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Original Article

Predictive value of CRP combined with peripheral blood cell ratio for the prognosis of advanced NSCLC

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Abstract: Lung cancer remains the leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for the vast majority. In recent years, the interaction between inflammation and tumorigenesis has become the focus of attention, which has also confirmed the importance of inflammatory markers such as C-reactive protein (CRP) in prognosis. In this study, we explored the effects of CRP, systemic inflammatory immune index (SII), and monocyte/lymphocyte ratio (MLR) on the prognosis of patients with advanced NSCLC. We conducted a retrospective study of 274 patients suffering from stage III/IV NSCLC. Among them, 224 patients served as the training set and 50 patients served as the validation set. The independent factors affecting PFS (Progression-Free Survival) and OS (Overall Survival) in the patients were analyzed by Cox regression. Our results showed that CPR (HR=1.691, P=0.004), SII (HR=1.960, P<0.001), MLR (HR=1.578, P=0.003), CEA (HR=1.845, P=0.006), NSE (HR=2.138, P=0.003) and adrenal metastasis (HR=2.896, P<0.003) were independent factors affecting the PFS of NSCLC patients. SII (HR=1.645, P=0.004), CEA (HR=2.021, P=0.002) and brain metastasis (HR=2.899, P<0.001) were independent factors affecting the OS of NLSCL patients. The DCA curve demonstrated that the prediction model provided better clinical net benefit in predicting patients' 6-month PFS and 12-month OS under different threshold probabilities. DeLong test showed no significant difference between AUCs of SII and risk score (P>0.05). Compared with CEA, SII and risk score had higher predictive value for patients' 6-month PFS and 12-month OS (P<0.05). In conclusion, the results of this study indicate that serum inflammatory factor SII can be used as an independent indicator to evaluate 6-month PFS and 12-month OS in patients with advanced NSCLC, and its predictive value is similar to that of the nomogram model.

Keywords: CRP, SII, MLR, advanced NSCLC, prognosis, nomogram

Introduction

Lung cancer (LC) is a leading malignant tumor worldwide, with rising incidence and mortality rates [1, 2]. According to China's National Cancer Registry Annual Report [3], there are about 780,000 new LC cases each year in China. Clinically, LC is categorized into small cell LC (SCLC) and non-small cell LC (NSCLC). NSCLC accounts for 85% of LC cases, making it the primary cause of cancer-related deaths globally [4].

NSCLC is a multifaceted disease that can be further categorized into squamous cell carcinoma, adenocarcinoma, and large cell carcinoma based on the specific sites of manifestation. Notably, the incidence of adenocarcinoma is on a steep rise, representing over 40% of NSCLC. In contrast, squamous cell carcinoma and large cell carcinoma account for 20%-30% and 10%-15%, respectively [5, 6]. Given the relentless escalation in LC incidence coupled with its alarming mortality rate, it has evolved into a paramount health threat for the Chinese populace, imposing immense challenges and social burdens on the public health sector.

The prognosis for NSCLC remains grim, with a significant portion of patients being diagnosed

at advanced stages, culminating in increased mortality [7]. As the tools like medical imaging, bronchoscopy, bronchial washing cytology, and histopathology have played an important role in NSCLC screening and early diagnosis, a profound comprehension of the biological characteristics and molecular mechanisms of NSCLC have catalyzed the evolution of innovative diagnostic tools and therapeutic interventions [8]. Yet, a consensus on clinical standards for NSCLC's prevention, early diagnosis, and treatment remains elusive. Serum biomarkers, given their ease operation, non-invasiveness, efficiency, and dynamic monitoring capabilities, hold paramount importance in NSCLC management, offering invaluable insights for clinical decision-making.

In the intricate landscape of malignant tumor development, inflammation emerges as a pivotal player, fostering tumor cell proliferation and angiogenesis [9]. The quest for the optimal inflammatory biomarker for tumor prognosis prediction has spurred a plethora of studies in recent times. Blood routine parameters, such as leukocyte and subgroup counts, offer a glimpse into the body's inflammatory status [10]. Comprehensive inflammatory indices rooted in these blood routine parameters have been linked with the prognosis of an array of malignant tumors [11]. The systemic immune-inflammation index (SII), a novel inflammatory index, incorporates three distinct inflammatory cells and is computed by multiplying the neutrophil count with the platelet count, followed by division by the lymphocyte count. This index, introduced by Hu et al. in 2014 [12], revealed that elevated SII values were indicative of an unfavorable prognosis in primary liver cancer patients. The monocyte to lymphocyte ratio (MLR) mirrors the equilibrium between tumor progression and inhibition within the body and has been associated with the prognosis of cancers like liver and breast cancer [13, 14]. C-reactive protein (CRP), an acute phase reactant protein predominantly synthesized by hepatocytes, significantly elevates in a majority of cancer patients [15]. Research indicates that CRP levels might be augmented by the stimulation of proinflammatory factors within the tumor microenvironment, thereby triggering a cascade of events leading to excessive cell proliferation and DNA damage [16].

Despite the extensive exploration of the prognostic significance of serum inflammatory factors across various cancers, the amalgamated application of comprehensive inflammatory indices such as SII, MLR, and CRP in gauging the prognosis of patients with advanced NSCLC remains in its infancy. In this study, we juxtaposed and scrutinized the efficacy of SII, MLR, and CRP against conventional tumor markers like CEA and NSE in determining the prognosis of patients with advanced NSCLC. Our findings underscore that SII, MLR, and CRP can more adeptly forecast patients' PFS and OS, paving the way for a novel prognostic evaluation paradigm for advanced NSCLC based on serum indicators.

Materials and methods

Ethical statement

The current study was conducted with the approval of the Binzhou Medical University Hospital Medical Ethics Committee (2021-4230).

Sample source

The data of 337 patients with advanced NSCLC who received treatment between January 2018 and January 2020 were retrospectively analyzed.

Inclusion and exclusion criteria

Inclusion criteria: 1) Patients with confirmed non-small cell lung cancer indicated by pathological and imaging examinations; 2) Patients with pathological type of adenocarcinoma or squamous cell carcinoma; 3) Patients that met AJCC 8th edition clinical stage III or IV [17]; 4) Patients unable to receive surgical treatment; 5) All patients received first-line chemotherapy with platinum-based doublet, the medication complied with guideline recommendations, and completed at least 2 cycles with an interval of no more than 1 month; 6) Patients with complete clinical data and follow-up imaging data that available for efficacy evaluation after chemotherapy.

Exclusion criteria: 1) Patients combined with other primary malignant tumors; 2) Patients with severe heart, liver, and kidney dysfunction; 3) Patients combined with various infectious

diseases or trauma; 4) Patients with a history of medication use before chemotherapy that may affect blood routine, such as glucocorticoids; 5) Patients combined with hematologic diseases or autoimmune diseases.

Group definition

The treatment efficacy was evaluated based on RECIST version 1.1 [18]. Complete response: In addition to the disappearance of all target lesions, pathological lymph nodes (whether target or non-target) also shrink to normal size and the short axis value is less than 10 mm; Partial response: The sum of the diameters of all target lesions decreases by at least 30% from baseline; Stable disease: Neither partial response nor progression criteria are met; Progression: The sum of the diameters of all target lesions increases by at least 20% from baseline, and the absolute value of the increase is greater than 5 mm, or new lesions appear. We categorized the patients with complete response, partial response, and stable disease into control group and the patients with progression into progression group.

Sample screening

Patients were screened according to the inclusion and exclusion criteria. Among them, 32 patients who did not meet the diagnosis of adenocarcinoma or squamous cell carcinoma were excluded according to the pathologic type criteria; 16 patients with stage III or IV disease were not excluded according to the clinical staging criteria; 9 patients who did not receive platinum-based doublet first-line chemotherapy or received less than 2 cycles of chemotherapy were also excluded; moreover, 4 patients with incomplete information that could not be evaluated and 2 patients with a combination of malignancies, severe organ dysfunction, or autoimmune diseases were excluded according to the criteria for patients with comorbid diseases. After stratified screening, a total of 54 patients who did not meet this criterion were excluded, and a total of 274 NSCLC patients who met all the prespecified screening criteria were finally included in this study. We divided the patients into 224 patients in the training group and 50 patients in the validation group according to a ratio of 8:2 (training group:validation group) (**Figure 1**).

Clinical data collection

According to the patients' electronic medical records and outpatient follow-up records, we obtained the patients' clinical data and laboratory examination indicators. The clinical data included gender, age, clinical stage, tumor location, T stage, N stage, pathological type, contralateral lung metastasis, pericardial metastasis, pleural metastasis, liver metastasis, brain metastasis, adrenal metastasis, bone metastasis, smoking history and chronic obstructive pulmonary disease (COPD). Laboratory data included pre-treatment WBC (white blood cell count), Hb (Hemoglobin), ALB (Albumin), FIB (Fibrinogen), CRP (C-Reactive Protein), SII (Systemic Immune-Inflammation Index), MLR (Monocyte-to-Lymphocyte Ratio), CEA (Carcinoembryonic Antigen) and NSE (Neuron Specific Enolase). The calculation formula for SII is N×P/L, and the calculation formula for MLR is M/L (Note: N: neutrophil, P: platelet, L: lymphocyte, M: monocyte). All the indicators were the test results on the first day of admission.

Follow-up

The last follow-up time was set as December 31, 2022. PFS (progression-free survival) is defined as the time from the start of a certain treatment to tumor progression (such as tumor enlargement or appearance of new metastatic lesions) or patient death (regardless of cause). OS (overall survival) is defined as the time from the start of a certain treatment to patient death (regardless of cause). The PFS and OS of patients were statistically analyzed. Follow-up was performed monthly for the first 3 months, then every 3 months thereafter, and every 4 months after the second year. All lung cancer patients underwent CT, MRI and other examinations of the corresponding parts after every 2 cycles of chemotherapy to evaluate the efficacy and disease progression. Based on the patient's progress in the third month, the patients were divided into the progression group and the control group.

Statistical analysis

Data processing was conducted using SPSS 26.0 software. Dichotomous variables were represented as ratios (frequencies) and analyzed using Chi-square tests. Measurement

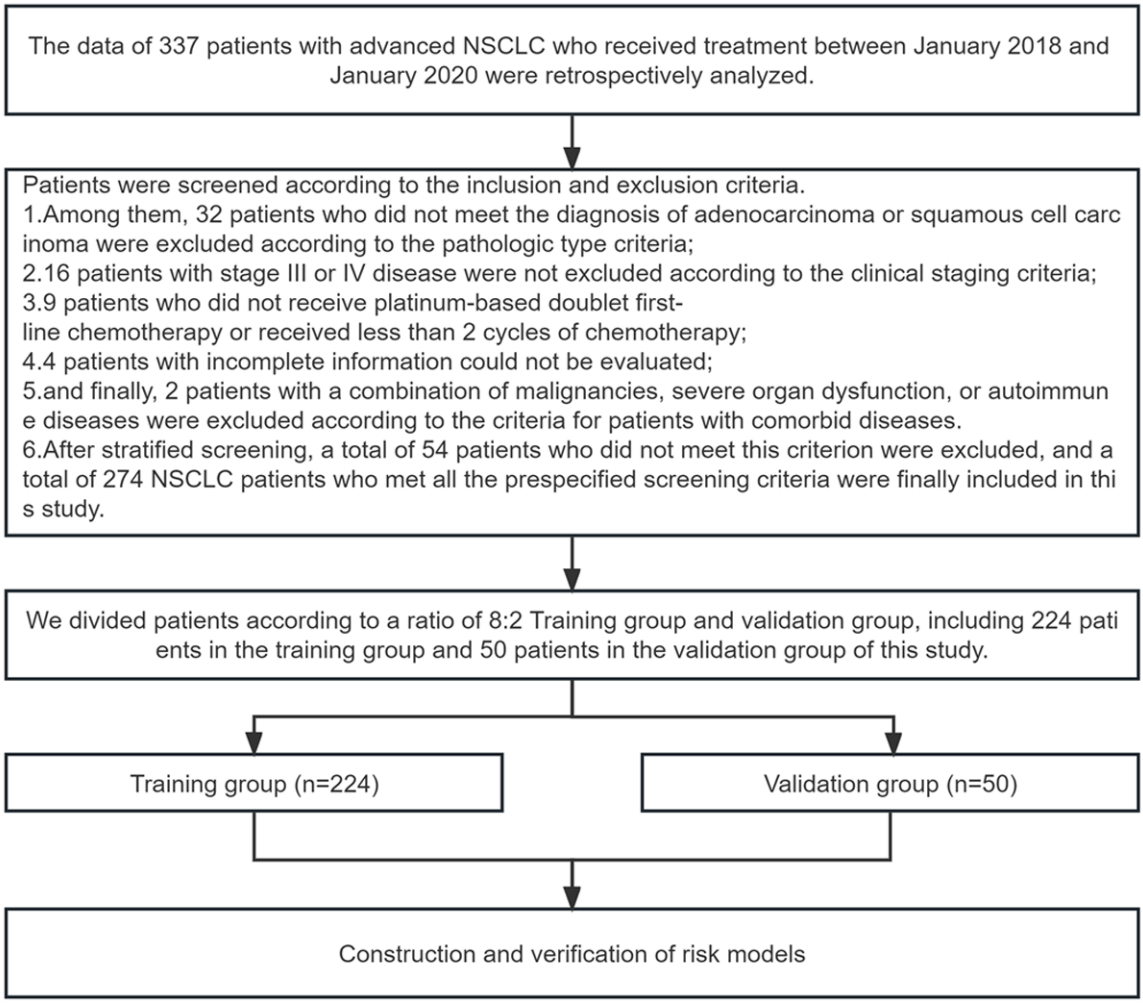

Figure 1. Flow chart of sample screening and model construction.

data were presented as mean ± standard deviation, and independent samples t-test was applied. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive value of various indicators for patient prognosis. Cox proportional hazards regression model was employed to analyze factors influencing the prognosis of NSCLC patients. Regarding the nomogram and DCA (Decision Curve Analysis method), we used R language (4.2.2) for the analysis where 'rms' program package was used to create the nomogram and 'rmda' program package was used for DCA. c-index was calculated using the 'rms' program package to calculate it. X-Tile software was used to determine the optimal survival cutoff value for the measured data. All tests were two-sided, and a *P*-value less than 0.05 was considered statistically significant.

Results

General information

This study included a total of 224 patients with advanced NSCLC, including 185 males and 39 females. According to clinical staging, there were 86 patients with stage III and 138 patients with stage IV. They were divided into progression group (64 cases) and control group (160 cases). In terms of age, there were 111 cases ≥60 years old and 113 cases <60 years old. Tumor locations were mainly central type (142 cases), T stages were mainly T3-4 (157 cases), and N stages were mainly N2-3 (175 cases). Pathological types were mainly adenocarcinoma (125 cases), followed by squamous carcinoma (99 cases). There were 20 cases with contralateral lung metastasis, 27 cases with

pericardial metastasis, 86 cases with pleural metastasis, 18 cases with liver metastasis, 25 cases with brain metastasis, 25 cases with adrenal metastasis, and 50 cases with bone metastasis. There were 60 cases with chronic obstructive pulmonary disease (COPD). Among them, 175 cases had a smoking history.

Comparison of clinical data between progression group and control group

Comparison of clinical data between the two groups found that the proportion of patients with stage III, adenocarcinoma, no pleural metastasis, liver metastasis, adrenal metastasis, bone metastasis and brain metastasis in the control group was significantly higher than that in the progression group (all P<0.05, **Table 1**). There were no significant differences in other clinical indicators (all P>0.05, **Table 1**).

Relationship between CRP, SII, MLR, tumor markers, and treatment efficacy

Patients were classified based on the optimal cutoff value of X-tile. Subsequent analysis of the relationship between each index and treatment efficacy revealed a significantly higher number of patients in the progression group with high expression of CRP, SII, MLR, CEA, and NSE compared to the control group (all P<0.001, **Table 2**).

Analysis of prognostic factors for patients' PFS

Univariate Cox analysis revealed that CRP (HR=2.315, P<0.001), SII (HR=2.796, P<0.001), MLR (HR=1.697, P<0.001), CEA (HR=2.849, P<0.001), NSE (HR=4.033, P<0.001), smoking history (HR=1.421, P=0.033), pathologic type (HR=1.536, P=0.002), liver metastasis (HR=1.921, P=0.008), brain metastasis (HR=3.281, P<0.001), adrenal metastasis (HR=2.449, P<0.001), and clinical staging (HR=0.679, P=0.005), significantly influenced patient PFS (**Table 3**). Furthermore, a multi-factor Cox regression analysis identified CRP (HR=1.691, P=0.004), SII (HR=1.960, P<0.001), MLR (HR=1.578, P=0.003), CEA (HR=1.845, P=0.006), NSE (HR=2.138, P=0.003), and adrenal metastasis (HR=2.896, P<0.001) as independent prognostic factors for patients' PFS (**Table 4**). These findings provide valuable insights for clinical prognosis assessment and the development of treatment strategies.

Analysis of prognostic factors for patients' OS

Univariate Cox analysis revealed that CRP (HR=1.820, P<0.001), SII (HR=2.273, P<0.001), MLR (HR=1.583, P=0.002), CEA (HR=2.670, P<0.001), NSE (HR=2.362, P<0.001), pathologic type (HR=1.542, P=0.002), liver metastasis (HR=1.903, P=0.009), brain metastasis (HR=3.257, P<0.001), adrenal metastasis (HR=2.063, P=0.001), and clinical staging (HR=0.743, P=0.031) significantly influenced patient OS (**Table 5**). Subsequently, multivariate Cox regression analysis demonstrated that SII (HR=1.645, P=0.004), CEA (HR=2.021, P=0.002), and brain metastasis (HR=2.899, P<0.001) independently affected patient OS (**Table 6**). These findings provide valuable insights for clinical prognosis assessment and treatment decisions.

The value of SII and CEA in predicting PFS and OS in NSCLC patients

To further explore the predictive value of SII and CEA for patients' 6-month PFS and 12-month OS, we conducted ROC curve analysis. The results revealed that at an SII of 775.150, the sensitivity and specificity for 6-month PFS were 83.75% and 54.17%, respectively, with an AUC of 0.683 (95% CI: 0.611-0.755). Similarly, at a CEA level of 40.050 μg/L, the sensitivity and specificity for 6-month PFS were 92.50% and 23.61%, respectively, but the AUC was 0.529 (95% CI: 0.452-0.605), indicating a lower predictive value. Regarding the prediction of 12-month OS, at an SII of 780.150, the sensitivity and specificity were 74.75% and 52.00%, respectively, with an AUC of 0.609 (95% CI: 0.534-0.684). For CEA at 26.950 μg/L, both the sensitivity and specificity were 74.75%, but the specificity was 37.60% and the AUC was 0.529 (95% CI: 0.454-0.605) (**Figure 2**; **Table 7**).

Nomogram prognostic model construction

Later, we developed a prediction model using a nomogram to forecast the 6-month PFS and 12-month OS of patients. This model was constructed based on independent prognostic factors identified through multivariable Cox regression analysis (**Figure 3A**, **3B**). The PFS chart had a C index of 0.707 (0.687-0.727, P<0.0001), while the OS chart had a C index of 0.627 (0.606-0.648, P<0.0001). ROC curve analysis

Table 1. Comparison of clinical data between progression group and control group

Factors	Control group (n=160)	Progression group (n=64)	x^2 value	*P* value
Gender			1.503	0.220
Male	129	56		
Female	31	8		
Age			2.445	0.117
≥60 years	74	37		
<60 years	86	27		
Clinical staging			25.397	<0.001
Stage III	78	8		
Stage IV	82	56		
Tumor site			2.926	0.087
Central	107	35		
Peripheral	53	29		
T-stage			2.759	0.096
T1-2	53	14		
T3-4	107	50		
N-stage			0	>0.999
N0-1	35	14		
N2-3	125	50		
Pathologic type			4.708	0.030
Adenocarcinoma	82	43		
Squamous cell carcinoma	78	21		
Contralateral lung metastasis			0.021	0.882
Yes	14	6		
No	146	58		
Pericardial metastasis			0.606	0.436
Yes	21	6		
No	139	58		
Pleural metastasis			10.058	0.002
Yes	51	35		
No	109	29		
Liver metastasis			13.918	0.001
Yes	6	12		
No	154	52		
Brain metastasis			21.436	<0.001
Yes	8	17		
No	152	47		
Adrenal metastasis			21.436	<0.001
Yes	8	17		
No	152	47		
Bone metastasis			14.483	<0.001
Yes	25	25		
No	135	39		
Smoking history			2.048	0.152
Yes	121	54		
No	39	10		
COPD			3.826	0.050
Yes	37	23		
No	123	41		

Note: COPD, chronic obstructive pulmonary disease.

Table 2. CRP, SII, MLR, and tumor markers with efficacy

Factors	Control group (n=160)	Progression group (n=64)	x^2 value	*P* value
CRP (mg/L)			61.717	<0.001
≥12.100	17	39		
<12.100	143	25		
SII			82.024	<0.001
≥789.700	31	54		
<789.700	129	10		
MLR			20.036	<0.001
≥0.510	34	33		
<0.510	126	31		
CEA (μg/L)			31.376	<0.001
≥41.400	8	21		
<41.400	152	43		
NSE (ng/mL)			36.674	<0.001
≥26.500	4	19		
<26.500	156	45		

Note: CRP, C-reactive protein; SII, systemic immune-inflammation index; MLR, monocyte-to-lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron specific enolase.

revealed that the AUC of risk score for predicting patient PFS was 0.715, and for predicting OS was 0.605 (**Figure 3C**; **Table 8**). The DCA curve demonstrated that the prediction model yielded favorable clinical net benefit across various threshold probabilities, confirming its effectiveness (**Figure 3D**).

External model validation

To test the generality of our model, we included an additional group of 50 patients with advanced NSCLC as a validation group. We first compared the baseline data of the patients who experienced progression and those who did not among the 50 patients. The results revealed significant differences between the two groups in terms of pathologic data, including type, brain metastasis, adrenal metastasis, and bone metastasis (all P<0.05, **Table 9**). However, there were no differences in other clinical data (all P>0.05). When comparing the baseline data of patients in the training group and the validation group, we found no differences in clinical data between the two groups (all P>0.05, **Table 10**). We calculated the ROC curve of the validation group model based on the beta coefficients of 6-month PFS and 12-month OS. The risk formula for 6-month PFS is CRP*0.639860124 + SII*0.83613-3444 + MLR*0.413880205 + CEA*0.321500044 + NSE*0.320666118 + adrenal metastasis*0.374129155. The risk formula for 12-month OS is SII*0.661431908 + CEA*0.313806623 + adrenal metastasis*1.048705535. The calculation results showed that the risk model had an AUC of 0.767 for 6-month PFS in the validation group, and an AUC of 0.641 for pre-existing OS (**Figure 4A**, **4B**). The C-index of the PFS plot was 0.711 (0.673-0.749, P<0.0001), while the C-index of the OS plot was 0.612 (0.568-0.656, P<0.0001). The DCA curve demonstrated that the prediction model provided better clinical net benefit in predicting patients' 6-month PFS and 12-month OS under different threshold probabilities (**Figure 4C**, **4D**), confirming its practicality. Finally, our comparison also revealed that comparing the C-index of the training set with that of the validation set for 6-month PFS by Delong's test showed no difference in the C-index between the two models (Z=0.026, P=0.979), and comparing the C-index of the training set with that of the validation set for 12-month OS also showed no difference in the C-index between the two models (Z=0.956, P=0.342).

Comparison of the value of individual indicators and risk models in predicting patient PFS and OS

At the end of the study, we conducted an analysis to determine the efficacy of individual indicators and risk models in predicting patients' 6-month PFS and 12-month OS. The Delong test was employed for this purpose. The findings revealed that there was no significant difference between SII and risk score (P>0.05). However, both SII and risk score demonstrated higher predictive value for patients' 6-month PFS and 12-month OS compared to CEA (**Table 11**, P<0.05).

Discussion

Although serum inflammatory markers have been extensively studied for their prognostic value in various cancers, their combined application in assessing the prognosis of patients with advanced NSCLC remains limited [19]. In

Table 3. Univariate Cox regression analysis of factors affecting PFS

Factors	β	SE	χ^2	P	HR	95% CI	
						Lower	Upper
WBC	-0.042	0.035	1.461	0.227	0.958	0.895	1.027
Hb	0.006	0.004	2.424	0.120	1.006	0.998	1.014
ALB	0.003	0.014	0.043	0.836	1.003	0.975	1.032
FIB	-0.053	0.066	0.646	0.422	0.949	0.834	1.079
CRP	0.840	0.158	28.368	<0.001	2.315	1.700	3.154
SII	1.028	0.146	49.319	<0.001	2.796	2.098	3.724
MLR	0.529	0.147	12.965	<0.001	1.697	1.272	2.262
CEA	1.047	0.207	25.659	<0.001	2.849	1.900	4.273
NSE	1.395	0.235	35.192	<0.001	4.033	2.544	6.394
Gender	0.257	0.178	2.102	0.147	1.293	0.913	1.832
Age	-0.005	0.007	0.435	0.510	0.995	0.981	1.010
Smoking history	0.352	0.165	4.529	0.033	1.421	1.028	1.965
Tumor Site	-0.138	0.140	0.971	0.324	0.871	0.662	1.146
T-stage	-0.194	0.147	1.738	0.187	0.824	0.617	1.099
N-stage	-0.184	0.164	1.258	0.262	0.832	0.604	1.147
Pathologic type	0.429	0.140	9.468	0.002	1.536	1.169	2.020
Contralateral lung metastasis	-0.085	0.237	0.129	0.719	0.919	0.578	1.460
Pericardial metastasis	-0.018	0.209	0.007	0.932	0.982	0.652	1.480
Pleural metastasis	0.187	0.138	1.838	0.175	1.206	0.920	1.580
Liver metastasis	0.653	0.248	6.953	0.008	1.921	1.182	3.120
Brain metastasis	1.188	0.222	28.743	<0.001	3.281	2.125	5.065
Adrenal metastasis	0.896	0.217	17.089	<0.001	2.449	1.602	3.744
Bone metastasis	0.285	0.161	3.127	0.077	1.330	0.970	1.824
Clinical staging	-0.387	0.138	7.804	0.005	0.679	0.518	0.891
COPD	0.115	0.152	0.572	0.449	1.122	0.833	1.512

Note: WBC, white blood cell count; Hb, hemoglobin; ALB, albumin; FIB, fibrinogen; CRP, C-reactive protein; SII, systemic immune-inflammation index; MLR, monocyte-to-lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron specific enolase; COPD, chronic obstructive pulmonary disease; OS, overall survival.

Table 4. Multivariate Cox regression analysis of factors affecting PFS

Factors	β	SE	χ^2	P	HR	95% CI	
						Lower	Upper
CRP	0.525	0.181	8.389	0.004	1.691	1.185	2.412
SII	0.673	0.171	15.413	<0.001	1.960	1.401	2.743
MLR	0.456	0.153	8.901	0.003	1.578	1.170	2.130
CEA	0.612	0.222	7.594	0.006	1.845	1.193	2.851
NSE	0.760	0.260	8.552	0.003	2.138	1.285	3.557
Smoking history	0.080	0.174	0.209	0.648	1.083	0.770	1.523
Pathologic type	0.240	0.147	2.677	0.102	1.272	0.954	1.696
Brain metastasis	0.353	0.256	1.892	0.169	1.423	0.861	2.352
Adrenal metastasis	1.063	0.234	20.720	<0.001	2.896	1.832	4.577
Clinical staging	0.448	0.233	3.696	0.055	1.565	0.991	2.470

Note: CRP, C-Reactive protein; SII, systemic immune-inflammation index; MLR, monocyte-to-lymphocyte Ratio; CEA, carcinoembryonic antigen; NSE, neuron specific enolase; PFS, progression-free survival.

this study, we investigated for the first time the relationships among routine laboratory indicators such as white blood cells, CRP, and lactate dehydrogenase, as well as the impact of short-

Table 5. Univariate Cox regression analysis of factors affecting OS

Factors	β	SE	χ^2	P	HR	95% CI	
						Lower	Upper
WBC	-0.045	0.035	1.631	0.202	0.956	0.892	1.025
Hb	0.007	0.004	2.886	0.089	1.007	0.999	1.015
ALB	0.001	0.014	0.004	0.949	1.001	0.973	1.030
FIB	-0.055	0.066	0.692	0.406	0.947	0.832	1.077
CRP	0.599	0.157	14.575	<0.001	1.820	1.338	2.475
SII	0.821	0.145	31.876	<0.001	2.273	1.709	3.022
MLR	0.460	0.147	9.826	0.002	1.583	1.188	2.110
CEA	0.982	0.207	22.513	<0.001	2.670	1.780	4.006
NSE	0.860	0.226	14.493	<0.001	2.362	1.517	3.677
Gender	0.251	0.178	1.990	0.158	1.286	0.907	1.823
Age	-0.001	0.007	0.025	0.875	0.999	0.985	1.013
Smoking history	0.307	0.165	3.462	0.063	1.359	0.984	1.879
Tumor Site	-0.089	0.140	0.410	0.522	0.914	0.695	1.202
T-stage	-0.139	0.146	0.905	0.341	0.870	0.653	1.159
N-stage	-0.183	0.163	1.249	0.264	0.833	0.605	1.148
Pathologic type	0.433	0.141	9.471	0.002	1.542	1.170	2.033
Contralateral lung metastasis	-0.149	0.236	0.397	0.529	0.862	0.542	1.369
Pericardial metastasis	0.032	0.206	0.024	0.876	1.033	0.689	1.548
Pleural metastasis	0.130	0.138	0.890	0.345	1.139	0.869	1.492
Liver metastasis	0.644	0.247	6.777	0.009	1.903	1.172	3.090
Brain metastasis	1.181	0.220	28.759	<0.001	3.257	2.115	5.014
Adrenal metastasis	0.724	0.216	11.269	0.001	2.063	1.352	3.149
Bone metastasis	0.205	0.161	1.617	0.203	1.228	0.895	1.685
Clinical staging	-0.297	0.138	4.646	0.031	0.743	0.567	0.973
COPD	0.001	0.153	0.000	0.997	1.001	0.742	1.350

Note: WBC, white blood cell count; Hb, hemoglobin; ALB, albumin; FIB, fibrinogen; CRP, C-reactive protein; SII, systemic immune-inflammation index; MLR, monocyte-to-lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron specific enolase; COPD, chronic obstructive pulmonary disease; OS, overall survival.

term chemotherapy on patients with advanced non-small cell lung cancer. According to our research findings, there were significant differences in the expression of inflammatory and immune markers such as SII, MLR, CRP, and tumor markers between patients responsive to chemotherapy and those with disease progression. Further detailed analysis revealed significant differences in clinical staging, pleura, bone, brain, liver, and adrenal distant metastasis rates between the progression group and the control group. This suggests that the inflammatory status, clinical stage, and metastatic state of patients with advanced NSCLC may affect the short-term efficacy of chemotherapy. Therefore, we speculate that inflammatory and tumor markers such as SII, MLR, and CRP, as well as the disease progression status, may be the keys in predicting chemotherapy sensitivity in these patients.

To further understand the factors influencing patients' OS and PFS, we employed Cox regression analysis to identify the prognostic factors affecting patient OS and PFS. The analysis revealed that CRP, SII, MLR, CEA, NSE, and Adrenal metastasis were independent prognostic factors affecting patient PFS. Meanwhile, SII, CEA, and Brain metastasis were independent prognostic factors affecting patient OS. A study by Hatanaka et al. [20] found that in patients with hepatocellular carcinoma treated with altizumab and bevacizumab, CRP≥1.0 mg/dL was significantly associated with PFS and OS. Additionally, Chen et al. [21] conducted a comprehensive retrospective analysis of 1,383 patients undergoing radical resection of colorectal cancer and found that patients with lower NLR, PLR, and SII levels had longer DFS and OS. In multivariate analysis, SII was identified as an independent prognostic factor for

Table 6. Multivariate Cox regression analysis of factors affecting OS

Factors	β	SE	χ^2	P	HR	95% CI	
						Lower	Upper
CRP	0.297	0.189	2.478	0.115	1.346	0.930	1.948
SII	0.498	0.171	8.453	0.004	1.645	1.176	2.301
MLR	0.296	0.153	3.738	0.053	1.345	0.996	1.816
CEA	0.704	0.223	9.992	0.002	2.021	1.307	3.127
NSE	0.019	0.262	0.005	0.942	1.019	0.610	1.704
Pathologic type	0.275	0.148	3.446	0.063	1.317	0.985	1.761
Liver metastasis	0.379	0.255	2.211	0.137	1.461	0.886	2.409
Brain metastasis	1.064	0.232	20.967	<0.001	2.899	1.838	4.572
Adrenal metastasis	0.161	0.238	0.458	0.499	1.175	0.737	1.873
Clinical staging	-0.116	0.147	0.618	0.432	0.891	0.667	1.189

Note: CRP, C-reactive protein; SII, systemic immune-inflammation index; MLR, monocyte-to-lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron specific enolase; OS, overall survival.

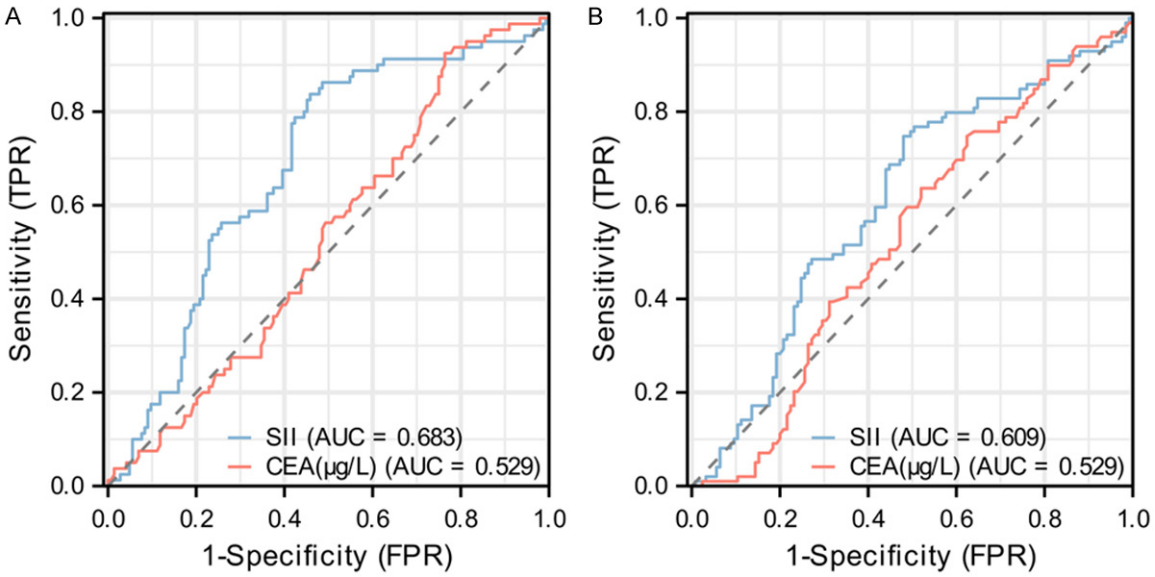

Figure 2. ROC curves of SII and CEA in predicting OS and PFS in advanced NSCLC patients. A. AUCs of SII and CEA in predicting 6-month PFS. B. AUCs of SII and CEA in predicting 12-month OS. Note: SII, systemic immune-inflammation index; CEA, carcinoembryonic antigen; PFS, progression-free survival; OS, overall survival; AUC, area under curve; ROC, receiver operating characteristic.

DFS and OS, even outperforming NLR and PLR in prognostic value. Ding et al. [22] also supported this, showing in a retrospective study of 30 patients with advanced cancer treated with immunotherapy that higher pre-treatment SII and PIN levels were associated with worse PFS and OS. These studies highlight the clinical significance of inflammatory markers in predicting tumor OS and PFS, consistent with our research findings.

In this study, we found that SII and CEA are common factors affecting OS and PFS. However, it remains unclear whether both are clinically valuable in predicting OS and PFS. We analyzed the predictive value of SII and CEA for 6-month PFS and 12-month OS in this study. The results revealed that the AUC of SII for predicting 6-month PFS was 0.683 and for 12-month OS was 0.529. In contrast, the AUC of CEA for predicting 6-month PFS was 0.609 and for 12-month OS was 0.529. This suggests that SII and CEA are not ideal for predicting patient survival. Recent studies have found that risk models have high clinical value for predicting and evaluating patient prognosis. For

Table 7. ROC curve analysis of SII and CEA in predicting PFS and OS

Variables	Time (month)	Status	Cut-off	Sensitivity	Specificity	AUC	95% CI	*P* value
SII	6	PFS	775.150	83.75%	54.17%	0.683	0.611-0.755	<0.001
CEA (μg/L)			40.050	92.50%	23.61%	0.529	0.452-0.605	0.479
SII	12	OS	780.150	74.75%	52.00%	0.609	0.534-0.684	0.005
CEA (μg/L)			26.950	74.75%	37.60%	0.529	0.454-0.605	0.426

Note: SII, Systemic Immune-Inflammation Index; CEA, Carcinoembryonic Antigen; PFS, Progression-Free Survival; OS, Overall Survival; AUC, area under curve; ROC, Receiver operating characteristic.

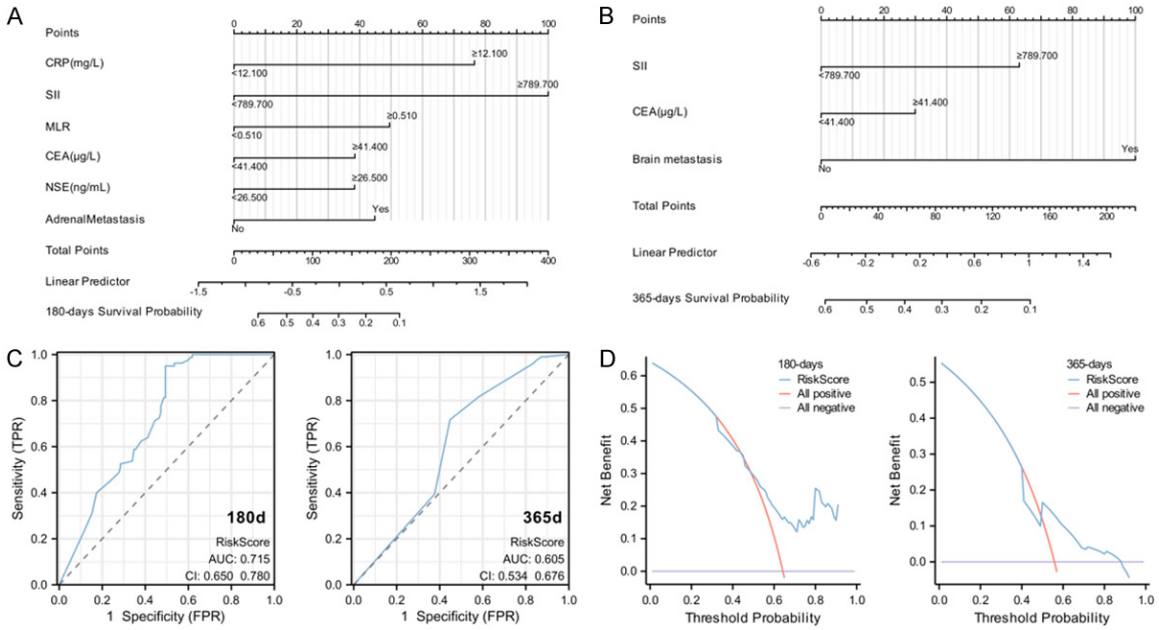

Figure 3. Nomogram in predicting 6-month PFS and 12-month OS. A, B. Nomogram predicting 6-month PFS and 12-month OS in patients with advanced NSCLC. C. ROC curve of nomogram model for predicting 6-month PFS and 12-month OS of patients. D. DCA curves for predictive prognostic modeling of line graph models. Note: CRP, C-reactive protein; SII, systemic immune-inflammation index; MLR, monocyte-to-lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron specific enolase; ROC, receiver operating characteristic; PFS, progression-free survival; OS, overall survival; DCA, decision curve analysis.

Table 8. Validation group versus the training group risk model in predicting the ROC curve parameters of patient PFS and OS

Variables	Time (month)	Status	Cut-off	Sensitivity	Specificity	AUC	95% CI	*P* value
Training group	6	PFS	1.426	95.00%	50.69%	0.715	0.650-0.780	<0.001
Validation group			0.786	69.57%	74.07%	0.767	0.636-0.897	0.001
Training group	12	OS	0.488	71.72%	55.20%	0.605	0.534-0.676	0.007
Validation group			0.488	66.67%	58.62%	0.641	0.503-0.780	0.090

instance, Wang et al. [23] successfully predicted postoperative outcomes in patients with pulmonary metastasis of colorectal cancer by constructing a nomogram model. In this study, we constructed a nomogram based on Cox regression prognostic factors to predict 6-month PFS and 12-month OS in patients. Through validation, it was found that this model has some value in predicting patient survival. However, at the end of the study, we found through the Delong test that the risk score and SII had no difference in predicting 6-month PFS and 12-month OS for patients. This indicates that although our risk score model was con-

Table 9. Training group baseline data

Factors	Control group (n=35)	Progression group (n=15)	x^2 value	*P* value
Gender			1.023	0.312
Male	28	10		
Female	7	5		
Age			0.192	0.662
≥60 years	14	7		
<60 years	21	8		
Clinical staging			0.599	0.439
Stage III	8	5		
Stage IV	27	10		
Tumor site			0.010	0.922
Central	18	9		
Peripheral	17	9		
T-stage			0.272	0.602
Central	7	4		
Peripheral	28	11		
N-stage			0.008	0.929
N0-1	5	2		
N2-3	30	13		
Pathologic type			4.667	0.030
Adenocarcinoma	21	4		
Squamous cell carcinoma	14	11		
Contralateral lung metastasis			0.577	0.447
Yes	5	1		
No	30	14		
Pericardial metastasis			0.017	0.897
Yes	2	1		
No	33	14		
Pleural metastasis			1.020	0.312
Yes	9	6		
No	26	9		
Liver metastasis			0.641	0.423
Yes	4	3		
No	31	12		
Brain metastasis			9.235	0.002
Yes	1	5		
No	34	10		
Adrenal metastasis			4.193	0.040
Yes	1	3		
No	34	12		
Bone metastasis			4.365	0.036
Yes	2	4		
No	33	11		
Smoking history			0.019	0.891
Yes	25	11		
No	10	4		
COPD			0.058	0.810
Yes	6	3		
No	29	12		

Table 10. Comparison of the baseline data between the training group and the validation group

Factors	Control group (n=160)	Progression group (n=50)	x^2 value	*P* value
Gender			1.172	0.279
Male	185	38		
Female	39	12		
Age			0.934	0.334
≥60 years	111	21		
<60 years	113	29		
Clinical staging			2.720	0.099
Stage III	86	13		
Stage IV	138	37		
Tumor site			1.526	0.217
Central	142	27		
Peripheral	82	23		
T-stage			1.256	0.262
T1-2	67	11		
T3-4	157	39		
N-stage			1.559	0.212
N0-1	49	7		
N2-3	175	43		
Pathologic type			0.556	0.456
Adenocarcinoma	125	25		
Squamous cell carcinoma	99	25		
Contralateral lung metastasis			0.449	0.503
Yes	20	6		
No	204	44		
Pericardial metastasis			1.536	0.215
Yes	27	3		
No	197	47		
Pleural metastasis			1.237	0.266
Yes	86	15		
No	138	35		
Liver metastasis			1.754	0.185
Yes	18	7		
No	206	43		
Brain metastasis			0.029	0.865
Yes	25	6		
No	199	44		
Adrenal metastasis			0.056	0.812
Yes	25	5		
No	199	45		
Bone metastasis			1.718	0.190
Yes	50	7		
No	174	43		
Smoking history			0.866	0.352
Yes	175	36		
No	49	14		
COPD			1.675	0.196
Yes	60	9		
No	164	41		
Progress			0.040	0.840
Yes	64	15		
No	160	35		

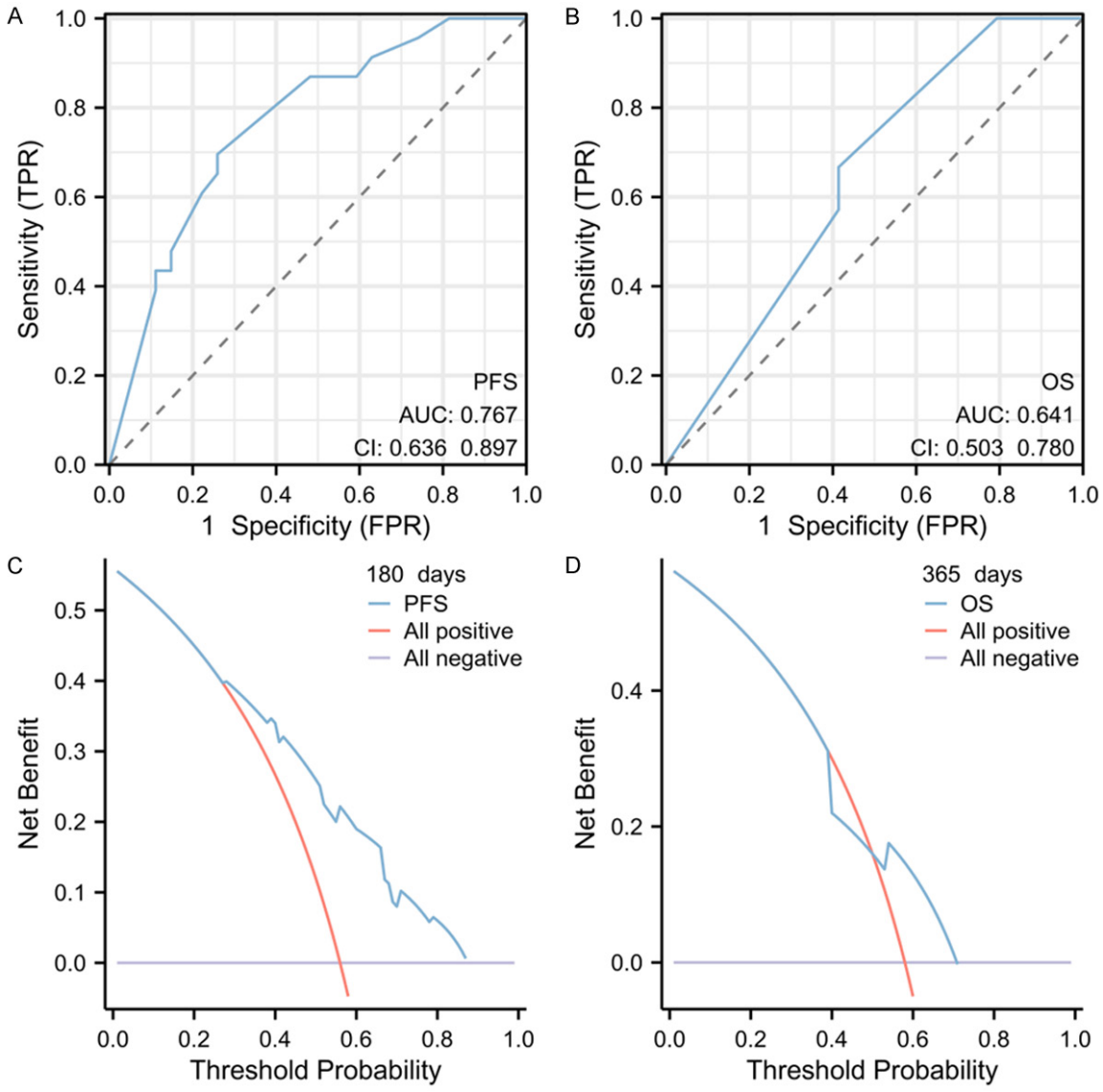

Figure 4. ROC curves and DCA curves assessing the efficacy of predictive models for patients' 6-month PFS and 12-month OS. A, B. ROC curve for the prediction of patient 6-month PFS and 12-month OS. C, D. DCA curves for predictive prognostic modeling of line graph models. Note: PFS, progression-free survival; OS, overall survival; ROC, receiver operating characteristic; DCA, decision curve analysis.

Table 11. The value of each index to predict PFS and OS in patients verified by Delong test

The test results on	Time (month)	Status	Z value	*P* value	AUC difference	95% CI	
						Lower	Upper
Risk Score - SII	6	PFS	0.976	0.329	0.032	-0.033	0.097
Risk Score - CEA			5.113	<0.001	0.186	0.115	0.258
SII - CEA			3.222	0.001	0.154	0.060	0.248
Risk Score - SII	12	OS	-0.091	0.927	-0.004	-0.087	0.079
Risk Score - CEA			3.427	0.001	0.135	0.058	0.212
SII - CEA			3.068	0.002	0.139	0.050	0.227

structed based on multiple prognostic factors, it did not offer predictive power beyond the known SII index. In other words, the SII index already covers most of the predictive informa-

tion in our model, making their predictive capabilities comparable. This also suggests that for patient prognosis prediction, the SII index may be sufficient, eliminating the need for a complex risk score model. This is beneficial for clinical practice as using a simple index can more quickly and conveniently predict patient outcomes. Previous research by He et al. [24] found that SII is a simple yet potent prognostic predictor after radical surgery for stage I-II gastric cancer. Furthermore, a meta-analysis [25] suggested that a high SII might be a promising poor prognostic predictor in patients with gynecological and breast cancers, especially ovarian cancer and triple-negative breast cancer. In line with previous research, SII is a promising high-level prognostic marker with the potential for optimizing individualized treatment plans for non-small cell lung cancer [26-28]. Compared to traditional tumor markers, it provides superior predictive power, but this claim still requires validation in larger sample studies.

However, there are some limitations to this study. First, this is a retrospective analysis based on existing data, which might introduce selection bias. Secondly, although a considerable patient sample was included, it is still relatively limited compared to the entire NSCLC patient population. This might limit our exploration of some rare but significant factors. Additionally, the study mainly utilizes single-center data, potentially affecting the generalizability of the results. Hence, even though this study offers some insights into the prognosis prediction for patients with NSCLC, further extensive, multi-center validation studies are needed before applying the findings to clinical practice. We look forward to subsequent research further investigating the prognostic biomarkers for NSCLC patients and providing a basis for individualized treatment.

In summary, the results of this study indicate that serum inflammatory factor SII can be used as an independent indicator to evaluate 6-month PFS and 12-month OS in patients with advanced NSCLC, and its predictive value is similar to that of the nomogram model.

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Disclosure of conflict of interest

None.

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