Combination of Baseline and Variation of Prognostic Nutritional Index Enhances the Survival Predictive Value of Patients With Advanced Non-Small Cell Lung Cancer Treated With Programmed Cell Death Protein 1 Inhibitor

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ABSTRACT

BACKGROUND: Low baseline prognostic nutritional index (PNI) scores are associated with poor survival for various malignancies; however, they vary based on the cohort and time resulting in inaccurate results. We determined the predictive value of the PNI score variations in addition to the baseline PNI scores for patients with advanced non-small cell lung cancer (NSCLC) who received programmed cell death protein 1 (PD-1) inhibitor.

METHODS: We retrospectively analysed 115 patients with advanced NSCLC who received PD-1 inhibitor. The median follow-up period was 28 months. Patients were clustered into four groups based on the combined PNI scores (combination of baseline and variation of PNI scores): ΔPNI-L-L, ΔPNI-L-H, ΔPNI-H-L, and ΔPNI-H-H subgroups. For instance, if PNI scores of patients with high baseline PNI score increased from baseline to 6 weeks after treatment, they were included in the ΔPNI-H-H subgroup. Cox regression models were used to identify the factors associated with survival.

RESULTS: The baseline PNI score was only related to the overall survival (OS) (P = .026), and not to the overall response rate (ORR) (P = .299) and progression-free survival (PFS) (P = .207). The ORR was associated with the combined PNI scores (P = .017). A multivariable Cox regression analysis confirmed that the combined PNI scores were independent factors for PFS (ΔPNI-L-H, 12 months, hazard ratio [HR] = 0.449, P = .009; ΔPNI-H-H, 14 months, HR = 0.500, P = .019; and ΔPNI-H-H, 17 months, HR = 0.390, P = .012; vs ΔPNI-L-L, 8 months) and OS (ΔPNI-L-H, 27 months, HR = 0.403, P = .019; ΔPNI-H-L, 28 months, HR = 0.369, P = .010; and ΔPNI-H-H, not reached, HR = 0.087, P = .002; vs ΔPNI-L-L, 15 months).

CONCLUSIONS: Patients with high baseline PNI and increased PNI score had the better survival outcome. On dynamic monitoring and comprehensive assessment, the combined PNI scores significantly enhanced the survival predictive ability of patients with NSCLC treated with PD-1 inhibitor.

KEYWORDS: Non-small cell lung cancer, prognostic nutritional index, programmed cell death protein 1 inhibitor, survival, baseline, variation

Introduction

Lung cancer has the highest mortality rate and the second highest incidence rate worldwide, accounting for 13% of all cancer diagnoses and 23% of all cancer-related deaths.1 Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers and commonly presents at an advanced stage during initial diagnosis. The use of programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) in targeted immuno-oncology has revolutionised and reformed the treatment pattern.2 Drugs targeting and binding to PD-1 and PD-L1 (such as nivolumab plus ipilimumab, pembrolizumab, atezolizumab, and cemiplimab) as first-line treatment for advanced or metastatic NSCLC with driver gene negativity have been approved by the United States Food and Drug Administration. The lack of predictive indicators is an important reason for unsatisfactory immunotherapy outcomes, unlike those in targeted therapy. At present, different methods to assess PD-L1 expression of pembrolizumab, nivolumab, durvalumab, and atezolizumab have been adopted in the clinic.3 In the real world, not all patients with positive PD-L1 and high tumour mutational burden (TMB) expression can benefit from immunotherapy. Some elderly, weak, or diseased patients are unable to undergo biopsy for assessing PD-L1 expression or TMB; thus, next-generation sequencing and whole exome

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sequencing are subsequently warranted, which could result in a huge economic burden on these patients. Therefore, finding more sensitive and affordable predictive biomarkers for anti-PD-1 in immunotherapy is warranted.

Although characteristics of the tumour itself and tumour microenvironment are important for determining the biomarkers of immunotherapy, host-related factors, particularly the nutritional and immune status, cannot be ignored. Recent studies have demonstrated that the nutritional and immune status of patients with tumours is equally important for cancer progression and prognosis.\(^\text{4,5}\)

The prognostic nutritional index (PNI) score is calculated using the serum albumin level and peripheral lymphocyte count,\(^\text{6}\) which can indicate the nutritional and immune status of patients with tumours. The PNI score possesses the characteristics of being non-invasive, has real-time acquisition, and is economical in the clinic, thereby ensuring convenient application and promotion. Several studies have confirmed that the PNI score is associated with the tumour response and prognosis of patients with NSCLC undergoing surgery, chemotherapy, or chemoradiotherapy.\(^\text{7-9}\) However, the correlation between the PNI score and immunotherapy remains poorly studied. A few studies have demonstrated that a low pre-treatment PNI score is closely correlated with early progression and is an independent risk factor for the survival of patients with advanced NSCLC receiving PD-1 inhibitor treatment.\(^\text{10,11}\)

Owing to cohort-dependence and time-dependence, the reported optimal PNI cut-off scores have been highly variable. Therefore, we could not apply the baseline PNI score to determine its predictive value for a given patient. This study determined the predictive value of PNI score variations in addition to baseline PNI scores for patients with NSCLC who received PD-1 inhibitor treatment.

**Methods**

**Patients**

We performed a retrospective analysis of all consecutive patients with NSCLC at the Shanghai Pulmonary Hospital between March 2017 and September 2018. Eligible patients for inclusion in this study had unresectable disease according to the International Association for the Study of Lung Cancer guidelines, Eighth Edition. All the patients had received anti-PD-1 antibody treatment for at least two treatment cycles. All the follow-up data of the patients were obtained.

Age at diagnosis, sex, baseline Eastern Cooperative Oncology Group Performance Status scale score, PD-L1 expression, date of progression, date of death, and date of last follow-up were obtained from the patients' electronic medical records. Routine blood test results and blood biochemical index score before treatment and six weeks after treatment (0 w and 6 w) were also collected. The neutrophil-to-lymphocyte ratio (NLR) score, defined as the absolute neutrophil count divided by the absolute lymphocyte count, was prospectively obtained.

The ΔNLR was defined as the variation between the baseline NLR value and the values collected at six weeks (after two treatment cycles). Although the cut-off values of the NLR score were not constant in all the studies, a value of 5 was widely applied and adopted for distinguishing between the high and low groups.\(^\text{12}\) PD-L1 expression of the tumour sample at diagnosis was detected by immunohistochemistry according to standard practice (clone 22C3; DAKO, Denmark). Considering the percentage of viable tumour cells with partial or complete membrane staining, the tumour proportion score (TPS) ≥ 1% was defined as PD-L1 positive status. This study was approved by the institutional ethical review board of the Shanghai Pulmonary Hospital (no. K22-241). The requirement for informed consent was waived by the ethical review board as this was a non-interventional study using anonymised collected data.

Tumour responses were estimated using the immune response evaluation criteria in solid tumour (iRECIST) guidelines. Progression-free survival (PFS) was defined as the time between the initiation of PD-1 inhibitor treatment and disease progression or death. Overall survival (OS) refers to total survival, that is, the time from the first diagnosis in our hospital to death for any reason or the last follow-up of the patient. The median follow-up period was 28.

**PNI**

The PNI score was defined as the serum albumin level (g/L) + 5 × peripheral lymphocytes (10⁹/L) within three days before each anti-PD-1 antibody treatment administration. These scores were retrospectively obtained in this study. The receiver-operating characteristic (ROC) curve was calculated based on the pre-treatment PNI score. The variable value corresponding to the maximum value of the Youden index was the PNI cut-off score. The APNI score was defined as the difference between the baseline PNI score and the PNI score at sixweeks (after two treatment cycles) collected before anti-PD-1 antibody treatment administration. Patients were clustered into four groups based on the combined PNI scores (combination of baseline and variation of PNI scores). If the PNI scores of the patients with a high baseline PNI score increased from baseline to sixweeks after treatment, they were included in the ΔPNI-H-H subgroup. Patients with high baseline PNI score who experienced a decrease in the PNI score after treatment were included in the ΔPNI-H-L subgroup. Patients with low baseline PNI score who experienced an increase in the PNI score after treatment were included in the ΔPNI-L-H subgroup; those who experienced a decrease in the PNI score after treatment were included in the ΔPNI-L-L subgroup (Figure 1).

**Statistical analysis**

Categorical variables are summarised as numbers and percentages and were compared using the chi-square or the Fisher
exact test. Continuous variables were analysed using the Student t-test. Survival curves were drawn using the Kaplan-Meier method to estimate the probability of PFS and OS. The Cox regression analysis with calculated hazard ratios (HRs) and 95% confidence interval (CI) was applied to adjust for potential confounders. A heatmap was used to demonstrate the trends of the PNI scores. Statistical significance was set at $P \leq 0.05$. IBM SPSS 22.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9.0.0 were used for the statistical analyses and graphing.

Results

Baseline patient characteristics

A total of 115 patients were enrolled in this study. Their baseline characteristics are summarised in Table 1. The median age at the time of diagnosis was 61.4 years ($\pm$ 8.3 years), and 83.4% (n = 96) were males. Lung adenocarcinoma accounted for most the cases (63.4%; n = 73). Squamous cell carcinoma was 26.1% (n = 30). Not otherwise specified (NOS) cancer was noted in 12 (10.4%) patients. Except for 14 patients (12.2%) with stage IIIB/IIIC, all the other patients were in stage IV. The most common metastatic sites were bone (40.8%; n = 47), lungs (30.4%; n = 35), pleura (21.7%; n = 25), and the central nervous system (10.4%; n = 12). Eight patients had adrenal gland metastases, eight had liver metastases, and another eight had distant lymph node metastasis.

In our group, except for four patients with Kirsten rat sarcoma virus (KRAS) mutation and one patient with epidermal growth factor receptor (EGFR) 20 insertion, no driver gene mutation was observed in the rest of the patients. Programmed death ligand 1 expression was found to be positive in fifty-nine (51.3%) patients. Sixty-four (55.6%) patients were treated according to first-line treatment. Patients who received immunotherapy (anti-PD-1) combined with chemotherapy, immunotherapy combined with antiangiogenesis treatment, and monotherapy accounted for 57.4% (n = 66), 15.6% (n = 18), and 27.0% (n = 31) of the total participants, respectively. Baseline characteristics of the patients are shown in Table 1.

The median PFS and OS for all the patients were 13 months (95% CI = 10.849-15.151) and 28 months (95% CI = 23.937-32.063), respectively. The survival rates of all the patients at one year and three years were 72.2% and 9.7%, respectively. The ROC curve showed that the PNI cut-off score was 48.775 (Figure 2A). The area under the ROC curve was 0.608 ($P = .046$), and the corresponding sensitivity and specificity were 0.604 and 0.629, respectively. According to the cut-off value (48.775), 55 patients (47.9%) had low pre-treatment (baseline) PNI scores and 60 patients (52.2%) had high pre-treatment (baseline) PNI scores. The relationship between the PNI scores and clinical characteristics of the patients is shown in Table 1. There were no significant differences in the baseline characteristics of the two groups.
Table 1. Baseline characteristics of the patients.

| CHARACTERISTICS                  | ALL PATIENTS (n) | %     | PNI >48.775 (n) | %     | PNI ≤48.775 (n) | %     | P  |
|---------------------------------|-----------------|-------|-----------------|-------|-----------------|-------|----|
| Total                           | 115             |       |                 |       |                 |       |    |
| Age                             |                 |       |                 |       |                 |       |    |
| <65                             | 78              | 67.8  | 44              | 73.3  | 34              | 61.8  | 0.187 |
| >65                             | 37              | 32.2  | 16              | 26.7  | 21              | 38.2  |    |
| Sex                             |                 |       |                 |       |                 |       |    |
| Male                            | 96              | 83.5  | 54              | 90.0  | 42              | 76.4  | 0.091 |
| Female                          | 19              | 16.5  | 6               | 10.0  | 13              | 23.6  |    |
| ECOG                            |                 |       |                 |       |                 |       |    |
| 0                               | 88              | 76.5  | 46              | 76.7  | 42              | 76.4  | 0.969 |
| 1-2 score                       | 27              | 23.5  | 14              | 23.3  | 13              | 23.6  |    |
| Histology                       |                 |       |                 |       |                 |       |    |
| LUAD                            | 73              | 63.5  | 40              | 66.7  | 33              | 60.0  | 0.674 |
| LUSC                            | 30              | 26.1  | 15              | 25.0  | 15              | 27.3  |    |
| Other                           | 12              | 10.4  | 5               | 8.3   | 7               | 12.7  |    |
| Stage                           |                 |       |                 |       |                 |       |    |
| IIIB/IIIC                       | 14              | 12.2  | 7               | 11.7  | 7               | 12.7  | 1.000 |
| IV                              | 101             | 87.8  | 53              | 88.3  | 48              | 87.3  |    |
| Metastatic sites                |                 |       |                 |       |                 |       |    |
| Lung                            | 35              | 30.4  | 16              | 26.7  | 19              | 34.5  | 0.796 |
| Pleura                          | 25              | 21.7  | 12              | 20.0  | 13              | 23.6  |    |
| Liver                           | 8               | 7.0   | 4               | 6.7   | 4               | 7.3   |    |
| Bone                            | 47              | 40.9  | 26              | 43.3  | 21              | 38.2  |    |
| CNS                             | 12              | 10.4  | 4               | 6.7   | 8               | 14.5  |    |
| Adrenal gland                   | 8               | 7.0   | 3               | 5.0   | 5               | 9.1   |    |
| Distant lymph node metastasis   | 8               | 7.0   | 5               | 8.3   | 3               | 5.5   |    |
| Line of therapy                 |                 |       |                 |       |                 |       |    |
| 1                               | 64              | 55.7  | 37              | 61.7  | 26              | 47.3  | 0.121 |
| >2                              | 51              | 44.3  | 23              | 38.3  | 29              | 52.7  |    |
| PD-L1 expression                |                 |       |                 |       |                 |       |    |
| Negative                        | 56              | 48.7  | 32              | 53.3  | 24              | 43.6  | 0.299 |
| Positive                        | 59              | 51.3  | 28              | 46.7  | 31              | 56.4  |    |
| Regimen                         |                 |       |                 |       |                 |       |    |
| Combination with chemotherapy   | 66              | 57.4  | 39              | 65.0  | 27              | 49.1  | 0.135 |
| Monotherapy                     | 31              | 27.0  | 15              | 25.0  | 16              | 29.1  |    |
| Combination with antiangiogenic  | 18              | 15.7  | 6               | 10.0  | 12              | 21.8  |    |

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PD-L1, programmed death ligand 1; PNI, prognostic nutritional index.
Correlation of tumour response and survival outcomes with baseline PNI scores

Based on the level of the baseline PNI scores, the overall response rates (ORRs) of the patients at high and low levels were 53.3% (32/60) and 43.6% (24/55), respectively; however, the difference was not statistically significant ($P = .299$). The disease control rates for the patients with high and low baseline PNI scores were 95% (57/60) and 94.5% (52/55), respectively (not significantly different; $P = .913$).

The PFS median values were 15 (95% CI = 12.926-17.074) and 10 (95% CI = 7.617-12.383) months for the patients with high and low baseline PNI scores, respectively. Although the difference was large, it was not statistically significant ($P = .207$). However, the baseline PNI scores were closely associated with the OS. The median OS of the patients at the high baseline level was much longer than that of the patients at the low baseline level (30 months [95% CI = 23.949-36.051] vs 19 months [95% CI = 8.414-29.586]; $P = .026$) (Figure 3A and B).

Correlation of the tumour response and survival outcomes with the variations of the PNI scores

We examined whether the variations in the PNI scores from baseline to six weeks correlated with the response to treatment. An increase in the PNI score was observed in 55 patients (defined as the $\Delta$PNI-H subgroup), whereas a decrease in the PNI score was observed in 60 patients (defined as the $\Delta$PNI-L subgroup). The ORR of the $\Delta$PNI-H subgroup (33/55; 60.0%) was higher than that of the $\Delta$PNI-L subgroup (23/60; 38.3%; $P = .025$). In addition, the difference in the disease control rate was not statistically significant ($P = .913$).

Furthermore, the patients were divided into two groups according to their tumour response. Increased PNI scores were more often observed in the partial response group (33/56; 58.9%) than in the stable disease group (19/53; 35.8%) ($P = .021$) (Figure 4). Patients in the $\Delta$PNI-L subgroup had significantly worse PFS and OS than those in the $\Delta$PNI-H subgroup (median PFS: 12 months [95% CI = 8.864-15.136] vs 15 months [95% CI = 10.420-19.580], $P = .037$; median OS: 25 months [95% CI = 19.974-30.026] vs 36 months [95% CI = 23.834-48.166], $P = .047$) (Figure 3C and D).

Predictive ability of the combination of baseline and variation of PNI scores

Patients were clustered into four groups based on the combined PNI scores (combination of baseline PNI scores and PNI score variations). The difference in the ORR of the four subgroups was statistically significant ($P = .017$): 78.9% (15/19, $\Delta$PNI-H-H subgroup), 41.5% (17/41, $\Delta$PNI-H-L subgroup), 50% (18/36, $\Delta$PNI-L-H subgroup), and 31.6% (6/19, $\Delta$PNI-L-L subgroup).

The PFS median values were 8 (95% CI = 5.867-10.133), 12 (95% CI = 7.076-16.924), 14 (95% CI = 12.101-15.899), and 17 (95% CI = 13.513-20.487) months for the $\Delta$PNI-L-L, $\Delta$PNI-L-H, $\Delta$PNI-H-L, and $\Delta$PNI-H-H subgroups, respectively ($P = .013$). The OS median values were 15 (95% CI = 11.855-18.145), 27 (95% CI = 13.397-40.603), 28 (95% CI = 24.032-31.968) months, and not reached for the $\Delta$PNI-L-L, $\Delta$PNI-L-H, $\Delta$PNI-H-L, and $\Delta$PNI-H-H subgroups, respectively ($P < .001$) (Figure 3E and F). Patients in the $\Delta$PNI-L-H subgroup had longer survival than those in the $\Delta$PNI-L-L subgroup (PFS: 12 months vs 8 months, $P = .019$; OS: 28 months vs 15 months, $P = .013$).
OS: 27 months vs 15 months, \( P = .035 \). For patients with a high baseline level (ΔPNI-H-H and ΔPNI-H-L subgroups), the difference between the PFS values was not statistically significant (\( P = .181 \)); however, a significant difference was found between their OS values (\( P = .018 \)). For patients with a decreased PNI score (ΔPNI-L-L and ΔPNI-L-L subgroups), the prognosis was worse for patients with a low baseline PNI score than for patients with a high PNI score (PFS: \( P = .009 \); OS: \( P = .007 \)). Considering patients with increased PNI scores (ΔPNI-L-H and ΔPNI-H-H), a significant difference was observed between the median OS values (\( P = .011 \)); however, no significant difference was observed in the median PFS values (\( P = .381 \)). Patients in the ΔPNI-L-H subgroup appear to have a similar survival rate to that of patients in the ΔPNI-H-L subgroup (PFS: 12 months vs 14 months, \( P = .572 \); OS: 27 months vs 28.0 months, \( P = .911 \)).

The area under the ROC curve of the combined PNI score (baseline PNI scores combined with the PNI score variations) was 0.652 (\( P = .005 \)). The sensitivity and specificity were 0.585 and 0.710, respectively (Figure 2B).

Cox regression model of the survival outcomes

According to the univariable analyses, the Eastern Cooperative Oncology Group Performance Status Scale Score (HR = 2.022; 95% CI = 1.344-3.043; \( P = .001 \)), PD-L1 expression positive (HR = 0.572; 95% CI = 0.376-0.870; \( P = .009 \)), NLR variation (HR = 1.529; 95% CI = 1.002-2.331; \( P = .049 \)), PNI variation (HR = 0.657; 95% CI = 0.435-0.992; \( P = .046 \)), and combined PNI (ΔPNI-L-H, HR = 0.442, 95% CI = 0.242-0.805, \( P = .008 \); ΔPNI-H-L, HR = 0.506, 95% CI = 0.285-0.899, \( P = .020 \); and ΔPNI-H-H, HR = 0.330, 95% CI = 0.160-0.680, \( P = .003 \); vs ΔPNI-L-L) were independent factors for PFS.
However, the Eastern Cooperative Oncology Group Performance Status Scale Score (HR = 2.384; 95% CI = 1.380-4.120; P = .002), positive PD-L1 expression (HR = 0.507; 95% CI = 0.292-0.881; P = .016), baseline NLR score (HR = 1.891; 95% CI = 1.083-3.302; P = .025), baseline PNI score (HR = 0.544; 95% CI = 0.313-0.944; P = .030), and combined PNI scores (ΔPNI-L-H, HR = 0.421, 95% CI = 0.198-0.894, P = .024; ΔPNI-H-L, HR = 0.410, 95% CI = 0.195-0.865, P = .019; and ΔPNI-H-H, HR = 0.079, 95% CI = 0.017-0.358, P = .001; vs ΔPNI-L-L) were independent factors for OS (Tables 2 and 3).

The factors that were significant in the univariable analyses were included in a multivariable Cox regression model. We found that the combined PNI scores were associated with the ORR (ΔPNI-H-H, HR = 0.079, 95% CI = 0.017-0.358, P = .019; and ΔPNI-H-L, HR = 0.087, 95% CI = 0.019-0.396, P = .002; vs ΔPNI-L-L). Eastern Cooperative Oncology Group Performance Status Scale Score (PFS, HR = 1.935, 95% CI = 1.272-2.944, P = .002; OS, HR = 2.115, 95% CI = 1.218-3.674, P = .008), positive PD-L1 expression (PFS, HR = 0.568, 95% CI = 0.372-0.869, P = .009; OS, HR = 0.493, 95% CI = 0.281-0.864, P = .014) were found as independent predictive indicators of PFS and OS in the multivariable analysis.

**Discussion**

The goal of this study was to discover and explore the correlation between the baseline PNI scores and PNI score variations with immunotherapy for lung cancer. To our knowledge, this is the first study investigating this relationship. We found the baseline PNI scores to be only relevant to the OS, and not to the ORR and PFS. Prognostic nutritional index score variations and combined PNI scores were associated with the ORR, PFS, and OS. A multivariable Cox regression analysis confirmed that only the combined PNI scores were independent risk factors for PFS and OS. The combination of the baseline and variation of the PNI scores significantly enhanced the survival predictive ability of patients with NSCLC treated with PD-1 inhibitor. These results can help clinicians in formulating better treatment strategy making.

The PNI was originally proposed by Smale et al. It is mainly used to evaluate the risk of recurrence and survival following surgical treatment; however, it has not been popularised owing to its complex calculation. Nevertheless, the formula used to calculate the PNI score has been simplified by Onodera et al based on the serum albumin level and lymphocyte count. Recently, a growing number of studies have used the PNI to determine the prognosis of patients with tumours, including lung cancer. As relatively a few studies exist on the PNI scores of patients with NSCLC, the optimal threshold of the PNI score has not been determined. Owing to the heterogeneity between patients and small sample sizes, the cut-off scores reported in different studies are diverse. The critical PNI score for NSCLC ranges from 45.0 to 52.5. In this study, the best PNI cut-off score calculated from the ROC curve was 48.775. However, owing to individual patient variation, a mere standard value across the board cannot be followed. Our research demonstrated that the median OS of patients with high baseline PNI scores was much longer than that of patients with low baseline PNI scores (30 months vs 19 months), similar to the results of some other studies. A meta-analysis revealed that a low PNI score was significantly associated with poor OS for patients with lung cancer.

However, some studies did not find an association between the baseline PNI scores and survival outcomes. The predictive efficacy of the baseline PNI is controversial. Therefore, studying PNI score variation during anti-PD-1 treatment is noteworthy. To the best of our knowledge, no previous studies have explored PNI score variations as predictors of NSCLC outcomes treated with PD-1. The baseline PNI scores did not influence the ORR and PFS in this study; however, the PNI score variations did demonstrate such an influence. Patients with an increased PNI score had an ORR of 60.0%, and median PFS of 15 months, whereas the ORR was 38.3% and median PFS was 12 months for patients with a decreased PNI score. An increase in the PNI score indicates a higher response to anti-PD-1 treatment. The nutritional statuses of patients of the same stage varied widely when they sought medical advice. This could imply that either the nutritional status of the patients were different before they got sick or the time from illness to the first visit was inconsistent. Some patients underwent further medical consultations owing to physical examination. Some patients visit a doctor as soon as they feel unwell,
Table 2. Cox regression analysis for progression-free survival (PFS).

|                                | UNIVARIABLE ANALYSIS |                       |                       |                       | MULTIVARIABLE ANALYSIS |                       |                       |                       |
|--------------------------------|----------------------|-----------------------|-----------------------|-----------------------|------------------------|-----------------------|-----------------------|-----------------------|
|                                | HR                   | 95% CI                | \( P \)               |                       | HR                    | 95% CI                | \( P \)               |                       |
| **PFS**                        |                      |                       |                       |                       |                        |                       |                       |                       |
| **Age**                        |                      |                       |                       |                       |                        |                       |                       |                       |
| \(< 65\)                       | 1                    |                       |                       |                       |                        |                       |                       |                       |
| \(\geq 65\)                    | 0.942                | 0.613-1.448           | 0.785                 |                       |                        |                       |                       |                       |
| **Sex**                        |                      |                       |                       |                       |                        |                       |                       |                       |
| Female                         | 1                    |                       |                       |                       |                        |                       |                       |                       |
| Male                           | 1.089                | 0.632-1.874           | 0.759                 |                       |                        |                       |                       |                       |
| **ECOG**                       |                      |                       |                       |                       |                        |                       |                       |                       |
| 0                              | 1                    |                       |                       |                       |                        |                       |                       |                       |
| 1-2 score                      | 2.022                | 1.344-3.043           | \(0.001\)            |                       | 1.935                  | 1.272-2.944           | \(0.002\)            |                       |
| **Histology**                  |                      |                       |                       |                       |                        |                       |                       |                       |
| LUSC                           | 1                    |                       |                       |                       |                        |                       |                       |                       |
| LUAD                           | 0.808                | 0.504-1.296           | 0.377                 |                       |                        |                       |                       |                       |
| Other                          | 1.318                | 0.659-2.637           | 0.435                 |                       |                        |                       |                       |                       |
| **Stage**                      |                      |                       |                       |                       |                        |                       |                       |                       |
| IIIIB/IIIC                     | 1                    |                       |                       |                       |                        |                       |                       |                       |
| IV                             | 1.105                | 0.573-2.133           | 0.766                 |                       |                        |                       |                       |                       |
| **Line of therapy**            |                      |                       |                       |                       |                        |                       |                       |                       |
| 1                              | 1                    |                       |                       |                       |                        |                       |                       |                       |
| \(\geq 2\)                    | 1.144                | 0.762-1.716           | 0.517                 |                       |                        |                       |                       |                       |
| **Regimen**                    |                      |                       |                       |                       |                        |                       |                       |                       |
| Combination with chemotherapy  | 1                    |                       |                       |                       |                        |                       |                       |                       |
| Monotherapy                    | 0.952                | 0.696-1.301           | 0.756                 |                       |                        |                       |                       |                       |
| Combination with antiangiogenic| 0.892                | 0.676-1.177           | 0.419                 |                       |                        |                       |                       |                       |
| **PD-L1 expression**           |                      |                       |                       |                       |                        |                       |                       |                       |
| Negative                       | 1                    |                       |                       |                       |                        |                       |                       |                       |
| Positive                       | 0.572                | 0.376-0.870           | \(0.009\)            |                       | 0.568                  | 0.372-0.869           | \(0.009\)            |                       |
| **Baseline NLR**               |                      |                       |                       |                       |                        |                       |                       |                       |
| Low                            | 1                    |                       |                       |                       |                        |                       |                       |                       |
| High                           | 1.148                | 0.720-1.830           | 0.563                 |                       |                        |                       |                       |                       |
| **Variation of NLR**           |                      |                       |                       |                       |                        |                       |                       |                       |
| Low                            | 1                    |                       |                       |                       |                        |                       |                       |                       |
| High                           | 1.529                | 1.002-2.331           | \(0.049\)            |                       |                        |                       |                       |                       |
| **Baseline PNI**               |                      |                       |                       |                       |                        |                       |                       |                       |
| Low                            | 1                    |                       |                       |                       |                        |                       |                       |                       |
Table 3. Cox regression analysis for overall survival (OS).

|                | UNIVARIABLE ANALYSIS | MULTIVARIABLE ANALYSIS |
|----------------|----------------------|------------------------|
|                | HR       | 95% CI     | P          | HR       | 95% CI     | P          |
| **OS**         |          |            |            |          |            |            |
| **Age (years)**|          |            |            |          |            |            |
| ≤65            |          |            |            |          |            |            |
| >65            | 1.232    | 0.706-2.149| 0.462      |          |            |            |
| **Sex**        |          |            |            |          |            |            |
| Female         | 1        |            |            |          |            |            |
| Male           | 1.181    | 0.575-2.423| 0.651      |          |            |            |
| **ECOG**       |          |            |            |          |            |            |
| 0              |          |            |            |          |            |            |
| 1-2 score      | 2.384    | 1.380-4.120| 0.002      | 2.115    | 1.218-3.674| 0.008      |
| **Histology**  |          |            |            |          |            |            |
| LUSC           | 1        |            |            |          |            |            |
| LUAD           | 1.030    | 0.530-2.003| 0.931      |          |            |            |
| Other          | 2.075    | 0.846-5.091| 0.111      |          |            |            |
| **Stage**      |          |            |            |          |            |            |
| IIIB/IIIC      |          |            |            |          |            |            |
| IV             | 1.269    | 0.540-3.196| 0.614      |          |            |            |
| **Line of therapy** |     |            |            |          |            |            |
| 1              | 1        |            |            |          |            |            |
| >2             | 0.976    | 0.568-1.677| 0.930      |          |            |            |

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed death ligand 1; PFS, progression-free survival; PNI, prognostic nutritional index.
whereas some delay diagnosis and treatment related to poor nutritional status owing to various causes, such as neglecting symptoms, strong tolerance to pain or discomfort, or lack of medical knowledge. Therefore, the nutritional status at the baseline of diagnosis cannot be used to comprehensively evaluate the prognosis. Prognostic nutritional index variation may not only evaluate short-term efficacy but also correlate with long-term prognosis.

Furthermore, we combined the baseline PNI scores and PNI score variations and found combined PNI score to be significant independent predictive factors of patients with NSCLC treated with PD-1 inhibitor on univariable and multivariable analysis. This study revealed that patients with low level of baseline PNI experienced decreased PNI, the prognosis of which is the worst (PFS: 8 months, OS: 15 months). Although patients with high level of baseline PNI score who showed increased PNI scores had the best survival outcomes (PFS: 17 months, OS: not reached). Patients with low baseline and increased variation appear to have a similar prognosis to that of the patients with high baseline and decreased variation (PFS: 12 months vs 14 months, OS: 27 months vs 28.0 months).

Based on the combined PNI scores, different strategies should be adopted. The status of patients in the PNI-L-L subgroup with low baseline PNI and increased variation, which could be attributed to insensitivity to immunotherapy, deteriorate during immunotherapy, and experienced unfavourable survival

### Table 3. (Continued)

|                  | UNIVARIABLE ANALYSIS | MULTIVARIABLE ANALYSIS |
|------------------|----------------------|------------------------|
|                  | HR | 95% CI     | P | HR | 95% CI     | P |
| Regimen          |    |            |   |    |            |   |
| Combination with chemotherapy | 1 |          |   |    |            |   |
| Monotherapy      | 0.958 | 0.641-1.432 | 0.836 |    |            |   |
| Combination with antiangiogenic | 0.961 | 0.663-1.393 | 0.834 |    |            |   |
| PD-L1 expression |    |            |   |    |            |   |
| Negative         | 1 |          |   |    |            |   |
| Positive         | 0.507 | 0.292-0.881 | **0.016** | 0.493 | 0.281-0.864 | **0.014** |
| Baseline NLR     |    |            |   |    |            |   |
| Low              | 1 |          |   |    |            |   |
| High             | 1.891 | 1.083-3.302 | **0.025** |    |            |   |
| Variation of NLR |    |            |   |    |            |   |
| Low              | 1 |          |   |    |            |   |
| High             | 1.297 | 0.742-2.266 | 0.361 |    |            |   |
| Baseline PNI     |    |            |   |    |            |   |
| Low              | 0.544 | 0.313-0.944 | **0.030** |    |            |   |
| High             | 0.576 | 0.331-1.004 | 0.052 |    |            |   |
| Variation of PNI |    |            |   |    |            |   |
| Low              | 1 |          |   |    |            |   |
| High             | 0.421 | 0.198-0.894 | **0.024** | 0.403 | 0.189-0.861 | **0.019** |
| Combined PNI     |    |            |   |    |            |   |
| ∆PNI-L-L         | 0.410 | 0.195-0.865 | **0.019** | 0.369 | 0.173-0.787 | **0.010** |
| ∆PNI-L-H         | 0.410 | 0.195-0.865 | **0.019** | 0.369 | 0.173-0.787 | **0.010** |
| ∆PNI-H-L         | 0.079 | 0.017-0.358 | **0.001** | 0.087 | 0.019-0.396 | **0.002** |

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD-L1, programmed death ligand 1; PNI, prognostic nutritional index.
rate. Thus, treatment strategies should be performed more carefully in these patients. Patients with high baseline and increased variation may have relative low tumour burden and higher response to anti-PD-1 treatment; thus, positive antitumour therapies can be performed. We conducted an in-depth research of the baseline PNI scores combined with the dynamic changes in the PNI score and found that the diagnostic efficiency of the ROC curve was better than that of the baseline PNI scores. A multivariable Cox regression analysis confirmed that combined PNI scores are independent risk factors for PFS and OS; however, the baseline PNI score is not an independent risk factor. Dynamic monitoring and comprehensive assessment of the PNI score may be useful for observing the curative effect and assessing the prognosis, thereby providing an individualised prognosis and implementing the progress of clinical treatment strategies, which cannot be determined by the baseline score alone.

The PNI score is an indicator of the immunologic and nutritional status of patients as it is composed of lymphocytes and albumin. Biological evidence has suggested that the PNI score is associated with the immunotherapy outcomes. Lymphocytes have a vital role in immune surveillance by inhibiting the proliferation, invasion, and migration of tumour cells, whereas a low lymphocyte count is related to an impaired antitumour response, CD8+ T-cell cytotoxicity, and impaired CD4+ helper T-cell function. Decreased lymphocyte production results in a weak immune response in tumour cells. For patients treated with nivolumab, a high absolute lymphocyte count was significantly and independently associated with a better PFS and OS. These findings confirm that high lymphocyte counts are significantly related to better clinical outcomes of the treated patients. Low albumin levels are associated with weight loss and malnutrition, which are significantly associated with unfavourable clinical outcomes.

Considering immunotherapy, serum albumin ≥3.5 g/dL was an independent predictor of disease control and survival, although it was not a predictor of the ORR of patients with NSCLC who received PD-1 inhibitor treatment. Serum albumin is suppressed by and reflects the chronic systemic inflammatory response. Malnutrition caused by increased tumour metabolism is the most common cause of immunodeficiency; malnutrition could result in a nutrient-deficient tumour microenvironment. The deficiency of essential nutrients can induce immune cells to alter metabolic programming and influence their functions. Dysfunctional metabolisms can also result in an immunosuppressive tumour microenvironment, thereby affecting the immune responses.

The PD-L1 expression is a universally acknowledged predictor. In this study, we also found that positive PD-L1 expression is also meaningful in multiple COX regression. After excluding the influence of PD-L1 expression, the combined PNI scores were still observed as significant predictors. Programmed death ligand 1 expression can reflect the tumour-related features, whereas the PNI scores may mirror the nutritional and immune status of the host. We also studied NLR, which was also demonstrated to impact the PFS and OS in the univariable analyses. However, in the final multiple regression, no significance was observed. The cut-off point value of 5, which was commonly used, may not be suitable for all patients. The predictive value of NLR indicator was uncertain. No consensus was reached and written into the guideline at present.

Despite the advantages of this study, it has several limitations. First, it was a single-centre retrospective study with a limited sample size, encompassing a certain extent of heterogeneous patient population (different patterns of immunotherapy). Second, the haematologic parameters may have been affected by certain concomitant medications that were not accounted for in this study. Further large-scale, prospective clinical studies are warranted to verify our conclusions.

Conclusions
In conclusion, we observed two key findings. First, the baseline PNI scores were only relevant to the OS, and not to the ORR and PFS. The PNI score variations were associated with the ORR, PFS, and OS. The combination PNI scores significantly enhanced the survival predictive ability of patients with NSCLC treated with PD-1 inhibitor compared with the baseline and variation scores of PNI alone. Second, four subgroups of patients with NSCLC with significantly different survival rates were divided based on the combined PNI scores, and patients with high baseline PNI and increased PNI scores had the best survival outcome. Therefore, baseline PNI scores should not be used as the sole predictor. The combined PNI scores – which are non-invasive, sensitive, and inexpensive – can be used as predictive indicators of patients with NSCLC treated with PD-1 inhibitor to guide personalised treatment.

Author Contributions
QF, JZ, and CZ contributed to the conceptualisation. QF and JY contributed to the methodology. JY and JL contributed to the software. QF and BC contributed to the validation. QD contributed to the formal analysis. JY contributed to the investigation. JZ contributed to the resources. YH contributed to the curation. QF contributed to the writing – original draft preparation. QF, YH, and JZ contributed to the writing – review and editing. QF contributed to the visualisation. JZ and CZ contributed to the supervision. CZ contributed to the project administration. All the authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate
This study was approved by the institutional ethical review board of the Shanghai Pulmonary Hospital (K22-241, 2022-6-15).
