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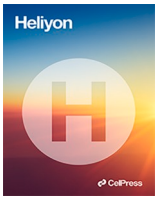

Review article

Predictive value of the prognostic nutritional index in advanced non-small cell lung cancer patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis

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A R T I C L E I N F O

Keywords:
Prognostic nutritional index
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Meta-analysis

A B S T R A C T

Purpose: The prognostic nutritional index (PNI), which is derived from the albumin concentration and absolute lymphocyte number, is an effective indicator of cancer patients' nutritional and immunological status. According to multiple studies, PNI was strongly linked to the prognosis of patients with non-small cell lung cancer (NSCLC). The predictive value of PNI for survival outcomes in NSCLC patients receiving immune checkpoint inhibitors (ICIs) is still in dispute at present. This meta-analysis is devoted to fill this information gap and investigate the predictive ability of PNI in NSCLC patients treated with ICIs.

Methods: The PubMed, Embase, Cochrane Library databases, and conference proceedings were searched for eligible studies without language restriction. Overall survival (OS) and progression-free survival (PFS) were included. The predictive value of PNI was estimated using hazard ratios and their 95% confidence intervals.

Results: Thirteen relevant retrospective cohort studies were included and these studies included 1119 patients with stage III-IV NSCLC. Lower PNI status was found to be an independent risk factor for worse survival outcomes in patients with NSCLC (OS HR = 2.68; 95%CI: 1.76–4.06; $P < 0.0001$; PFS HR = 1.84; 95%CI: 1.39–2.42; $P < 0.0001$). According to the subgroup analysis, PNI was similarly connected to OS in most subgroups of NSCLC patients receiving ICIs, except for those receiving chemoimmunotherapy or first-line treatment, and those with a cut-off value < 45.

Conclusion: Our findings indicated that lower PNI was associated with poorer prognosis in NSCLC patients undergoing ICI therapy. Further prospective research with bigger patient groups is required.

Systematic Review Registration: International Prospective Register of Systematic Reviews (PROSPERO), identifier CRD42022327528.

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1. Introduction

Lung cancer remains the leading cause of cancer-related deaths worldwide [1] and approximately 85% of lung cancer is non-small-cell lung cancer (NSCLC). Owing to the absence of clinical symptoms, the majority of patients with NSCLC are diagnosed at an advanced stage, resulting in a low 5-year survival rate [2]. Immune checkpoint inhibitors (ICIs), particularly anti-programmed death receptor-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors, have completely changed the treatment paradigm for NSCLC patients [3–5]. Despite the fact that some patients respond to ICIs treatment, the majority of patients fail to experience any benefit. Generally, PD-1 inhibitor monotherapy produces a clinical response only in 20% of patients with NSCLC [3,4]. Therefore, it is essential to distinguish and validate predictive markers for screening patients who are most suitable for ICIs treatment.

The PD-L1 expression and tumor mutational burden (TMB) score are the two most clinically acknowledged and recognized biomarkers for ICIs efficacies [6–8]. The expression of PD-L1 as detected by immunohistochemistry (IHC) in tumor cells is the first FDA-approved biomarker for selecting beneficial patients with NSCLC receiving ICIs [9]. First-line pembrolizumab treatment for advanced NSCLC patients with high PD-L1 expression showed a substantial survival benefit [6,10]. However, in CheckMate-057, regardless of PD-L1 level, a prognostic advantage was reported for second-line nivolumab treatment [4]. Similarly, number of independent investigations indicated that TMB remained insufficiently predictive, due to its dynamic, heterogenous and methodology-affecting characteristics [11,12].

In addition to tumor features, the prognosis of patients with advanced NSCLC can also be predicted by patient-related parameters [13–25]. The prognostic nutritional index (PNI) was created for the first time in 1980 to estimate perioperative risk for gastrointestinal surgeries [26]. In patients with early-stage NSCLC, PNI was shown to be useful in predicting postoperative recurrence and prognosis [27]. Moreover, it has been shown that pre-treatment PNI is strongly linked with progression free survival (PFS) and overall survival (OS) in patients with NSCLC who received chemotherapy or chemoradiotherapy [28–30]. However, there is no conclusive conclusion addressing the potential predictive values of PNI in NSCLC patients treated with ICIs. For the past few years, the ability of PNI to forecast the survival of NSCLC patients receiving ICIs has been investigated by several research. Therefore, it is necessary to integrate these studies to provide preliminary insight into this subject.

In this study, we included all pertinent retrospective cohort studies and performed a meta-analysis of them to clarify the predictive and clinical impact of PNI on NSCLC patients receiving ICIs treatment, thereby providing strong evidence for practical clinical decision-making.

2. Methods

2.1. Guidelines and registration

This meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement [31]. The International Prospective Register of Systematic Reviews (PROSPERO) received this meta-analysis for registration: number CRD42022327528.

2.2. Eligibility criteria

Studies were considered if the following criteria were met: 1) The research comprised patients with pathologically determined NSCLC; 2) Studies explored the predictive capability of PNI that was calculated by serum albumin levels and peripheral lymphocyte counts; 3) Retrospective or prospective studies contained the HR and accompanying 95% confidence interval (95%CI) for the OS or PFS; 4) Retrospective or prospective studies published before August 2022.

Studies meeting the following criteria were excluded: 1) reviews, conference abstracts, case reports, letters, or comments; 2) laboratory testing of clinical samples, cell lines, or animals; 3) inadequate data of PNI.

2.3. Data extraction

First author, year of publication, study design, region, sample size, biological sex, PNI cutoff value, treatment regimen, treatment lines and results with HRs and their associated95%CIs of high versus low PNI for OS and PFS were retrieved independently by two researchers from the eligible studies. Discussion and agreement were used to settle any disputes.

2.4. Study quality assessment

Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the study's quality. Each study was given a number ranging from 0 (worst) to 9 (best). Studies receiving a score of 6 or less were deemed to be of low quality, while those receiving a score of 7 or above were deemed to be of excellent quality [32].

2.5. Statistical analysis

The present meta-analysis was assessed by R 4.1.3 software. HRs calculated from multivariate analyses were extracted preferentially where available. Univariate HRs were used instead if multivariate HRs were not available. According to heterogeneity, the

random effect or fixed-effect model was merged with pooled HRs and 95% CIs. Q tests and I^2 statistics were used to evaluate heterogeneity. $P < 0.05$ and/or $I^2 > 50\%$ were defined as significant heterogeneity and random effect model was further to used. Otherwise, we chose the fixed-effect model. In accordance with the sample size, region, treatment regimen, treatment line and PNI cut-off value, subgroup analyses were performed. For subgroup analysis of cut-off value, the stratification was based on the median of the cut-off values used in the included studies [33,34]. Sensitivity analysis, in which one study was removed at a time, was performed to evaluate the stability of the results. Finally, publication bias was evaluated by funnel plots. If funnel plot asymmetry was suggested by a visual assessment, we would perform exploratory analyses (e.g. Rücker's arcsine test for dichotomous data) to further investigate funnel plot asymmetry [35,36].

3. Results

3.1. Study selection

Our database and manual searches retrieved a total of 173 publications, of which 38 were excluded due to duplication. We initially screened the abstracts and titles for eligibility. Of the 135 studies that were assessed for eligibility, 23 met our inclusion criteria. Then, by reading the full text, we further filter the selected studies. Ultimately, a total of 13 studies were included in the meta-analysis. Fig. 1 displays a flow chart of the studies' selection process.

3.2. Characteristics of the included studies

The key characteristics of the included studies are listed in Table 1. A total of 13 studies comprising 1119 patients were included for meta-analysis, all of which were retrospective cohort studies [13–25]. Among all included studies, nine were conducted in Asia [14–16,18–23] and four in Europe [13,17,24,25]; patients with stage III-IV NSCLC were enrolled in each study. The sample size of these studies ranged from 24 to 237. The cut-off values of PNI varied from 40 to 50.

3.3. Correlation between PNI and survival in NSCLC

In a total of 11 studies, the OS andPFS outcomes were reported. The heterogeneity analyses indicated the presence of heterogeneity, hence the random effect model was employed. The results indicated that lower pretreatment PNI was associated with worse OS in NSCLC patients treated with ICIs (HR = 2.68; 95%CI: 1.76–4.06; $P < 0.0001$; I2 = 91.0%, $P < 0.0001$) (Fig. 2A). In addition, decreased

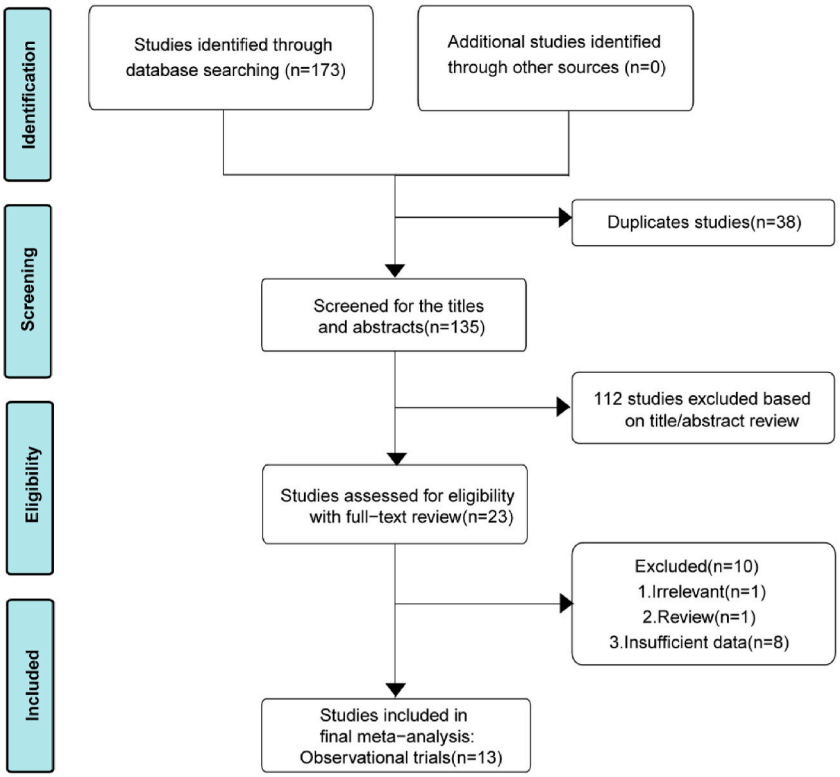


Fig. 1. Flow chart of study selection and design.

Table 1
Summary of studies included in the present meta-analysis.

Authors	Year	Study design	N	Gender (M/F)	Age	Region	Stage	Treatment	Line	Cut-off value	Outcomes	NOS
Lihong	2019	Retrospective	102	87/15	62	Asia	III-IV	Nivo, Pemb, Toripa, Sinti	un-selected	45	OS,PFS	7
Taichi	2020	Retrospective	24	7/17	64.5 (54.8–74.2)	Asia	III-IV	Atezo	>1	40	OS	5
Cipriano	2020	Retrospective	34	27/17	67 (34–79)	Europe	IV	Immunotherapy	un-selected	50	OS	4
Shi	2021	Retrospective	103	68/35	66	Asia	III-IV	Immunotherapy/Chemoimmunotherapy	un-selected	45	OS,PFS	7
Cinzia	2021	Retrospective	44	26/18	70 (42–83)	Europe	III-IV	Pemb	1	45.1	PFS	8
Taisuke	2021	Retrospective	36	31/5	68.5	Asia	III-IV	Chemoimmunotherapy	1	40	OS,PFS	6
Junichi	2021	Retrospective	73	52/21	70.9 (46–89)	Asia	III-IV	Nivo, Pemb,Atezo	un-selected	43	OS,PFS	7
Yuri	2021	Retrospective	34	29/5	72 (55–81)	Asia	IV	Chemoimmunotherapy	1	40	OS,PFS	6
Na	2021	Retrospective	123	98/25	59.9 (48.6–71.2)	Asia	IV	Nivo, Pemb, Sinti, Camre, Toripa	un-selected	46.05	OS,PFS	6
Cipriano	2021	Retrospective	52	42/10	NR	Europe	IV	Immunotherapy	un-selected	50	OS,PFS	4
Stares	2022	Retrospective	219	109/110	69	Europe	III-IV	Pemb	1	45	OS,PFS	8
Satomi	2022	Retrospective	237	187/187	69 (62–73)	Asia	IV	Chemoimmunotherapy	un-selected	40.35	OS,PFS	7
Naoki	2022	Retrospective	38	30/8	75 (45–86)	Asia	III-IV	Pemb	1	40	PFS	6

N, number; M, male; F, female; NR, not reported; OS, overall survival; PFS, progression-free survival; Nivo, Nivolumab; Pemb, Pembrolizumab; Toripa, Toripalimab; Sinti, Sintilimab; Camre, Camrelizumab; Atezo, Atezolizumab; NOS, Newcastle-Ottawa quality assessment Scale.

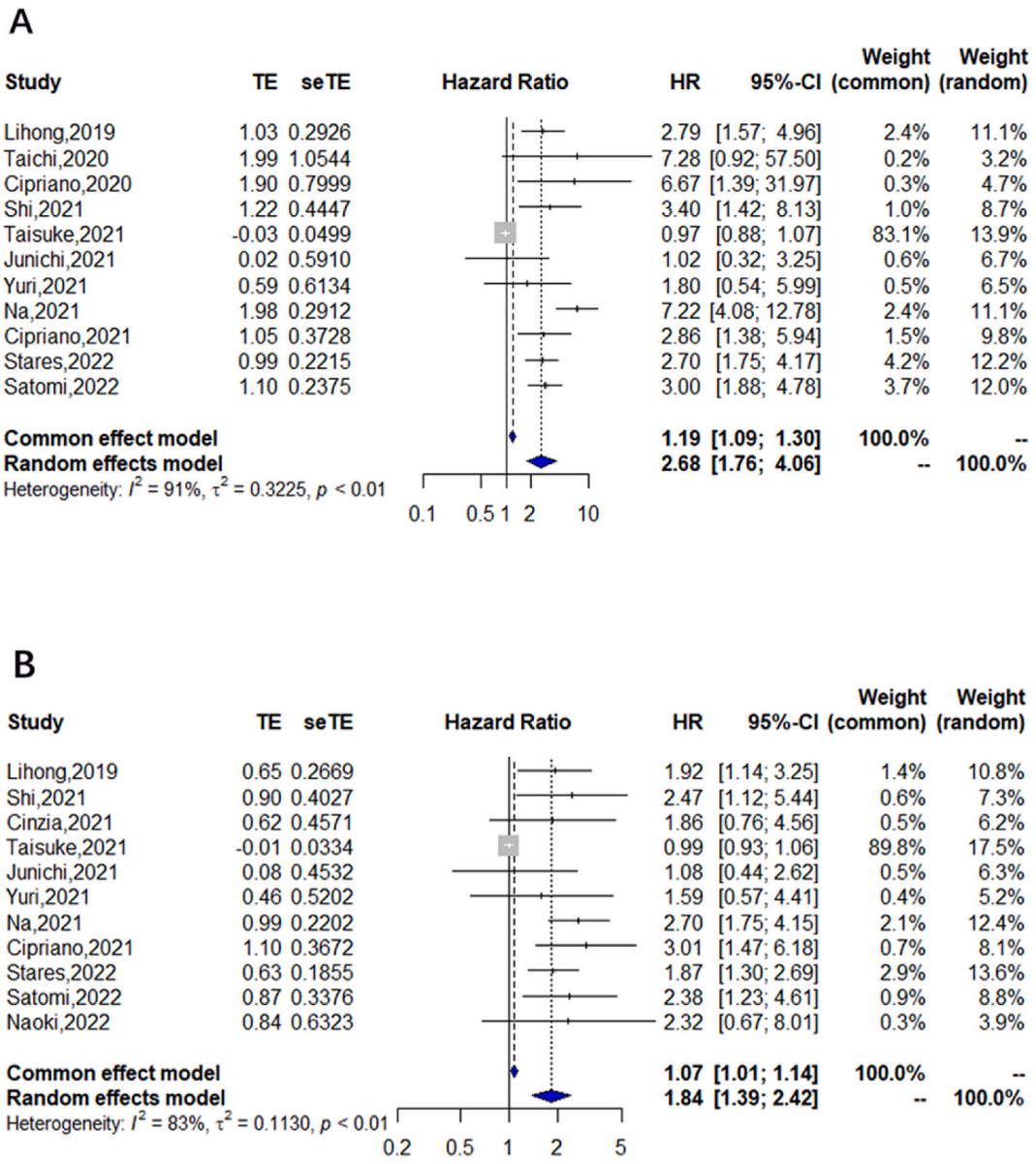


Fig. 2. Forest plot for the association between PNI and (A) overall survival (OS), (B) progression-free survival (PFS).

pretreatment PNI was linked to poorer PFS as well (HR = 1.84; 95%CI: 1.39–2.42; P < 0.0001; I2 = 82.9%, P < 0.0001) (Fig. 2B).

3.4. Subgroup analysis

In order to identify factors associated with heterogeneity, we performed subgroup analyses stratified by sample size, region, treatment regimen, treatment line, PNI cut-off value (stratified by median value as described in the Methods section) and NOS score. In the majority of stratified analyses, a lower PNI was associated with worse OS in NSCLC patients receiving ICIs treatment. However, this relationship was not statistically significant in the chemoimmunotherapy subgroup, the first-line treatment subgroup and the cut-off value < 45 subgroup (Table 2). Notably, the subgroup analysis based on cut-off values revealed a statistically significant difference between the two subgroups (P = 0.04). In the cut-off value ≥ 45 subgroup, pooled HR demonstrated that patients with low PNI had a worse OS compared to those with high PNI, (HR = 3.63; 95%CI: 2.47–5.31; P < 0.0001; I2 = 45.1%, P < 0.0001), whereas no difference was observed between patients with low and high PNI in the cut-off value < 45 subgroup (HR = 1.72; 95%CI: 0.91–3.24; P = 0.10; I2 = 84.6%, P < 0.0001).

Table 2
Subgroup analyses based on a random effects model.

	N	Association		Heterogeneity	
		HR (95%CI)	p value	I2 (%)	p value
Sample size					
<100	6	1.94 [1.01; 3.71]	0.04	72.80%	<0.01
≥100	5	3.48 [2.41; 5.04]	<0.01	53.00%	0.07
Region					
Asia	8	2.52 [1.46; 4.35]	<0.01	91.90%	<0.01
Europe	3	2.87 [2.00; 4.13]	<0.01	0.00%	0.55
Treatment regimen					
Mono-Immunotherapy	7	3.35 [2.11; 5.30]	<0.01	56.50%	0.03
Chemoimmunotherapy	3	1.67 [0.77; 3.62]	0.19	91.10%	<0.01
Un-selected	1	3.40 [1.42; 8.13]	–	–	–
Line					
>1	1	7.28 [0.92; 57.50]	–	–	–
1	3	1.61 [0.78; 3.29]	0.20	90.60%	<0.01
Un-selected	7	3.35 [2.25; 4.99]	<0.01	51.90%	0.05
Cut-off value					
<45	5	1.72 [0.91; 3.24]	0.09	84.60%	<0.01
≥45	6	3.62 [2.47; 5.31]	<0.01	45.10%	0.11
Study quality					
<7	6	3.01 [1.39; 6.52]	<0.01	92.10%	<0.01
≥7	5	2.73 [2.11; 3.53]	<0.01	0.00%	0.53

HR, hazard ratio; CI, confidence interval.

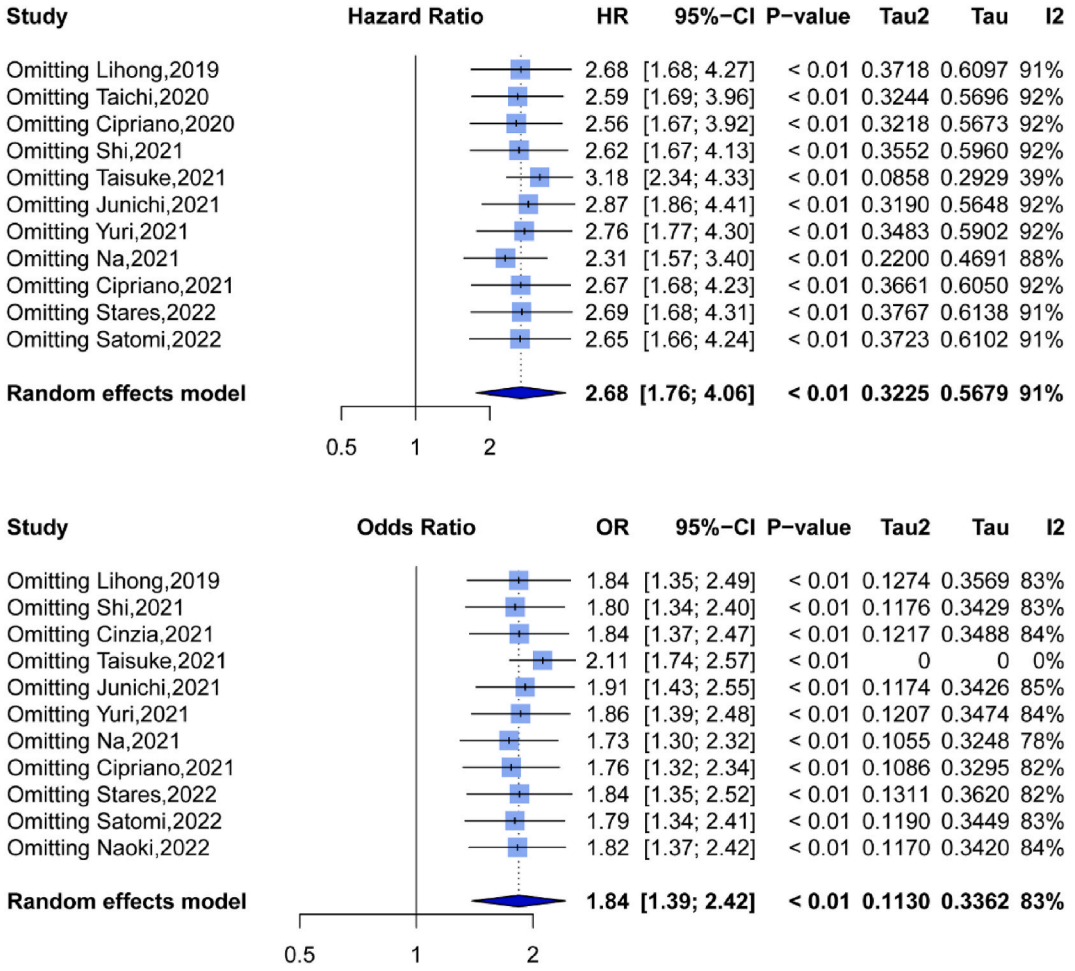
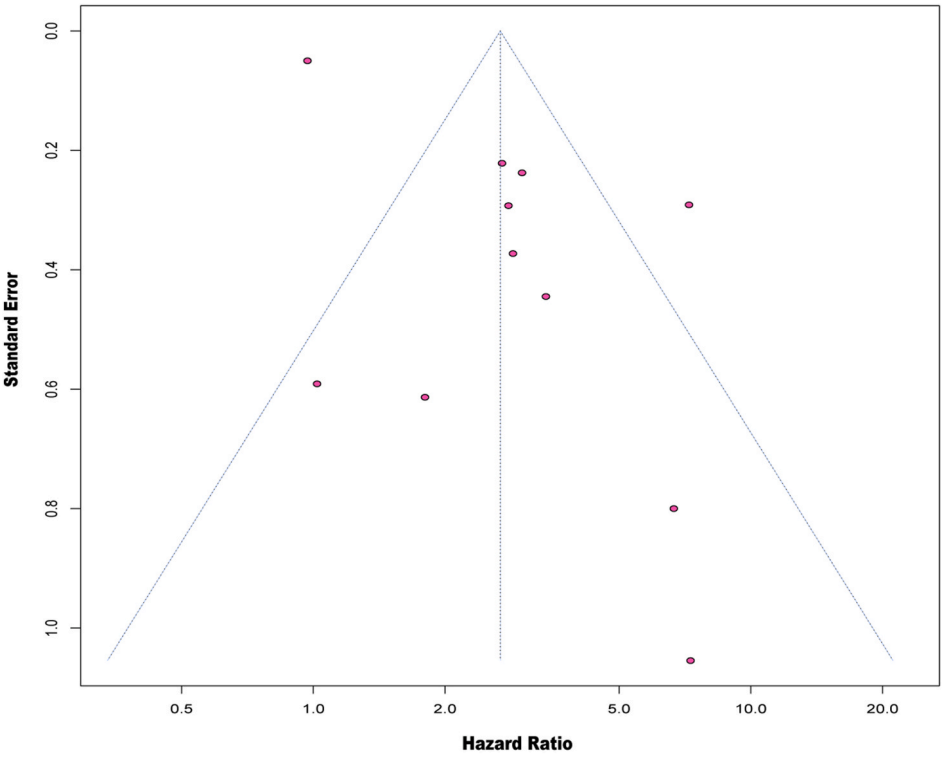


Fig. 3. Sensitivity analysis for the association between PNI and (A) overall survival (OS), (B) progression-free survival (PFS).



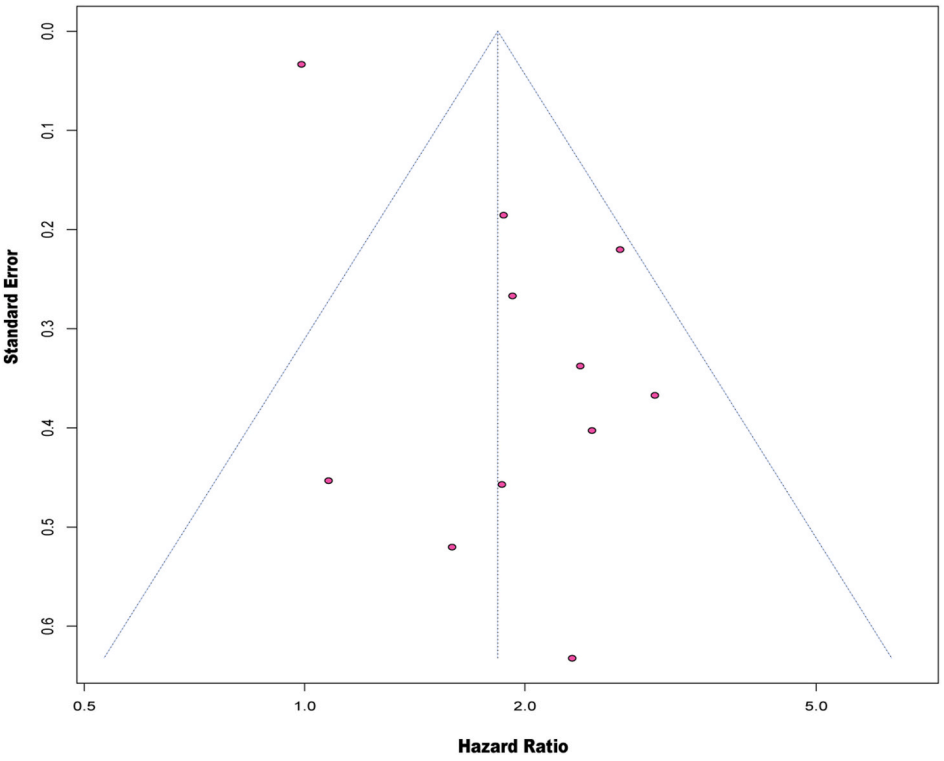


Fig. 4. Funnel plot for (A) overall survival (OS) and (B) progression-free survival (PFS).

3.5. Sensitivity analysis

We conducted a sensitivity analysis by removing one study at a time and computed the combined HR. The pooled HRs and 95% CIs indicated that no research substantially influenced OS or PFS (Fig. 3A and B), demonstrating the stability and dependability of our findings in this meta-analysis.

3.6. Publication bias

The funnel plots for publication bias showed some asymmetry (Fig. 4A and B). Arcsine tests were therefore carried out to better examine the publication bias. The P values of the Arcsine tests indicated that there were no discernible biases in the pooled HRs for OS and PFS ($P = 0.2576$ for OS; $P = 0.1544$ for PFS).

4. Discussion

This systematic review and meta-analysis provided first-of-its kind evidence for the association between PNI and the prognosis of patients with NSCLC receiving ICIs. The PFS and OS data gathered from the included studies were pooled for statistical analysis. Collectively, the findings of the present research suggested that a lower PNI was associated with poorer outcomes (OS and PFS) in NSCLC patients receiving ICIs treatment. In the subgroup analyses, it was revealed that lower PNI remained a risk factor for worse OS in certain subgroups (i.e., region, sample size, tumor stage, histology, and study quality). The subgroup analysis in the chemo-immunotherapy and first-line therapy scenario was based solely on data from three studies. The results of this analysis should be treated with caution due to the small number of research included. In light of the limited number of included trials, this stratified result should be interpreted with some caution. Notably, there is currently no gold standard to define the optimal cut-off value for PNI [13,14]. Nevertheless, our results indicated that the cut-off value of 45 or above was more valuable for predicting the prognosis of NSCLC patients undergoing ICI therapy.

As an effective immune-nutritional marker, PNI is determined based on serum albumin and lymphocyte count and reflects both immunological and nutritional status. Several potential mechanisms may account for the observed association between increased PNI and worse prognosis in NSCLC patients treated with ICIs. On the one hand, serum albumin has been proven to be a reliable indicator of patients' nutritional condition [37]. Malnutrition is one of the main causes for immunodeficiency and profoundly affects the anti-tumor immune responses [38,39]. Hypoalbuminemia implies poor nutritional status, impairs immunological function, including humoral and cell-mediated immunity as well as antigen-presenting cell activities, thus correlating with poor prognosis for cancer patients [40]. On the other hand, lymphocytes play a fundamental role in suppressing tumor growth and progression via direct effects on cancer cells or indirect effects on the tumor microenvironment [41]. Numerous studies have shown that lymphocytopenia is related with impaired anti-tumor immune response, and lymphocyte count level can be utilized as an indicator to predict the overall treatment outcomes in cancer patients [42,43]. In a single-center retrospective study of 268 patients with advanced NSCLC, those with lymphopenia (absolute lymphocyte count < 1000 cells/mm3) had poor performance status and extensive disease when receiving immunotherapy. In addition, the results from multivariate analysis demonstrated that lymphopenia was associated with unfavorable prognosis and poor response to ICIs [44]. Overall, as a potential biomarker, PNI has excellent application prospects in the field of antitumor immunotherapy.

Exploring biomarkers of responses to ICIs will facilitate the development of precise or personalized treatment strategies, which will improve the efficacy of ICIs. The expression of PD-L1 level is the most common clinically used and approved biomarker for ICIs treatment [6,9]. Certain hematological parameters can also reflect immune status of different cancers, and thus have the predictive potential for ICIs effectiveness. PNI has been found to have possible correlations with PD-L1 expression. For example, high expression of PD-L1 and malnutrition are both associated with immunosuppression [45,46]. Riki and his colleagues found a negative correlation between PD-L1 expression and PNI [47], with one possible explanation being that both inflammatory factors and nutritional status regulate the metabolism and function of immune cells [48–50]. A number of studies have elucidated that hematological markers, such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR) and PNI have high predictive values for the efficacy of ICIs treatment in patients with NSCLC [51–54]. These markers have the advantages of being reliable, inexpensive, and easy to obtain. Additionally, researchers have reported that PNI is a more useful biomarker than CRP or NLR by comparing the AUC value, sensitivity and specificity [55]. Therefore, PNI exhibits substantial clinical potential as a biomarker to predict the prognosis for NSCLC patients receiving ICIs treatment.

Several limitations, however, must be taken into account when interpreting our findings. First, the majority of included studies had a retrospective design, which is a potential source of bias; Second, we observed considerable heterogeneity across studies. Although subgroup and sensitivity analyses were performed, the main source of heterogeneity was not identified. That may be attributed to the fact that different cut-off values were employed in the analyzed studies. Third, our subgroup analysis demonstrated that setting the cutoff value of PNI at 45 or above might have a greater predictive effect for the efficacy of ICIs treatment in patients with NSCLC. However, considering that the range for 45 and above is still broad, it is necessary to conduct large-scale clinical studies to obtain more precise cut-off value for achieving optimal predictive effects.

5. Conclusion

In conclusion, our study provides evidence that a reduced PNI level is associated with worse survival outcomes in NSCLC patients

undergoing ICIs treatment, which may help clinicians to predict the prognosis of NSCLC patients and to choose the optimal treatments. More comprehensive, better designed, and prospective studies are needed to verify our results.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

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Declaration of competing interest

All authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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