Original Article

Blood biomarkers to predict the efficacy of neoadjuvant chemo-immunotherapy in non-small cell lung cancer patients

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Background: Neoadjuvant chemo-immunotherapy has increased the number of patients with advanced lung cancer eligible for surgery. However, only a small number of such patients respond to this approach. Intensive research is being conducted to identify biomarkers to predict the efficacy of neoadjuvant chemo-immunotherapy. Among these, blood predictive biomarkers are particularly promising, and have the advantages of being both non-invasive and cost effective. This study aims to evaluate the predictive value of blood biomarkers in determining the efficacy of neoadjuvant chemo-immunotherapy for patients with non-small cell lung cancer (NSCLC), addressing a critical need for more personalized treatment strategies in clinical practice.

Methods: We retrospectively collected the data of 199 NSCLC patients who received neoadjuvant chemo-immunotherapy from January 1, 2021 to December 31, 2023, at Zhejiang Cancer Hospital. We then analyzed the performance of blood biomarkers in predicting the efficacy of neoadjuvant chemo-immunotherapy.

Results: The patients in the major pathological response (MPR) group had significantly higher pre-treatment squamous cell carcinoma antigen (SCCA) levels, and a significantly lower post-treatment platelet-lymphocyte ratio (PLR) than those in the non-MPR group. For patients with higher pre-treatment SCCA levels, the 1- and 2-year event-free survival (EFS) rates were 97.87% [95% confidence interval (CI): 94.99–100.00%] and 93.21% (95% CI: 84.32–100.00%), respectively. In those with lower pre-treatment SCCA levels, the 1- and 2-year EFS rates were 91.39% (95% CI: 84.93–98.35%) and 82.24% (95% CI: 72.42–93.39%), respectively. The survival analysis showed that higher pre-treatment SCCA levels were correlated with improved EFS (P=0.02) in patients receiving neoadjuvant chemo-immunotherapy. Conversely, for patients undergoing surgery alone, high pre-treatment SCCA levels were correlated with a poorer prognosis [disease-free survival (DFS), P=0.001]. These findings confirm the value of SCCA levels in predicting which patients will have a more favorable response to neoadjuvant chemo-immunotherapy.

In patients receiving neoadjuvant chemo-immunotherapy, a high post-treatment PLR indicated a poorer prognosis (P=0.02). The Cox regression analysis indicated that the pre-treatment SCCA level (P=0.04) and post-treatment PLR (P=0.04) were independent predictive factors of EFS.

Conclusions: In patients receiving neoadjuvant chemo-immunotherapy, high pre-treatment SCCA levels and low post-treatment PLRs were significantly associated with better efficacy and survival. Thus, these biomarkers could be used to guide the choice of treatment modalities.

Keywords: Squamous cell carcinoma antigen (SCCA); platelet-lymphocyte ratio (PLR); chemo-immunotherapy; non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer is one of the most prevalent and deadly cancers worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 80–85% of all lung cancer cases (1). Over half of NSCLC patients present with either advanced or metastatic diseases at the time of diagnosis (2). Immune checkpoint inhibitors (ICIs), notably including programmed cell death protein-1 (PD-1) and programmed death-ligand-1 (PD-L1) inhibitors, have significantly altered the treatment landscape and prognosis of patients with advanced NSCLC (3). In advanced lung cancer, immunotherapy may be used as neoadjuvant therapy. Patients with PD-L1 ≥50% may receive monotherapy with immunotherapy, while those with PD-L1 levels <50% may be treated with chemo-immunotherapy. However, patients with PD-L1 ≥50% only represent a minority of NSCLC patients. Further, real-world studies have confirmed that chemo-immunotherapy has better efficacy than immunotherapy alone (4,5). Consequently, neoadjuvant chemo-immunotherapy has emerged as a standard therapeutic paradigm for advanced NSCLC (4,5).

However, only a minority of patients derive benefits from neoadjuvant chemo-immunotherapy. Given that advanced NSCLC patients may experience rapid progression due to ineffective treatment, predicting the efficacy of neoadjuvant chemo-immunotherapy is crucial (6,7). Tumor PD-L1 and the tumor mutational burden (TMB) have been established as feasible biomarkers in predicting the efficacy of immunotherapy in lung cancer patients (8). Despite the potential utility of the aforementioned biomarkers in clinical settings, these biomarkers have significant limitations. First, the availability and accessibility of tumor biopsy samples are limited, as current companion diagnostic assays necessitate testing on tissue samples. Second, the intrinsic heterogeneity of tumors can lead to considerable variability in the evaluation of PD-L1 expression, TMB, and other biomarkers, depending on the specific section of the tissue biopsy analyzed. Third, there may be other underlying molecular mechanisms involved in the response to ICIs that have not yet been evaluated (9-11).

The NADIM II trial showed that patients with low

Highlight box

Key findings

- The patients with higher pre-treatment squamous cell carcinoma antigen (SCCA) levels had significantly better event-free survival rates.
- A lower post-treatment platelet-lymphocyte ratio (PLR) was associated with improved survival outcomes.
- The pre-treatment SCCA level and post-treatment PLR are independent predictive factors for the efficacy of neoadjuvant chemo-immunotherapy.

What is known, and what is new?

- Neoadjuvant chemo-immunotherapy has improved the surgical outcomes of advanced lung cancer patients, but effective response prediction remains a challenge.
- This study showed that the pre-treatment SCCA level and post-treatment PLR can serve as novel blood biomarkers that can predict the efficacy and prognosis of neoadjuvant chemo-immunotherapy in non-small cell lung cancer patients.

What is the implication, and what should change now?

- The findings suggest that monitoring SCCA levels and the PLR could help clinicians to tailor neoadjuvant chemo-immunotherapy for patients, optimizing patient outcomes.
- Clinical protocols should incorporate the measurement of the SCCA level and PLR to guide treatment decisions and improve prognosis predictions for lung cancer patients.

baseline circulating tumor DNA (ctDNA) levels experienced significantly enhanced progression-free survival (PFS) and overall survival (OS) than those with high ctDNA levels (12). Similarly, the CheckMate 816 trial revealed that ctDNA clearance is associated with extended event-free survival (EFS) (13). Nonetheless, the limited size of these clinical trial cohorts might have introduced bias. Additionally, the cost of biomarker testing remains a significant concern.

Blood routine test and tumor marker detection are routinely conducted for lung cancer patients, and have the advantages of being both non-invasive and cost effective. The objective of this study is to investigate whether the results of such tests can serve as reliable predictors of the efficacy of neoadjuvant chemo-immunotherapy in lung cancer patients. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-717/rc).

Methods

Patient data collection and organization

Patients diagnosed with stage T1–4, N0–2, M0 NSCLC who underwent surgical resection at Zhejiang Cancer Hospital between January 1, 2021 and December 31, 2023 were identified from prospectively collected lung cancer database. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have T1–4, N0–2, M0 stage NSCLC, deemed potentially resectable for curative intent by the lung cancer multidisciplinary team (MDT) at Zhejiang Cancer Hospital; (II) be aged 18 to 75 years with an Eastern Cooperative Oncology Group performance status (ECOG-PS) score ≤2; (III) have not undergone prior treatment of chemotherapy, targeted therapy, radiotherapy, or surgery; (IV) have an absence of epidermal growth factor receptor and anaplastic lymphoma kinase mutations; and (V) have normal organ function. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had not undergone curative resection after neoadjuvant chemo-immunotherapy; (II) were unsuitable for neoadjuvant chemo-immunotherapy; (III) had a history of other malignancies; and/or (IV) had been diagnosed with small cell lung cancer (SCLC) or mixed lung cancers that included SCLC components.

Before initiating treatment, these patients underwent positron emission tomography-computed tomography (PET-CT) and brain imaging using computed tomography (CT) or magnetic resonance imaging. For patients suspected of having N2 disease, endobronchial ultrasound-guided transbronchial needle aspiration was performed. Patients received at least two cycles of neoadjuvant therapy, which included PD-1/PD-L1 inhibitors (Table S1) combined with platinum-based doublet chemotherapy, before undergoing surgery. Subsequently, the lung cancer MDT at Zhejiang Cancer Hospital assessed their eligibility for surgical resection. Surgery took place 3 to 4 weeks after the cessation of neoadjuvant chemo-immunotherapy.

A total of 199 patients who met the enrollment criteria were selected for inclusion in the study. To evaluate the prognostic value of the pre-treatment squamous cell carcinoma antigen (SCCA) level in individuals undergoing surgical treatment alone, the data of 129 patients who underwent surgery without neoadjuvant therapy were retrospectively collected. The enrollment process is depicted in *Figure 1*. The neoadjuvant cohort and surgery cohort were derived from the same institutional database, but from different recruitment periods (2021–2023 for the neoadjuvant cohort, and 2008–2018 for the surgery cohort) and different study designs. All the study procedures were conducted in accordance with the Declaration of Helsinki (as revised in 2013), and were approved by the Ethics Committee of Zhejiang Cancer Hospital (No. IRB-2024-328). The requirement of individual consent for this retrospective analysis was waived.

Assessment of major pathological response (MPR) and clinical staging

The proportion of residual tumor in the primary tumor site was assessed by experienced pathologists using standard hematoxylin and eosin staining. The MPR and non-MPR classifications were established based on the patients' pathologic response to neoadjuvant chemo-immunotherapy. Patients with 10% or less residual viable tumor postoperatively were allocated to the MPR group, and the remaining patients were allocated to the non-MPR group. Clinical staging was based on the 8th edition of the tumor, node, metastasis (TNM) Classification of the International Association for the Study of Lung Cancer.

Collection of peripheral blood laboratory data

We conducted a retrospective analysis of pre-treatment serum tumor markers, including neuron-specific enolase (NSE), carbohydrate antigen 125 (CA125),

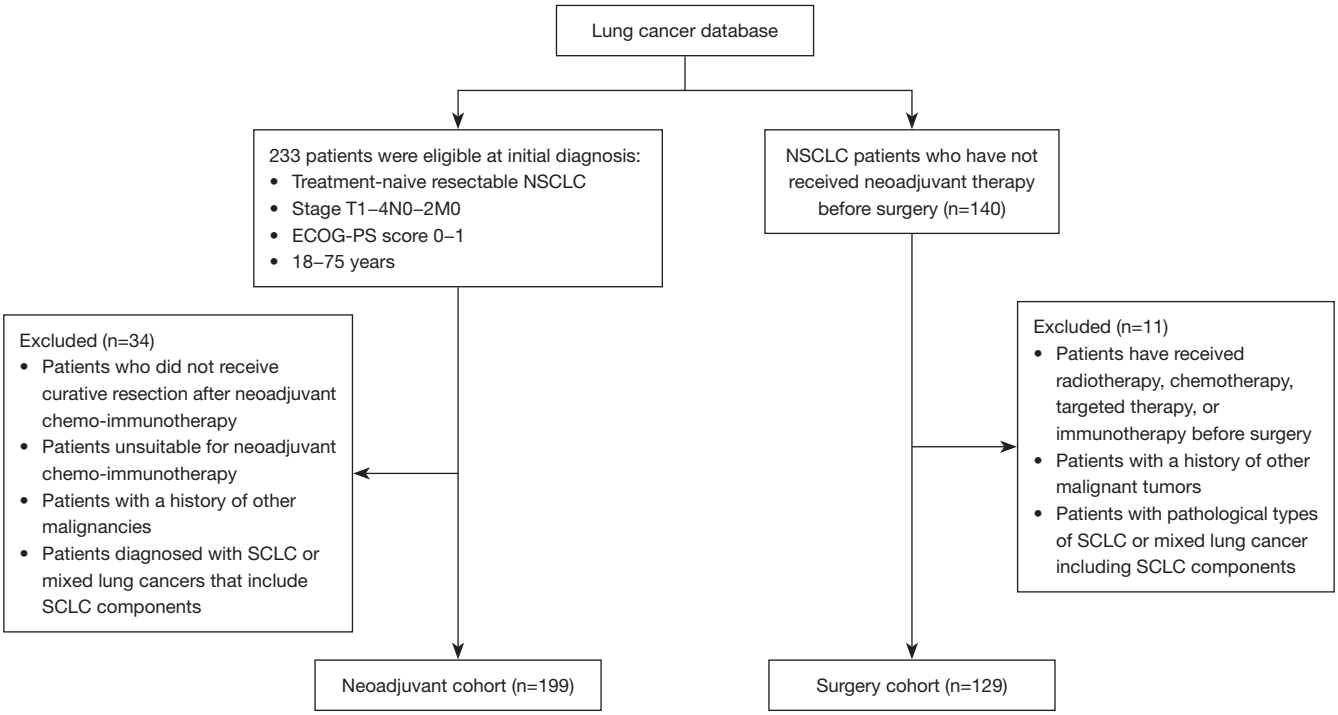

Figure 1 Study enrollment process. NSCLC, non-small cell lung cancer; ECOG-PS, Eastern Cooperative Oncology Group performance status; SCLC, small cell lung cancer.

carcinoembryonic antigen (CEA), cytokeratin 19 (CK19), progastrin-releasing peptide (ProGRP), SCCA, and ferritin, alongside peripheral blood inflammation-based biomarkers. These inflammation markers included the eosinophil fraction (EF), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute platelet count, monocyte count, and albumin levels (g/L), which were assessed both before treatment and 4–6 weeks after neoadjuvant chemo-immunotherapy. The neutrophil-lymphocyte ratio (NLR) was determined by the ANC to ALC ratio. The platelet-lymphocyte ratio (PLR) was determined by dividing the absolute platelet count by the ALC. The systemic immune-inflammation index (SII) was the product of the absolute platelet count and NLR. The monocyte-to-lymphocyte ratio (MLR) was calculated by dividing the monocyte count by the ALC. The prognostic nutritional index (PNI) was defined as the albumin level plus the total ALC multiplied by five. Further, we assessed the relative changes in these biomarkers before and after neoadjuvant chemo-immunotherapy, calculated as the post-treatment value ratio to the pre-treatment value for each marker, and denoted as the r-EF, r-NLR, r-PLR, r-SII, r-MLR, and r-PNI, respectively.

Follow-up

Patients undergoing neoadjuvant chemo-immunotherapy at Zhejiang Cancer Hospital were scheduled for routine follow-up examinations. Tumor CT imaging was performed every three months during the first year, every four months during the second year, and biannually thereafter. The final follow-up date for the patients included in the study occurred in January 2024. Due to the insufficient follow-up time for the neoadjuvant chemo-immunotherapy cohort, we used EFS as a surrogate for OS. EFS was defined as the interval from the initiation of neoadjuvant chemo-immunotherapy to the date of disease progression that precluded definitive surgery, local or distant recurrence, occurrence of a second primary cancer, or death from any cause, whichever occurred first. The patients in the surgery cohort were monitored over a 3-year follow-up period. OS was defined as the time from surgery to the date of death (from any cause), or to the date that the patient was last known to be alive. Disease-free survival (DFS)

Table 1 Baseline characteristics of NSCLC patients receiving neoadjuvant chemo-immunotherapy included in the study

Variables	Non-MPR (N=75)	MPR (N=124)	P value
Gender, n (%)			<0.001
Female	17 (22.7)	4 (3.2)	
Male	58 (77.3)	120 (96.8)	
Age (years), n (%)			0.20
<65	38 (50.7)	50 (40.3)	
≥65	37 (49.3)	74 (59.7)	
Smoking history, n (%)			<0.001
Never smoker	35 (46.7)	23 (18.5)	
Smoker or ex-smoker	40 (53.3)	101 (81.5)	
BMI, n (%)			0.45
Normal weight	53 (70.7)	95 (76.6)	
Under/overweight	22 (29.3)	29 (23.4)	
Pre-CT tumor size (mm), mean (SD)	43.3 (21.3)	49.9 (19.5)	0.03
cN, n (%)			0.09
N0	11 (14.7)	32 (25.8)	
N+	64 (85.3)	92 (74.2)	
Clinical stage, n (%)			0.04
I	2 (2.7)	10 (8.1)	
II	32 (42.7)	33 (26.6)	
III	41 (54.7)	81 (65.3)	
Tumor location, n (%)			0.91
LLL	13 (17.3)	20 (16.1)	
LUL	19 (25.3)	35 (28.2)	
RLL	20 (26.7)	28 (22.6)	
RML	1 (1.3)	4 (3.2)	
RUL	22 (29.3)	37 (29.8)	
Histological type, n (%)			<0.001
LUAD	36 (48.0)	18 (14.5)	
LUSC	39 (52.0)	106 (85.5)	

NSCLC, non-small cell lung cancer; MPR, major pathological response; BMI, body mass index; CT, computed tomography; SD, standard deviation; cN, clinical N stage; LLL, left lower lung; LUL, left upper lung; RLL, right lower lung; RML, right middle lung; RUL, right upper lung; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.

was calculated from the date of surgery to either disease recurrence or death from any cause.

Statistical analyses

The statistical analyses were conducted using R (version 4.3.1, R Core Team 2024) and SPSS (version 29.0, IBM Corp., Armonk, NY, USA). The differences in the categorical variables between the MPR and non-MPR groups were assessed by Chi-squared tests and Fisher-Freeman-Halton exact tests. The continuous data from the patients in both groups were compared using the *t*-test. The Wilcoxon rank-sum test was used to examine differences in peripheral blood laboratory data between these groups. The cut-off points for the serum tumor markers and peripheral blood inflammation-based biomarkers were determined using the "pROC" package in R. A logistic regression analysis was performed to identify the predictors of the MPR. Kaplan-Meier (KM) survival curves and log-rank test were applied to evaluate the correlation between these biomarkers and survival. The independent prognostic value of the biomarker was determined by univariate and multivariate Cox regression analyses. In the Cox regression analysis, variables with P values of less than 0.05 in the univariate Cox regression analysis were subsequently incorporated into the multivariate analysis. The variables potentially related to prognosis were also considered for inclusion in the multivariate analysis.

Results

Patient characteristics

Our study comprised 199 patients who were stratified into the MPR and non-MPR groups based on their postoperative pathological assessments (*Table 1*). There were no significant differences between the two groups in terms of age, body mass index (BMI), clinical N stage (cN), or tumor location. The MPR group had a higher proportion of male patients (96.8% *vs.* 77.3%) and a lower proportion (3.2% *vs.* 22.7%) of female patients than the non-MPR group (P<0.001). Compared to patients without an MPR, those with an MPR tended to have a smoking history (81.5% *vs.* 53.3%, P<0.001). Additionally, the non-MPR group had a smaller tumor size (43.3 *vs.* 49.9 mm, P=0.03) and a lower proportion of stage I disease (2.7% *vs.* 8.1%, P=0.04) than

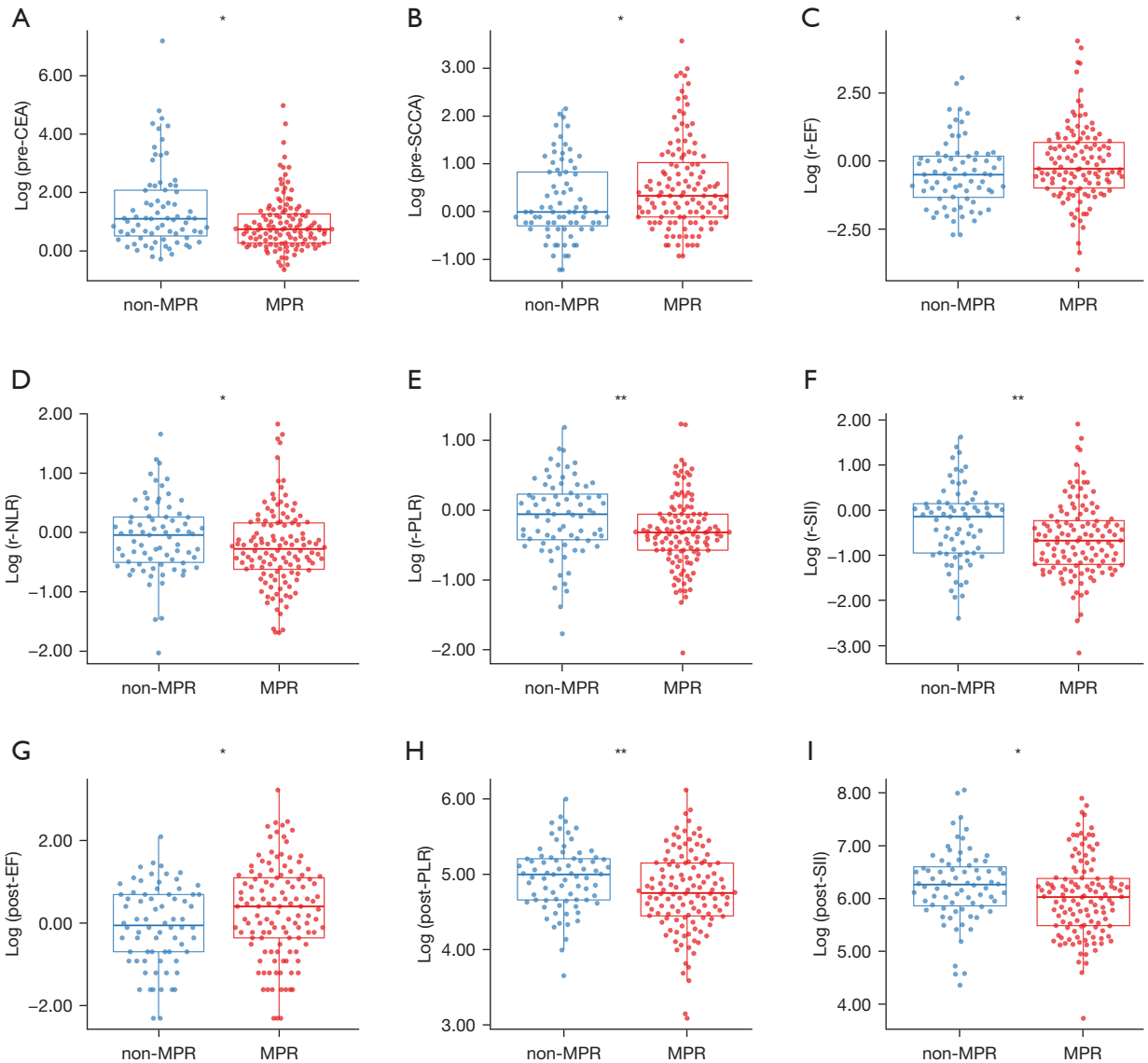

Figure 2 Distribution characteristics of serum tumor markers (A,B) and peripheral blood inflammation-based biomarkers (C-I) in the MPR group and the non-MPR group. *, P<0.05; **, P<0.01. MPR, major pathological response; CEA, carcinoembryonic antigen; SCCA, squamous cell carcinoma antigen; r, relative; EF, eosinophil fraction; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammation index.

the MPR group. In relation to the histological type, the lung squamous cell carcinoma (LUSC) patients accounted for 85.2% of the patients in the MPR group and 52.0% in the non-MPR group (P<0.001).

Distribution of peripheral blood markers in the MPR and non-MPR groups

Before initiating neoadjuvant chemo-immunotherapy, CEA was significantly lower in patients in the MPR group than the non-MPR group (median 2.1 *vs.* 3.0, P=0.01). Conversely, the SCCA level (median 1.4 *vs.* 1.0, P=0.01) was significantly higher in the MPR group than the non-MPR group. The effect of neoadjuvant chemo-immunotherapy on peripheral blood inflammation-based biomarkers revealed variations in the r-EF (median MPR: 0.7 *vs.* non-MPR: 0.5, P=0.03), r-NLR (median MPR: 0.8 *vs.* non-MPR: 1.0, P=0.047), r-PLR (median MPR: 0.7 *vs.* non-MPR:

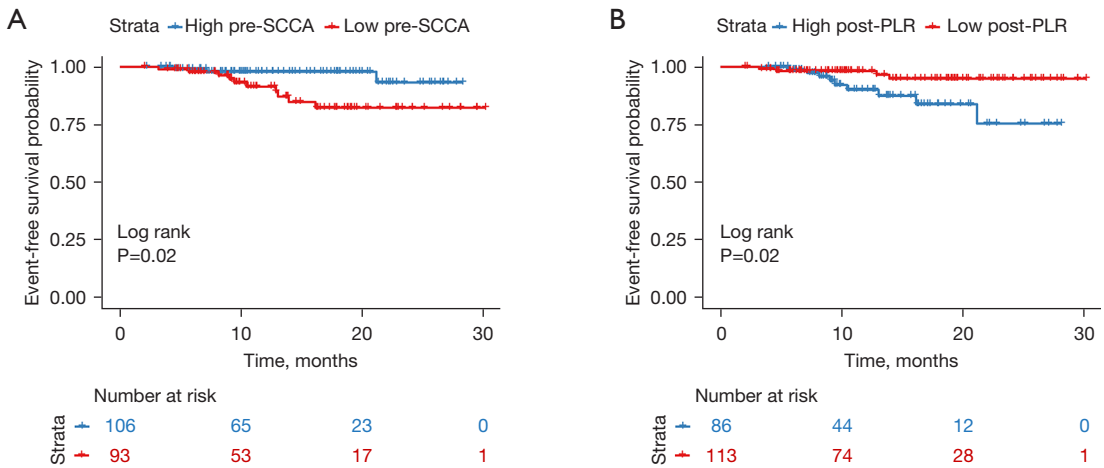

Figure 3 The relationship between the pre-treatment SCCA level (A) and the post-treatment PLR (B) with patients' EFS. SCCA, squamous cell carcinoma antigen; PLR, platelet-lymphocyte ratio; EFS, event-free survival.

0.9, P=0.004), r-SII (median MPR: 0.5 *vs.* non-MPR: 0.9, P=0.004), post-treatment EF (median MPR: 1.4 *vs.* non-MPR: 0.9, P=0.03), post-treatment PLR (median MPR: 116.0 *vs.* non-MPR: 148.2, P=0.009), and post-treatment SII (median MPR: 416.0 *vs.* non-MPR: 526.1, P=0.01) (*Figure 2* and Table S2). However, before treatment, no significant differences in these biomarkers were detected (Figure S1). The patients were categorized into high and low groups according to the optimal cut-off values of the serum tumor markers and peripheral blood inflammatory biomarkers (Table S3).

Predictive value of blood biomarkers for MPR

We found that the high SCCA group had a higher rate of MPR (P=0.005). Conversely, the high PLR group had a lower rate of MPR (P=0.005) (Figure S2). The univariate logistic regression analysis showed that the pre-treatment NSE, CEA, CK19, ProGRP, SCCA, and ferritin, r-EF, r-NLR, r-PLR, r-SII, r-MLR, r-PNI, pre-treatment MLR, post-treatment EF, post-treatment NLR, post-treatment PLR, and post-treatment SII had predictive value in terms of the MPR (all P<0.05) (Table S4). However, in the multivariate logistic regression analysis, only smoking history (P=0.01) and pre-treatment NSE (P=0.04) were independent predictors of MPR (Table S5). Multicollinearity within the model was assessed using the variance inflation factor (VIF), which was below 10 for all variables (Table S6).

Predictive value of blood biomarkers in patients receiving neoadjuvant chemo-immunotherapy

The association between EFS and the biomarkers was investigated using KM survival curves and log-rank tests (Figure S3). For patients with higher pre-treatment SCCA levels, the 1- and 2-year EFS rates were 97.87% [95% confidence interval (CI): 94.99–100.00%] and 93.21% (95% CI: 84.32–100.00%), respectively. In those with lower pre-treatment SCCA levels, the 1- and 2-year EFS rates were 91.39% (95% CI: 84.93–98.35%) and 82.24% (95% CI: 72.42–93.39%), respectively. For patients with a higher post-treatment PLR, the 1- and 2-year EFS rates were 90.03% (95% CI: 82.63–98.09%) and 75.36% (95% CI: 58.94–96.36%), respectively. In those with a lower post-treatment PLR, the 1- and 2-year EFS rates were 98.16% (95% CI: 95.67–100.00%) and 94.86% (95% CI: 89.88–100.00%), respectively. It was observed that patients with higher pre-treatment SCCA levels (P=0.02) exhibited a more favorable prognosis, while those with a higher post-treatment PLR (P=0.02) following neoadjuvant chemo-immunotherapy experienced worse outcomes (*Figure 3*). The multivariate Cox regression analysis demonstrated that the pre-treatment SCCA levels (P=0.04) and the post-treatment PLR (P=0.04) were independent prognostic factors of EFS in patients (*Table 2*).

We also analyzed the prognostic differences between the MPR group and the non-MPR group, and found that the MPR group had a better prognosis (P=0.01). For patients in the MPR group, the 1- and 2-year EFS rates were 97.27%

Table 2 Univariate and multivariate Cox analyses of EFS

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender: male (*vs.* female)	0.57 (0.13–2.60)	0.47	0.88 (0.10–7.61)	0.91
Age: ≥65 years (*vs.* <65 years)	1.26 (0.41–3.85)	0.69	1.90 (0.57–6.30)	0.29
Smoking history: ever (*vs.* never)	0.89 (0.27–2.88)	0.84	3.15 (0.54–18.29)	0.20
BMI: under/overweight (*vs.* normal weight)	1.58 (0.48–5.14)	0.45	1.68 (0.48–5.89)	0.42
Clinical stage: III (*vs.* I/II)	1.39 (0.43–4.52)	0.59	2.06 (0.49–8.68)	0.33
Tumor location: LUL/RLL/RML/RUL (*vs.* LLL)	0.87 (0.19–3.89)	0.86	–	–
	0.50 (0.08–3.02)	0.45	–	–
	0.00 (0.00–Inf)	>0.99	–	–
	0.77 (0.17–3.44)	0.73	–	–
Pre-CT tumor size: ≤50 mm (*vs.* >50 mm)	1.37 (0.42–4.44)	0.60	0.99 (0.24–3.97)	0.98
Histological type: LUSC (*vs.* LUAD)	0.38 (0.13–1.15)	0.09	0.98 (0.20–4.74)	0.98
MPR: yes (*vs.* no)	0.25 (0.08–0.80)	0.02	0.25 (0.06–0.99)	0.048
Pre-NSE: low (*vs.* high)	1.40 (0.47–4.18)	0.55	–	–
Pre-CA125: low (*vs.* high)	0.53 (0.16–1.72)	0.29	–	–
Pre-CEA: low (*vs.* high)	0.73 (0.24–2.18)	0.57	–	–
Pre-CK19: low (*vs.* high)	1.49 (0.41–5.40)	0.55	–	–
Pre-ProGRP: low (*vs.* high)	0.72 (0.22–2.33)	0.58	–	–
Pre-SCCA: low (*vs.* high)	4.01 (1.10–14.58)	0.04	4.73 (1.09–20.47)	0.04
Pre-ferritin: low (*vs.* high)	2.12 (0.70–6.40)	0.18	–	–
r-EF: low (*vs.* high)	0.94 (0.29–3.05)	0.92	–	–
r-NLR: low (*vs.* high)	0.44 (0.15–1.34)	0.15	–	–
r-PLR: low (*vs.* high)	0.41 (0.14–1.22)	0.11	–	–
r-SII: low (*vs.* high)	0.55 (0.18–1.65)	0.29	–	–
r-MLR: low (*vs.* high)	0.78 (0.25–2.39)	0.67	–	–
r-PNI: low (*vs.* high)	1.28 (0.43–3.84)	0.66	–	–
Pre-EF: low (*vs.* high)	1.89 (0.62–5.78)	0.27	–	–
Pre-NLR: low (*vs.* high)	0.97 (0.32–2.89)	0.95	–	–
Pre-PLR: low (*vs.* high)	1.50 (0.49–4.59)	0.48	–	–
Pre-SII: low (*vs.* high)	1.89 (0.62–5.80)	0.27	–	–
Pre-MLR: low (*vs.* high)	0.97 (0.30–3.15)	0.96	–	–
Pre-PNI: low (*vs.* high)	0.80 (0.27–2.42)	0.70	–	–
Post-EF: low (*vs.* high)	0.81 (0.25–2.63)	0.72	–	–
Post-NLR: low (*vs.* high)	0.40 (0.09–1.80)	0.23	–	–
Post-PLR: low (*vs.* high)	0.28 (0.08–0.90)	0.03	0.26 (0.07–0.97)	0.04
Post-SII: low (*vs.* high)	0.95 (0.31–2.91)	0.93	–	–
Post-MLR: low (*vs.* high)	0.68 (0.21–2.20)	0.52	–	–
Post-PNI: low (*vs.* high)	1.69 (0.47–6.16)	0.42	–	–

EFS, event-free survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; LUL, left upper lung; RLL, right lower lung; RML, right middle lung; RUL, right upper lung; LLL, left lower lung; CT, computed tomography; LUSC, lung squamous cell carcinoma; LUAD, lung adenocarcinoma; MPR, major pathological response; NSE, neuron-specific enolase; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; CK19, cytokeratin 19; ProGRP, progastrin-releasing peptide; SCCA, squamous cell carcinoma antigen; r, relative; EF, eosinophil fraction; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammation index; MLR, monocyte-to-lymphocyte ratio; PNI, prognostic nutritional index.

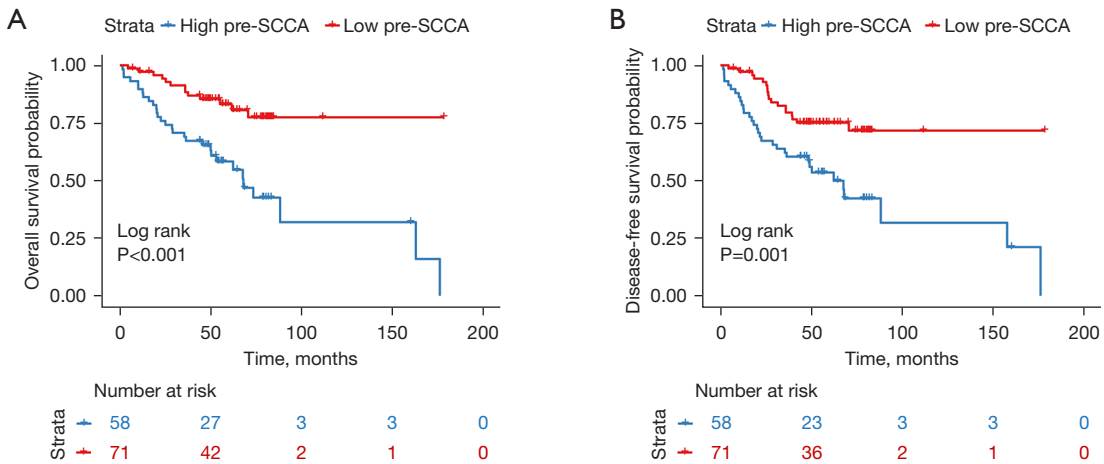

Figure 4 The relationship between pre-treatment SCCA levels and OS (A) and DFS (B) in patients. SCCA, squamous cell carcinoma antigen; OS, overall survival; DFS, disease-free survival.

(95% CI: 94.25–100.00%) and 95.65% (95% CI: 91.38–100.00%), respectively. For those in the non-MPR group, the 1- and 2-year EFS rates were 90.66% (95% CI: 83.08–98.93%) and 71.70% (95% CI: 53.20–96.70%), respectively. A further subgroup analysis showed that among all the patients, those in the MPR group with high SCCA levels had the most favorable prognosis, while those in the non-MPR group with low SCCA levels had the worst prognosis (P=0.02). Similarly, patients in the non-MPR group with high PLR levels had the worst outcomes (P<0.001) (Figure S4).

Prognostic value of SCCA in patients undergoing surgery alone

To assess whether the improved survival in the neoadjuvant cohort with high pre-treatment SCCA levels was attributable to the prognostic value of the SCCA across all therapies, we included a cohort of patients who received surgery only. The baseline characteristics of the 129 patients are shown in Table S7. The survival analysis showed that elevated SCCA levels were linked to a worse prognosis (OS, P<0.001; DFS, P=0.001) (*Figure 4*). However, this association was significantly different in the neoadjuvant cohort, where high SCCA levels were correlated with a better prognosis. For patients with high pre-treatment SCCA levels, the 1-, 3-, and 5-year OS and DFS rates were 89.70% (95% CI: 82.20–97.80%) and 68.97% (95% CI: 58.03–81.96%) and 58.30% (95% CI: 46.40–73.20%), and 82.76% (95% CI: 73.59–93.07%) and 62.07% (95% CI: 50.76–75.90%) and 53.47% (95% CI: 41.65–68.66%), respectively. For patients with low pre-treatment SCCA levels, the 1-, 3-, and 5-year OS and DFS rates were 97.16% (95% CI: 93.36–100.00%) and 88.33% (95% CI: 81.04–96.27%) and 83.11% (95% CI: 74.36–92.90%), and 97.16% (95% CI: 93.36–100.00%) and 79.50% (95% CI: 70.47–89.68%) and 75.08% (95% CI: 65.48–86.09%), respectively. The multivariate Cox analysis confirmed that the pre-treatment SCCA level was an independent indicator of worse OS (P=0.048) and DFS (P=0.047) (Tables S8,S9).

Discussion

Numerous clinical trials have shown that ICIs, either as monotherapy or in combination with chemotherapy, exhibit good clinical efficacy in the neoadjuvant setting for NSCLC (4,14). As patients with PD-L1 expression ≥50% represent a minority of patients, and neoadjuvant immunotherapy alone is less effective than neoadjuvant chemo-immunotherapy, the latter has emerged as the standard treatment approach for advanced NSCLC (4,5). However, only a small subset of patients benefit from neoadjuvant chemo-immunotherapy (15,16). Therefore, the identification of biomarkers capable of predicting patients' responses to neoadjuvant chemo-immunotherapy is crucial.

Currently, PD-L1 expression and the TMB are widely used to predict the response of patients with solid tumors to immunotherapy. However, when neoadjuvant immunotherapy regimens are combined with chemotherapy, the effectiveness of PD-L1 expression and TMB in predicting the treatment outcomes of resectable NSCLC patients is

Table 3 Baseline characteristics of patients grouped by pre-SCCA levels

Variables	High pre-SCCA (N=106)	Low pre-SCCA (N=93)	P value
MPR, n (%)			0.006
No	30 (28.3)	45 (48.4)	
Yes	76 (71.7)	48 (51.6)	
Gender, n (%)			<0.001
Female	3 (2.8)	18 (19.4)	
Male	103 (97.2)	75 (80.6)	
Age (years), n (%)			0.02
<65	38 (35.8)	50 (53.8)	
≥65	68 (64.2)	43 (46.2)	
Smoking history, n (%)			0.009
Never smoker	22 (20.8)	36 (38.7)	
Smoker or ex-smoker	84 (79.2)	57 (61.3)	
BMI, n (%)			0.66
Normal weight	77 (72.6)	71 (76.3)	
Under/overweight	29 (27.4)	22 (23.7)	
Pre-CT tumor size (mm), mean (SD)	51.1 (17.9)	43.2 (22.3)	0.007
cN, n (%)			0.053
N0	29 (27.4)	14 (15.1)	
N+	77 (72.6)	79 (84.9)	
Clinical stage, n (%)			0.33
I	6 (5.7)	6 (6.5)	
II	30 (28.3)	35 (37.6)	
III	70 (66.0)	52 (55.9)	
Tumor location, n (%)			0.52
LLL	18 (17.0)	15 (16.1)	
LUL	26 (24.5)	28 (30.1)	
RLL	27 (25.5)	21 (22.6)	
RML	1 (0.9)	4 (4.3)	
RUL	34 (32.1)	25 (26.9)	
Histological type, n (%)			<0.001
LUAD	10 (9.4)	44 (47.3)	
LUSC	96 (90.6)	49 (52.7)	

SCCA, squamous cell carcinoma antigen; MPR, major pathological response; BMI, body mass index; CT, computed tomography; SD, standard deviation; cN, clinical N stage; LLL, left lower lung; LUL, left upper lung; RLL, right lower lung; RML, right middle lung; RUL, right upper lung; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.

limited, and their testing methods are both complex and expensive (12,17,18). Conversely, blood predictive biomarkers offer the advantages of being inexpensive, convenient, and non-invasive. Our study revealed that the pre-treatment SCCA level and post-treatment PLR could predict tumor response, and these biomarkers could serve as independent prognostic factors for patients receiving neoadjuvant chemo-immunotherapy.

SCCA, a serine protease inhibitor belonging to the Ovoinhibitor family, has long been recognized as a serum marker for diagnosing advanced squamous cell carcinoma in various organs (19). Elevated SCCA levels in NSCLC patients, which have now been established to be an independent prognostic factor for lung cancer, are associated with decreased DFS and OS, and are correlated with PD-L1 expression (20,21), which we again confirmed in our study of the patients receiving surgery alone. Additionally, this study was the first to find that the pre-treatment SCCA level had both predictive and prognostic value in patients undergoing neoadjuvant chemo-immunotherapy. The patients with high pre-treatment SCCA levels were more prone to achieve an MPR and to have better EFS. However, in the patients who received surgery alone, higher pre-treatment SCCA levels were correlated with a worse prognosis. These findings further support its value as a valid biomarker for predicting patients' responses to neoadjuvant chemo-immunotherapy.

LUSC generally has higher SCCA levels than other lung cancer subtypes (22,23). In this study, 90.6% of the patients in the high pre-treatment SCCA group had LUSC (*Table 3*). Previous research has shown that LUSC patients derive greater survival benefits from immunotherapy, either monotherapy or combination therapy, than lung adenocarcinoma (LUAD) patients (24). Indeed, in our study, more LUSC patients achieved an MPR than LUAD patients (73% *vs.* 33%, P<0.001) (*Table 1*). Compared with LUAD, LUSC has more $CD8^+$ tumor-infiltrating lymphocytes and less $Foxp3^+$ regulatory T cells, which may partly explain the superior effectiveness of neoadjuvant chemo-immunotherapy in LUSC (25,26). Additionally, research has shown that LUSC patients have a higher TMB and higher neoantigen levels than LUSC patients, which provides further biological insight into the enhanced therapeutic response in LUSC (27).

Our analysis revealed a higher proportion of males in the high pre-treatment SCCA group (97.2% *vs.* 80.6%, P<0.001) (*Table 3*). A previous study showed that male patients achieved more favorable outcomes from ICIs

than female patients (28). In our neoadjuvant chemo-immunotherapy cohort, the high-level SCCA group had a significantly higher proportion of smokers (79.2% *vs.* 61.3%, P=0.009) (*Table 3*). Studies have shown that smokers have an elevated TMB and higher PD-L1 expression, and thus may benefit more from ICIs (29,30). Additionally, a greater proportion of the patients in the high pre-treatment SCCA group were N0 (27.4% *vs.* 15.1%, P=0.053) (*Table 3*). Lymph node metastasis induces immunosuppression by stimulating the induction of regulatory T cells and altering dendritic cell phenotypes, resulting in impaired $CD8^+$ T cell responses, which are critical for anti-tumor immunity (31).

Inflammation plays a critical role in cancer development and progression. Recent studies have emphasized the value of inflammation-based biomarkers in peripheral blood for predicting patients' pathologic responses to immunotherapy. Notably, a previous study highlighted that the NLR had better predictive accuracy in terms of the pathologic response than the TMB and PD-L1 expression (32). Additionally, earlier findings showed that both the NLR and PLR could predict the prognosis of NSCLC patients undergoing nivolumab treatment (33). A comprehensive meta-analysis of 15 studies confirmed that the SII is a reliable biomarker of both the pathologic response and patient outcomes in cancer therapy (34). Further, a detailed examination of various inflammation-based biomarkers, including the NLR, PLR, SII, MLR, and PNI, before and after neoadjuvant immunotherapy, revealed that they were associated with the pathologic response and patient prognosis (35). However, research into the significance of inflammatory markers in neoadjuvant immunochemotherapy, a standard treatment for advanced lung cancer, remains limited. Consequently, investigating the effects of these markers on treatment efficacy is critical. This study thoroughly evaluated the predictive and prognostic values of these biomarkers in a cohort undergoing neoadjuvant immunochemotherapy, and suggested that the PLR may be a potential biomarker for predicting outcomes.

A study has shown that platelets contribute to tumor growth, development, and expansion via non-inflammatory pathways and angiogenesis, notably through the stimulation of MMP9 synthesis, adhesion molecules, and growth factors (36). Further, platelets play a crucial role in shielding tumor cells from $CD8^+$ T cell-mediated immune surveillance and facilitate their adherence to the endothelium at metastatic locations (37). These mechanisms could explain the phenomenon observed in our research and our finding that a high post-treatment PLR was linked to worse patient outcomes. Given the prognostic importance of the PLR in NSCLC patients receiving neoadjuvant chemo-immunotherapy, those with higher PLRs should receive more aggressive adjuvant therapy after surgery. Recent research has combined the PLR with tertiary lymphoid structures, nutritional markers, and metabolic parameters from PET-CT to predict the outcomes of NSCLC patients after neoadjuvant immunotherapy (38-40).

Our study had certain limitations. First, this study was conducted at a single center, which might affect the generalizability of our findings. Second, the follow-up period for the neoadjuvant chemo-immunotherapy cohort was short. Third, the retrospective design of our study may introduce biases such as selection bias and information bias. To address these biases, future research should consider prospective study designs and include larger, multi-center cohorts to enhance the generalizability and reliability of the findings. Finally, the mechanisms underlying the predictive value of the pre-treatment SCCA level and the post-treatment PLR for the efficacy of neoadjuvant chemo-immunotherapy remain unclear and warrant further investigation. However, our study was the first to identify the significance of the SCCA level in predicting the efficacy of neoadjuvant chemo-immunotherapy, and it is one of the few studies to explore the relationship between neoadjuvant chemo-immunotherapy and inflammatory markers.

Conclusions

This study investigated the predictive and prognostic value of peripheral blood laboratory markers in patients receiving neoadjuvant chemo-immunotherapy. A high pre-treatment SCCA and a low post-treatment PLR were found to be significantly correlated with a good pathologic response; thus, these markers could serve as independent prognostic indicators in patients undergoing neoadjuvant chemo-immunotherapy. Using these biomarkers, an integrated prediction model could be developed that leverages these and other biomarkers to guide treatment strategies for patients with advanced NSCLC in the future.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-717/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Zhejiang Cancer Hospital Ethics Committee (No. IRB-2024-328), and the requirement of individual consent for this retrospective analysis was waived.

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