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Original Article

Value of prognostic nutritional index and controlling nutritional status score for advanced non-small cell lung cancer patients receiving PD-1 inhibitors

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Abstract: Objective: To explore the value of preoperative prognostic nutritional index (PNI) and controlling nutritional status (CONUT) score in predicting response and prognosis of patients with advanced non-small cell lung cancer (NSCLC) receiving programmed cell death protein 1 (PD-1) inhibitors. Methods: A retrospective study was conducted in patients who received PD-1 inhibitors for advanced NSCLC. Patients were assigned by immunotherapy effects into response (partial and complete response, pCR) group (n=52) and non-response (non-pCR) group (n=132). The pathological and clinical data were collected for statistical analysis of factors influencing the immunotherapeutic response. The diagnostic value of PNI and CONUT score for response was assessed. The overall survival (OS) was observed over a 3-year follow-up. COX regression analysis was performed to identify risk factors affecting the survival. The effects of different PNI and CONUT scores on the survival were observed. Results: Multivariate regression analysis showed that, the tumor-node-metastasis (TNM) stage (P=0.001), PNI (P<0.001), and CONUT score (P<0.001) were associated with response. The non-pCR group had a higher 3-year mortality rate and a shorter 3-year OS than the pCR group (P<0.001). COX regression analysis showed that low PNI and high CONUT score were risk factors for poor prognosis. Further analysis showed that patients with low PNI and high CONUT score had lower 3-year survival rates (P=0.005, P<0.001). Conclusion: High TNM stage, PNI<50, and CONUT score ≥5 are risk factors for poor response in patients with advanced NSCLC receiving PD-1 inhibitors, and low PNI and high CONUT score suggest poor prognosis.

Keywords: Non-small cell lung cancer, prognostic nutritional index, controlling nutritional status score, PD-1 inhibitor, response, prognosis, correlation

Introduction

Lung cancer remains the most prevalent malignancy globally, accounting for 18% of all cancer-related deaths worldwide and significantly impacting human health [1, 2]. In China, lung cancer is still the highest in morbidity and mortality compared with other malignancies [3, 4]. Non-small cell lung cancer (NSCLC) represents the majority of lung cancers (80%-85%) [4]. NSCLC in its early stages often goes undetected due to its asymptomatic features, with approximately one-third of cases being diagnosed at an advanced stage [5-7]. Historically, for most of the patients with advanced NSCLC who were ineligible for surgery, individualized treatment such as traditional chemoradiotherapy and targeted therapy are adopted; however, the response varies and the overall prognosis is poor [8, 9]. For instance, gemcitabine combined with cisplatin is a standard treatment regimen for advanced NSCLC but is associated with significant adverse reactions, leading to poor tolerability and prognosis [10]. Immune checkpoint inhibitors, by enhancing the anti-tumor immune response and restoring the immune response of tumor patients, have become a new treatment strategy for advanced NSCLC. At present,

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monotherapy with anti-programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors or in combined with platinum-based chemotherapy, has become the standard first-line treatment for advanced NSCLC [11]. This approach has effectively improved patients' progression-free survival (PFS) and overall survival (OS), as well as quality of life [12-14].

Recent studies have increasingly validated the significance of nutritional status in NSCLC patient prognosis, alongside traditional factors such as pathological type and tumor size [15, 16]. Prognostic nutritional index (PNI) is a clinical index reflecting the immune and nutritional status. PNI is proven to be associated with the prognosis of various malignancies, and patients with gastric cancer or oral cancer at a low PNI have significantly decreased OS [17, 18]. Controlling nutritional status (CONUT) score provides an assessment of nutritional status of patients according to their daily nutrients and energy consumption under normal physiological conditions based on the human metabolism and nutritional requirements. Study has shown that CONUT score can be applied to assess the short-term response of patients with gastric cancer undergoing laparoscopic treatment [19].

Despite the established importance of these nutritional indices, there is a relative paucity of research, both in China and internationally, on the predictive value of PNI and CONUT scores for the prognosis of patients with advanced NSCLC treated with PD-1 inhibitors. This study aims to fill this gap by collecting pre-treatment PNI and CONUT scores from patients with advanced NSCLC receiving PD-1 inhibitors at our hospital and exploring their correlations with treatment response and prognosis.

Materials and methods

General data

The clinical data of 184 patients with advanced NSCLC receiving PD-1 inhibitors in our hospital from January 2017 to April 2020 were collected for retrospective analysis. This study was approved by the Ethics Committee of Affiliated Hospital of Hubei Medical College.

Inclusion criteria

Patients included met the following criteria: pathological diagnosis of NSCLC with a PD-L1 tumor proportion score (TPS) ≥50% [20]; clinical stage IIIb-IV [21]; no prior tumor-related treatment; an Eastern Cooperative Oncology Group (ECOG) score of 0-2, with an estimated survival time exceeding 3 months; no other driver mutations; complete clinical records and follow-up data.

Exclusion criteria

Patients with the following conditions were excluded: heart, liver, lung, or kidney insufficiency; ongoing or previous chemotherapy treatments; other malignancies; abnormal coagulation or bone marrow function; allergies to PD-1 inhibitors or chemotherapy drugs; acute or chronic infectious diseases, hemorrhagic or autoimmune disorders; recent or ongoing antibiotic treatment; or those taking lipid-lowering medications.

Data extraction

The relevant clinical data of enrolled patients were extracted by searching for the medical records of patients in the inpatient and outpatient systems, including lymphocyte count, serum albumin, total cholesterol at admission and follow-up.

The lymphocyte count, serum albumin, and total cholesterol of patients with stage IIIb-IV NSCLC on Day 1 after admission were collected to further calculate the PNI and CONUT indicators, and all patients were treated with PD-1 inhibitor monotherapy or combined with chemotherapy.

One month post-chemotherapy, the tumor volume (a×b) was calculated by multiplying the maximum diameter (a) and its perpendicular maximum diameter (b), according to the Response Evaluation Criteria in Solid Tumors (RECIST) [22]. Tumor responses were classified according to the tumor volume observed through color ultrasound prior to and post treatment with PD-1 inhibitors. The classifications included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR: disappearance of all target lesions, no new lesions, and normalization

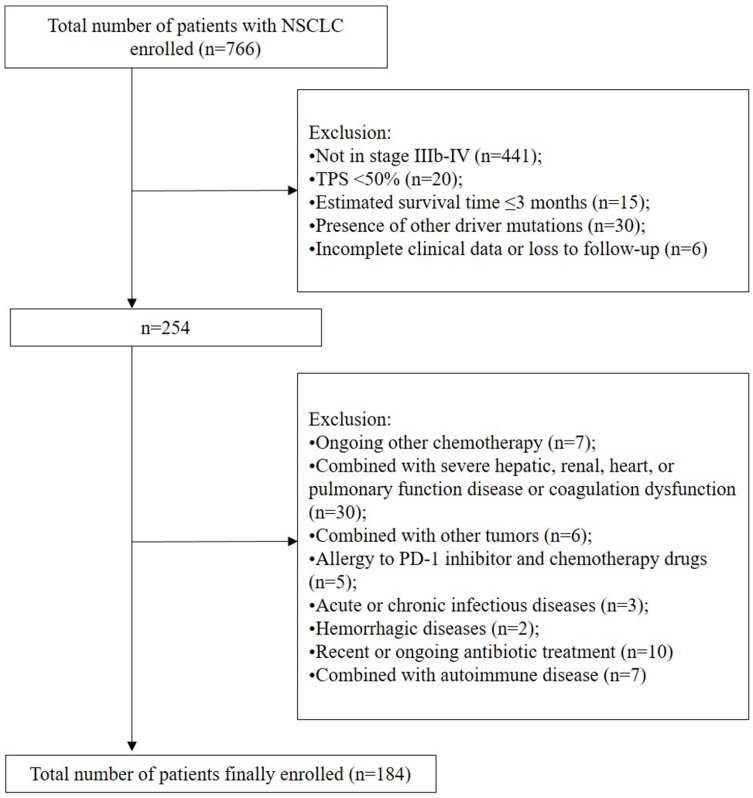

Figure 1. Flow chart for patient selection. NSCLC: non-small cell lung cancer; TPS: tumor proportion score; PD-1: programmed cell death protein 1.

of tumor markers for at least 4 weeks; PR: at least a 30% reduction in the sum of the maximum diameters of target lesions, sustained for at least 4 weeks; SD: reduction in tumor size that does not meet the criteria for PR; PD: an increase in the sum of the maximum diameters of target lesions by at least 20%, or the appearance of new lesions. According to the evaluation results as per RECIST, patients were divided into the response (PR+CR, pCR) group and the non-response (SD+PD, non-pCR) group, with the response (pCR) group showing clincal benefits from the treatment.

A comprehensive 3-year follow-up, concluded in June 2023, was conducted via telephone or during outpatient visits. Patients with stable condition regularly visited the outpatient clinic once every 3 months. If a scheduled visit was missed, the patients or their family members were contacted by telephone to update their health condition. The follow-up was terminated in case of death, and the OS of patients was recorded.

Outcome measures

Pre-treatment PNIs were compared between the two groups. PNI=5× Lymphocyte count ($\times 10^9$/L) + serum albumin (g/L) [23]. PNI≥50 indicates normal nutritional status, and PNI<50 suggests malnutrition. CONUT score was determined by serum albumin, total lymphocyte count, and total cholesterol level. The specific scoring criteria are as follows: Serum albumin levels of ≥35 g/L, 30-34.9 g/L, 25-29.9 g/L, and <25 g/L were scored as 0, 2, 4, and 6 points, respectively; total lymphocyte count of $\geq 1.60\times 10^9$/L, $(1.20\text{-}1.59)\times 10^9$/L, $(0.8\text{-}1.19)\times 10^9$/L, and $<0.8\times 10^9$/L, and total cholesterol of ≥180 mg/dL, 140-179 mg/dL, 100-139 mg/dL, and <100 mg/dL were scored as 0, 1, 2, and 3 points, respectively. The total CONUT score was calculated as the sum of scores of the three indicators [17]. The nutritional status was classified as normal (0-1 point), mild malnutrition (2-4 points), moderate malnutrition (5-8 points), and severe malnutrition (9-12 points).

Deaths including those from advanced NSCLC itself or from NSCLC-related complications were observed during the 3-year follow-up.

The survival and specific time of death were collected by telephone follow-up. COX regression was performed to analyze related risk factors, and the effect of pre-treatment PNI and CONUT score on the survival of patients with advanced NSCLC receiving PD-1 inhibitors was observed. See **Figure 1** for the specific flow chart.

Statistical analysis

SPSS 22.0 statistical software was used for data analysis. Continuous variables conforming to normal distribution were analyzed by independent sample *t* test. Measurement data with

Table 1. Comparison of clinical data between the two groups ($\bar{x}$ ± sd/n (%))

Item	pCR group (n=52)	Non-pCR group (n=132)	χ^2/t/Z	P
Gender			0.003	0.959
Male	40	102		
Female	12	30		
Age (years)			0.703	0.402
≥60	28 (53.85)	80 (60.61)		
<60	24 (46.15)	52 (39.39)		
Smoking			0.432	0.551
Yes	32 (61.54)	88 (66.67)		
No	20 (38.46)	44 (33.33)		
Pathological type			0.233	0.890
Squamous carcinoma	28 (53.85)	66 (50.00)		
Adenocarcinoma	22 (42.31)	60 (45.45)		
Other	2 (3.85)	6 (4.55)		
TNM stage			11.580	0.001
IIIb-c	22 (42.31)	24 (18.18)		
IV	30 (57.69)	108 (81.82)		
ECOG score			0.294	0.588
0-1	42 (80.77)	111 (84.09)		
2	10 (19.23)	21 (15.91)		
Number of metastatic sites			4.968	0.026
<3	47 (90.38)	100 (75.76)		
≥3	5 (9.62)	32 (24.24)		
PD-L1 expression			1.046	0.593
Negative	5 (9.62)	20 (15.15)		
Weakly positive	22 (42.31)	55 (41.67)		
Strongly positive	25 (48.07)	57 (43.18)		
Treatment regimen			0.086	0.769
Monotherapy	22 (42.31)	59 (44.70)		
Combined chemotherapy	30 (57.69)	73 (55.30)		
BMI (kg/m^2)	23.06±2.64	22.73±2.83		
PNI	44.85±5.62	39.53±6.07	4.482	<0.001
CONUT score	2.88±1.91	4.58±2.46	5.467	<0.001

Note: pCR: partial and complete response; TNM: tumor-node-metastasis; ECOG: Eastern Cooperative Oncology Group; PD-L1: programmed cell death ligand 1; BMI: body mass index; PNI: prognostic nutritional index; CONUT: controlling nutritional status.

non-normal distribution were compared between the two groups using the Mann-Whitney *U* test. Categorical data were analyzed by Pearson's chi-square test. Factors affecting the therapeutic effect of PD-1 inhibitors were analyzed by a binary logistic regression model, including only variables showing significant differences. According to whether the patient was benefited from the treatment, the receiver operating characteristic (ROC) curve was plotted by PNI and CONUT scores, and the area under the ROC curve (AUROC) was calculated. The 3-year survival of the two groups was observed by survival analysis. The correlation between PNI, CONUT score and the prognosis of patients with advanced NSCLC receiving PD-1 inhibitors was analyzed by the multivariate COX regression method. P<0.05 was considered statistically significant.

Results

Comparison of clinical data

Among the 184 patients with NSCLC who were treated with PD-1 inhibitors, 52 patients achieved a response (pCR group, all 52 patients with PR), and 132 patients had no response (non-pCR group, 110 patients with SD and 22 patients with PD). Comparison of clinical data showed that the number of metastatic sites, tumor-node-metastasis (TNM) stage, and CONUT score in the pCR group were lower than those in the non-pCR group, while the PNI was higher than that in the non-pCR group (P<0.01; **Table 1**).

Factors influencing the response of patients with advanced NSCLC receiving PD-1 inhibitors

Multivariate binary logistic regression analysis was used to assess factors influencing response to PD-1 inhibitors in patients with advanced NSCLC, with the presence of pCR as the dependent variable (1= presence, 0= absence). The results showed that TNM stage (OR: 1.523; 95% CI: 1.215-2.152, P=0.009), PNI (OR: 0.854; 95% CI: 0.800-0.912, P< 0.001), and CONUT score (OR: 1.422; 95% CI: 1.201-1.683, P<0.001) significantly influenced the response to treatment (**Table 2**).

Table 2. Factors influencing the response of patients with advanced NSCLC receiving PD-1 inhibitors

Variable	OR (95% CI)	P
Constant	-	<0.001
TNM stage	1.523 (1.215-2.152)	0.009
PNI	0.854 (0.800-0.912)	<0.001
CONUT score	1.422 (1.201-1.683)	<0.001

Note: Number of metastatic sites ≥3=1, and <3=0; TNM stage IV=1, and stage IIIb-c=0. Other numerical indicators were substituted with normal values. NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; OR: odds ratio; CI: confidence interval; TNM: tumor-node-metastasis; PNI: prognostic nutritional index; CONUT: controlling nutritional status.

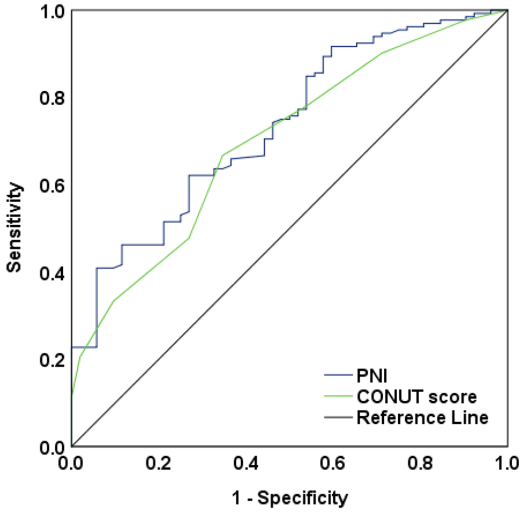

Figure 2. Diagnostic value of PNI and CONUT score for response of patients with advanced NSCLC receiving PD-1 inhibitors. PNI: prognostic nutritional index; CONUT: controlling nutritional status; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1.

Diagnostic value of PNI and CONUT score for response of patients with advanced NSCLC receiving PD-1 inhibitors

The AUROC of PNI and CONUT score for predicting the response of patients with advanced NSCLC receiving PD-1 inhibitors was 0.732 and 0.698, respectively. The cut-off values of PNI and CONUT score were 46.67 and 3.5, respectively. The respective Youden indices were 0.321 and 0.323, with the specificity of 0.917 and 0.654 and the sensitivity of 0.404 and 0.667, respectively (**Figure 2**).

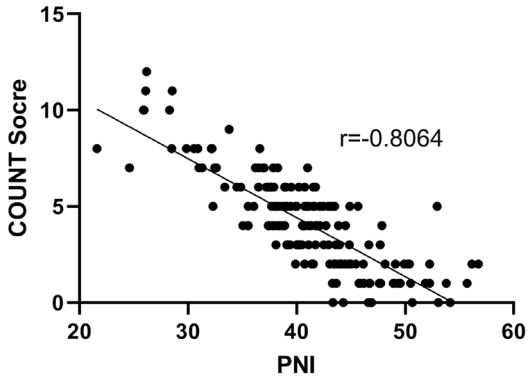

Figure 3. Correlation between PNI and CONUT scores. PNI: prognostic nutritional index; CONUT: controlling nutritional status.

Correlation between PNI and CONUT score

The PNI was negatively correlated with CONUT score (r=-0.8064, P<0.001; **Figure 3**).

Comparison of deaths within 3 years

The 3-year mortality rate was 61.54% (32/52) in the pCR group, which was significantly lower than 80.30% (106/132) in the non-pCR group (**Table 3**). The mean OS was 9.3 months in the non-pCR group, which was significantly shorter than 14.5 months in the pCR group (χ^2=12.451, P<0.001; **Figure 4**).

COX regression analysis of factors influencing prognosis of patients with advanced NSCLC receiving PD-1 inhibitors

The multivariate COX regression analysis showed that CONUT score was a risk factor for death in patients with advanced NSCLC receiving PD-1 inhibitors, while PNI was a protective factor (**Table 4**). The interaction index of PNI*CONUT produced an S index of 1.150, suggesting a positive interaction (calculated as [exp (0.120-0.337 + 1.195) - 1]/[exp (0.120) + exp (-0.337) - 2]). Thus, PNI*CONUT could serve as an independent risk factor for prognosis.

Correlation between different levels of PNI and CONUT score and the prognosis of patients with advanced NSCLC receiving PD-1 inhibitors

According to the definitions of PNI and CONUT score, their cut-off values were 50 and 5 points, respectively. The cohort included 38 patients

Table 3. Comparison of 3-year mortality between the two groups (n (%))

Group	1-year mortality rate	2-year mortality rate	3-year mortality rate
pCR (n=52)	16 (30.77)	29 (55.77)	32 (61.54)
Non-pCR (n=132)	81 (61.36)	104 (78.79)	106 (80.30)
χ^2	14.008	9.866	7.005
P	<0.001	0.002	0.008

Note: χ^2 represents chi-square test. pCR: partial and complete response.

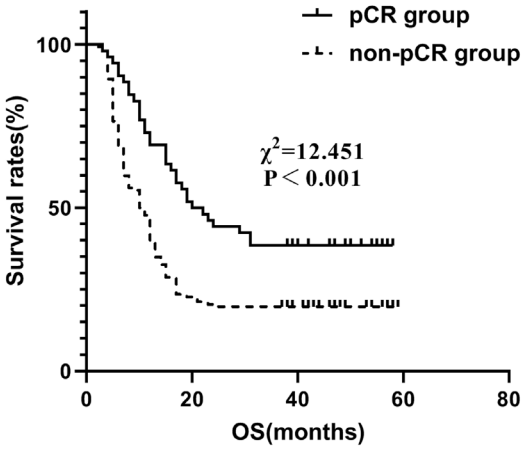

Figure 4. Comparison of the 3-year survival rate between the two groups. pCR: partial and complete response; OS: overall survival.

with high PNI and 146 patients with low PNI; 78 patients with high CONUT score and 106 patients with low CONUT score. Survival analysis showed that patients with high PNI and low CONUT score had higher survival rates (χ^2= 56.102, P<0.001; χ^2=35.152, P<0.001; **Figure 5**).

Discussion

Nutritional and immune statuses are of great importance in predicting the therapeutic effect and prognosis in cancer patients. Serum albumin level reflects the nutritional status of patients, while lymphocytes reflect the immune status. Therefore, the PNI calculated by the above two indicators can be used to comprehensively evaluate the nutritional and immune statuses of the patients. A previous study showed that the PNI value was closely related to the OS of patients with esophageal cancer (P=0.0075) and may become a new reliable biomarker for predicting the prognosis of esophageal cancer [24]. For patients undergoing surgical treatment for gastric cancer, higher PNI value was related to a longer PFS (P=0.010), while lower PNI value corresponded with shorter OS (P<0.001). Additionally, PNI may help predict postoperative morbidity and mortality risk, aiding in identifying gastric cancer patients who might benefit from perioperative nutritional support [25]. Another study on the relationship between PNI value and OS in a small sample of patients with stage III/IV NSCLC receiving platinum-based chemotherapy revealed that lower PNI values were linked to shorter OS [26]. However, there is no definitive clinical evidence confirming the relationship between PNI and the therapeutic effect of immune therapy in patients with advanced NSCLC. The CONUT score, which evaluates blood lipids, has shown potential relevance in studies on NSCLC. Among patients with EGFR-mutated NSCLC, those with higher total cholesterol levels experienced a 63% reduction in mortality risk compared with those with lower levels (P=0.001), indicating that higher cholesterol level is associated with better OS in patients with NSCLC [27]. Another study including patients with NSCLC treated with PD-1 inhibitors showed that increased cholesterol levels were associated with improved PFS and OS [28]. Conversely, the therapeutic effect of tumor immunotherapy increased with the decrease in cholesterol levels, and a lower cholesterol level before immunotherapy was related to better anti-tumor effect [29]. PNI and CONUT score may have a certain correlation with the therapeutic effect of PD-1 inhibitors.

This study included patients with advanced NSCLC receiving PD-1 inhibitors to investigate their response to immunotherapy. The regression analysis showed that TNM, PNI, and CONUT score were factors influencing the therapeutic effect of immunotherapy, among which high TNM associates with aggressive tumor proliferation and invasion, often leading to reduced sensitivity to immunotherapy, a finding consistent with previous study results [30]. Nutritional indicators play an important role in the occurrence, invasion, and metastasis of tumors [31]. Good nutritional status before treatment can reduce the incidence of chemotherapy-related side effects, improve the thera-

Table 4. COX regression analysis of factors influencing prognosis of patients with advanced NSCLC receiving PD-1 inhibitors

Variables	β	SE	Wald value	OR (95% CI)	P
PNI	-0.113	0.013	102.891	0.876 (0.853-0.898)	<0.001
CONUT score	0.274	0.033	67.021	1.315 (1.232-1.405)	<0.001
PNI*CONUT	1.195	3.477	23.439	2.563 (2.142-3.564)	<0.001

Note: NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; OR: odds ratio; CI: confidence interval; PNI: prognostic nutritional index; CONUT: controlling nutritional status.

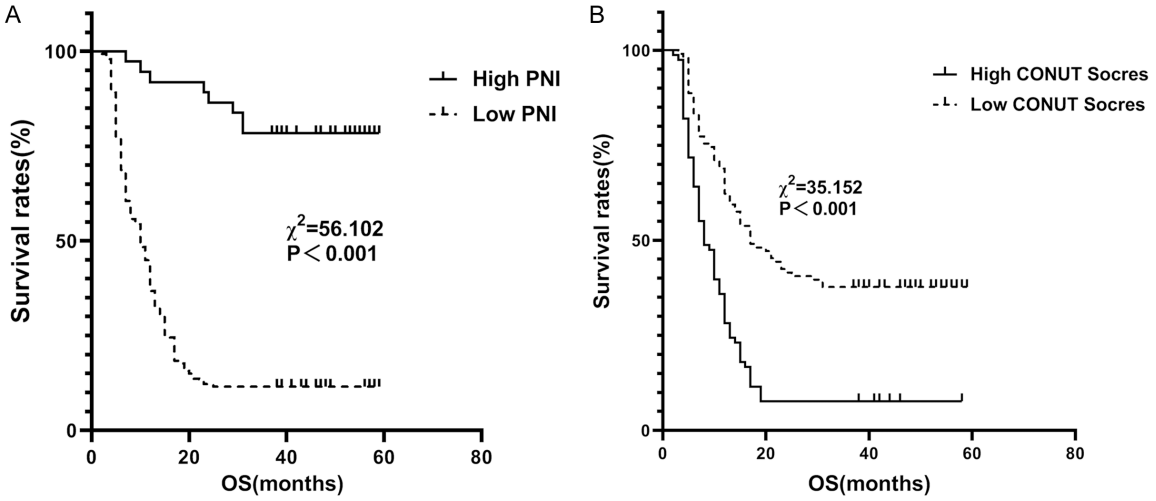

Figure 5. Correlation between different levels of PNI and CONUT scores and prognosis. A: Survival curve of different levels of PNI; B: Survival curve of different CONUT scores. PNI: prognostic nutritional index; CONUT: controlling nutritional status; OS: overall survival.

peutic effect, and prolong the survival of patients [32, 33]. Both PNI and CONUT score are indicators of nutritional status. PNI is calculated by serum albumin and lymphocyte count. Many studies have confirmed that hypoproteinemia is an important factor for poor prognosis of tumor patients [23, 34]. Similarly, studies on lung cancer also demonstrated that patients with good nutritional status had a better prognosis [35, 36]. Lymphocytes are vital for activating cytotoxic T cells, which can inhibit the proliferation and migration of malignant tumor cells [37]. CONUT score, which incorporates total cholesterol based on PNI, provides a comprehensive evaluation of a patient's nutritional status [38]. Studies on the blood lipid level that abnormalities in these levels can trigger oxidative stress, insulin resistance, and inflammatory response, all of which may contribute to the tumor development [39]. CONUT has been shown to offer significant insight into short-term response in patients with gastric cancer undergoing laparoscopic treatment [19]. Another study showed that pre-treatment CONUT and PNI level had an impact on the OS and treatment response in the patients with ovarian cancer undergoing chemotherapy [40]. At present, there is a scarcity of studies exploring the value of CONUT and PNI in predicting prognosis of patients with advanced NSCLC receiving PD-1 inhibitors. This study confirms that pre-treatment CONUT and PNI levels are correlated with therapeutic effect, which aligns with the above findings.

Further analysis showed that patients with low PNI and high CONUT score had a reduced 3-year survival rate. A retrospective study showed that low PNI (≤46) was an independent risk factor for decreased OS of patients with NSCLC [41]. Another study also revealed that patients with high PNI scores (≥49.17) had better OS compared with patients with low PNI scores (<49.17) [42]. A study assessing the prognosis of 127 patients with NSCLC using PNI and systemic immune-inflammation index

(SII) found that both low PNI and high SII indicated poor prognosis [43]. CONUT score has a certain predictive value for postoperative pulmonary complications in resectable NSCLC [44], and can enhance the accuracy of survival prediction in lung cancer patients [45]. In this study, the thresholds defined by CONUT score and PNI were used as the cut-off values, with both low PNI and high CONUT score indicating poor prognosis, aligning with findings from previous studies.

The ROC analysis and survival analysis conducted in this study showed that patients with poor nutritional status had worse chemotherapy effect and prognosis. Previous studies have shown that increased neutrophil secretion can promote tumor growth, stimulate angiogenesis, and enhance tumor cell invasion [46]. Lymphocytes play an important role in the body's immunoregulation, influencing tumor microenvironment to inhibit the migration and micrometastasis of malignant tumors [47]. As tumor progression can increase the consumption of serum albumin, the prognosis of malnourished tumor patients is poor [48, 49].

Despite the findings, there are some limitations in this study. As a single-center study, there might be selection bias in data collection, which warrants future multi-center study. The small sample size of this study can be further expanded to better observe the effects of PNI and CONUT scores on the response and prognosis of patients with advanced NSCLC receiving PD-1 inhibitors. The mechanisms and influencing factors that lead to changes in PNI and CONUT scores in patients with advanced NSCLC should be further investigated. Moreover, the follow-up period in this study was relatively short and should be extended to comprehensively evaluate the effect of PNI and CONUT scores on the response and prognosis of patients with advanced NSCLC receiving PD-1 inhibitors.

In conclusion, high TNM stage, PNI (<50), and CONUT score (≥5) are risk factors for poor response in patients with advanced NSCLC receiving PD-1 inhibitors. Low PNI and high CONUT score are indicative of poor prognosis in patients with advanced NSCLC, and they may not benefit from the treatment with PD-1 inhibitors.

Disclosure of conflict of interest

None.

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