 (62.9%) were current or former smokers. The most common tumor location was the left upper lobe (31.4%), whereas the least common was the right lower lobe (10%). At the time of diagnosis, brain metastases were present in 19 out of 70 patients (27.1%), while bone metastases were present in 30 out of 70 patients (42.9%). The clinical and demographic data of the patients are summarized in Table 1.

Table 1. Basic sociodemographic and clinicopathological characteristics of patients with extensive-stage lung cancer

Variable	All patients, (n=70)	
Age (year), n (%)	<65	36 (51.4)
	≥65	34 (48.6)
Sex, n (%)	Male	59 (84.3)
	Female	11 (15.7)
ECOG PS, n (%)	0-1	49 (70.0)
	2	21 (30.0)
Smoking status, n (%)	Non-smoker	26 (37.1)
	Smoker	44 (62.9)
Comorbidity, n (%)	None	34 (48.6)
	Present	36 (51.4)
Tumor location, n (%)	Left	34 (48.6)
	Right	36 (51.4)
Brain metastasis, n (%)	None	51 (72.9)
	Present	19 (27.1)
Bone metastasis, n (%)	None	40 (57.1)
	Present	30 (42.9)
Mortality, n (%)	None	13 (18.6)
	Present	57 (81.4)
PIV, n (%)	<825	35 (50.0)
	≥825	35 (50.0)
SII, n (%)	<829.5	21 (30.0)
	≥829.5	49 (70.0)
NLR, n (%)	<5.5	45 (64.3)
	≥5.5	25 (35.7)

ECOG PS: Eastern Cooperative Oncology Group performance status, PIV: Pan-immune-inflammation value, SII: Systemic inflammation index, NLR: Neutrophil to lymphocyte ratio

Cut-Off Values of the Laboratory Parameters

The PIV, SII, and NLR indices were assessed for their predictive efficacy with respect to mortality using ROC curve analysis (Figure 1). The highest area under the ROC curve (AUC) values were found for PIV at 0.83 (95% CI: 0.65-1.0), SII at 0.90 (95% CI: 0.81-0.99), and NLR at 0.81 (95% CI: 0.67-0.95). Optimal cutoff values, determined using the maximum Youden index, were 825 for PIV, 829.5 for SII, and 5.5 for NLR. Clinicopathological features and laboratory parameters, including prognostic indices, were compared between the low- and high-PIV cohorts (Table 2). Statistically significant associations were observed between PIV and mortality, SII, and NLR; however, no significant associations were found with other variables.

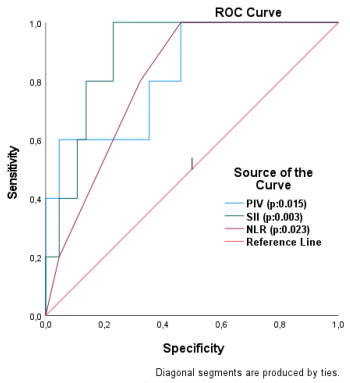

Figure 1. Comparison of the capability of PIV, SII, and NLR to predict mortality in extensive-stage lung cancer using ROC curve analysis

PIV: Pan-immune-inflammation value, SII: Systemic inflammation index, NLR: Neutrophil to lymphocyte ratio, ROC: Receiver operating characteristic

Table 2. The relationship between PIV groups and patient clinicopathological characteristics

Variables		PIV		
		Low <825	High ≥825	p*
Age (year), n (%)	<65	17 (48.6)	19 (54.3)	0.406
	≥65	18 (51.4)	16 (45.7)	
Sex, n (%)	Male	27 (77.1)	32 (91.4)	0.094
	Female	8 (22.9)	3 (8.6)	
ECOG PS, n (%)	0-1	23 (65.7)	26 (74.3)	0.301
	2	12 (34.3)	9 (25.7)	
Smoking Status, n (%)	Non-smoker	11 (31.4)	15 (42.9)	0.267
	Smoker	24 (68.6)	20 (57.1)	
Comorbidity, n (%)	None	18 (51.4)	16 (45.7)	0.406
	Present	17 (48.6)	19 (54.3)	
Tumor location, n (%)	Left	18 (51.4)	16 (45.7)	0.406
	Right	17 (48.6)	19 (54.3)	
Brain metastasis, n (%)	None	24 (68.6)	27 (77.1)	0.296
	Present	11 (31.4)	8 (22.9)	
Liver metastasis, n (%)	None	20 (57.1)	20 (57.1)	0.595
	Present	15 (42.9)	15 (42.9)	
Mortality, n (%)	None	10 (28.6)	3 (8.6)	0.018
	Present	25 (71.4)	32 (91.4)	
SII, n (%)	<829.5	21 (60.0)	0 (0.0)	<0.001
	≥829.5	14 (40.0)	35 (100.0)	
NLR, n (%)	<5.5	29 (82.9)	16 (45.7)	<0.001
	≥5.5	6 (17.1)	19 (54.3)	

PIV: Pan-immune-inflammation value, ECOG PS: Eastern Cooperative Oncology Group performance status, SII: Systemic inflammation index, NLR: Neutrophil to lymphocyte ratio, *statistical significance, (p<0.05)

Survival Analysis

In an average follow-up duration of 13.2 months (95% CI: 2.1-51.0), progression occurred in 65 patients (92.8%), and 57 patients (81.4%) died. The median OS of the study cohort was found to be 17 months. OS was 18.0 months (95% CI:

11.45-24.68) in patients with low PIV and 10.5 months (95% CI: 8.44-12.58) in patients with high PIV. Patients with low PIV exhibited significantly longer OS than those with high PIV (p=0.047). The median PFS of the patients was found to be 8.4 months. PFS was 12.0 months (95% CI: 6.30-17.96) in patients with low PIV and 6.7 months (95% CI: 5.36-7.96) in patients with high PIV. Although PFS in the low-PIV group was longer than that in the high-PIV group, no statistically significant relationship was observed (p=0.081). The Kaplan-Meier survival curves for OS and PFS stratified by low and high PIV groups are shown in Figures 2 and 3, respectively.

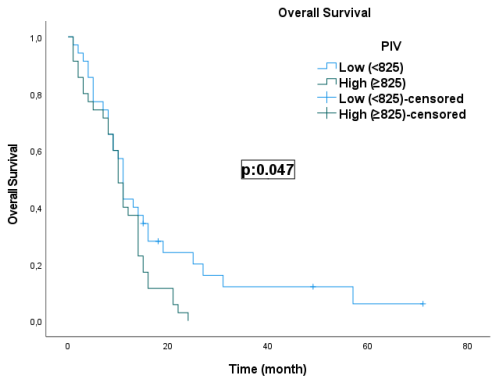

Figure 2. Kaplan-Meier curve illustrating the OS for low and high PIV groups

OS: Overall survival, PIV: Pan-immune-inflammation value

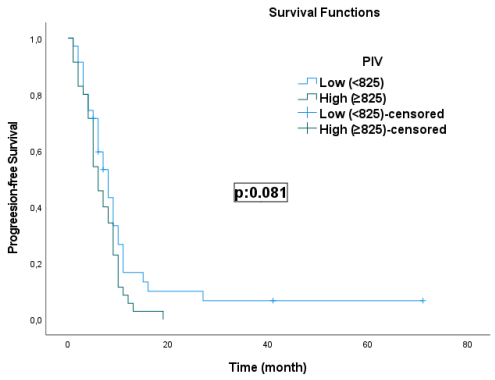

Figure 3. Kaplan-Meier curve illustrating the PFS for low and high PIV groups

PFS: Progression-free survival, PIV: Pan-immune-inflammation value

The clinical and laboratory parameters affecting OS in patients with ES-SCLC were investigated using a univariate Cox proportional hazards model (Table 3). In univariate analysis, liver metastasis, SII, and NLR were significantly associated with OS (p<0.05). In multivariate analysis, the presence of liver metastasis and SIRI remained significantly associated with OS (p<0.05). Consequently, both the presence of liver metastasis and high SII were identified as poor prognostic factors associated with a lower OS.

The clinical and laboratory parameters affecting PFS in patients with ES-SCLC were investigated using a univariate Cox proportional hazards model (Table 4). In the univariate analysis, both SII and NLR were significantly associated with PFS (p<0.05). However, in the multivariate analysis, no significant relationship was observed (Table 4).

Table 3. Cox regression model of overall survival in patients with ES-SCLC

	Overall survival							
	Univariate				Multivariate			
	HR (95% CI for HR)			p*	HR (95% CI for HR)			p*
Age	0.924	0.565	1.513	0.754	1.229	0.688	2.197	0.486
Sex	1.024	0.533	1.970	0.943	0.912	0.417	1.995	0.817
Comorbidity	0..870	0.534	1.415	0.574	0.876	0.434	1.867	0.386
Smoking status	1.386	0.399	4.817	0.607	0.259	0.061	1.096	0.066
Tumor location	0.803	0.489	1.321	0.388	1.124	0.441	2.863	0.807
ECOG PS	1.282	0.607	2.706	0.515	1.553	0.951	2.537	0.078
Brain metastasis	1.163	0.105	12.858	0.902	1.456	0.675	7.230	0.320
Liver metastasis	1.917	1.000	3.675	0.049	4.473	1.548	12.924	0.006
PIV	1.630	0.976	2.721	0.062	0.783	0.379	1.617	0.509
SII	3.008	1.569	5.767	<0.001	3.106	1.159	8.323	0.024
NLR	2.596	1.531	4.400	0.001	1.641	0.848	3.177	0.142

ES-SCLC: Extensive-stage small-cell lung cancer, ECOG PS: Eastern Cooperative Oncology Group performance status, PIV: Pan-immune-inflammation value, SII: Systemic inflammation index, NLR: Neutrophil to lymphocyte ratio, HR: Hazard ratio, CI: Confidence interval, *statistical significance, (p<0.05)

Table 4. Cox regression model of progression-free survival in patients with ES-SCLC

	Progression-free Survival							
	Univariate				Munivariate			
	HR (95% CI for HR)			p*	HR (95% CI for HR)			p*
Age	0.945	0.580	1.541	0.821	0.782	0.439	1.394	0.404
Sex	0.885	0.462	1.696	0.712	1.069	0.491	2.327	0.867
Comorbidity	1.092	0.670	1.781	0.723	1.071	0.613	1.871	0.809
Smoking status	2.207	0.646	7.540	0.207	0.973	0.214	4.433	0.972
Tumor location	0.878	0.536	1.437	0.604	0.940	0.356	2.484	0.901
ECOG PS	1.222	0.585	2.553	0.593	1.179	0.736	1.888	1.179
Brain metastasis	1.855	0.986	3.489	0.055	2.606	0.930	7.306	0.069
Liver metastasis	1.065	0.652	1.740	0.800	2.173	0.548	7.122	0.326
PIV	1.505	0.915	2.476	0.108	0.847	0.418	1.714	0.644
SII	2.165	1.186	3.951	0.012	2.085	0.861	5.052	0.104
NLR	2.041	1.207	3.451	0.008	1.723	0.908	3.267	0.096

ES-SCLC: Extensive-stage small-cell lung cancer, ECOG PS: Eastern Cooperative Oncology Group performance status, PIV: Pan-immune-inflammation value, SII: Systemic inflammation index, NLR: Neutrophil to lymphocyte ratio, HR: Hazard ratio, CI: Confidence interval, *statistical significance, (p<0.05)

DISCUSSION

In early-stage SCLC, effective treatment options such as surgery or curative radiotherapy remain standard; however, in advanced stages, despite the clinical outcomes improved with ICIs, survival remains limited. Despite the development of ICIs and targeted therapies identified in recent clinical trials for advanced-line treatment, OS remains unfortunately limited to approximately 12-15 months. As treatment progresses, tolerability diminishes due to side effects, accompanied by nutritional deficiencies and reduced quality of life, leading to parallel declines in treatment responses.

Given the aggressive clinical course of this disease, there is an essential need for predictive markers capable of anticipating treatment responses and clinical outcomes.

Examining the evolution of cancer and prognostic biomarker research over the past decade, initially, the field focused on designing marker combinations based on immune-inflammation to enhance cancer prognosis, such as NLR, PLR, and MLR. Subsequently, this phase was followed by the development of indices that utilize multiple parameters to further refine prognostic assessments such as SII and PIV. In a study conducted by Kucuk et al.,[21] the prognostic significance of PIV was assessed in patients with limited-stage SCLC before concurrent chemoradiotherapy (C-CRT) and prophylactic cranial irradiation (PCI). The results revealed that patients with PIV <417 exhibited significantly longer PFS and OS than those with PIV ≥417, highlighting the potential of PIV as an independent prognostic biomarker in patients with LS-SCLC undergoing C-CRT and PCI. In a study conducted by Topkan et al.,[22] the prognostic significance of PIV was investigated in patients with stage IIIB/C NSCLC undergoing C-CRT. The results revealed that patients with high PIV had significantly shorter median PFS and OS than those with low PIV, indicating the potential of PIV as an independent predictor of outcomes in stage IIIB/C NSCLC patients undergoing C-CRT. In a study conducted by Zhai et al.,[23] the predictive value of PIV was investigated in patients undergoing neoadjuvant immunotherapy for NSCLC. The results revealed that patients with pathological complete response (pCR) had a significantly longer disease-free survival (DFS) than those without pCR. As a result of the statistical analyses, it was demonstrated that PIV may have a strong predictive performance regarding the efficacy of neoadjuvant immunotherapy and pCR for NSCLC. The PIV also studied and has been found to be prognostic in patients with NSCLC undergoing ICI and in those with ALK-positive NSCLC.[24,25]

Numerous studies have explored the impact of SII on clinical outcomes in lung cancer. In a meta-analysis encompassing nine studies and a total of 2,441 patients, pretreatment SII was found to be significantly associated with poorer OS, DFS, PFS, and cancer-specific survival in NSCLC patients.[26] Additionally, the prognostic significance of SII has been found in NSCLC patients treated with nivolumab,[5] resected NSCLC patients,[20,27] NSCLC patients receiving neoadjuvant chemotherapy,[28] and NSCLC patients treated with C-CRT.[29]

The findings of this study support the notion that high PIV values are statistically significantly associated with poorer OS outcomes in patients with ES-SCLC, highlighting the potential use of PIV as a prognostic biomarker in ES-SCLC. For PFS, the results, although clinically significant, did not reach statistical significance. Statistically significant relationships were observed between PIV and mortality, SII, and NLR, once again underscoring the interaction between inflammation and cancer progression in ES-SCLC patients. According to ROC curve analysis, when examining the predictive capacity for mortality in ES-SCLC, SII was found to be superior to both PIV and NLR. Univariate and multivariate analyses demonstrated that the impact of PIV on clinical outcomes in ES-SCLC was not as strong as that of SII. It was found that both the SII and the NLR have significant associations with PFS and OS. However, the relatively small size of the study cohort may affect the generalizability of these results. Additionally, the presence of liver metastasis and high SII were identified as independent poor prognostic factors associated with lower OS, emphasizing the importance of considering both systemic inflammation and disease burden when making treatment decisions. The findings of this study are consistent with previous research on the relationship between PIV and lung cancer prognosis.[18] The ease of calculating PIV using routine blood tests makes it an attractive option for integration into clinical practice, which can aid clinicians in risk stratification and treatment selection for ES-SCLC patients.

Limitations

There were some limitations in the current study. Its retrospective design and single-center nature could affect the balanced distribution of cases, the application of more detailed statistical analyses, and the generalizability of the results. This index, based on a multivariate formula, includes markers that may indirectly influence each other. Additionally, some of these markers may activate intrinsic chemokines or cytokines in the body, potentially affecting immune responses and the clinical course of cancer through different mechanisms. The lack of internationally accepted standard cut-off values for each marker can also be considered a limitation. Furthermore, certain issues may have been overlooked, such as mild infections without clinical symptoms at the time of parameter measurements, individual differences in immune system changes, variable transient fluctuations in marker levels, and the absence of an internal validation group. The possibility of bias in PIV groups due to differences in advanced-line treatment options should also be considered. In the future, designing studies based on larger cohorts and including an internal validation group may provide more accurate and convincing information regarding the prognostic significance and predictive capacity of PIV.

CONCLUSION

This study provides evidence supporting the prognostic significance of PIV in patients with ES-SCLC who received standard chemotherapy with or without ICIs. PIV, along with other inflammatory markers, holds promise as a valuable tool for predicting clinical outcomes and guiding personalized treatment approaches for this aggressive form of lung cancer. Further research is warranted to validate these findings and to explore the potential integration of PIV into routine clinical practice for the management of ES-SCLC.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the University of Health Sciences Antalya Training and Research Hospital Clinical Researches Ethics Committee (Date: 14.12.2023, Decision No: 17/4).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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