BMC Cancer

RESEARCH Open Access

Peripheral blood inflammatory biomarkers neutrophil/ lymphocyte ratio, platelet/ lymphocyte ratio and systemic immune-inflammation index/albumin ratio predict prognosis and efficacy in non-small cell lung cancer patients receiving immunotherapy and opioids

Yan Lei[1†], Chengsong Cao[1†], Rui Tang[2] and Yong Liu[1*]

Abstract

Objective The study aimed to assess the value of pretreatment peripheral blood neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and systemic immune-inflammation index/albumin ratio (SII/ALB) for predicting immunotherapy prognosis and efficacy in Non-small cell lung carcinoma (NSCLC) treated with Immune checkpoint inhibitors (ICIs) and opioids.

Methods A total of 78 NSCLC patients received ICIs and opioids were retrospectively collected. The optimal cut-off values were determined by receiver operating characteristic curves. The univariate and multivariate analysis investigated the effects of NLR, PLR, and SII/ALB on patients prognosis.

Results NLR and PLR had predictive value of efficacy. SII/ALB > 17.79 was an independent risk factor for worse outcomes.

Conclusion PLR and SII/ALB have predictive value of efficacy, but NLR was not. SII/ALB > 17.79 suggests a poor prognosis following immunotherapy in NSCLC patients receiving ICIs and opioids.

Keywords Peripheral blood inflammatory marker, Immune checkpoint inhibitors, Opioids, Cancer pain, Non-small cell lung cancer, Prognostic value

†Yan Lei and Chengsong Cao Co-first authors.

*Correspondence:
Yong Liu
lyly.7011@163.com

[1]Department of Oncology, Xuzhou Central Hospital, Xuzhou Clinical School of Xuzhou Medical University, Xuzhou, Jiangsu, China
[2]School of Public Health, Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia

Lung cancer remains one of the leading causes of cancer-related mortality worldwide [1]. Non-small cell lung carcinoma (NSCLC) accounts for 85-90% of all lung cancer cases, with a diverse range of treatment options available. Several immune checkpoint inhibitors (ICIs) have been approved for first- and second-line treatment of advanced NSCLC. Compared to traditional chemotherapy, ICIs, whether used as monotherapy or in combination with standard chemotherapy, have demonstrated improved survival rates. However, in clinical practice, while focusing on the tumor itself, it is equally crucial to address the symptoms caused by cancer, particularly cancer-related pain. Approximately 58.2% of patients with advanced lung cancer experience pain, which is one of the most distressing symptoms contributing to depression and anxiety [2]. For patients with moderate to severe cancer pain, the use of opioids is essential. However, studies have shown that opioids may reduce both overall survival (OS) and progression-free survival (PFS) in patients undergoing immunotherapy [3], and may negatively impact the efficacy of ICIs in NSCLC patients [4]. Opioids exhibit a dual role in their effects on immune function: they can directly suppress immune responses, yet they may also indirectly improve immune function by alleviating pain [5], thereby influencing the prognosis and efficacy of immunotherapy [6, 7]. Currently, clinical biomarkers such as programmed death-ligand 1 (PD-L1) expression, tumor mutational burden (TMB), and microsatellite instability (MSI) status [8, 9] are used to predict the efficacy of immunotherapy. However, these biomarkers lack specificity for cancer pain patients, are costly, and require sufficient tumor tissue samples. Therefore, there is an urgent need to identify an economical, convenient, and readily accessible predictive biomarker to address the limitations of existing indicators.

Routine blood tests can provide multiple indicators reflecting the inflammatory status of cancer patients, such as absolute neutrophil count, platelet count, and absolute lymphocyte count, as well as derived ratios including the neutrophil-to-lymphocyte ratio (NLR) [10, 11], platelet-to-lymphocyte ratio (PLR) [12, 13], and systemic immune-inflammation index to albumin ratio (SII/ALB) [14]. These composite indicators reflect the immune, inflammatory, and nutritional status of cancer patients and represent novel prognostic markers for malignancies. Given the significance of peripheral blood inflammatory markers in the context of NSCLC, we explored the predictive value of pretreatment blood inflammatory markers in assessing the efficacy of immunotherapy in NSCLC through retrospective analysis. These findings may assist clinicians in predicting the efficacy of immunotherapy in NSCLC patients and in devising appropriate treatment plans to control disease progression and alleviate symptoms, thereby improving patients' quality of life. However, there is a lack of reported studies on peripheral blood inflammatory markers in NSCLC patients concurrently receiving opioids and immunotherapy. Therefore, this retrospective study aims to investigate the prognostic value of peripheral blood inflammatory markers in NSCLC patients with cancer pain undergoing ICIs treatment.

Materials & methods

Patients

The medical records of 78 patients with NSCLC cancer pain treated with ICIs at Xuzhou Central Hospital from September 01, 2021 to September 01, 2023 were retrospectively analyzed. The inclusion criteria for patients were as follows: (1) aged ≥ 18 years; (2) with moderate-to-severe cancer pain and a numerical rating scale (NRS) score ≥ 4 points; (3) receiving opioid therapy; (4) patients with blood data within 30 days before the first ICI injection; and (5) having at least one lesion amenable to impact measurement according to the Response Evaluation Criteria in Solid tumors (RECIST) V1.1. The exclusion criteria for patients were as follows: (1) those who could not be followed up continuously; (2) those who had a history of infection within 14 days before immunotherapy; (3) those who did not have blood test results within 1 month before the first ICI treatment; and (4) those who did not have imaging data to evaluate the treatment effect. This study was approved by the Ethics Committee of Xuzhou Central Hospital (XZXY-LK-20230822-0144).

Data collection

The clinical and pathological data of the included patients were collected through electronic medical records. A combination of electronic medical records, internet hospitals, telephone calls, letters and outpatient re-examinations were used to record the diagnosis and treatment, laboratory test and imaging results and survival data. The final follow-up visit was ended on 1 September 2023.A numerical rating scale (NRS) 0–10 was used to rate the pain intensity of the patients.The clinical data included patient information and albumin, neutrophil, lymphocyte, and platelet count from routine blood results within 1 week before NLR, PLR, and SII/ALB are calculated according to the following formulas: NLR: neutrophil count/lymphocyte count; PLR: platelet count/lymphocyte count and SII/ALB: platelet count × neutrophil count/lymphocyte count/albumin.

To evaluate the diagnostic value of the biomarkers, receiver operating characteristic (ROC) curves were used to compare the sensitivity, specificity, optimal cut-off value and area under the curve (AUC) of each tested indicator with the gold standard of 'evaluating whether the best efficacy is effective'. The Youden index was calculated as follows: sensitivity + specificity-1. When the Youden index was the largest, this value was taken as the

optimal cut-off value and the sensitivity and specificity of the index were the best. A cut-off value higher than the optimal cutoff was used for the high subgroup, and a value lower than the optimal cutoff was used for the low subgroup.

The efficacy is evaluated according to the RECIST V1.1 which can be classified as complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD). Objective response rate (ORR) and disease control rate (DCR) were used to assess the post-treatment efficacy: (1) ORR = (CR + PR) / (CR + PR + SD + PD) × 100% and (2) DCR = (CR + PR + SD) / (CR + PR + SD + PD) × 100%.The prognosis was evaluated based on PFS which was defined as the time from the start of immunotherapy to disease progression or death due to any cause.

Statistical analysis

SPSS v. 25.0 software was used for analysis. Comparisons of grouped data were made using the Chi-square (χ^2) test. The optimal cut-off values for the NLR, PLR, and SII/ALB were derived from the optimal Youden index through ROC curves.

The Kaplan-Meier method was used to construct survival curves and calculate survival rates. The log-rank test was used to perform single-factor analysis and the Cox proportional hazards regression model was used to perform multivariate analyses. A difference of $p < 0.05$ was considered to indicate statistical significance.

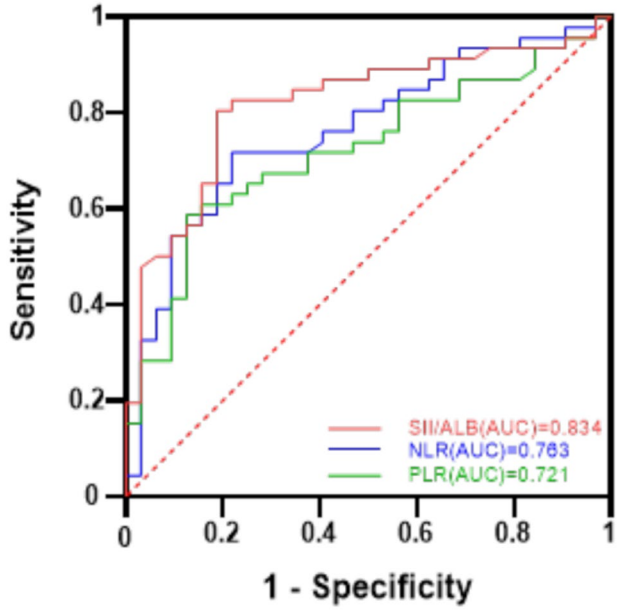

Fig. 1 The receiver operating characteristic curves of systemic immune-inflammation-to-albumin, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio NSCLC patients receiving immunotherapy and opioids

Results

Determination of the optimal cut-off values of the NLR, PLR, and SII/ALB

The results of the ROC curve analysis showed that the optimal cut-off value of the NLR was 3.985 with an AUC of 0.763. Similarly, the optimal cut-off value of the PLR was 195.005 with an AUC of 0.721. The optimal cut-off value of SII/ALB was 17.79 with an AUC of 0.834. Based on the optimal cut-off values, patients were categorized into a high NLR subgroup and low NLR subgroup, a high PLR subgroup and low PLR subgroup and a high SII/ALB subgroup and low SII/ALB subgroup.(Fig. 1).

Patient characteristics

According to the inclusion and exclusion criteria, a total of 78 NSCLC patients (27 females, 34.6%; 51 males, 65.4%) treated with ICIs and opioids from September 01, 2021, to September 01, 2023, were enrolled in this study. The relationship between NLR, PLR, and SII/ALB and various clinical characteristics of patients was analyzed using the χ^2 test. The NLR was significantly correlated with smoking History($P = 0.026$), Eastern Cooperative Oncology Group performance status(ECOG PS)($P < 0.001$), combined medication with ICIs ($P = 0.046$), and adverse events ($P = 0.032$). The PLR was significantly correlated with smoking history ($P = 0.020$), ECOG PS ($P < 0.001$), disease stage ($P = 0.008$), lines of ICI treatment ($P = 0.004$), combined medication with ICIs ($P = 0.003$), and adverse events ($P < 0.001$). The SII/ALB was correlated with histological types ($P = 0.025$), ECOG PS($P < 0.001$), disease stage ($P = 0.007$), lines of ICI treatment ($P = 0.002$), combined medication with ICIs ($P = 0.002$), and adverse events ($P < 0.001$).(Table 1).

Efficacy evaluation

The Chi-square test was used to assess the associations between the NLR, PLR, SII/ALB and the ORR, DCR of immunotherapy for NSCLC patients treated with ICIs and opioids. The results showed that patients in the low SII/ALB subgroup had a better ORR (35.14%; $p = 0.007$) and a better DCR (72.97%; $p = 0.003$) and that patients in the low PLR subgroup had a better DCR (65.31%; $p = 0.019$) (Table 2).

Survival curve

The Kaplan-Meier method was used to plot survival curves and calculate survival rates was assessed using the log-rank test. The Kaplan-Meier survival curve demonstrated that an increased NLR, PLR, and SII/ALB were associated with decreased PFS. The low NLR(11.45 vs. 5.76 months, HR = 0.1367; 95% CI: 0.0674–0.2773, $P < 0.001$), PLR(13.1 vs. 5.21 months, HR = 0.073; 95% CI: 0.0345–0.1546, $P < 0.001$), and SII/ALB(13.1 vs. 5.7 months, HR = 0.0812; 95% CI: 0.0415–0.1591, $P < 0.001$)

Table 1 Clinic and pathologic features of 78 NSCLC patients receiving immunotherapy and opioids

Characteristics	Total	NLR-Low	NLR-High	*P*	PLR-Low	PLR-High	*P*	SII/ALB-Low	SII/ALB-High	*P*
	N = 78(%)	*N* = 47(%)	*N* = 31(%)		*N* = 49(%)	*N* = 29(%)		*N* = 37(%)	*N* = 41(%)	
Sex										
Female	27(34.6)	16(34)	11(35.5)	0.896	15(30.6)	12(41.4)	0.334	15(40.5)	12(29.3)	0.296
Male	51(65.4)	31(66)	20(64.5)		34(69.4)	17(58.6)		22(59.5)	29(70.7)	
Age										
≤ 60	32(41)	18(38.3)	14(45.2)	0.546	19(38.8)	13(44.8)	0.599	18(48.6)	14(34.1)	0.194
>60	46(59)	29(61.7)	17(54.8)		30(61.2)	16(55.2)		19(51.4)	27(65.9)	
Histological types										
SCC	26(33.3)	19(40.4)	7(22.6)	0.102	17(34.7)	9(31)	0.740	17(45.9)	9(22%)	0.025
Non-SCC	52(66.7)	28(59.6)	24(77.4)		32(65.3)	20(69)		20(54.1)	32(78%)	
Smoking History										
Yes	46(59.0)	23(48.9)	23(74.2)	0.026	24(49)	22(75.9)	0.020	18(48.6)	28(68.3)	0.078
No	32(41.0)	24(51.1)	8(25.8)		25(51)	7(24.1)		19(51.4)	13(31.7)	
ECOG PS										
0–1	49(62.8)	37(78.7)	12(38.7)	<0.001	42(85.7)	7(24.1)	<0.001	37(100)	12(29.3)	<0.001
2	29(37.2)	10(21.3)	19(61.3)		7(14.3)	22(75.9)		0	29(70.7)	
NRS Scores										
4–6	62(79.5)	37(78.7)	25(80.6)	0.837	40(81.6)	22(75.9)	0.542	29(78.4)	33(80.5)	0.818
7–10	16(20.5)	10(21.3)	6(19.4)		9(18.4)	7(24.1)		8(21.6)	8(19.5)	
Disease stage										
III	34(43.6)	24(51.1)	10(32.3)	0.101	27(55.1)	7(24.1)	0.008	22(59.5)	12(29.3)	0.007
IV	44(56.4)	23(48.9)	21(67.7)		22(44.9)	22(75.9)		15(40.5)	29(70.7)	
ICIs types										
PD-1/PD-L1	75(96.2)	45(95.7)	30(96.8)	0.817	47(95.9)	28(96.6)	0.888	35(94.6)	40(97.6)	0.496
Others	3(3.8)	2(4.3)	1(3.2)		2(4.1)	1(3.4)		2(5.4)	1(2.4)	
ICIs lines of treatments										
1	38(48.7)	27(57.4)	11(35.5)	0.058	30(61.2)	8(27.6)	0.004	25(67.6)	13(31.7)	0.002
≥ 2	40(51.3)	20(42.6)	20(64.5)		19(38.8)	21(72.4)		12(32.4)	28(68.3)	
ICIs combined medication										
ICIs+opioids	36(46.2)	26(55.3)	10(32.3)	0.046	29(59.2)	7(24.1)	0.003	24(64.9)	12(29.3)	0.002
ICIs+opioids+others	42(53.8)	21(44.7)	21(67.7)		20(40.8)	22(75.9)		13(35.1)	29(70.7)	
opioids doses(mg/d)										
<30	38(48.7)	27(57.4)	11(35.5)	0.058	28(57.1)	10(34.5)	0.125	22(59.5)	16(39)	0.071
≥ 30	40(51.3)	20(42.6)	20(64.5)		21(42.9)	19(65.5)		15(40.5)	25(61)	
Adverse event										
Grade1-2	58(74.4)	39(83)	19(61.3)	0.032	43(87.8)	15(51.7)	<0.001	37(100)	21(51.2)	<0.001
Grade > 2	20(25.6)	8(17)	12(38.7)		6(12.2)	14(48.3)		0	20(48.8)	
PD-L1 expression										
Positive	24(30.8)	16(34.0)	8(25.8)	0.441	15(30.6)	9(31)	0.969	12(32.4)	12(29.3)	0.762
Negative	54(69.2)	31(66.0)	23(74.2)		34(69.4)	20(69)		25(67.6)	29(70.7)	
EGFR/ALK mutation										
Positive	25(32.1)	14(29.8)	11(35.5)	0.598	15(30.6)	10(34.5)	0.723	12(32.4)	13(31.7)	0.945
Negative	53(69.7)	33(70.2)	20(64.5)		34(69.4)	19(65.5)		25(67.6)	28(68.3)	
Lung surgery										
Yes	27(34.6)	16(34)	11(35.5)	0.896	17(34.7)	10(34.5)	0.985	13(35.1)	14(34.1)	0.927
No	51(65.4)	31(66)	20(64.5)		32(65.3)	19(65.5)		24(64.9)	27(65.9)	

Table 2 Relationship of NLR, PLR, AndSII/ALB with ORR and DCR of immunotherapy in NSCLC receiving ICIs and opioids

Group	*N*	ORR	χ^2	*P*	DCR	χ^2	*P*
SII/ALB							
<17.79	37	13(35.14)	7.349	0.007	27(72.97)	9.061	0.003
≥ 17.79	41	4(9.76)			16(39.02)		
NLR							
≤ 3.985	47	13(27.66)	2.386	0.122	28(59.57)	0.945	0.331
>3.985	31	4(12.90)			15(48.39)		
PLR							
≤ 195.005	49	14(28.57)	3.551	0.06	32(65.31)	5.519	0.019
>195.005	29	3(10.34)			11(37.93)		

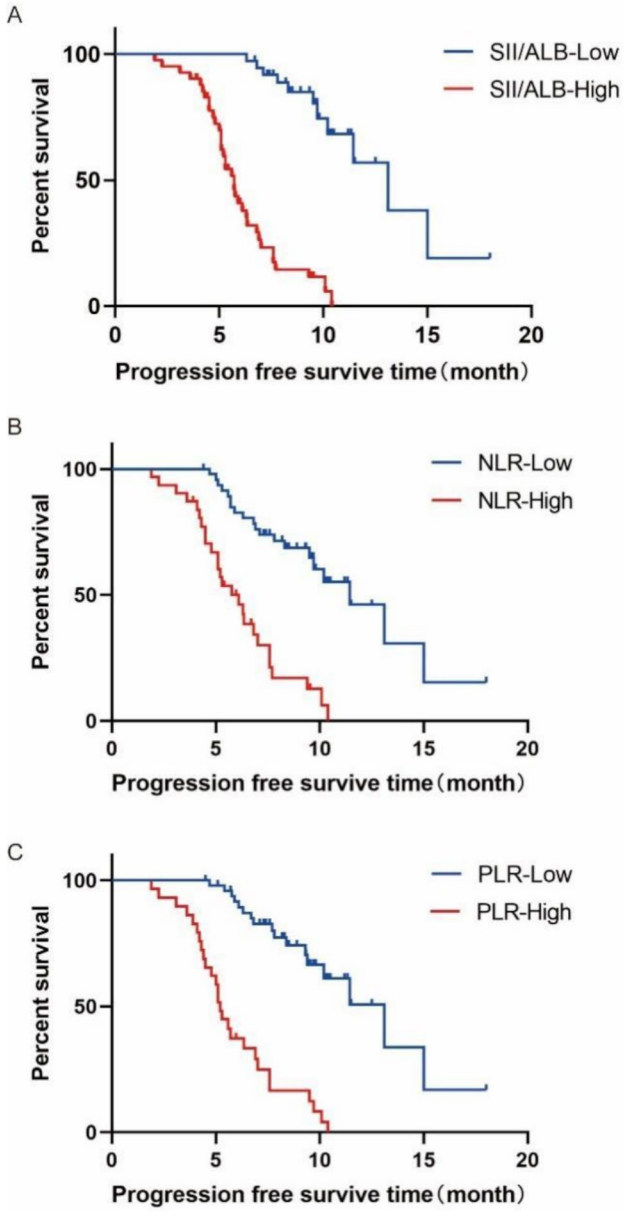

Fig. 2 Kaplan–Meier estimates of progression free survival according to SII/ALB **(A)**, NLR **(B)**, PLR **(C)**

group had longer PFS after opioid treatment than the high group.(Fig. 2).

Univariate and multivariable Cox regression analysis models

The univariate Cox regression analysis results revealed that patients with a NRS score of 7–10 ($p = 0.004$), stage IV disease ($p = 0.025$), and a high SII/ALB ratio ($p < 0.001$) had significantly shorter PFS times, indicating that these indices were associated with poor PFS prognosis after immunotherapy in NSCLC patients treated with ICIs and opioids.

Multivariate Cox proportional hazards model analysis revealed that a NRS score of 7–10 ($p = 0.007$), stage IV disease ($p < 0.001$), and a high SII/ALB ratio ($p < 0.001$) were found to be independent risk factors for poor PFS in NSCLC patients treated with ICIs and opioids.(Table 3).

Discussion

To the best of our knowledge, this is the first study to investigate the prognostic value of hematological markers in predicting outcomes for NSCLC patients with cancer pain undergoing ICI therapy. While most previous research has primarily focused on the efficacy of immunotherapy itself, there has been limited attention on NSCLC patients experiencing cancer pain. This study offers an initial exploration into the potential of hematological markers as predictive tools for guiding immunotherapy in this specific patient population. Our findings demonstrate that pre-treatment levels of NLR, PLR, and SII/ALB are significantly associated with both prognosis and treatment efficacy in NSCLC patients with cancer pain receiving ICI therapy.

This retrospective study enrolled in 78 NSCLC patients who received ICIs and opioids. First, the peripheral blood inflammatory markers NLR, PLR and SII/ALB had predictive value for the efficacy of immunotherapy in NSCLC patients receiving opioids and the AUC of the SII/ALB was 0.834 which was better than that of the NLR or PLR. Second, the high NLR, PLR, and SII/ALB groups exhibited significantly higher proportions of patients with ECOG PS ≥ 2 and Grade > 2 adverse events,

Table 3 Univariate and multivariate Cox proportional hazard regression model survival analysis of SII/ALB, NLR, PLR for PFS

characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR(95% CI)	*P*
Gender(female vs. male)	1.494(0.596–3.75)	0.392		
Age(≤ 60 vs. >60 years)	1.747(0.65–4.7)	0.269		
Histological types(SCC vs. non-SCC)	1.653(0.563–4.847)	0.36		
Smoking history(yes vs. no)	0.498(0.191–1.297)	0.153		
ECOG PS (0–1 vs. 2)	0.131(0.012-1.4)	0.093		
NRS(4–6 vs. 7–10)	0.17(0.051–0.559)	***0.004***	0.327(0.146–0.736)	***0.007***
Stage(III vs. IV)	0.051(0.004–0.691)	***0.025***	0.061(0.021–0.183)	***<0.001***
ICIs tyes(PD-1/PD-L1 vs. others)	4.859(0.392–60.214)	0.218		
ICIs lines of treatments(1 vs. ≥2)	0.093(0.006–1.332)	0.08		
ICIs combinded medication(Yes or No)	31.303(0.534-1836.401)	0.097		
opioids dose(mg/d)(<30 vs.≥30)	0.656(0.286–1.504)	0.319		
Adverse reaction(grade1-2 vs. 3–4)	0.786(0.255–2.425)	0.675		
PD-L1expression(Positive vs. Negative)	1.227(0.537-2.8)	0.628		
EGFR/ALK mutation(Positive vs. Negative)	0.771(0.343–1.735)	0.53		
Lung surgery(Yes vs. No)	1.946(0.882–4.295)	0.099		
NLR(≤ 3.99 vs. >3.99)	0.465(0.179–1.205)	0.115		
PLR(≤ 195.01 vs. >195.01)	1.25(0.493–3.171)	0.638		
SII/ALB(≤ 17.79 vs. >17.79)	0.039(0.007–0.21)	***<0.001***	0.026(0.009–0.075)	***<0.001***

indicating poorer overall health status in these groups. Third, according to the optimal cut-off value patients with NSCLC receiving opioids in the SII/ALB-low subgroup (SII/ALB ≤ 17.79) had a better ORR and DCR after immunotherapy (35.14 and 72.97%; $p < 0.05$). Fourth, univariate and multivariate Cox proportional hazards model analysis showed that NRS scores 7–10, stage IV, and SII/ALB>17.79 were independent risk factors for poor PFS from immunotherapy in NSCLC patients treated with opioids.

NSCLC patients with a NRS score of 7–10 exhibit poorer prognoses compared to those with an NRS score of 4–6. This correlation is likely due to the fact that higher NRS scores reflect more severe cancer pain, which is associated with elevated levels of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α. These cytokines are closely linked to the onset and prognosis of cancer pain in these patients [15]. Furthermore, baseline cancer pain has been identified as a negative prognostic factor in lung cancer patients undergoing immunotherapy [16]. Notably, the development of breakthrough pain in patients with baseline cancer pain is associated with even worse survival outcomes. Additionally, the clinical stage of the disease plays a critical role in prognosis; later stages, particularly stage IV, are linked to poorer outcomes [17]. Advanced-stage cancers generally exhibit a diminished response to immunotherapy, likely due to the secretion of immune-suppressive cytokines, such as TGF-β and IL-10, which drive systemic inflammation and immune suppression [18], thereby weakening the body's immune response against tumor cells.

The prognostic value of the SII/ALB is better than that of the NLR and PLR in NSCLC patients with cancer pain receiving ICIs. However, relevant clinical studies using peripheral blood inflammatory markers to predict and assess the predictive value of three different peripheral blood inflammatory markers for efficacy and prognosis in NSCLC patients treated with ICIs and opioids not been reported. The results of univariate and multivariate survival analyses showed that the SII/ALB>17.79 was an independent risk factor affecting the prognosis of NSCLC patients treated with ICIs and opioids. These findings suggest a potential interplay between systemic inflammation, nutritional status, and immune function, collectively influencing tumor progression and clinical outcomes. Inflammation may exacerbate malnutrition by enhancing catabolic processes and impairing nutrient absorption, while malnutrition, in turn, can amplify inflammatory responses [19]. In the context of malignancy, excessive levels of pro-inflammatory cytokines synergistically impair hepatic albumin synthesis [20].Collectively, these mechanisms highlight the close relationship between albumin levels and systemic inflammation.

In tumor-associated acute inflammation, neutrophils, the most abundant leukocytes, are often the first immune cells to infiltrate inflammatory sites, demonstrating robust homing capabilities toward tumor regions [21]. Platelets, on the other hand, support cancer stem cell survival [22] and protect tumor cells from the cytotoxic effects of chemotherapeutic agents [23]. Through direct interactions with cancer cells and mediation of epithelial-mesenchymal transition (EMT), platelets further

promote cancer cell adhesion, proliferation, and invasion, exacerbating tumor aggressiveness [24].

The difference between high and low PD-L1 expression on the prognosis of NSCLC patients treated with ICIs and opioids was not statistically significant in this retrospective study. Possible reasons for this situation include tumor patient heterogeneity, the objectivity of PD-L1 testing, and differences in the disease states of the included populations [25]. Because the current PD-L1 expression cannot comprehensively and accurately predict the efficacy and prognosis of immunotherapy for NSCLC treated with ICIs and opioids, we conducted this retrospective study with the expectation that screening for other metrics would help us predict the efficacy and prognosis of immunotherapy for NSCLC patients receiving opioids.

In summary, the clinical outcomes of NSCLC patients with cancer pain receiving ICIs are influenced by a combination of factors, including tumor burden, systemic inflammatory status, and nutritional and immune conditions. Therefore, a comprehensive assessment of these factors is essential to accurately predict patient prognosis, identify high-risk populations, and develop tailored treatment strategies aimed at optimizing outcomes and prolonging survival.

In this study, we preliminarily identified that a high SII/ALB ratio is associated with poor prognosis and diminished immunotherapy response, suggesting its potential as a prognostic biomarker for NSCLC patients with cancer pain undergoing ICIs treatment. However, this study has several limitations. First, the use of ROC curve-derived cut-off values for PFS remains controversial, as there is currently no standardized approach. Larger-scale studies are needed to establish consensus on optimal thresholds. Second, this study did not dynamically monitor longitudinal changes in NLR, PLR, SII/ALB levels, or NRS pain scores, thereby limiting the ability to fully assess the impact of these changes on prognosis. Finally, the single-center, retrospective design with a relatively small sample size may introduce selection bias, potentially limiting the generalizability of the findings. Future large-scale, multicenter prospective studies are warranted to validate these results and further elucidate the prognostic significance of these biomarkers, thereby enhancing the robustness and clinical applicability of the finding.

Conclusion

The study confirmed the predictive value of peripheral blood inflammatory markers for the efficacy of immunotherapy in NSCLC patients treated with ICIs and opioids and suggested that the SII/ALB > 17.79 was an independent risk factor for poor prognosis after immunotherapy in NSCLC patients treated with ICIs and opioids. In this study, we assessed the prognostic value of peripheral blood inflammatory markers for immunotherapy efficacy in NSCLC patients with ICIs and opioids and screened the best peripheral blood inflammatory marker predictors and the best cut-off values through comparative analysis of different peripheral blood inflammatory markers, thereby providing a new and effective reference and evaluation index for evaluating the efficacy and outcomes of immunotherapy in NSCLC patients treated with ICIs and opioids.

Abbreviations

NLR	Neutrophil/lymphocyte ratio
PLR	Platelet/lymphocyte ratio
SII/ALB	Systemic immune-inflammation index/albumin ratio
NSCLC	Non-small cell lung carcinoma
ICIs	Immune checkpoint inhibitors
OS	Overall survival
PFS	Progression-free survival
PD-L1	Programmed death-ligand 1
TMB	Tumor mutational burden
MSI	Microsatellite instability
NRS	Numerical rating scale
RECIST V1.1	Response Evaluation Criteria in Solid tumors V1.1
ROC	Receiver operating characteristic
AUC	Area under the curve
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Disease progression
ORR	Objective response rate
DCR	Disease control rate
ECOG PS	Eastern Cooperative Oncology Group performance status
EMT	Epithelial-mesenchymal transition

Acknowledgements

Thank you for all support from the XuZhou Central Hospital and the University of Queensland.

Author contributions

All authors contributed to the method conception and program design of this study. The research data collection, organization and statistical analysis were performed by Y Lei and R Tang. The research data and statistical results proofreading was done by Y Lei and CS Cao. The first draft and revision of the manuscript was written by Y Lei and Y Liu. All the authors participated in the final proofreading of the manuscript and confirmed that there was no relevant conflict of interest.

Funding

This work was supported by the Innovation Team Project of Xuzhou Medical University (XYFC2021006); and Key Project of Xuzhou Municipal Health Commission (XWKYHT20210589). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of Xuzhou Central Hospital. The patients/participants provided their written informed consent to participate in this study. All methods were conducted in accordance with relevant guidelines and regulations. All informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Received: 21 February 2024 / Accepted: 1 April 2025
Published online: 10 April 2025

References

1. Cai L, Zhu CX, Zhang XL, et al. [Interpretation of global lung cancer statistics] [J]. Zhonghua Liu Xing Bing Xue Za Zhi. 2024;45(4):585–90.
2. Walling AM, Weeks JC, Kahn KL, et al. Symptom prevalence in lung and colorectal cancer patients [J]. J Pain Symptom Manage. 2015;49(2):192–202.
3. Iglesias-Santamaría A. Impact of antibiotic use and other concomitant medications on the efficacy of immune checkpoint inhibitors in patients with advanced cancer [J]. Clin Transl Oncol. 2020;22(9):1481–90.
4. Guo H, Li Y, Lin J, et al. A novel investigation into the negative impact of opioid use on the efficacy of immune checkpoint inhibitors in advanced non-small cell lung cancer patients [J]. Int Immunopharmacol. 2024;129:111611.
5. Prasetya RA, Metselaar-Albers M, Engels F. Concomitant use of analgesics and immune checkpoint inhibitors in non-small cell lung cancer: A pharmacodynamics perspective [J]. Eur J Pharmacol. 2021;906:174284.
6. Li H, Zhang L, Yang F, et al. Impact of concomitant medications on the efficacy of immune checkpoint inhibitors: an umbrella review [J]. Front Immunol. 2023;14:1218386.
7. Cani M, Bironzo P, Garetto F et al. Immune checkpoint inhibitors and opioids in patients with solid tumours: is their association safe?? A systematic literature review [J]. Healthc (Basel), 2022, 11(1).
8. Zhao J, Zhuang W, Sun B et al. Prediction performance comparison of biomarkers for response to immune checkpoint inhibitors in advanced non-small cell lung cancer [J]. Thorac Cancer, 2024.
9. Cuppens K, Baas P, Geerdens E, et al. HLA-I diversity and tumor mutational burden by comprehensive next-generation sequencing as predictive biomarkers for the treatment of non-small cell lung cancer with PD-(L)1 inhibitors [J]. Lung Cancer. 2022;170:1–10.
10. Giustini N, Bazhenova L. Recognizing prognostic and predictive biomarkers in the treatment of Non-Small cell lung cancer (NSCLC) with immune checkpoint inhibitors (ICIs) [J]. Lung Cancer (Auckl). 2021;12:21–34.
11. Li Y, Zhang Z, Hu Y, et al. Pretreatment Neutrophil-to-Lymphocyte ratio (NLR) May predict the outcomes of advanced Non-small-cell lung cancer (NSCLC) patients treated with immune checkpoint inhibitors (ICIs) [J]. Front Oncol. 2020;10:654.
12. Zhou K, Cao J, Lin H, et al. Prognostic role of the platelet to lymphocyte ratio (PLR) in the clinical outcomes of patients with advanced lung cancer receiving immunotherapy: A systematic review and meta-analysis [J]. Front Oncol. 2022;12:962173.
13. Zhang N, Jiang J, Tang S, et al. Predictive value of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in non-small cell lung cancer patients treated with immune checkpoint inhibitors: A meta-analysis [J]. Int Immunopharmacol. 2020;85:106677.
14. Yan L, Kang P, Cao C, et al. Prognostic value of systemic immune-inflammation index/albumin ratio for immunotherapy-treated patients receiving opioids [J]. PLoS ONE. 2024;19(6):e0305119.
15. Zhang B, Fang WT, Zhong H. [Introduction to the 9(th) edition of TNM classification for lung cancer] [J]. Zhonghua Zhong Liu Za Zhi. 2024;46(3):206–10.
16. Peng Y, Qi Q, Zhu M, et al. Plasma levels of 12 different cytokines correlate to PD-1 inhibitor combined chemotherapy responses in advanced non-small-cell lung cancer patient [J]. Int Immunopharmacol. 2023;124(Pt A):110888.
17. Ruan GT, Ge YZ, Xie HL, et al. Association between systemic inflammation and malnutrition with survival in patients with cancer Sarcopenia-A prospective multicenter study [J]. Front Nutr. 2021;8:811288.
18. Damavandi N, Zeinali S. Association of xenobiotic-metabolizing enzymes (GSTM1 and GSTT 1), and pro-inflammatory cytokines (TNF-α and IL-6) genetic polymorphisms with non-alcoholic fatty liver disease [J]. Mol Biol Rep. 2021;48(2):1225–31.
19. Duran-Güell M, Garrabou G, Flores-Costa R, et al. Essential role for albumin in preserving liver cells from TNFα-induced mitochondrial injury [J]. Faseb J. 2023;37(3):e22817.
20. Zhou H, Lu X, Huang J, et al. Induction of trained immunity protects neonatal mice against microbial sepsis by boosting both the inflammatory response and antimicrobial activity [J]. J Inflamm Res. 2022;15:3829–45.
21. Zippoli M, Ruocco A, Novelli R, et al. The role of extracellular vesicles and interleukin-8 in regulating and mediating neutrophil-dependent cancer drug resistance [J]. Front Oncol. 2022;12:947183.
22. Sowannakul A, Rodpenpear N, Ekbhum P, et al. Prognostic value of the Neutrophil-to-Lymphocyte ratio, platelet-to-Lymphocyte ratio, and platelet count for Platinum-Sensitive recurrent epithelial ovarian cancer [J]. Asian Pac J Cancer Prev. 2023;24(11):3765–71.
23. Oncul S, Cho MS. Interactions between platelets and tumor microenvironment components in ovarian cancer and their implications for treatment and clinical outcomes [J]. Cancers (Basel), 2023, 15(4).
24. Wang X, Zhao S, Wang Z, et al. Platelets involved tumor cell EMT during circulation: communications and interventions [J]. Cell Commun Signal. 2022;20(1):82.
25. Schoenfeld AJ, Rizvi H, Bandlamudi C, et al. Clinical and molecular correlates of PD-L1 expression in patients with lung adenocarcinomas [J]. Ann Oncol. 2020;31(5):599–608.

Publisher's note