Received: 14 December 2021 | Revised: 27 January 2022 | Accepted: 8 February 2022

DOI: 10.1002/jcla.24300

RESEARCH ARTICLE

WILEY

Prognostic value of prognostic nutritional index and its variations in advanced non-small-cell lung cancer patients treated with anlotinib monotherapy

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Abstract

Background: Anlotinib is a third-line or further therapy for advanced non-small-cell lung cancer (NSCLC). However, the lack of simple biomarkers to predict the curative effect of anlotinib creates significant unmet needs in exploring the markers. This study aimed to explore the relationship between the prognostic nutritional index (PNI) and its variations and efficacy of anlotinib.

Methods: Data for patients with advanced NSCLC who received anlotinib were collected at Ningbo Medical Center Lihuili Hospital. The data included the values of pretreatment PNI (pre-PNI), posttreatment PNI (post-PNI), and ΔPNI (post-PNI minus the pre-PNI). The Kaplan–Meier method was used to generate survival curves, whereas univariate and multivariate Cox regression analyses were used to analyze survival predictors.

Results: A high disease control rate was associated with a high pre-PNI ($p = 0.007$), high post-PNI ($p = 0.000$), and high ΔPNI ($p = 0.006$). Univariable analysis revealed that pre-PNI ≤41.80, post-PNI ≤42.48, and ΔPNI ≤0.20 were significant risk factors for poor survival. According to the multivariate analysis, progression-free survival (PFS) in patients with post-PNI ≤42.48 was significantly shorter than in patients with higher values (median PFS: 1.5 months vs. 4.0 months, $p = 0.010$).

Conclusions: Pre-PNI, ΔPNI, and post-PNI were found to be predictive factors for response in advanced NSCLC patients treated with anlotinib as a third-line or further treatment. Only post-PNI was a reliable predictor of PFS. Therefore, PNI and its variations, particularly post-PNI, are affordable and accessible predictors of NSCLC patients treated with anlotinib in clinical work.

KEYWORDS
anlotinib, non-small-cell lung cancer, prognostic factor, prognostic nutritional index, treatment response

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1 | BACKGROUND

Lung cancer is the second most prevalent and the leading cause of cancer deaths worldwide, accounting for 13% of all cancer diagnoses and 23% of all cancer-related deaths. Non-small-cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases, and most of them present with advanced metastatic disease with a 5-year overall survival (OS) rate of only 5%–20%.[1,2] The rapid development in systemic therapy such as chemotherapy, targeted therapy, and immunotherapy, as well as advances in local treatment including intensity modulate radiation therapy have considerably prolonged the survival time and enhanced the quality of life of advanced NSCLC patients. Meanwhile, those improvements make anti-tumor therapy as an exclusive support treatment to be necessary after two or more recommended standard treatment lines.

The Chinese Society of Clinical Oncology (CSCO) has approved anlotinib as a third-line therapy for advanced NSCLC. Anlotinib is a novel tyrosine kinase inhibitor (TKI) that acts on tumor angiogenesis and proliferating signal.[3] A random multicenter phase III study (ALTER0303)[4] reported that when compared to a control, anlotinib is associated with a 4-month increase in median progress rate (mPFS), and a 3.3-months improvement in median overall survival (mOS). The most common grade three or higher adverse events among the anlotinib group were hypertension, hyponatremia, and elevated γ-glutamyltransferase. However, these events were always regulated appropriately within safety limits, implying that anlotinib is a safe and effective target drug for third-line or further therapy. The efficacy of anlotinib, as a multiple target drug, differentiates it from the single-target EGFR-TKI. The shortest response duration for patients who reached the disease control rate (DCR) in the ALTER0303 trial was 1.5 months, and the longest response duration was at least 18 months. Furthermore, post-third-line therapy treatment in advanced NSCLC is so different from the original treatment that patients need new drugs that are both safer and more effective. Therefore, it is critical to identify a viable and excellent predictor to assist in identifying patients who will benefit most from anlotinib monotherapy. Wang et al. reviewed and analyzed the prognostic factors of the ALTER0303 trial and concluded that the common adverse reactions of anlotinib treatment were closely related to patient prognosis.[5] Previous studies have shown that certain elements, such as CD31-labeled activated circulating endothelial cells, KLK5, and L1CAM levels, may be potential biomarkers for effectively predicting anlotinib in NSCLC patients.[6,7] However, the lack of certain simple and convenient biomarkers to predict the curative effect in patients treated with anlotinib creates significant unmet needs in exploring markers to predict the clinical outcomes of anlotinib.

Nutrition and immune status are now well understood to play critical roles in disease progression and treatment response in various cancer patients.[8-10] The prognostic nutritional index (PNI), first proposed by Onodera T[11] in 1984, is the most recommended marker of immunonutrition status to predict treatment response and prognosis in a variety of cancers, including lung cancer.[12-17] Because PNI is calculated by combining the serum albumin levels and serum lymphocyte count, it can be easily measured using relatively inexpensive and convenient tests. Numerous articles[14,18-21] have been published on the relationship between pretreatment PNI and the prognosis of NSCLC chemoradiotherapy, surgery, and immunotherapy. Furthermore, researchers believe that pretreatment PNI (pre-PNI) is a useful biomarker for predicting the prognosis of patients with advanced-stage small-cell lung cancer who are being treated with anlotinib.[22] However, we found no reports on the predictive value of PNI and its variations in advanced NSCLC patients treated with anlotinib.

In this study, we retrospectively analyzed the prognostic and predictive role of PNI and its variations in advanced NSCLC patients receiving anlotinib as a third-line or further treatment. The aim was to stratify and select individual markers that are potentially reliable and convenient for patients.

2 | METHODS

2.1 | Patient selection and data collection

We retrospectively reviewed the data of patients with advanced NSCLC who received anlotinib as the third-line or further treatment at Ningbo Medical Center Lihuili Hospital from July 2018 to December 2020, with an initial oral dose of 10–12 mg/day. In case of dangerous treatment-related activities, the dose of anlotinib was reduced to 8–10 mg daily. A total of 96 patients were enrolled. The inclusion criteria were as follows: i. Pathological diagnosis of stage IV NSCLC (recurrent or metastatic); ii. conventional standard for receiving two standard system therapy plans; iii. treatment with anlotinib as a monotherapy for more than two weeks; and iv. serum albumin and serum lymphocyte count data were taken immediately before treatment and 2–4 weeks after treatment. We calculated PNI as serum albumin (g/L) $+5 \times$ serum lymphocyte count ($\times 10^9$ /L). Pre-PNI was defined as the period within two weeks before treatment, whereas posttreatment PNI (post-PNI) was within two to four weeks after treatment. The difference between post-PNI and pre-PNI was considered ΔPNI.

2.2 | Therapeutic response assessment and follow-up

Follow-up evaluation, including B-ultrasound and computed tomography, was performed three or six weeks after anlotinib administration, according to the solid tumor efficacy evaluation criteria (RECIST). Systemic check was performed per every two cycles of anlotinib treatment. Diagnostic tests were performed whenever recurrence was suspected. Disease control rate (DCR) was defined as the percentage of evaluated patients who achieved complete response (CR), partial response (PR), and stable disease (SD). Regardless of the

cause or the end of the follow-up period, objective response rate (ORR) was defined as the percentage of patients assessing CR and PR and calculated as overall survival (OS) from the start of treatment until death. Progression-free survival (PFS) was defined as the time from the beginning of treatment to progression or the last follow-up.

2.3 | Statistical analysis

Statistical analysis was conducted using SPSS (Version 26.0, IBM). The best cutoff values for the receiver operating characteristic (ROC) curves of pre-PNI, post-PNI, and ΔPNI were determined for progression results. Survival curves were drawn using Fisher's exact or Chi-square test and Kaplan–Meier method. Any differences were determined using univariable and multivariable Cox regression. Variables with a *P* value of <0.1 in the univariable analysis were considered for inclusion in the multivariable logistic regression model. The statistical significance threshold was set as $p < 0.05$.

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics are summarized in Table 1. The major driver of change was EGFR mutations, which were found in 15 (15.6%) of the 96 patients. The ECOG score was more than two in 30 (31.3%) patients. Except for adenocarcinoma and squamous cell carcinoma, two cases were pathologically diagnosed as adenosquamous in nature. The majority of patients (76.9%) were taking 12 mg of anlotinib daily.

The median follow-up period was 6.2 months (ranging from 1.1 to 22.4 months), and by the end of the period, 76 (79.2%) patients had died, and all the patients had a relapse. Six (6.3%), 59 (61.4%), and 31 (32.3%) patients achieved PR, SD, and PD, respectively. None of the patients achieved a CR. DCR and ORR were obtained by 67.7% and 6.3% patients, respectively. The median PFS and OS for all patients were 2.5 and 6.4 months, respectively.

3.2 | Optimal cutoff values for pre-PNI, post-PNI, and ΔPNI

The ROC curves were used to determine the optimal threshold for pre-PNI, post-PNI, and ΔPNI for all patients in this study. The optimal cutoff value for pre-PNI was 41.80, and the area under the curve (AUC) was 0.650 ($p = 0.018$, 95% CI: 0.533–0.767), with sensitivity and specificity of 0.708 and 0.419, respectively. The optimal cutoff value for post-PNI was 42.48, with an AUC of 0.793 ($p = 0.000$, 95% CI: 0.699–0.886), sensitivity of 0.692, and specificity of 0.194. The optimal cutoff value for ΔPNI was 0.20, with an AUC of 0.652 ($p = 0.016$, 95% CI: 0.533–0.772), sensitivity of 0.523, and specificity of 0.226. The ROC curves are presented in Figure 1A–C.

TABLE 1 Characteristics of the patients

Characteristics	Patients (%)
Age (years)	
Median	61
Range	32–84
<65	60 (62.5%)
≥65	36 (37.5%)
Gender	
Male	74 (77.1%)
Female	22 (22.9%)
Performance status (ECOG)	
0–1	66 (68.8%)
2–3	30 (31.2%)
Pathology	
Adenocarcinoma	46 (47.9%)
Squamous carcinoma and others	48 (50.0%)
Adenosquamous	2 (2.1%)
Driver gene EGFR/ c-met	
Mutant type	16 (16.7%)
Wild type	80 (83.3%)
Metastasis sites	
≤3	51 (53.1%)
>3	45 (46.9%)
History of tumor surgery	
Yes	42 (43.8%)
No	54 (56.2%)
Number of previous treatment lines	
3	56 (58.3%)
>3	40 (41.7%)

3.3 | Correlation between prognostic nutritional index variations and clinicopathological parameters and treatment response

Fifty-nine (61.5%) patients had a high pre-PNI >41.80, whereas the remaining had a pre-PNI ≤41.80. Fifty-one (53.1%) patients had a high post-PNI >42.48, whereas 45 (46.9%) patients had a post-PNI ≤42.48. Furthermore, 41 (42.7%) patients had a high ΔPNI (> 0.20), whereas 55 (57.3%) had a low ΔPNI (≤0.20). A high DCR was correlated with a high pre-PNI ($p = 0.007$), high post-PNI ($p = 0.000$), and high ΔPNI ($p = 0.006$). However, there was no significant correlation between ORR and any of the indices. A detailed description of the analysis of the treatment response of the pre-PNI, post-PNI, and ΔPNI is provided in Tables 2 and 3.

3.4 | Factors associated with prognosis

The univariable analysis indicated that pre-PNI ≤41.80, post-PNI ≤42.48, and ΔPNI ≤0.20 were significant risk factors for poor PFS and

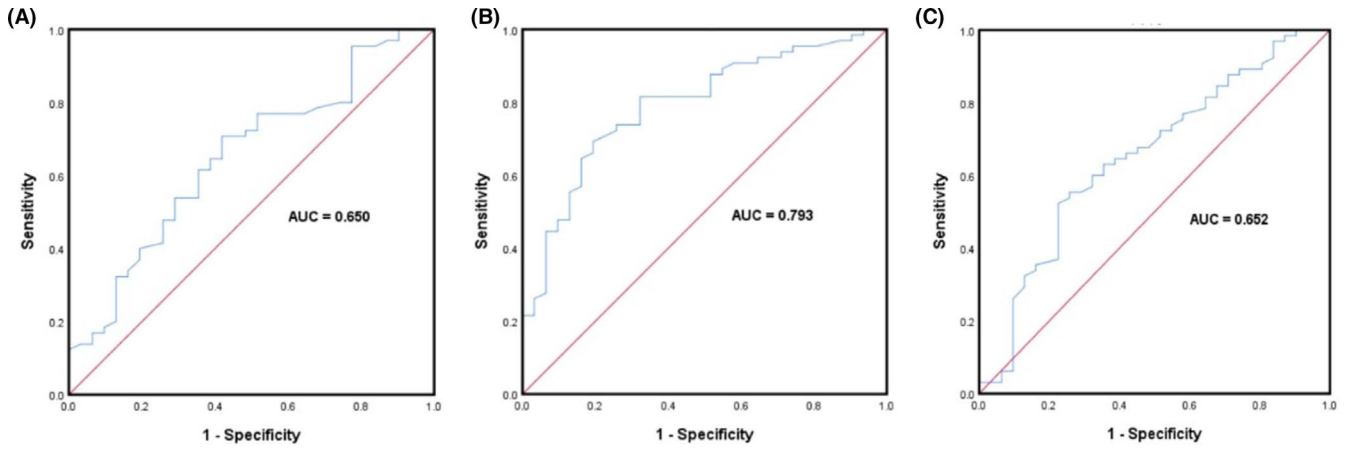

FIGURE 1 (A) Receiver operating curves for treatment response showing the optimum cutoff values for pre-PNI. (B) Receiver operating curves for treatment response showing the optimum cutoff values for post-PNI. (C) Receiver operating curves for treatment response showing the optimum cutoff values for ΔPNI.

TABLE 2 Association of pre-PNI, post-PNI, and ΔPNI with clinicopathological characteristics

	Pre-PNI			Post-PNI			ΔPNI		
Characteristics	**≤41.80**	**>41.80**	***p*-value**	**≤42.48**	**>42.48**	***p*-value**	**≤0.20**	**>0.20**	***p*-value**
Age (years)									
<65	22 (22.9%)	38 (39.6%)	0.626	26 (27.1%)	34 (35.4%)	0.369	36 (37.5%)	24 (25.0%)	0.489
≥65	15 (15.6%)	21 (21.9%)		19 (19.8%)	17 (17.7%)		19 (19.8%)	17 (17.7%)	
Gender									
Male	31 (32.3%)	43 (44.8%)	0.216	37 (38.5%)	37 (38.5%)	0.260	43 (44.8%)	31 (32.3%)	0.767
Female	6 (6.3%)	16 (16.6%)		8 (8.3%)	14 (14.7%)		12 (12.5%)	10 (10.4%)	
Pathology									
Adenocarcinoma	17 (17.7%)	29 (30.2%)	0.760	23 (24.0%)	23 (24.0%)	0.556	27 (28.1%)	19 (19.8%)	0.790
Squamous carcinoma and others	20 (20.8%)	30 (31.3%)		22 (22.9%)	28 (29.1%)		28 (29.2%)	22 (22.9%)	
Performance status									
0–1	28 (29.2%)	38 (39.6%)	0.246	34 (35.4%)	32 (33.3%)	0.177	41 (42.7%)	25 (26.0%)	0.156
2–3	9 (9.4%)	21 (21.8%)		11 (11.5%)	19 (19.8%)		14 (14.6%)	16 (16.7%)	
Driver gene EGFR/ALK/c-met									
Mutant type	5 (5.2%)	11 (11.5%)	0.512	6 (6.3%)	10 (10.4%)	0.410	9 (9.4%)	7 (7.3%)	0.926
Wild type	32 (33.3%)	48 (50.0%)		39 (40.6%)	41 (42.7%)		46 (47.9%)	34 (35.4%)	
Number of metastases									
≤3	21 (21.9%)	30 (31.3%)	0.572	26 (27.1%)	25 (26.0%)	0.391	33 (34.4%)	18 (18.8%)	0.118
>3	16 (16.7%)	29 (30.1%)		19 (19.8%)	26 (27.1%)		22 (22.9%)	23 (23.9%)	
History of tumor surgery									
No	21 (21.9%)	33 (34.4%)	0.937	27 (28.1%)	27 (28.1%)	0.487	30 (31.3%)	24 (25.0%)	0.697
Yes	16 (16.7%)	26 (27.0%)		18 (18.8%)	24 (25.0%)		25 (26.0%)	17 (17.7%)	
Number of previous treatment lines									
3	20 (20.8%)	36 (37.5%)	0.501	24 (25.0%)	32 (33.3%)	0.351	30 (31.3%)	26 (27.1%)	0.383
>3	17 (17.7%)	23 (24.0%)		21 (21.9%)	19 (19.8%)		25 (26.0%)	15 (15.6%)	

OS (Table 4). Patients with pre-PNI >41.80 had significantly longer mPFS (3.8 months vs. 2.0 months, HR: 0.579, 95% CI: 0.380–0.881, $p = 0.011$; Figure 2A) and mOS (7.9 months vs. 4.4 months, HR: 0.457, 95% CI: 0.289–0.722, $p = 0.001$; Figure 2B) than other patients. In patients with post-PNI >42.48, mPFS (4.0 months vs. 1.5 months, HR: 0.406, 95% CI: 0.265–0.623, $p = 0.000$; Figure 3A) and mOS (10.4 months vs. 4.4 months, HR: 0.376, 95% CI: 0.236–0.598, $p = 0.000$; Figure 3B) were significantly longer than in patients with

TABLE 3 Associations of pre-PNI, post-PNI, and ΔPNI with treatment response

Treatment response	pre-PNI			post-PNI			ΔPNI		
	≤41.80	>41.80	*p*-value	≤42.48	>42.48	*p*-value	≤0.20	>0.20	*p*-value
PR	2 (2.1%)	4 (4.2%)	0.025	1 (1.0%)	5 (5.2%)	0.000	4 (4.2%)	2 (2.1%)	0.012
SD	17 (17.7%)	42 (43.8%)		19 (19.8%)	40 (41.7%)		27 (28.1%)	32 (33.3%)	
PD	18 (18.8%)	13 (13.4%)		25 (26.0%)	6 (6.3%)		24 (25.0%)	7 (7.3%)	
ORR	2.1%	4.2%	1.000	1.0%	5.2%	0.209	4.2%	2.1%	1.000
DCR	19.8%	47.9%	0.007	20.8%	46.9%	0.000	32.3%	35.4%	0.006

TABLE 4 Univariable analysis of factors associated with progression-free survival and overall survival

	Progression-free survival			Overall survival		
Prognostic factors	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)						
<65	1			1		
≥65	0.974	0.639–1.484	0.902	0.987	0.644–1.515	0.954
Gender						
Female	1			1		
Male	1.169	0.721–1.893	0.527	1.157	0.713–1.878	0.555
Pathology						
Squamous carcinoma and others	1			1		
Adenocarcinoma	0.847	0.555–1.292	0.440	0.855	0.558–1.311	0.473
Performance status						
0–1	1			1		
2–3	1.020	0.659–1.579	0.929	1.041	0.669–1.619	0.860
Driver gene EGFR/c- met						
Wild type	1			1		
Mutant type	1.175	0.684–2.017	0.559	1.184	0.685–2.046	0.545
Metastasis sites						
≤3	1			1		
>3	0.993	0.663–1.488	0.974	0.910	0.561–1.477	0.704
History of tumor surgery						
No	1			1		
Yes	0.887	0.590–1.335	0.567	0.844	0.521–1.368	0.492
Number of previous treatment lines						
3	1			1		
>3	1.022	0.679–1.540	0.915	1.006	0.662–1.530	0.976
pre-PNI						
≤41.80	1			1		
>41.80	0.579	0.380–0.881	0.011	0.457	0.289–0.722	0.001
post-PNI						
≤42.48	1			1		
>42.48	0.406	0.265–0.623	0.000	0.376	0.236–0.598	0.000
ΔPNI						
≤0.20	1			1		
>0.20	0.673	0.445–1.017	0.045	0.558	0.347–0.897	0.016

lower post-PNI values. Patients with ΔPNI >0.20 had significantly longer mPFS (3.0 months vs. 2.1 months, HR: 0.673, 95% CI: 0.445–1.017, $p = 0.045$; Figure 4A) and mOS (7.9 months vs. 5.8 months, HR: 0.558, 95% CI: 0.347–0.897, $p = 0.016$; Figure 4B) than those with ΔPNI ≤0.20. According to the multivariable analysis, post-PNI ≤42.48 was the only independent risk factor for poor PFS ($p = 0.010$). It also showed a clear trend in poor OS, but it was not statistically significant ($p = 0.077$). Accordingly, pre-PNI ≤41.80 and ΔPNI ≤0.20 were not independent risk factors for PFS or OS (Table 5).

4 | DISCUSSION

Numerous studies indicate that inflammation plays as an important role in tumorigenesis and development.[23,24] Serum albumin, which reflects the nutritional status, has been associated with inflammation and is considered to predict survival in several types of cancers.[25-28] Lymphocytes act as the basic cells of the immune system, which include humoral and cellular immunity, and they are effective against tumor cells.[23] Furthermore, the lymphocyte level is linked to the treatment efficacy and prognosis in a variety of tumors.[29-32] Moreover, VEGF/VEGFR axis is considered relevant in regulating multiple tumor-infiltrating lymphocytes that contain CD4+, CD8 + Treg.[33-36] Anlotinib is a small multi-target tyrosine kinase inhibitor of VEGFR1-3, FGFR1-4, and PDGFRα-β, among others. Among these, VEGFR is the most important inhibitory target.[37,38] Due to the aforementioned reasons, we focused on PNI in NSCLC patients who received anlotinib treatment in this study.

In comparison with the ALTER0303 study, this research exhibited a slightly worse outcome in DCR (67.7%) and survival (mOS 6.4 months). We speculate that the reasons for this discrepancy are due to more advanced disease, worse ECOG scores, and

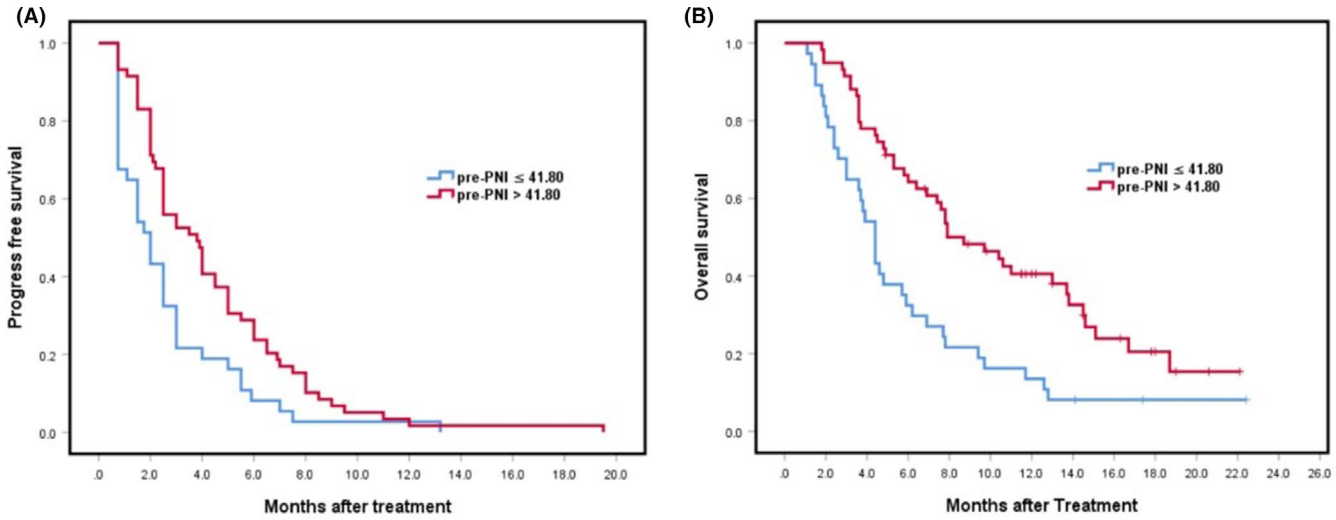

FIGURE 2 (A) Association of pre-PNI (≤41.80 vs. >41.80) with progression-free survival ($p = 0.011$). (B). Association of pre-PNI (≤41.80 vs. >41.80) with overall survival ($p = 0.001$).

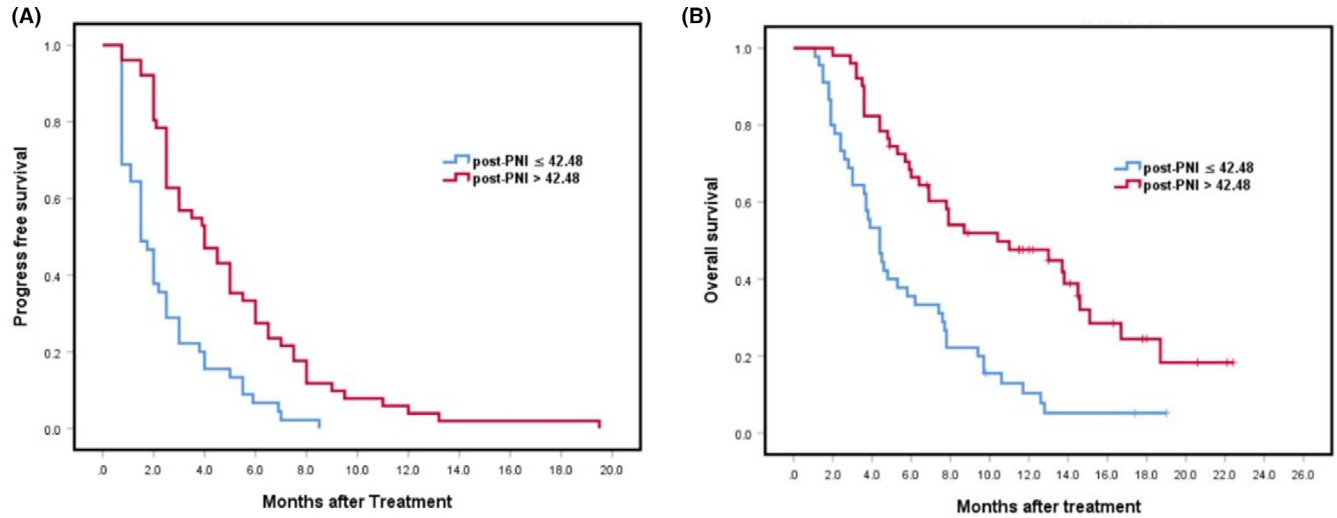

FIGURE 3 (A) Association of post-PNI (≤42.48 vs. >42.48) with progression-free survival ($p = 0.000$). (B) Association of post-PNI (≤42.48 vs. >42.48) with overall survival ($p = 0.000$).

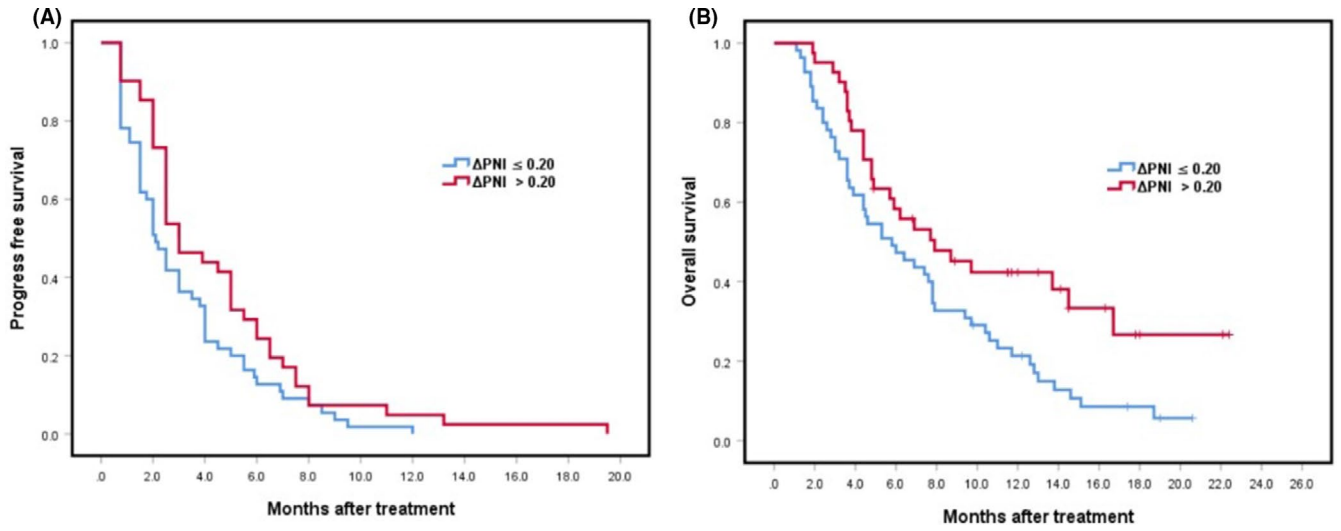

FIGURE 4 (A) Association of ΔPNI (≤0.20 vs. >0.20) with progression-free survival ($p = 0.045$). (B) Association of ΔPNI (≤0.20 vs. >0.20) with overall survival ($p = 0.016$).

TABLE 5 Multivariable analysis of factors associated with progression-free survival and overall survival

Prognostic factors	Progression-free survival			Overall survival		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Pre-PNI (≤41.80 vs. >41.80)	0.803	0.484–1.333	0.396	0.596	0.340–1.044	0.070
Post-PNI (≤42.48 vs. >42.48)	0.477	1.036–2.603	0.010	0.569	0.304–1.063	0.077
ΔPNI (≤0.20 vs. >0.20)	0.871	1.268–2.477	0.577	0.686	0.393–1.196	0.184

posterior line therapy in our study. Jingjing Liu et al.[22] discovered a link between anlotinib treatment response and pre-PNI in SCLC. In this study, based on the optimal cutoff values calculated from ROC curves, we noticed a similar connection between the anlotinib treatment response and the pre-PNI in NSCLC, as well as the post-PNI and ΔPNI. Therefore, PNI was considered to be a better clinical index for predicting the treatment response to anlotinib therapy in lung cancer. Our results uncovered that pre-PNI, post-PNI, and ΔPNI had prognostic values for prognosis based on the univariable analysis. However, pre-PNI ≤41.80 and ΔPNI ≤0.20 were not independent risk factors for PFS or OS according to the multivariable analysis. Post-PNI ≤42.48 was shown to be an independent novel prognostic marker for mPFS (1.5 months vs. 4.0 months, $p = 0.010$). Unfortunately, the difference in OS was statistically insignificant (4.4 months vs. 10.4 months, $p = 0.077$), which may be due to various artificial uncontrollable factors such as irregular PNI cutoff values, individual differences in nutritional status, diseases, and others. Therefore, post-PNI may be the most appropriate clinical index to predict the prognosis of anlotinib among the three elements. Notably, the independent prognostic relevance of PNI in advanced NSCLC patients receiving anlotinib monotherapy has not been carried out before this study.

The best cutoff value cannot be expressed simply as a median or average number because of the different diseases, patients, and treatments. At present, a majority of studies have selected a relative specific population based on the ROC curves, while discovering a variety of cutoff values from different therapies. Yakup Bozkaya et al.[19] reported that patients with pre-PNI ≥46.7 had a better OS in palliative chemotherapy for advanced NSCLC. However, the significant cutoff value of pre-PNI varied in surgery (48.0), radiochemotherapy (40.5), and immunotherapy (46.05).[18,20,21] This study focused on patients with advanced NSCLC who were treated with anlotinib and determined that the best cutoff values of pre-PNI and post-PNI were 41.80 and 42.48, respectively.

This research has certain limitations. First, our cohort was a single-center retrospective in nature with a relatively limited sample size, which may lead to bias. When there were not so many independent variables and the sample size was not so large, it was more suitable for the logistic analysis of this research. Like other similar studies,[39,40] it ensured the accuracy of statistical methods and further reduced bias. Second, the lack of an independent verification group resulted in an imperfect clinical application of the cutoff values. However, these studies[21,22] lacking such verification were also persuasive at present. Finally, different initial treatments and follow-up treatments or lack of, and other unknown elements may potentially result in different outcomes. We analyzed that there was no significant difference in the general characteristics including surgery or not and third-line or further lines, so as to reduce the unavoidable bias of such retrospective studies, as did some other studies.[21,41] Despite these limitations, this is the first study, to the best of

our knowledge, to evaluate the therapeutic response and prognostic significance of PNI and its variations in third-line or further anlotinib therapy for advanced NSCLC patients. We have also demonstrated post-expected value of PNI on the regimen.

5 | CONCLUSION

This study showed that post-PNI status is an independent predictor of PFS in patients with advanced NSCLC who receive anlotinib as their third-line or ongoing treatment, whereas neither pre-PNI nor ΔPNI is a predictor. Except for pre-PNI, the results indicated that ΔPNI and post-PNI are predictive factors for responsiveness to anlotinib as a third-line or further treatment in patients with advanced NSCLC. Therefore, for NSCLC patients treated with anlotinib in clinical work, PNI and its variations are affordable and accessible predictors, especially post-PNI. However, more studies are required to verify and support these conclusions.

ACKNOWLEDGEMENTS

The first author appreciates his beloved wife Chen Wang (Department of Gastroenterology, Ningbo Medical Center Lihuili Hospital) for supporting his work.

AUTHOR CONTRIBUTIONS

(I) Tian Chen and Mengqiu Tang contributed to conception and design. (II) Zhenfei Xiang contributed to administrative support. (III) Tian Chen and Gaofeng Liang contributed to provision of study materials or patients. (IV) Xiaoyu Xu contributed to collection and assembly of data. (V) Jinxian He contributed to data analysis and interpretation. (VI) All authors contributed to manuscript writing. (VII) All authors made final approval of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA: A Cancer J Clin*. 2020;70(1):7-30.
2. Arbour KC, Riely GJ. Systemic therapy for locally advanced and metastatic non-small cell lung cancer: a review. *JAMA*. 2019;322(8):764-774.
3. Sun Y, Niu W, Du F, et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. *J Hematol Oncol*. 2016;9(1):105.
4. Han B, Li K, Wang Q, et al. Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: the ALTER 0303 Phase 3 randomized clinical trial. *JAMA Oncol*. 2018;4(11):1569-1575.
5. Wang J, Zhao Y, Wang Q, et al. Prognostic factors of refractory NSCLC patients receiving anlotinib hydrochloride as the third- or further-line treatment. *Cancer Biol Med*. 2018;15(4):443-451.
6. Liu Z, Wang J, Meng Z, et al. CD31-labeled circulating endothelial cells as predictor in anlotinib-treated non-small-cell lung cancer: analysis on ALTER-0303 study. *Cancer Med*. 2018;7(7):3011-3021.
7. Lu J, Shi Q, Zhang L, et al. Integrated transcriptome analysis reveals KLK5 and L1CAM predict response to anlotinib in NSCLC at 3rd line. *Fron Oncol*. 2019;9:886.
8. Mayne ST, Playdon MC, Rock CL. Diet, nutrition, and cancer: past, present and future. *Nat Rev Clin Oncol*. 2016;13(8):504-515.
9. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity*. 2004;21(2):137-148.
10. Arrieta O, Michel Ortega RM, Villanueva-Rodríguez G, et al. Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: a prospective study. *BMC Cancer*. 2010;10:50.
11. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi*. 1984;85(9):1001-1005.
12. Sun K, Chen S, Xu J, et al. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol*. 2014;140(9):1537-1549.
13. Yang Y, Gao P, Song Y, et al. The prognostic nutritional index is a predictive indicator of prognosis and postoperative complications in gastric cancer: a meta-analysis. *Eur J Surg Oncol*. 2016;42(8):1176-1182.
14. Shoji F, Morodomi Y, Akamine T, et al. Predictive impact for postoperative recurrence using the preoperative prognostic nutritional index in pathological stage I non-small cell lung cancer. *Lung Cancer (Amsterdam, Netherlands)*. 2016;98:15-21.
15. Pinato DJ, North BV, Sharma R. A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: the prognostic nutritional index (PNI). *Br J Cancer*. 2012;106(8):1439-1445.
16. Kim KH, Hwang HK, Kang IC, et al. Oncologic impact of preoperative prognostic nutritional index change in resected pancreatic cancer following neoadjuvant chemotherapy. *Pancreatology*. 2020;20(2):247-253.
17. Hao J, Chen C, Wan F, et al. Prognostic value of pre-treatment prognostic nutritional index in esophageal cancer: a systematic review and meta-analysis. *Front Oncol*. 2020;10:797.
18. Ozdemir Y, Topkan E, Mertsoylu H, et al. Low prognostic nutritional index predicts poor clinical outcomes in patients with stage iiib non-small-cell lung carcinoma undergoing chemoradiotherapy. *Cancer Manage Res*. 2020;12:1959-1967.
19. Bozkaya Y, Köstek O, Sakin A, et al. Is the prognostic nutritional index a prognostic and predictive factor in metastatic non-small cell lung cancer patients treated with first-line chemotherapy? *Supp Care Cancer*. 2020;28(5):2273-2282.
20. Okada S, Shimada J, Kato D, et al. Clinical significance of prognostic nutritional index after surgical treatment in lung cancer. *Ann Thor Surg*. 2017;104(1):296-302.
21. Liu N, Jiang A, Zheng X, et al. Prognostic nutritional index identifies risk of early progression and survival outcomes in advanced non-small cell lung cancer patients treated with PD-1 INHIBITORS. *J Cancer*. 2021;12(10):2960-2967.
22. Liu J, Li S, Zhang S, et al. Pretreatment prognostic nutritional index is a prognostic marker for extensive-stage small cell lung cancer patients treated with anlotinib. *J Thorac Dis*. 2020;12(10):5765-5773.
23. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. *Nature*. 2008;454(7203):436-444.

24. Landskron G, De la Fuente M, Thuwajit P, et al. Chronic inflammation and cytokines in the tumor microenvironment. *J Immunol Res*. 2014;2014: 149185.
25. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. *Nutr J*. 2010;9:69.
26. Dalia S, Chavez J, Little B, et al. Serum albumin retains independent prognostic significance in diffuse large B-cell lymphoma in the post-rituximab era. *Ann Hematol*. 2014;93(8):1305-1312.
27. Wu M, Pan Y, Jia Z, et al. Preoperative plasma fibrinogen and serum albumin score is an independent prognostic factor for resectable stage II-III gastric cancer. *Dis Markers*. 2019;2019:9060845.
28. Blomstrand H, Green H, Fredrikson M, et al. Clinical characteristics and blood/serum bound prognostic biomarkers in advanced pancreatic cancer treated with gemcitabine and nab-paclitaxel. *BMC Cancer*. 2020;20(1):950.
29. Zhang J, Huang SH, Li H, et al. Preoperative lymphocyte count is a favorable prognostic factor of disease-free survival in non-small-cell lung cancer. *Med Oncol (Northwood, London, England)*. 2013;30(1):352.
30. Wild AT, Ye X, Ellsworth SG, et al. The association between chemoradiation-related lymphopenia and clinical outcomes in patients with locally advanced pancreatic adenocarcinoma. *Am J Clin Oncol*. 2015;38(3):259-265.
31. Fang P, Jiang W, Davuluri R, et al. High lymphocyte count during neoadjuvant chemoradiotherapy is associated with improved pathologic complete response in esophageal cancer. *Radiother Oncol*. 2018;128(3):584-590.
32. Davuluri R, Jiang W, Fang P, et al. Lymphocyte nadir and esophageal cancer survival outcomes after chemoradiation therapy. *Int J Radiat Oncol Biol Phys*. 2017;99(1):128-135.
33. Huang H, Langenkamp E, Georganaki M, et al. VEGF suppresses T-lymphocyte infiltration in the tumor microenvironment through inhibition of NF-κB-induced endothelial activation. *FASEB J*. 2015;29(1):227-238.
34. Malo CS, Khadka RH, Ayasoufi K, et al. Immunomodulation mediated by anti-angiogenic therapy improves CD8 T cell immunity against experimental glioma. *Front Oncol*. 2018;8:320.
35. Tada Y, Togashi Y, Kotani D, et al. Targeting VEGFR2 with Ramucirumab strongly impacts effector/ activated regulatory T cells and CD8(+) T cells in the tumor microenvironment. *J Immunother Cancer*. 2018;6(1):106.
36. de Aguiar RB, de Moraes JZ. Exploring the immunological mechanisms underlying the anti-vascular endothelial growth factor activity in tumors. *Front Immunol*. 2019;10:1023.
37. Shen G, Zheng F, Ren D, et al. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. *J Hematol Oncol*. 2018;11(1):120.
38. Cheng JD, Chai LX, Zhao ZP, et al. Efficacy and safety of anlotinib for patients with advanced NSCLC who progressed after standard regimens and the preliminary analysis of an efficacy predictor. *Cancer Manage Res*. 2020;12:5641-5650.
39. Roeleveld PP, Guijt D, Kuijper EJ, et al. Ventilator-associated pneumonia in children after cardiac surgery in The Netherlands. *Intensive Care Med*. 2011;37(10):1656-1663.
40. Uema D, Alves C, Mesquita M, et al. Carcinoid heart disease and decreased overall survival among patients with neuroendocrine tumors: a retrospective multicenter latin american cohort study. *J Clin Med*. 2019;8(3):405.
41. Diem S, Schmid S, Krapf M, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer (Amsterdam, Netherlands)*. 2017;111:176-181.

How to cite this article: Chen T, Liang G, Xiang Z, He J, Xu X, Tang M. Prognostic value of prognostic nutritional index and its variations in advanced non-small-cell lung cancer patients treated with anlotinib monotherapy. *J Clin Lab Anal*. 2022;36:e24300. doi:10.1002/jcla.24300