Am J Cancer Res 2026;16(3):920-936
www.ajcr.us /ISSN:2156-6976/ajcr0171303

Original Article

Predictive value of the systemic immune-inflammation index and geriatric nutritional risk index on the efficacy of immunotherapy and survival prognosis in advanced non-small cell lung cancer: a retrospective study

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Received January 7, 2026; Accepted March 18, 2026; Epub March 25, 2026; Published March 30, 2026

Abstract: Objective: To investigate the predictive value of the systemic immune-inflammation index (SII) and geriatric nutritional risk index (GNRI) for immunotherapy efficacy and survival prognosis in advanced non-small cell lung cancer (NSCLC). Methods: This retrospective study enrolled 152 patients with advanced NSCLC who received immunotherapy. Patients were divided into effective (n = 106) and ineffective (n = 46) groups based on treatment response. Pretreatment SII, GNRI, and programmed cell death-ligand 1 (PD-L1) levels were compared between groups. Multivariate logistc regression identified factors influencing immunotherapy efficacy. Receiver operating characteristic curve analysis evaluated the predictive value of these indicators. Kaplan-Meier method analyzed the relationship between SII, GNRI, and progression-free survival (PFS)/overall survival (OS). Cox regression analyzed their impact on survival and interaction. Results: The effective group had significantly lower pretreatment SII but higher GNRI and PD-L1 than the ineffective group (all $P<0.05$). All three indicators significantly influenced immunotherapy efficacy (all $P<0.05$). SII combined with GNRI yielded a higher AUC (0.879) for predicting efficacy than SII alone (0.778), GNRI alone (0.699), or PD-L1 alone (0.707). Patients with high SII (≥418.67) had worse 2-year OS and shorter median PFS/OS than those with low SII (all $P<0.05$). Patients with low GNRI (<97.89) had worse outcomes than those with high GNRI (≥97.89) (all $P<0.05$). SII ≥418.67 and GNRI <97.89 were independent risk factors for poor survival (both $P<0.05$), with significant interaction between them. Conclusions: SII and GNRI are closely associated with immunotherapy efficacy in advanced NSCLC, and their interaction influences patient survival.

Keywords: Systemic immune-inflammation index, geriatric nutritional risk index, non-small cell lung cancer, immunotherapy, objective response rate, survival prognosis

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1], with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all lung cancer cases [2]. NSCLC typically presents no obvious symptoms in its early stages. Consequently, many patients are diagnosed at an advanced stage and have already missed the window for surgical intervention. In recent years, immune checkpoint inhibitors (ICIs), a novel form of anti-tumor immunotherapy, have achieved breakthroughs in the treatment of various cancers, including lung cancer [3]. In particular, ICIs targeting programmed cell death protein 1 (PD-1) or programmed cell death-ligand 1 (PD-L1) have, to some extent, transformed the treatment landscape for advanced NSCLC, offering some patients the possibility of prolonged survival [4]. Although ICIs have greatly changed the treatment landscape for NSCLC patients, not all patients derive benefit from them. This has prompted researchers to continuously explore biomarkers capable of predicting ICIs efficacy. At present, immunohistochemical detection of PD-L1 expression in tumor tissues is a common method for evaluating whether cancer patients are suitable for immunotherapy [5]. However, immunohistochemical detection has certain limitations. For instance, the results are highly susceptible to subjective interpretation by evaluators, and intratumoral heterogeneity can introduce bias into the assessment of

https://doi.org/10.62347/QMNU5628

PD-L1 expression levels. Consequently, PD-L1 alone is not yet a reliable predictor of ICIs efficacy in tumors. Although many studies have explored combining PD-L1 with other biomarkers-such as tumor mutational burden or tumor-infiltrating lymphocytes-to improve predictive accuracy, such combination strategies remain under investigation [6, 7]. However, such combined predictors typically rely on the acquisition of tumor tissue. In clinical practice, limitations such as insufficient tissue quantity, variable sample quality, and the high cost of gene sequencing restrict their broader application. Therefore, developing cost-effective and practical alternatives to replace tissue-based detection has become a key focus of current research.

Related research shows that the non-specific activation of the immune system can lead to off-target immune and inflammatory responses, which can affect almost any organ or system, resulting in patients becoming insensitive to immunotherapy or developing drug resistance after a period of treatment [8]. Inflammation is a key feature of the tumor microenvironment [9] and, to a certain extent, promotes the occurrence and progression of malignant tumors. The systemic immune-inflammation index (SII) is a composite inflammatory biomarker derived from peripheral blood platelet, neutrophil and lymphocyte counts [10]. It can accurately reflect the balance between tumor-induced inflammatory response and anti-tumor immune response. However, in the NSCLC population, it is important to note that patients are often older and many may present with malnutrition [11]. The geriatric nutritional risk index (GNRI) is a composite indicator based on serum albumin and body weight, which can effectively reflect an individual's nutritional status [12]. When the GNRI is too low, it often impairs host immune function and exacerbates the systemic inflammatory response, which in turn promotes the progression of cancer cachexia and reduces patient tolerance to immunotherapy. This suggests that changes in GNRI not only affect SII in patients with cancer but also influence the efficacy and prognosis of immunotherapy. Compared with tissue-based detection methods (e.g., PD-L1 expression), SII and GNRI offer the advantages of being minimally invasive and suitable for repeated assessment. However, there remains a lack of systematic evaluation regarding the predictive value of SII and GNRI for both the efficacy of immunotherapy and the prognosis of patients with advanced NSCLC. The purpose of this study was to explore the effects of SII and GNRI on the efficacy and prognosis of patients with advanced NSCLC receiving immunotherapy, in order to provide reference for clinical practice.

Material and methods

Sample size estimation

First, the sample size was calculated based on the events per variable (EPV) criterion [13]. The initial number of analytic variables in this study was 12, so the EPV was set to 12. The final regression variables were limited to no more than 3. Subsequently, combining previous literature reports, about 66% to 68% of advanced cancer patients can benefit from ICIs treatment [14, 15], meaning their condition can be controlled. Therefore, this study assumes that approximately 70% of advanced NSCLC patients receive ICIs treatment and achieve disease condition. The required sample size was calculated using the following formula: sample size = (number of regression variables × EPV)/(1 - event occurrence rate), i.e., sample size = (3 × 12)/(1-0.7) ≈ 120. Assuming a data missing rate of 10%, a total of 132 samples are required. The final sample size included in the study is 152, which meets the needs of statistical analysis.

Research subjects

Using a retrospective design, data were collected and analyzed from NSCLC patients who received immunotherapy in the Oncology Department of Suzhou Ninth People's Hospital from January 2019 to October 2023. This study was approved by the ethics committee of Suzhou Ninth People's Hospital.

Inclusion criteria: (1) Compliant with the 2016 edition of the Expert Consensus on the Diagnosis and Treatment of Advanced Primary Lung Cancer in China [16], and confirmed by pathology as NSCLC; (2) Patients with tumor node metastasis staging ranging from stage IIIB to IV who are no longer suitable for surgical treatment; (3) Age ≥60 years; (4) Eastern Cooperative Oncology Group performance status (ECOG) 0-2; (5) No prior anti-tumor treatment before initial diagnosis; (6) No diseases that may significantly affect peripheral blood inflammatory indicators and nutritional status before treatment, such as lung infection, sepsis, cardiovascular disease, or diabetes.

Exclusion criteria: (1) History of immunotherapy-related diseases; (2) Combined brain metastasis with unstable condition; (3) Concurrent autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis; (4) Expected survival time before immunotherapy less than 6 months; (5) Presence of other malignant tumors in addition to NSCLC; (6) Diseases that could significantly affect peripheral blood inflammation indicators before treatment, such as pulmonary infection or sepsis.

Data collection

Clinical data: By reviewing the patient's electronic medical records, the following information was collected: age, gender, body mass index (BMI), smoking history, ECOG score before treatment, pathological type, tumor stage, number of distant metastases (such as bone, liver, adrenal gland, pleura, axillary lymph nodes, mediastinal lymph nodes, etc.), treatment year, PD-L1 expression before treatment, SII before treatment, GNRI before treatment, and treatment method.

PD-L1 expression detection: An appropriate amount of tumor tissue was obtained through biopsy. The wax block containing the most tumor tissue was identified, and anti-detachment white slices were cut and dried in an oven. A fully automated immunohistochemical staining instrument (manufacturer: Roche, model: BenchMark ULTRA) was used to perform PD-L1 immunohistochemical staining on the slices. First, PD-L1 secondary antibody reagent (Maixin company, clone number MXR006) was added dropwise to obtain fully stained slices. The stained sections were washed three times with phosphate buffered saline, dehydrated with gradient ethanol, and sealed with neutral gum. PD-L1 interpretation used the tumor proportion score, which is calculated by dividing the number of PD-L1 positive tumor cells by the total number of tumor cells and multiplying by 100-that is, the percentage of partially or completely membrane-stained (positive) tumor cells among all viable tumor cells.

SII calculation: By reviewing the routine blood test results before immunotherapy, data on patients' peripheral blood neutrophil, lymphocyte, and platelet counts were obtained. The specific testing method was as follows: 5 mL of fasting venous blood was collected from the patient and placed in an ethylenediaminetetraacetic acid anticoagulant tube. The sample was allowed to stand at room temperature for 10 minutes and then centrifuged at 3000 r/min for 10 minutes. The upper serum layer was collected. A fully automatic blood cell analyzer (manufacturer: Sysmex, model: XN-9000) was used to measure neutrophil, lymphocyte, and platelet counts in the serum. SII was calculated according to the formula: SII = platelet count × neutrophil count/lymphocyte count ($\times 10^9$/L).

GNRI calculation: By reviewing the serum albumin test results before immunotherapy, data on patients' serum albumin levels were obtained. The specific testing method was as follows: 5 mL of fasting venous blood was collected from the patient and placed in an ethylenediaminetetraacetic acid anticoagulant tube. The sample was allowed to stand at room temperature for 10 min and then centrifuged at 3000 r/min for 10 min. The upper serum layer was collected. An automatic biochemical analyzer (manufacturer: Roche Diagnostics GmbH, model: Cobas 8000 C702) was used to detect serum albumin levels. Combined with the patient's height (cm) and weight before immunotherapy, GNRI was calculated according to the formula: GNRI = 1.489 × serum albumin (g/L) + 41.7 × [actual body weight (kg)/ideal body weight (kg)]. The ideal weight in this study refers to the method of [17], that is, ideal body weight for men = height - 100 - [(height - 150)/4]; ideal body weight for women = height - 100 - [(height - 150)/2].

Treatment methods

After determining the pathological type of NSCLC, tissue samples were retained for molecular detection, and treatment was guided according to molecular typing. For advanced NSCLC patients with positive driver genes, including epidermal growth factor receptor mutations and murine sarcoma virus oncogene homolog B1-V600 gene mutations, targeted therapy with corresponding inhibitors was administered. For patients with advanced NSCLC without driver genes and with non-squamous cell carcinoma, pemetrexed plus platinum-based combination therapy with cetuximab was given. For advanced NSCLC patients without driver genes and with squamous cell carcinoma, treatment with albumin-bound paclitaxel plus carboplatin combined with cetuximab was given. Stage IIIB patients simultaneously received chest radiotherapy, with a radiation field including the primary lesion, metastatic lymph nodes, and regional draining lymph nodes, at a dose of 2.0 Gy per fraction, once daily, with a total radiation dose of 60-70 Gy over 6-8 weeks. The dose of pemetrexed was 500 mg/m^2 every 3 weeks; the dose of sintilimab was 200 mg every 3 weeks, continued until the patient developed intolerance or disease progression; the dose of cisplatin was 75 mg/m^2 every 3 weeks; carboplatin area under the curve (AUC) = 5-6 every 3 weeks; the dose of albumin-bound paclitaxel was 100 mg/m^2 (administered on days 1, 8, and 15, respectively).

Observation indicators

(1) Therapeutic efficacy: Treatment efficacy was evaluated based on imaging results (including computed tomography and magnetic resonance imaging) before and after immunotherapy. Efficacy was assessed every 2 treatment cycles. After 4 cycles of treatment, according to the Response Evaluation Criteria in Solid Tumors 1.1 criteria [18], response was classified as complete response (CR): complete clearance of target lesions; partial response (PR): ≥30% decrease in the sum of the longest diameter of target lesions compared to baseline; stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD); and PD: ≥20% increase in the sum of the longest diameter of target lesions compared to the smallest sum on study. Patients with CR, PR and SD were included in the effective group, and patients with PD were included in the ineffective group.

(2) Adverse reactions: Adverse reactions related to immunotherapy were recorded, mainly including vomiting, diarrhea, liver injury, immune pneumonia, arthritis, hyperthyroidism or hypothyroidism, and the incidence of adverse reactions was calculated. The grading of immunotherapy-related toxic side effects was evaluated according to the National Cancer Institute-Common Terminology Criteria for Adverse Events v4.0, ranging from mild to severe (grades 1-5).

(3) Prognostic follow-up: Patients with advanced NSCLC were followed up regularly via outpatient visits, telephone, and online communication. Follow-up was performed once a month in the first year and once every 3 months in the second year. The maximum follow-up time for each patient was 2 years. The follow-up deadline was October 2025. Progression-free survival (PFS) was recorded, and 2-year overall survival (OS) and survival rate were calculated. PFS was defined as the time from the date of pathological diagnosis to the last follow-up or the date when tumor progression was detected by imaging examination. OS was defined as the time from the beginning of treatment to the first documentation of all-cause death or the last follow-up. PFS and OS were calculated on a monthly basis.

Statistical analysis

Statistical analysis was performed using SPSS 27.0 software. Normally distributed continuous variables were expressed as mean ± standard deviation, and comparisons between two groups were conducted using the t-test. Skewed distribution continuous variables were expressed as median with interquartile range [M (P_{25}-P_{75})], and comparisons between two groups were conducted using the Mann-Whitney *U* test. Categorical variables were expressed as counts and percentages [*n* (%)], and comparisons between two groups were conducted using the chi-square (χ^2) test. Multivariate logistic regression analysis was used to identify factors influencing the efficacy of immunotherapy in advanced NSCLC. Receiver operating characteristic (*ROC*) curve analysis was performed to evaluate the predictive value of each index for immunotherapy efficacy. The Delong test was used to compare differences in AUC. The Kaplan-Meier method was used to analyze the relationship between SII, GNRI and PFS/OS in patients with advanced NSCLC. Univariate and multivariate Cox regression analyses were performed to determine whether SII and GNRI were risk factors for survival prognosis. Cox regression models were also used to analyze additive and multiplicative interactions between SII and GNRI on patient prognosis. The excel table developed by Andersson *et al*. [19] was used to calculate interaction evaluation indicators [relative excess risk due to interaction (RERI), attribution proportion due to interaction (AP), and synergy index (S)]. If the 95% confidence interval (CI) for RERI and AP did not include 0, and the 95% CI for S did not include 1, an additive interaction between the two factors was considered present. A *P-value* <0.05 was considered statistically significant.

Results

General information and clinical features

A total of 152 NSCLC patients were included in this study, with a mean age of 65.51±8.34 years and a mean BMI of 23.09±1.74 kg/m^2. There were 98 male patients and 54 female patients. There were 86 patients with a smoking history and 66 without. The ECOG score was 0-1 in 61 cases and 2 in 91 cases. There were 70 cases of squamous cell carcinoma and 82 cases of adenocarcinoma. There were 45 cases of stage IIIB and 107 cases of stage IV. There were 59 cases with ≥3 distant metastasis sites and 93 cases with <3 distant metastasis sites. Regarding treatment year, there were 60 cases from 2019 to 2021 and 92 cases from 2022 to 2023. There were 26 cases of immunotherapy alone, 52 cases of immunotherapy combined with chemotherapy, 29 cases of immunotherapy combined with chemotherapy plus targeted therapy, and 45 cases of immunotherapy combined with chemotherapy plus radiotherapy. The expression level (TPS) of PD-L1 in tumor cells ranged from 3% to 95%, with a median of 48.5%. Efficacy evaluation: there were 2 cases of CR, 49 cases of PR, 55 cases of SD, and 46 cases of PD. Therefore, the effective group included 106 cases (CR + PR + SD) and the ineffective group included 46 cases (PD). Safety evaluation: a total of 47 cases of adverse reactions occurred, with an incidence rate of 30.92% (47/152). Among them, 14 patients had nausea/vomiting, 6 had skin reactions, 8 had fever, 4 had hypothyroidism, 5 had liver injury, 7 had pneumonia, and 3 had thrombocytopenia. The grade of adverse events was 1-2. When adverse reactions were detected, patients were able to continue treatment after timely symptomatic management.

Relationship between general clinical characteristics and immunotherapy efficacy

Univariate analysis showed that age, BMI, gender, smoking history, ECOG score, pathological type, tumor stage, number of distant metastases, treatment year, and treatment method were not correlated with immunotherapy efficacy (all *P*>0.05), as shown in **Table 1**.

Relationship between the expression levels of SII, GNRI and PD-L1 and immunotherapy efficacy

The pretreatment SII value in the effective group was significantly lower than that in the ineffective group, while the pretreatment GNRI and PD-L1 expression levels were significantly higher than those in the ineffective group (all *P*<0.05), as shown in **Table 2**. Whether immunotherapy was effective (0 = yes, 1 = no) was used as the dependent variable, and SII, GNRI, and PD-L1 were included in the multivariate logistic regression analysis. The results showed that the expression levels of SII, GNRI, and PD-L1 were all influencing factors for immunotherapy efficacy in advanced NSCLC patients (all *P*<0.05), as shown in **Table 3**. This indicates that the expression levels of SII, GNRI, and PD-L1 are associated with the outcome of immunotherapy in patients with advanced NSCLC.

Predictive efficacy of SII, GNRI and PD-L1 expression levels for immunotherapy efficacy in advanced NSCLC

According to ROC curve analysis, the AUC value of SII for predicting immunotherapy efficacy in advanced NSCLC was 0.778, the AUC value of GNRI was 0.699, and the AUC value of PD-L1 expression level was 0.707, as shown in **Figure 1**. Based on the Youden index, the optimal cut-off value of SII was 418.67, the optimal cut-off value of GNRI was 97.89, and the optimal cut-off value of PD-L1 was 46.57%. The corresponding sensitivity and specificity are shown in **Table 4**.

Comparison of the predictive efficacy of SII combined with GNRI versus PD-L1 expression level for immunotherapy efficacy in advanced NSCLC

According to ROC curve analysis, the AUC value of SII combined with GNRI for predicting immu-

Table 1. Relationship between general clinical characteristics and immunotherapy efficacy

Clinical features	Effective group (*n* = 106)	Ineffective group (*n* = 46)	t/χ^2 value	*P* value
Age (years)	65.76±7.92	64.94±7.81	0.559	0.557
BMI (kg/m²)	23.18±1.43	22.87±1.35	1.248	0.214
Gender			0.059	0.808
Male	69 (65.09)	29 (63.04)		
Female	37 (34.91)	17 (36.96)		
Smoking history			0.521	0.470
Yes	62 (58.49)	24 (52.17)		
No	44 (41.51)	22 (47.83)		
ECOG score			0.786	0.375
0-1	45 (42.45)	16 (34.78)		
2	61 (57.55)	30 (65.22)		
Pathological type			1.272	0.259
Squamous cell carcinoma	52 (49.06)	18 (39.13)		
Adenocarcinoma	54 (50.94)	28 (60.87)		
Tumor stage			1.958	0.162
Phase IIIB	35 (33.02)	10 (21.74)		
Phase IV	71 (66.98)	36 (78.26)		
Number of distant metastasis sites			2.255	0.133
≥3	37 (34.91)	22 (47.83)		
<3	69 (65.09)	24 (52.17)		
Treatment year			1.054	0.305
2019-2021	39 (36.79)	21 (45.65)		
2022-2023	67 (63.21)	25 (54.35)		
Treatment method			3.223	0.358
Immunotherapy alone	21 (19.81)	5 (10.87)		
Immunotherapy + chemotherapy	38 (35.85)	14 (30.43)		
Immunotherapy + chemotherapy + targeted therapy	19 (17.92)	10 (21.74)		
Immunotherapy + chemotherapy + radiotherapy	28 (26.42)	17 (36.96)		

Notes: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status.

Table 2. Relationship between SII, GNRI and PD-L1 expression levels and immunotherapy efficacy

Indicator	Effective group (*n* = 106)	Ineffective group (*n* = 46)	*t* value	*P* value
SII	409.54±97.65	492.86±129.07	4.359	<0.001
GNRI	106.48±13.71	97.27±11.95	3.950	<0.001
PD-L1 level (%)	51.39±15.88	42.76±12.94	3.190	0.002

Notes: SII, systemic immune-inflammation index; GNRI, geriatric nutritional risk index; PD-L1, programmed cell death-ligand 1.

Table 3. Multivariate logistic regression analysis of factors influencing immunotherapy efficacy in advanced NSCLC

Indicator	β	SE	Wald χ^2	*P* value	OR (95% CI)
SII	0.604	0.204	8.766	0.003	1.829 (1.228-2.726)
GNRI	0.543	0.208	6.815	0.009	1.721 (1.145-2.588)
PD-L1	0.351	0.159	4.873	0.027	1.420 (1.039-1.941)

Notes: SII, systemic immune-inflammation index; GNRI, geriatric nutritional risk index; PD-L1, programmed cell death-ligand 1; SE, standard error; OR, odds ratio; CI, confidence interval; NSCLC, non-small cell lung cancer.

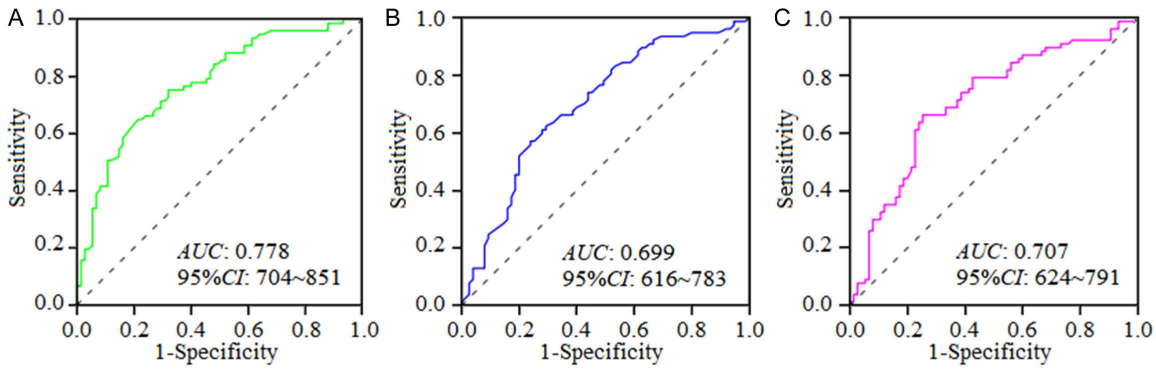

Figure 1. ROC curves of SII, GNRI, and PD-L1 expression levels for predicting immunotherapy efficacy in advanced NSCLC (A: ROC curve of SII; B: ROC curve of GNRI; C: ROC curve of PD-L1). Note: AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; SII, systemic immune-inflammation index; GNRI, geriatric nutritional risk index; PD-L1, programmed cell death-ligand 1; NSCLC, non-small cell lung cancer.

Table 4. ROC parameters of SII, GNRI and PD-L1 expression levels for predicting immunotherapy efficacy in advanced NSCLC

Indicator	AUC	Cut-off value	Sensitivity (%)	Specificity (%)	*P* value	95% CI
SII	0.778	418.67	0.791	0.712	<0.001	0.704-0.851
GNRI	0.699	97.89	0.639	0.736	<0.001	0.616-0.783
PD-L1 (%)	0.707	46.57	0.642	0.727	<0.001	0.624-0.791

Notes: SII, systemic immune-inflammation index; GNRI, geriatric nutritional risk index; PD-L1, programmed cell death-ligand 1; ROC, receiver operating characteristic; NSCLC, non-small cell lung cancer; AUC, area under the curve; CI, confidence interval.

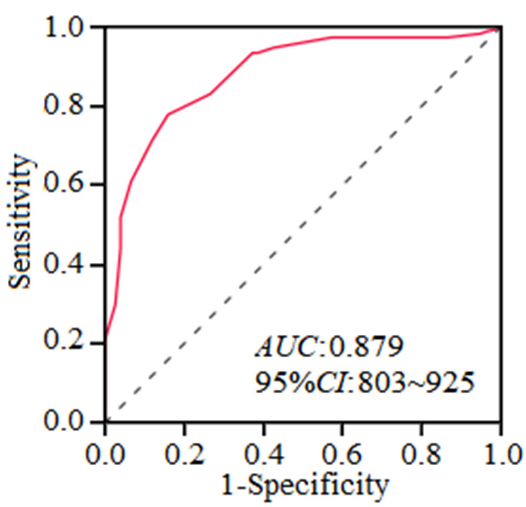

Figure 2. ROC curve of SII combined with GNRI for predicting immunotherapy efficacy in advanced NSCLC. Note: AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; SII, systemic immune-inflammation index; GNRI, geriatric nutritional risk index; NSCLC, non-small cell lung cancer.

notherapy efficacy in advanced NSCLC was 0.879, as shown in **Figure 2**. Based on the Youden index, the sensitivity and specificity of SII combined with GNRI were 0.846 and 0.819 respectively. The DeLong test showed that the AUC value of SII combined with GNRI was significantly higher than that of SII alone (0.778) and GNRI alone (0.699), with statistically significant differences (Z = -2.062, -3.416, both *P*<0.05). Additionally, it was significantly higher than the AUC value of PD-L1 alone (0.707), with a statistically significant difference (Z = -3.512, *P*<0.05), as shown in **Table 5**. This suggests that the combination of SII and GNRI is more effective in evaluating immunotherapy outcomes in advanced NSCLC patients and may serve as a potential alternative to tissue-based PD-L1 detection.

Relationship between SII and survival prognosis in patients with advanced NSCLC

The follow-up period for 152 patients with advanced NSCLC ranged from 8 to 24 months, with a median overall follow-up time of 17 months. No patients were lost to follow-up, and a total of 65 patients died during the follow-up period. The 2-year OS rate was 57.24%

Table 5. Comparison of AUC values of various indicators for predicting immunotherapy outcomes in advanced NSCLC

Item 1	Item 2	AUC difference	Standard error	95% CI	*Z* value	*P* value
SII	GNRI	0.078	0.283	-0.030-0.187	1.411	0.158
SII	PD-L1	0.070	0.282	-0.028-0.168	1.409	0.159
GNRI	PD-L1	-0.008	0.294	-0.139-0.123	-0.119	0.905
SII	SII combined with GNRI	-0.101	0.257	-0.197--0.005	-2.062	0.039
GNRI	SII combined with GNRI	-0.179	0.267	0.282--0.077	-3.416	0.001
PD-L1	SII combined with GNRI	-0.172	0.266	0.267--0.076	-3.512	0.001

Notes: SII, systemic immune-inflammation index; GNRI, geriatric nutritional risk index; PD-L1, programmed cell death-ligand 1; NSCLC, non-small cell lung cancer; AUC, area under the curve; CI, confidence interval.

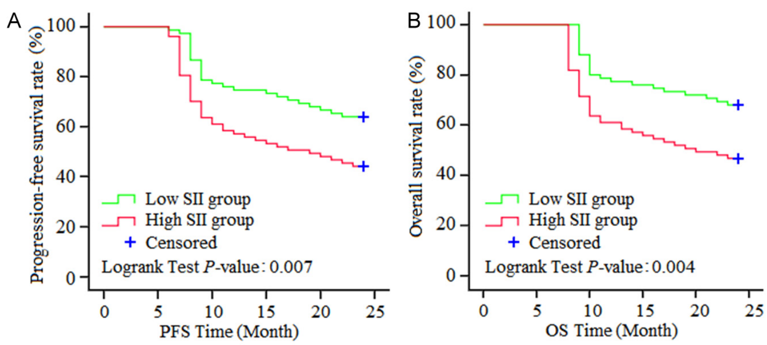

Figure 3. Kaplan-Meier curves for survival in advanced NSCLC patients stratified by SII (A: PFS; B: OS). Note: NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; SII, systemic immune-inflammation index.

(87/152). Using the optimal cut-off value of SII for predicting immunotherapy outcome (418.67) as the threshold, patients were divided into a low SII group (SII <418.67, n = 75) and a high SII group (SII ≥418.67, n = 77). In the low SII group, 24 patients died, the 2-year OS rate was 68% (51/75), the median PFS was 18.4 (15.4-23.1) months, and the median OS was 20.3 (10.4-23.8) months. In the high SII group, 41 patients died, the 2-year OS rate was 46.75% (36/77), the median PFS was 15.2 (13.6-22.3) months, and the median OS was 17.1 (9.1-22.4) months. Compared with the low SII group, the high SII group had a significantly worse 2-year OS rate (χ^2 = 7.007, *P* = 0.008) and shorter median PFS and OS (log-rank χ^2 =7.231 and 8.396, respectively; both *P*<0.05), as shown in **Figure 3**.

Relationship between GNRI and survival prognosis in advanced NSCLC patients

Using the optimal cut-off value of GNRI for predicting immunotherapy outcome (97.89) as the threshold, patients were divided into a low GNRI group (GNRI <97.89, n = 95) and a high GNRI group (GNRI ≥97.89, n = 57). In the low GNRI group, there were 53 deaths, with a 2-year OS rate of 44.21% (42/95), a median PFS of 15.1 (13.8-22.4) months, and a median OS of 16.8 (9.1-22.8) months. In the high GNRI group, there were 12 deaths, with a 2-year OS rate of 78.95% (45/57), a median PFS of 18.6 (15.9-23.2) months, and a median OS of 21.8 (13.5-23.5) months. Compared with the high GNRI group, the low GNRI group had a significantly poorer 2-year OS rate (χ^2 = 17.563, *P*<0.001) and shorter median PFS and OS (log-rank χ^2 = 15.819 and 18.746, respectively; both *P*<0.001), as shown in **Figure 4**.

Univariate analysis of factors affecting the survival prognosis of advanced NSCLC patients

Using the survival status of advanced NSCLC patients during follow-up after immunotherapy (0 = survival, 1 = death) as the dependent variable, all features in **Table 1** were included as independent variables in univariate and multivariate Cox regression analysis. The assigned values are shown in **Table 6**. Univariate Cox regression analysis showed that smoking history, tumor stage, number of distant metastases, SII, and GNRI were significantly associated with the survival prognosis of advanced NSCLC patients (all *P*<0.05), as shown in **Table 7**. Variables with statistical significance in univariate analysis were subsequently included in

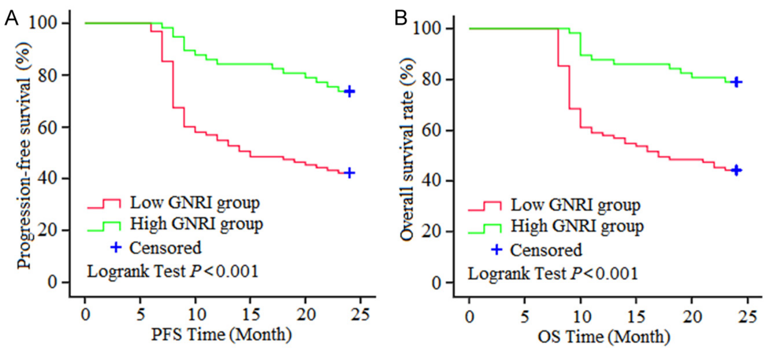

Figure 4. Kaplan-Meier curves for survival in advanced NSCLC patients stratified by GNRI (A: PFS; B: OS). Note: NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; GNRI, geriatric nutritional risk index.

multivariate Cox regression analysis. The results showed that SII ≥418.67 and GNRI <97.89 were independent risk factors for survival prognosis in advanced NSCLC patients (both $P<0.05$), as shown in **Table 8**.

Analysis of the interaction between SII and GNRI

Using SII and GNRI as interaction terms, the multiplicative and additive interactions between the two in predicting immunotherapy prognosis in advanced NSCLC patients were analyzed. The results show that, after controlling for related confounding factors (age, gender, smoking history, ECOG score, pathological type, tumor stage, number of distant metastasis sites, immunotherapy regimen, and PD-L1 expression level), the impact of SII and GNRI on prognostic outcomes exhibited both additive interaction [RERI = 4.073, 95% CI: 1.351-7.943; AP = 0.785, 95% CI: 0.387-1.287; S = 1.796, 95% CI: 1.406-7.121)] and multiplicative interaction (OR for multiplicative interaction = 3.407, 95% CI: 1.295-6.650), as shown in **Table 9**.

Discussion

The early symptoms of NSCLC are insidious and not easily detected, resulting in most patients being diagnosed at an advanced stage. At this point, clinical treatment becomes more challenging, and adjuvant therapies such as radiotherapy and chemotherapy are often required, yet clinical efficacy remains poor. Some stu dies have pointed out that ICIs are safer and more effective than chemoradiotherapy alone [20], and the combination of ICIs with chemotherapy can significantly prolong patient OS [21], which has become an important treatment strategy for advanced NSCLC. Therefore, tumor PD-L1 expression is frequently used as a predictive biomarker in immunotherapy-related research to screen patients who may benefit from immunotherapy. However, conflicting conclusions exist regarding the relationship between PD-L1 expression and clinical benefit. For example, clinical trials have shown that patients with PD-L1 expression levels ≥50% are considered ideal candidates for immunotherapy and can demonstrate more significant therapeutic responses [22]. Conversely, some studies have found that patients can benefit from immunotherapy regardless of PD-L1 expression level [23]. These findings suggest that PD-L1 expression level is not the sole predictive indicator. Numerous factors may influence immunotherapy efficacy, including individual nutritional status, anti-tumor immune capacity within the tumor microenvironment, and tumor burden, all of which may impact treatment outcomes [24]. Therefore, identifying biomarkers associated with immunotherapy efficacy and survival prognosis in advanced NSCLC is of great significance for improving therapeutic outcomes and prognosis in this patient population.

Inflammation plays a significant role in promoting the occurrence and development of malignant tumors. SII is a composite index based on peripheral blood platelet, neutrophil, and lymphocyte counts, which can effectively reflect the balance between immune and inflammatory responses in the body [25]. Upon activation, platelets release a large amount of pro-inflammatory cytokines, which promote tumor angiogenesis, induce epithelial-mesenchymal transition in tumor cells, and facilitate tumor cell invasion and migration, including enabling tumor cells to evade host immune surveillance [26]. Neutrophils release cytokines and chemokines (such as interleukin-6 and tumor necrosis factor-alpha), promoting tumor cell proliferation, invasion, and metastasis [27].

Table 6. Assignment of variables for Cox regression analysis

Variable	Assignment
Age	0 = <65 years; 1 = ≥65 years
Gender	0 = Female; 1 = Male
BMI	0 = ≥18.5 kg/m^2; 0 = <18.5 kg/m^2
Smoking history	0 = No; 1 = Yes
ECOG score	0 = 0-1; 1 = 2
Pathological type	0 = Squamous cell carcinoma; 1 = Adenocarcinoma
Tumor stage	0 = Stage IIIB; 1 = Stage IV
Number of distant metastasis sites	0 = <3 sites; 1 = ≥3 sites
Treatment year	0 = 2022-2023; 1 = 2019-2021
Treatment method	0 = Immunotherapy + chemotherapy + radiotherapy; 1 = Immunotherapy alone; 2 = Immunotherapy + chemotherapy; 3 = Immunotherapy + chemotherapy + targeted therapy
SII	0 = <418.67; 1 = ≥418.67
GNRI	0 = ≥97.89; 1 = <97.89

Notes: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status; SII, systemic immune-inflammation index; GNRI, geriatric nutritional risk index.

Table 7. Univariate Cox regression analysis of factors affecting survival prognosis in advanced NSCLC patients

Variable	*β*	SE	Wald χ^2	*P* value	HR	95% CI
Age	0.331	0.595	0.309	0.578	1.392	0.434-4.468
Gender	0.234	0.343	0.465	0.495	1.264	0.645-2.474
BMI	0.325	0.240	1.834	0.176	1.384	0.865-2.214
Smoking history	0.653	0.324	4.062	0.044	1.921	1.018-3.626
ECOG score	0.278	0.314	0.784	0.376	1.320	0.714-2.442
Pathological type	0.195	0.479	0.166	0.684	1.215	0.829-1.781
Tumor stage	0.686	0.322	4.539	0.033	1.986	1.056-3.732
Number of distant metastasis sites	0.702	0.317	4.904	0.027	2.017	1.084-3.755
Treatment year	0.654	0.395	2.741	0.098	1.923	0.887-4.170
Treatment method						
Immunotherapy alone	0.345	0.390	0.783	0.402	1.412	0.658-3.031
Immunotherapy + chemotherapy	0.327	0.434	0.568	0.451	1.387	0.592-3.248
Immunotherapy + chemotherapy + targeted therapy	0.291	0.462	0.397	0.529	1.338	0.541-3.310
SII	0.785	0.291	7.277	0.007	2.192	1.239-3.877
GNRI	0.706	0.284	6.179	0.013	2.026	1.161-3.536

Notes: NSCLC, non-small cell lung cancer; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status; SII, systemic immune-inflammation index; GNRI, geriatric nutritional risk index; SE, standard error; HR, hazard ratio; CI, confidence interval.

Lymphocytes play an anti-tumor role by recognizing and killing tumor cells, serving as the primary effector cells in immunotherapy [28]. Studies have found that in advanced NSCLC patients receiving immunotherapy, elevated baseline neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are closely associated with poorer PFS and OS [29, 30]. However, it remains unclear whether these indicators can effectively predict immunotherapy efficacy in patients with advanced NSCLC. Fest et al. [31] pointed out that SII, as a comprehensive indicator combining platelets, neutrophils, and lymphocytes, can more comprehensively reflect the host's immune status and inflammatory response. Its predictive value may be superior to neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, and it is an indepen-

Table 8. Multivariate Cox regression analysis of factors affecting survival prognosis in advanced NSCLC patients

Variable	β	SE	Wald χ^2	*P* value	HR	95% CI
Smoking history	0.304	0.178	2.917	0.087	1.355	0.956-1.921
Stage IV tumor	0.547	0.304	3.238	0.072	1.728	0.952-3.136
≥3 distant metastasis sites	0.456	0.241	3.580	0.058	1.578	0.984-2.529
SII ≥418.67	0.628	0.253	6.161	0.013	1.874	1.141-3.077
GNRI <97.89	0.603	0.261	5.338	0.021	1.827	1.095-3.049

Notes: NSCLC, non-small cell lung cancer; SII, systemic immune-inflammation index; GNRI, geriatric nutritional risk index; SE, standard error; HR, hazard ratio; CI, confidence interval.

Table 9. Analysis of the interaction between SII and GNRI in predicting immunotherapy prognosis in advanced NSCLC patients

Factor 1	Factor 2	Prognosis		OR (95% CI)	OR (95% CI)[i]
		Survival	Death		
SII	GNRI	87	65	-	-
<418.67	≥97.89	31	5	Reference	Reference
<418.67	<97.89	20	19	1.175 (0.442-3.354)	1.074 (0.386-3.295)
≥418.67	≥97.89	14	7	1.261 (0.543-3.406)	1.174 (0.453-3.309)
≥418.67	<97.89	22	34	1.485 (0.867-4.732)	1.402 (0.942-4.651)
Interaction effect	Additive model	RERI		4.262 (1.208-8.165)	4.073 (1.351-7.943)
		AP		0.672 (0.419-1.373)	0.785 (0.387-1.287)
		S		1.874 (1.385-7.271)	1.796 (1.406-7.121)
	Multiplicative model	$OR_{multiplicative}$		3.531 (1.342-6.987)	3.407 (1.295-6.650)

Notes: [i]Adjusted for confounding factors (age, gender, smoking history, ECOG score, pathological type, tumor stage, number of distant metastasis sites, immunotherapy regimen, and PD-L1 expression level). NSCLC, non-small cell lung cancer; SII, systemic immune-inflammation index; GNRI, geriatric nutritional risk index; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; S, synergy index; CI, confidence interval; OR, odds ratio; ECOG, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death-ligand 1.

dent risk factor for the occurrence and development of solid tumors. Li et al. [32] reported that SII was significantly correlated with major pathological response in NSCLC patients receiving neoadjuvant chemoimmunotherapy. This aligns with the findings of the present study, in which the pretreatment SII value in the effective immunotherapy group was significantly lower than that in the ineffective group. The underlying rationale may be as follows: The efficacy of immunotherapy in NSCLC patients is entirely dependent on the presence of functionally intact T cells within the body. A high pretreatment SII level indicates an elevated neutrophil count, which predisposes to an inflammatory environment dominated by neutrophils releasing substantial amounts of reactive oxygen species, arginase-I, and other substances. These factors directly inhibit T cell proliferation and cytotoxic function, promote overexpression of immune checkpoint molecules such as PD-1 and TIM-3 on T cells, driving them into an "exhausted" state. Even with PD-1/PD-L1 inhibitors, reactivation becomes difficult, thereby limiting immunotherapy efficacy. Additionally, patients with high SII levels exhibit a strong systemic inflammatory response, which may accelerate tumor progression and impact response rates to immunotherapy by promoting tumor angiogenesis, accelerating tumor cell proliferation, and suppressing immune responses. Further analysis revealed that pretreatment SII value is a factor influencing immunotherapy efficacy in advanced NSCLC patients, indicating a correlation between pretreatment SII levels and treatment outcomes. However, ROC curve analysis identified an optimal pretreatment SII cut-off value of 418.67 in this study, which was considerably lower than the SII cut-off values reported in recent NSCLC immunotherapy studies (range: 490.86-1618.04) [33]. This discrepancy may be attributable to factors such as patient demographic characteristics (limited to the elderly population in this study), disease stage distribution, treatment regimens, and differences in laboratory measurement methods across institutions.

Excessive inflammation (i.e., high SII levels) often increases energy consumption and catabolism within the body, leading to muscle wasting and hypoalbuminemia. This causes malnutrition, which weakens immune system function and, in turn, exacerbates the chronic inflammatory state [34]. Therefore, the metabolic damage caused by the inflammatory response, which often affects the body's nutritional status, should not be overlooked clinically [35]. Nutrition is a crucial determinant of immune responses; malnutrition can directly damage the immune system and suppress immune function [36]. Consequently, when investigating the relationship between SII and immunotherapy outcomes in NSCLC patients, an assessment of the patient's nutritional status should be incorporated simultaneously. GNRI is a nutritional assessment tool proposed by Bouillanne et al. [37] which is calculated based on serum albumin and BMI. The lower the GNRI, the higher the individual's risk of malnutrition. Currently, GNRI is commonly used clinically to assess the nutritional status and mortality risk of elderly patients [38]. Lv et al. [39] found that GNRI is associated with poor prognosis in malignant tumors, and during the treatment of malignant tumors, GNRI should be used as a predictive indicator of adverse outcomes in tumor treatment. In this study, we found that the pretreatment GNRI of NSCLC patients in the effective immunotherapy group was significantly higher than that in the ineffective group. The reason may be that malnutrition is one of the driving factors for tumor development. Under the influence of the tumor microenvironment, the body may experience negative energy balance and muscle tissue loss due to insufficient nutritional intake and increased energy consumption, affecting patient tolerance to immunotherapy and resulting in many patients being at nutritional risk. When receiving immunotherapy, the drug dose may be reduced or discontinued prematurely, affecting therapeutic efficacy. Further analysis revealed that GNRI values were influencing factors for immunotherapy efficacy in patients with advanced NSCLC, indicating that pretreatment GNRI levels are associated with immunotherapy outcomes. ROC curve analysis demonstrated that the AUC value of SII combined with GNRI for predicting immunotherapy efficacy in advanced NSCLC (0.879) was higher than that of SII alone (0.778), GNRI alone (0.699), and PD-L1 alone (0.707). The underlying rationale may be as follows: In the tumor microenvironment, excessively activated immune cells (such as neutrophils) release large amounts of pro-inflammatory cytokines, increasing systemic inflammatory responses and triggering widespread metabolic disturbances. This leads to elevated energy expenditure even at rest, pushing the body into a state of high catabolism and low synthesis. The body consumes significant amounts of energy and protein, which readily triggers nutritional risk and lowers the GNRI. Conversely, the presence of malnutrition risk (i.e., low GNRI) impairs lymphopoiesis, reduces lymphocyte counts, weakens anti-tumor immune function, and diminishes the ability to counteract inflammatory responses, thereby driving up the SII. This suggests a vicious cycle formed by the interaction between SII and GNRI. For NSCLC patients who rely entirely on a healthy immune system, high SII and low GNRI indices are likely to become important factors that interfere with immunotherapy efficacy and prognosis. Therefore, the combination of SII and GNRI demonstrates superior predictive performance. Furthermore, baseline tumor burden, tumor stage, and other factors influence PD-L1 expression. PD-L1 expression itself is highly heterogeneous, varying significantly across different tumor tissues and even within different regions of the same tumor. This variability directly affects the sensitivity of PD-L1 as a biomarker for assessing benefit from tumor immunotherapy. In contrast, compared with PD-L1 expression level, the combination of SII and GNRI offers advantages in predicting immunotherapy efficacy in NSCLC patients. It is recommended that in clinical practice, venous blood be drawn from patients before initiating immunotherapy (prior to any treatment) to obtain SII and GNRI values for early assessment of potential benefit; simultaneously, changes in SII and GNRI should be monitored before and at the end of each treatment cycle.

In many solid tumors, high SII levels are closely associated with shorter OS [40]; in a meta-analysis focusing specifically on the NSCLC population, high SII levels were also found to be significantly correlated with poorer OS [41]. In the context of immunotherapy prognosis for advanced NSCLC patients, this study found that the 2-year survival rate of patients with high SII levels was worse than that of patients with low SII levels, and the median PFS and OS were also shorter in the high SII group. The reason may be that high SII levels indicate a profile with more neutrophils, more platelets, and fewer lymphocytes. When there are too many neutrophils in the body, they secrete high levels of matrix metalloproteinases, thereby degrading the basement membrane and extracellular matrix formed by type IV collagen, destroying the normal tissue barrier, and facilitating tumor cell invasion and migration. Fewer lymphocytes result in reduced capacity to identify and eliminate tumor cells, leading to poor prognosis. Abundant platelets act as a reservoir and source of important pro-angiogenic factors such as vascular endothelial growth factor and platelet-derived growth factor, supporting continuous tumor growth by promoting neovascularization in tumor tissues. GNRI is a composite indicator reflecting weight changes and serum albumin levels. Shimasaki et al. [42] found that in advanced NSCLC patients receiving immunotherapy, the lower the GNRI value, the higher the risk of death. This directly supports the survival analysis of the present study, which found that advanced NSCLC patients with low GNRI had significantly poorer 2-year survival rates and shorter PFS and OS. The reason may be that low GNRI directly impairs immune function, exacerbates systemic inflammatory response, and leads to multiple intertwined biological pathways such as severe systemic inflammation and immune suppression, which together constitute the pathological basis for shortened survival in advanced NSCLC patients. Therefore, Cox regression analysis revealed that SII $\geq$418.67 and GNRI <97.89 are both risk factors for survival prognosis in advanced NSCLC patients. Furthermore, interaction analysis demonstrated multiplicative and additive interactions between SII and GNRI in the prognosis of advanced NSCLC patients. The underlying rationale may be as follows: High SII levels are primarily driven by neutrophilia and lymphopenia. Excessive neutrophil counts promote tumor microangiogenesis, tumor tissue remodeling, and tumor cell metastasis by secreting substances such as vascular endothelial growth factor and matrix metalloproteinases; reduced lymphocyte counts indicate impaired adaptive immune surveillance, allowing tumor cells to escape immune clearance. Low GNRI, primarily driven by hypoalbuminemia and low body weight [43], is also a core manifestation of cancer cachexia, characterized by continuous loss of skeletal muscle mass, leading to decreased physical performance, increased treatment-related toxicity, and deteriorated quality of life. Additionally, protein-energy malnutrition directly impairs immune cell generation, reduces immunity, and undermines the foundation for anti-tumor treatment. Studies have shown that the inflammatory state associated with high SII levels releases large amounts of pro-inflammatory cytokines (such as interleukin-6 and tumor necrosis factor-alpha), which can cause cachexia, directly leading to muscle wasting, lipolysis, and loss of appetite, resulting in weight loss and malnutrition [44], thereby affecting patient prognosis. Conversely, low GNRI reduces treatment tolerance by impairing immune function, exacerbating systemic inflammation, and driving cachexia progression, collectively impacting the immunotherapy response rate in patients with advanced NSCLC. Thus, low GNRI and high SII often coexist and mutually exacerbate each other: malnutrition aggravates immune dysfunction, while systemic inflammation promotes muscle breakdown and inhibits albumin synthesis, deepening malnutrition and forming a vicious cycle that accelerates disease progression and ultimately affects patient survival. Therefore, prior to immunotherapy for advanced NSCLC, if SII levels can be controlled and nutritional status improved, it may help enhance immunotherapy efficacy and improve patient survival prognosis.

This study has the following limitations: (1) It is a retrospective study from a single institution, with a relatively small sample size and limited representativeness; (2) This study only included elderly patients with advanced NSCLC aged $\geq$60 years, and the results cannot be generalized to non-elderly patients or other types of lung cancer; (3) Due to the lack of external data, the predictive value of combining SII and GNRI for immunotherapy outcomes in NSCLC patients has not been externally validated; (4) This study included NSCLC patients who received immunotherapy from 2019 to 2023 (a relatively long time span), and the results may be indirectly affected by changes in immunotherapy regimens during the study period; (5) To minimize the influence of potential confounding factors, strict inclusion and exclusion criteria were applied to screen patients. However, it remains difficult to completely eliminate the effects of certain comorbidities that may influence nutritional status and inflammation during treatment, as well as the impact of some medications (such as antibiotics and corticosteroids) used during immunotherapy on SII components and treatment efficacy; (6) Given the current obesity paradox in immunotherapy for advanced NSCLC [45], there is a complex nonlinear relationship between BMI and prognosis. Since GNRI is calculated based on serum albumin and BMI, this may potentially confound the association of GNRI with outcomes. In response to these limitations, future multicenter, prospective studies are needed, with expanded sample size and external validation (e.g., validating findings in NSCLC cohorts from different regions and institutions). Additionally, dynamic monitoring of SII and GNRI changes throughout treatment, as well as tracking BMI variations, should be incorporated to gain a more comprehensive understanding of the impact of SII and GNRI on immunotherapy outcomes in advanced NSCLC.

Conclusion

In summary, the combination of SII and GNRI can effectively predict immunotherapy efficacy in advanced NSCLC and is associated with patient survival prognosis. Implementing interventions such as controlling inflammation and improving nutritional status in patients with high SII and low GNRI may enhance immunotherapy outcomes and improve prognosis in advanced NSCLC.

Acknowledgements

This study was supported by the "Promoting Health through Science and Education" Project of Wujiang District, Suzhou City (No. WWK20-2317); and 2023 Academy-level Research Start-up Fund Project (No. YK202320).

Disclosure of conflict of interest

None.

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