Original Article

A novel inflammatory nutrient index for predicting survival outcomes in patients with non-small cell lung cancer

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Background: Lung cancer is one of the most common contributors to cancer-related deaths worldwide. This study aimed to develop a new blood index on the basis of the patient's systemic inflammation and nutritional status, which can be used to predict the prognosis of patients with non-small cell lung cancer (NSCLC).

Methods: Pre-treatment blood markers were analyzed in 556 NSCLC patients from 2010 to 2019. A least absolute shrinkage and selection operator (LASSO) method was used to select indicators to establish a new integrated biomarker (PNAGR). Kaplan-Meier survival curves were used to assess the prognostic impact of platelet-to-lymphocyte ratio (PLR), albumin (ALB), and the PNAGR. The prognostic value was verified using univariate and multivariate Cox analyses.

Results: We used four biomarkers including PLR, ALB, 1/albumin-to-globulin ratio (1/AGR), and neutrophil/albumin-to-globulin ratio (N/AGR) were used to screen for the PNAGR using LASSO. Patients with high PNAGR demonstrated lower overall survival (OS) compared to those with low PNAGR. In both univariate and multivariate analyses, PNAGR was revealed as an independent prognostic factor for OS. The predictive power of PNAGR [area under the curve (AUC): 0.753] was higher than that of the metrics alone.

Conclusions: PNAGR is a novel and effective clinical prognostic tool with good clinical predictive value for NSCLC patients.

Keywords: Non-small cell lung cancer (NSCLC); overall survival (OS); PNAGR

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Introduction

According to the latest global epidemiological data for lung cancer, it is estimated that there would be 2.2 million new cases and 1.8 million deaths in 2020, indicating that lung cancer remains one of the most common cancer-related deaths worldwide (1,2). Non-small cell lung cancer (NSCLC) is the most common pathological subtype of lung cancer, accounting for approximately 85% of all lung cancer cases (3). The continuous development of immunotherapy and targeted therapy for lung cancer provides a guiding direction for optimizing clinical treatment and improves the prognosis of patients to a certain extent (4). However, the prognosis of NSCLC remains poor, as most patients have reached terminal stages by their initial diagnosis (5). Furthermore, the current tumor, node, metastasis (TNM) staging system is the most commonly used parameter in treatment decision-making and predicting outcomes in NSCLC patients; however, it does not take into account the biological diversity of tumors, which leads to heterogeneous treatment outcomes in patients with the same TNM

staging. Therefore, it is urgent to accurately prognostically assess needs via more valid biomarkers.

Carcinogenesis is a chronic inflammatory process; the inflammatory microenvironment is significant in various tumor biology aspects, and there is a strong association between systemic inflammation response and mortality in advanced patients (6). Lymphocytes, neutrophils (N), monocytes (M), and platelets (PLT), as important components of inflammatory factors in the tumor microenvironment, are important in the development and prognosis of common tumors (7). Several studies have demonstrated that biomarkers, including neutrophil-to-lymphocyte ratio (NLR) (8), platelet-to-lymphocyte ratio (PLR) (9), systemic immune-inflammation index (SII) (10), and systemic inflammation response index (SIRI) (11), predict the NSCLC prognosis, yet there is still a lack of a prognostic assessment tool encompassing other significant factors. Nutritional status affects key cellular and molecular processes underlying cancer phenotypes, and malnutrition can cause muscle loss and cachexia, as well as impair tolerance and response to cooperative antitumor therapy, increasing the risk of treatment interruption, and decreasing survival (12). Multiple studies have shown that malnutrition is very prevalent in NSCLC patients and pervasive across disease and treatment trajectories (13,14). Several recent findings have shown that prognostic nutritional index (PNI) (15), albumin (ALB) (16), and albumin-to-globulin ratio (AGR) score (17) are as closely related to the prognosis of NSCLC as they are to numerous other solid tumors. Therefore, this study proposed to construct a novel prognostic indicator, PNAGR, according to the integration of inflammatory markers and nutritional scores, clinical significance was evaluated in NSCLC patients, yielding valuable research evidence was provided for the NSCLC management in the prediction and decision-making personal aspects. We present this article in accordance with the STARD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-91/rc).

Highlight box

Key findings

- The PNAGR is a novel and effective clinical prognostic tool for non-small cell lung cancer (NSCLC) patients.

What is known and what is new?

- Lung cancer remains one of the most common cancer-related deaths worldwide.
- The PNAGR is associated with prognostic significance for NSCLC patients.

What is the implication, and what should change now?

- By using the least absolute shrinkage and selection operator method to establish a new comprehensive biomarker (PNAGR), we are expected to find that it has good clinical predictive value for NSCLC patients and provide new strategies and methods for the prognosis of NSCLC.

Methods

Participants

We retrospectively collected patients diagnosed with NSCLC from January 2010 to December 2019 in Qingdao Municipal Hospital. The inclusion criteria were as follows: (I) pathologically diagnosed with NSCLC in Qingdao Municipal Hospital; (II) complete clinical, pathological, and imaging data. The exclusion criteria were as follows: (I) significant infection in the last month or receiving anti-inflammatory treatment in the month before enrollment; (II) combining with serious heart, liver, kidney, and blood system diseases; (III) combining with other tumors; (IV) key Information missing and loss to follow-up surveys. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Qingdao Municipal Hospital (No. 2022yxy077) and individual consent for this retrospective analysis was waived.

Data collection

The hospital collected clinical and laboratory data from the patients and used routine blood tests to measure the N, lymphocyte, PLT, M, hemoglobin (Hb), ALB, and globulin (GLB) counts of the patients during the week before diagnosis. We calculated NLR, derived NLR (dNLR), PLR, derived PLR (dPLR), lymphocyte-to-monocyte ratio (LMR), SII, SIRI, PNI, 1/albumin-to-globulin (1/AGR), and neutrophil/albumin-to-globulin ratio (N/AGR).

Case follow-up

Follow-up began on the date of diagnosis and ended on 31 December 2021. Follow-up methods included outpatient or inpatient review and telephone follow-up. Follow-up included follow-up treatment, outcome, recurrence, and time to death. The definition of overall survival (OS) was

the period from diagnosis until death from any other cause or the last follow-up visit. The median follow-up duration was 41.34 months, and 261 (about 46.9%) patients had died by the end of the study.

Statistical analysis

The software of the least absolute shrinkage and selection operator (LASSO) and R was applied the "glmnet" package to screen the most beneficial hematological prognostic utility, then these were further invested for the PNAGR constructed with respective LASSO regression coefficients. PLR, ALB, N/AGR, 1/AGR, and optimal threshold values for PNAGR were selected through X-tile software (Rimm Lab, Yale School of Medicine, New Haven, CT, USA). Kaplan-Meier survival analysis was applied for survival curves plotted, and the log-rank test was employed to compare survival between different groups. The predictive value of PLR, ALB, 1/AGR, N/AGR, and PNAGR for OS was assessed using receiver operating characteristic (ROC) curves. Univariate and multivariate regression analyses were conducted to screen for independent prognostic factors. The analysis and plotting of data were performed with SPSS 26.0.1 (IBM Corp., Armonk, NY, USA), Graph Pad Prism 7.1.0 (GraphPad Software, San Diego, CA, USA), and R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was determined at P<0.05.

Results

General characteristics of the study population

The baseline data of 556 patients with lung cancer were included, covering the demographic data of the patients and the corresponding mortality outcomes. The 556 patients included 339 males (60.9%) and 217 females (39.0%), with a mean age of 62 years (range, 56–67 years). The columns labeled "Outcomes" in *Table 1* show the number of people in the mortality group and their proportion in the corresponding category. A total of 261 patients died, of whom 192 (73.56%) were male, 182 (69.7%) were diagnosed with adenocarcinoma, and the maximum tumor diameter was 4.4 cm (range, 3.2–6 cm). Additionally, 84.6% of patients had already progressed at their initial diagnosis. This included 81 (31.0%) patients at the III stage and 140 (53.6%) patients at the IV stage, which accounted for a large proportion of the deaths. Meanwhile, we listed the blood indicators such as WBC count, N, M, PLT, ALB, Hb, and GLB, which are detailed in *Table 1*.

Correlation analysis of blood indicators

Firstly, we performed a correlation analysis of 20 pre-treatment blood indicators; *Figure 1* demonstrates the degree of correlation between each blood indicator, and the significance is reflected by the color shades. Among them, N and WBC [correlation coefficient (Cor) =0.91, P<0.001], N and neutrophil × albumin to hemoglobin (NA/Hb) (Cor =0.93, P<0.001) showed high correlation. The results of the test showed a significant correlation between preoperative N and SII (Cor =0.80, P<0.001), SIRI (Cor =0.80, P<0.001), NLR (Cor =0.77, P<0.001), dNLR (Cor =0.78, P<0.001), N/AGR (Cor =–0.83, P<0.001), and neutrophils × monocytes to (albumin-to-globulin ratio) (NM/AGR) (Cor =0.83, P<0.001).

Then, the optimal lambda value was determined according to a LASSO Cox regression model, and the value was found at the smallest lambda minimum mean square error (*Figure 2A*,*2B*). Indicators with non-zero coefficients were screened among the 20 predictor variables as ALB, GLB/ALB, PLR, and NA/Hb (*Table 2*). Thus, the composite indicator PNAGR was expressed as PNAGR = (−0.022192924 × ALB) + (1.784334721 × 1/AGR) + (0.002003093 × PLR) − (2.460231314 × N/AGR). Based on this formula, the best cut-off values for PNAGR indices obtained from X-tile software were used as 0.8.

Association between PNAGR and clinicopathological features

A total of 469 [84.03% (males, 267; females, 202)] patients showed low PNAGR, and 87 [15.7% (males, 72; females, 15)] patients showed high PNAGR. PNAGR was significantly correlated with gender, age, pathological classification, smoking, metastasis, stage, WBC, the count among N, M, and PLT types, ALB, Hb, and GLB were significantly correlated (*Table 3*).

Impact of preoperative blood markers on patient prognosis

The assessment of each biomarker prognostic value indicated that patients with high PNAGR levels had worse OS compared to those with low PNAGR values (P<0.001, *Figure 3A*). Similarly, lung cancer patients with high 1/AGR and PLR values had lower OS rates (P<0.001, *Figure 3B*,*3C*). Patients

Table 1 Baseline characteristics of all patients

Characteristics	Patients (n=556)	Outcomes (n=261)	P value
Sex, n (%)			<0.001
Female	217 (39.03)	69 (26.44)	
Male	339 (60.97)	192 (73.56)	
Age (years), n (%)			0.04
<60	229 (41.19)	88 (33.72)	
≥60	327 (58.81)	173 (66.28)	
Pathological classification, n (%)			0.006
Adenocarcinoma	437 (78.60)	182 (69.73)	
Non-adenocarcinoma	119 (21.40)	79 (30.27)	
History of smoking, n (%)			0.04
No	306 (55.04)	123 (47.13)	
Yes	250 (44.96)	138 (52.87)	
Metastasis, n (%)			<0.001
M0	393 (70.68)	121 (46.36)	
M1	163 (29.32)	140 (53.64)	
Tumor location, n (%)			0.64
U	308 (55.40)	140 (53.64)	
M/L	248 (44.60)	121 (46.36)	
Stage, n (%)			<0.001
I	184 (33.09)	10 (3.83)	
II	84 (15.11)	30 (11.49)	
III	126 (22.66)	81 (31.03)	
IV	162 (29.14)	140 (53.64)	
Tumor diameter, cm, median [IQR]	3.2 [1.8, 5]	4.4 [3.2, 6]	<0.001
WBC, 10^9/L, median [IQR]	6.61 [5.3775, 8.29]	7.4 [6.22, 8.75]	<0.001
N, 10^9/L, median [IQR]	3.97 [2.9675, 5.245]	4.72 [3.84, 5.94]	<0.001
M, 10^9/L, median [IQR]	0.44 [0.33, 0.56]	0.5 [0.38, 0.63]	<0.001
PLT,10^9/L, median [IQR]	238 [193.75, 296.5]	268 [213, 326]	<0.001
ALB, g/L, median [IQR]	39.405 [36.288, 42.38]	38.05 [34.67, 41.09]	<0.001
Hb, g/L, median [IQR]	135.5 [123.75, 145]	133 [121, 144]	0.11
GLB, g/L, median [IQR]	28.945 [25.98, 32.712]	30.14 [26.46, 33.7]	0.02

U, upper; M/L, middle/lower; IQR, interquartile range; WBC, white blood cell; N, neutrophil; M, monocyte; PLT, platelet; ALB, albumin; Hb, hemoglobin; GLB, globulin.

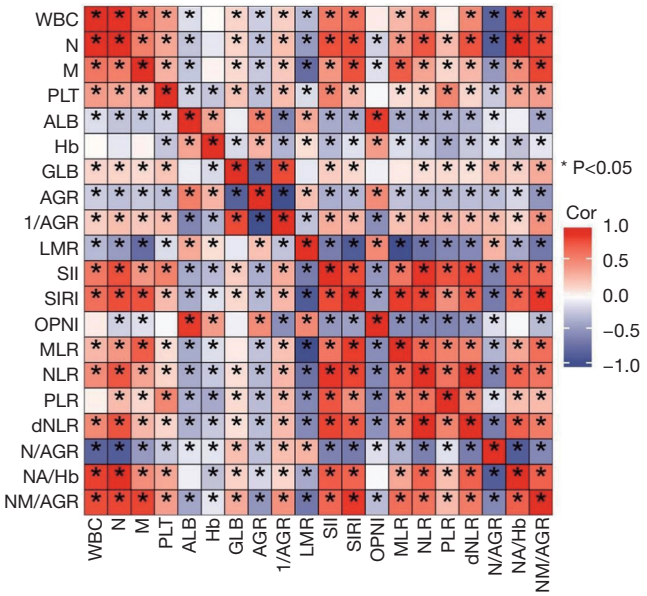

Figure 1 Correlation heatmap of 20 hematological indices. Cor, correlation coefficient; WBC, white blood cell; N, neutrophil; M, monocyte; PLT, platelet; ALB, albumin; Hb, hemoglobin; GLB, globulin; AGR, albumin-to-globulin ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; OPNI, Onodera's prognostic nutritional index; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; N/AGR, neutrophil/albumin-to-globulin ratio; NA/Hb, neutrophil × albumin to hemoglobin; NM/AGR, neutrophils × monocytes to (albumin-to-globulin ratio).

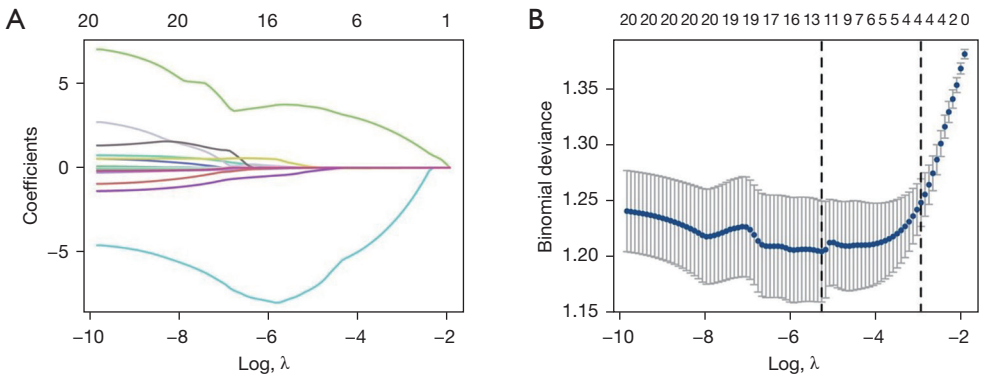

Figure 2 Construction of the PNAGR indicator using the LASSO regression model. (A) The curve of LASSO coefficients for 20 variables. The x-axis is the logarithm (lambda) and the y-axis is the partial regression coefficient. Each line represents a variable coefficient. (B) The optimal parameter (lambda) in the LASSO model was selected based on the minimum criterion using 10-fold cross-validation and filtered to correspond to the four variables corresponding to log(lambda)-1SE. LASSO, least absolute shrinkage and selection operator.

with low ALB and N/AGR values had a worse prognosis compared to those with high ALB and N/AGR values (P<0.001, *Figure 3D,3E*).

Further, we found that patients with high PNAGR levels had later clinical staging compared to those with low PNAGR values (*Table 3*), so we analyzed the prognostic value of each biomarker for patients with stage III and IV. Patients with high PNAGR levels had worse OS survival compared to patients with low PNAGR values (P<0.001, *Figure 4A*), and similarly, lung cancer patients with high 1/AGR and PLR

Table 2 LASSO regression to construct PNAGR indicator

Variable	Lambda.min	Lambda.1se
(Intercept)	0.1924648	−0.411830918
WBC (10^9/L)	0.000457085	0
N (10^9/L)	0	0
M (10^9/L)	0.024603092	0
PLT (10^9/L)	−0.00058334	0
ALB (g/L)	−0.021415616	−0.022192924
Hb (g/L)	0.000265962	0
GLB (g/L)	0	0
AGR	−0.030117739	0
1/AGR	3.69200367	1.784334721
LMR	0	0
SII	0	0
SIRI	0	0
OPNI	−0.022017563	0
MLR	0	0
NLR	0	0
PLR	0.005356582	0.002003093
dNLR	−0.305186079	0
N/AGR	−7.511799757	−2.460231314
NA/Hb	0.169077178	0
NM/AGR	0	0

LASSO, least absolute shrinkage and selection operator; WBC, white blood cell; N, neutrophil; M, monocyte; PLT, platelet; ALB, albumin; Hb, hemoglobin; GLB, globulin; AGR, albumin-to-globulin ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; OPNI, Onodera's prognostic nutritional index; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; N/AGR, neutrophil/albumin-to-globulin ratio; NA/Hb, neutrophil × albumin to hemoglobin; NM/AGR, neutrophils × monocytes to (albumin-to-globulin ratio).

values had poorer survival (P<0.001, P=0.03, *Figure 4B,4C*). The group with low ALB values had a poorer prognosis than those with high ALB values (P<0.001, *Figure 4D*). However, there was no significant difference in the prognosis of patients in the group with different expression levels of N/AGR (P=0.18, *Figure 4E*).

PNAGR is an independent prognostic factor in NSCLC patients

In the Cox univariate and multivariate analyses (*Table 4*), PNAGR scores showed a significant association with survival outcomes. In these models, the hazard ratio (HR) was higher in the group with high PNAGR values (≥0.8) compared to patients with low PNAGR values (<0.8), with 4.274 [95% confidence interval (CI): 3.246–5.629, P<0.001] and 1.935 (95% CI: 1.227–3.052, P=0.005), respectively. Meanwhile, the HR values of the group with low N/AGR values (≤0.2) were 1.748 (95% CI: 1.351–2.261, P<0.001) and 1.323 (95% CI: 1.003–1.746, P=0.047), respectively. The above indicated that PNAGR and N/AGR were the prognostic factors with independence in NSCLC patients (when P=0.005, P=0.047). PNAGR may be associated with risk factors for patient OS.

The predictive power of PNAGR for patient prognosis

Diagnostic ROC curves showed that compared with 1/AGR [area under the curve (AUC): 0.659], PLR (AUC =0.644), ALB (AUC =0.657), and N/AGR (AUC =0.622), PNAGR (AUC =0.753) possessed more accurate diagnostic ability (*Figure 5A*). Meanwhile, time-dependent ROC curves showed that PNAGR had better predictive efficacy than 1/AGR, PLR, ALB, and N/AGR (12 months, AUC =0.79; 36 months, AUC =0.77; 60 months, AUC =0.75) (*Figure 5B-5F*).

On the same note, we further analyzed the predictive ability of each biomarker for the prognosis of patients with stage III and IV. Compared with other biomarkers, PNAGR (AUC =0.655) possessed more accurate diagnostic ability (*Figure 6A*). Meanwhile, time-dependent ROC curves showed that PNAGR had better predictive efficacy than 1/AGR, PLR, ALB, and N/AGR at 12 months (AUC =0.713) and 36 months (AUC =0.690) (*Figure 6B-6F*).

Discussion

There is growing evidence that systemic inflammation is a significant factor in the development and progression of cancer (18,19). In recent years, various blood markers have been investigated for the assessment of systemic inflammation and prediction of malignancy and clinical outcomes. PLR has been identified as a representative indicator of systemic inflammation from abundant studies and investigated for its prognostic value in various cancers such as NSCLC (20),

Table 3 Relationships between the PNAGR and clinicopathological features

Characteristics	PNAGR		
	<0.8 (n=469)	≥0.8 (n=87)	P value
Sex, n (%)			<0.001
Female	202 (36.3)	15 (2.7)	
Male	267 (48.0)	72 (12.9)	
Age (years), n (%)			<0.001
<60	208 (37.4)	21 (3.8)	
≥60	261 (46.9)	66 (11.9)	
Pathological classification			<0.001
Adenocarcinoma	387 (69.6)	50 (9.0)	
Non-adenocarcinoma	82 (14.7)	37 (6.7)	
History of smoking, n (%)			<0.001
No	279 (50.2)	27 (4.9)	
Yes	190 (34.2)	60 (10.8)	
Metastasis, n (%)			<0.001
M0	351 (63.1)	42 (7.6)	
M1	118 (21.2)	45 (8.1)	
Tumor location, n (%)			0.78
U	261 (46.9)	47 (8.5)	
M/L	208 (37.4)	40 (7.2)	
Stage, n (%)			<0.001
I	182 (32.7)	2 (0.4)	
II	73 (13.1)	11 (2.0)	
III	97 (17.4)	29 (5.2)	
IV	117 (21.0)	45 (8.1)	
WBC, 10^9/ L, median [IQR]	6.32 [5.25, 7.78]	8.41 [6.75,10.235]	<0.001
N, 10^9/L, median [IQR]	3.73 [2.77, 4.81]	6 [4.515, 7.49]	<0.001
M, 10^9/L, median [IQR]	0.42 [0.32, 0.53]	0.6 [0.44, 0.765]	<0.001
PLT,10^9/L, median [IQR]	227 [188, 276]	323 [268, 375]	<0.001
ALB, g/L, median [IQR]	40.21 [37.65, 43.13]	32.7 [29.73, 35.56]	<0.001
Hb, g/L, median [IQR]	137 [127, 146]	120 [108, 134]	<0.001
GLB, g/L, median [IQR]	28.26 [25.47, 31.23]	33.7 [30.79, 39.04]	<0.001

U, upper; M/L, middle/lower; WBC, white blood cell; IQR, interquartile range; N, neutrophils; M, monocytes; PLT, platelets; ALB, albumin; Hb, haemoglobin; GLB, globulin.

ovarian cancer (21), and gastric cancer (22). Neutrophils play a critical role in carcinogenesis, as neutrophils release matrix metalloproteinase-9 (MMP-9), which degrades the extracellular matrix, stimulating the release of vascular endothelial growth factor (VEGF), and promotion of angiogenesis (23). Additionally, MMP-9 induces the release of reactive oxygen species (ROS) and induces the mutation of precancerous epithelial cells, causes DNA damage, which

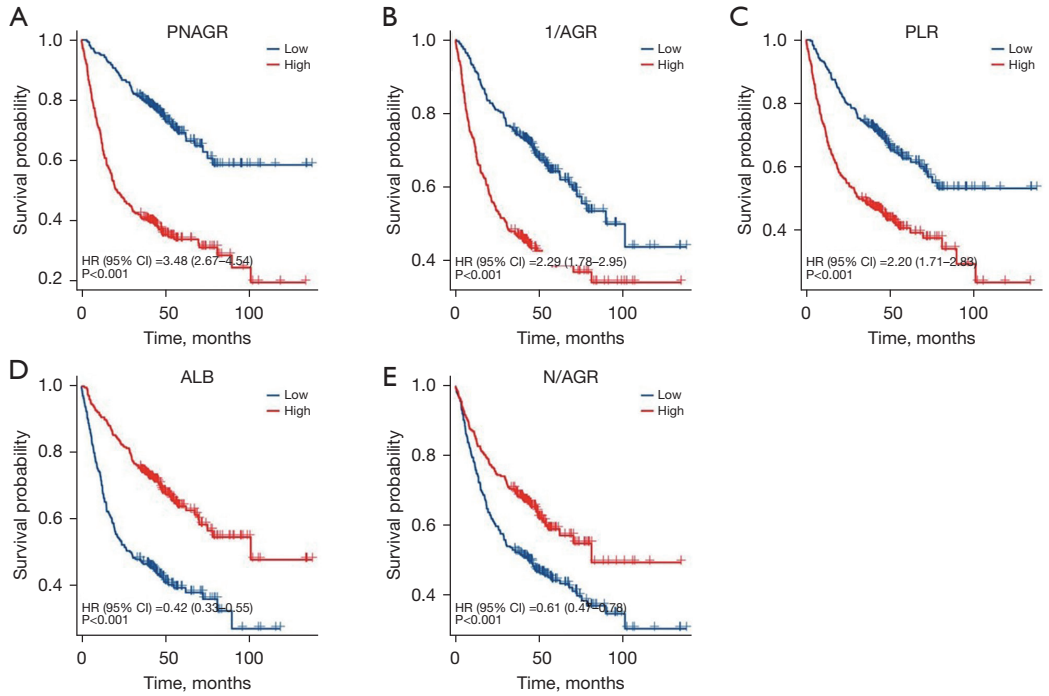

Figure 3 OS Kaplan-Meier survival curves for NSCLC patients stratified by PNAGR (A), 1/AGR (B), PLR (C), ALB (D), and N/AGR (E) levels. HR, hazard ratio; CI, confidence interval; 1/AGR, 1/albumin-to-globulin ratio; PLR, platelet-to-lymphocyte ratio; ALB, albumin; N/AGR, neutrophil/albumin-to-globulin ratio; OS, overall survival; NSCLC, non-small cell lung cancer.

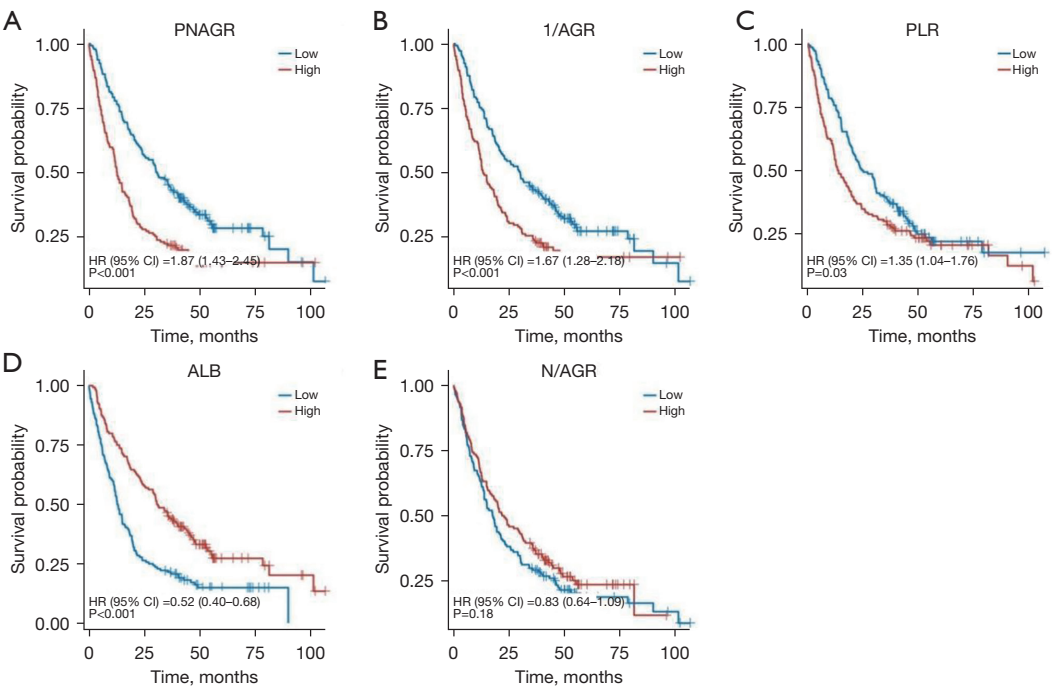

Figure 4 OS Kaplan-Meier survival curves for NSCLC stage III and IV patients stratified by PNAGR (A), 1/AGR (B), PLR (C), ALB (D), and N/AGR (E) levels. HR, hazard ratio; CI, confidence interval; 1/AGR, 1/albumin-to-globulin ratio; PLR, platelet-to-lymphocyte ratio; ALB, albumin; N/AGR, neutrophil/albumin-to-globulin ratio; OS, overall survival; NSCLC, non-small cell lung cancer.

Table 4 Univariate and multivariate analysis for OS

Characteristics	Total (N=556)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Sex					<0.001
Female	217	Reference		Reference	
Male	339	2.042 (1.550–2.690)	<0.001	2.062 (1.421–2.991)	
Age (years)					0.11
<60	229	Reference		Reference	
≥60	327	1.576 (1.219–2.037)	<0.001	1.238 (0.950–1.613)	
History of smoking					0.18
No	306	Reference		Reference	
Yes	250	1.466 (1.149–1.870)	0.002	0.800 (0.576–1.111)	
Pathological classification					0.92
Adenocarcinoma	437	Reference		Reference	
Non-adenocarcinoma	119	1.795 (1.377–2.341)	<0.001	1.016 (0.751–1.376)	
Tumor diameter (cm)					0.03
<3.0	243	Reference		Reference	
≥3.0	313	4.292 (3.156–5.836)	<0.001	1.453 (1.044–2.023)	
Metastasis					>0.99
M0	393	Reference		Reference	
M1	163	5.651 (4.402–7.253)	<0.001	0.000 (0.000–Inf)	
Tumor location					
U	308	Reference			
M/L	248	1.074 (0.842–1.370)	0.564		
Stage					<0.001
I	184	Reference		Reference	<0.001
II	84	7.001 (3.421–14.328)	<0.001	4.817 (2.302–10.077)	>0.99
III	126	17.331 (8.978–33.455)	<0.001	12.332 (6.282–24.207)	
IV	162	37.295 (19.576–71.054)	<0.001	12362485.0295 (0.000–Inf)	
ALB (g/L)					0.77
>35.9	430	Reference		Reference	
≤35.9	126	2.397 (1.849–3.108)	<0.001	1.056 (0.740–1.507)	
1/AGR					0.85
<1	496	Reference		Reference	
≥1	60	3.663 (2.676–5.013)	<0.001	1.046 (0.649–1.684)	

Table 4 *(continued)*

Table 4 *(continued)*

Characteristics	Total (N=556)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
PLR					0.07
<223.8	496	Reference		Reference	
≥223.8	60	2.927 (2.126–4.031)	<0.001	1.380 (0.977–1.950)	
N/AGR					0.047
>0.2	249	Reference		Reference	
≤0.2	307	1.748 (1.351–2.261)	<0.001	1.323 (1.003–1.746)	
PNAGR, n (%)					0.005
<0.8	469	Reference		Reference	
≥0.8	87	4.274 (3.246–5.629)	<0.001	1.935 (1.227–3.052)	

OS, overall survival; HR, hazard ratio; CI, confidence interval; U, upper; M/L, middle/lower; ALB, albumin; 1/AGR, 1/albumin-to-globulin ratio; PLR, platelet-to-lymphocyte ratio; N/AGR, neutrophil/albumin-to-globulin ratio.

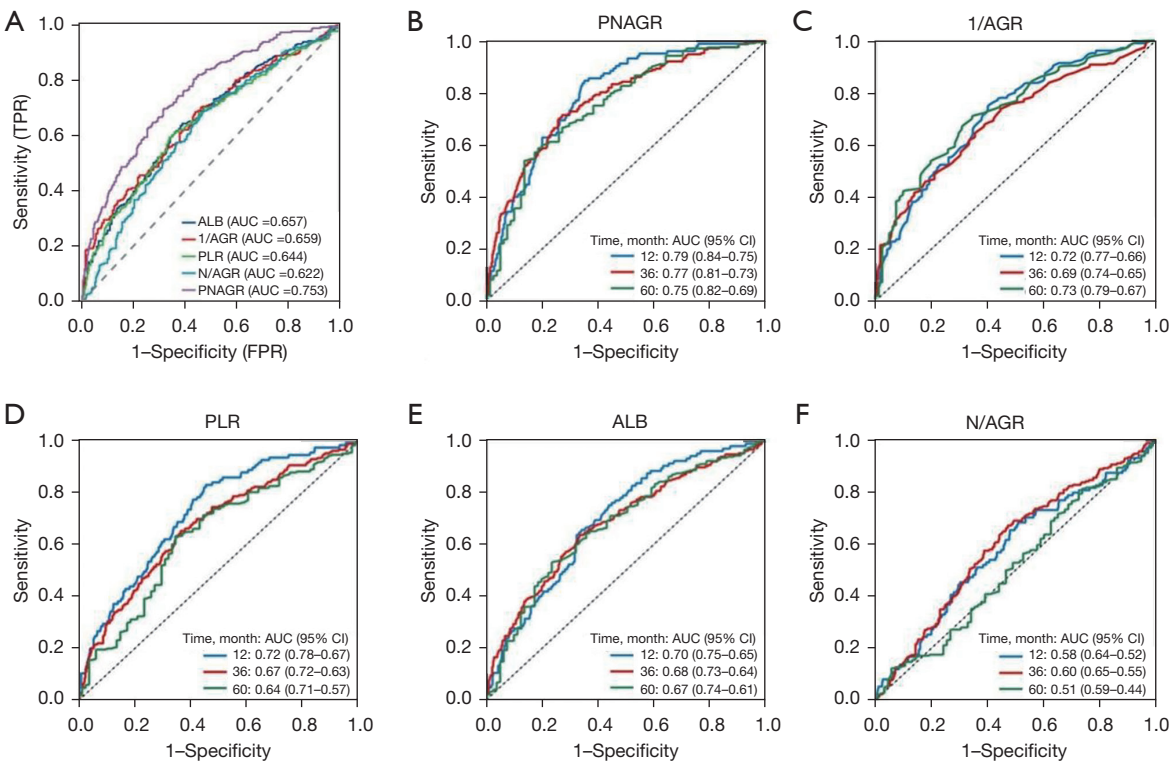

Figure 5 ROC curves for diagnostic and prognostic indicators of NSCLC. (A) Diagnostic ROC curves. (B-F) PNAGR, 1/AGR, PLR, ALB, and N/AGR and time-dependent ROC curves. TPR, true positive rate; FPR, false positive rate; ALB, albumin; 1/AGR, 1/albumin-to-globulin ratio; PLR, platelet-to-lymphocyte ratio; N/AGR, neutrophil/albumin-to-globulin ratio; AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; NSCLC, non-small cell lung cancer.

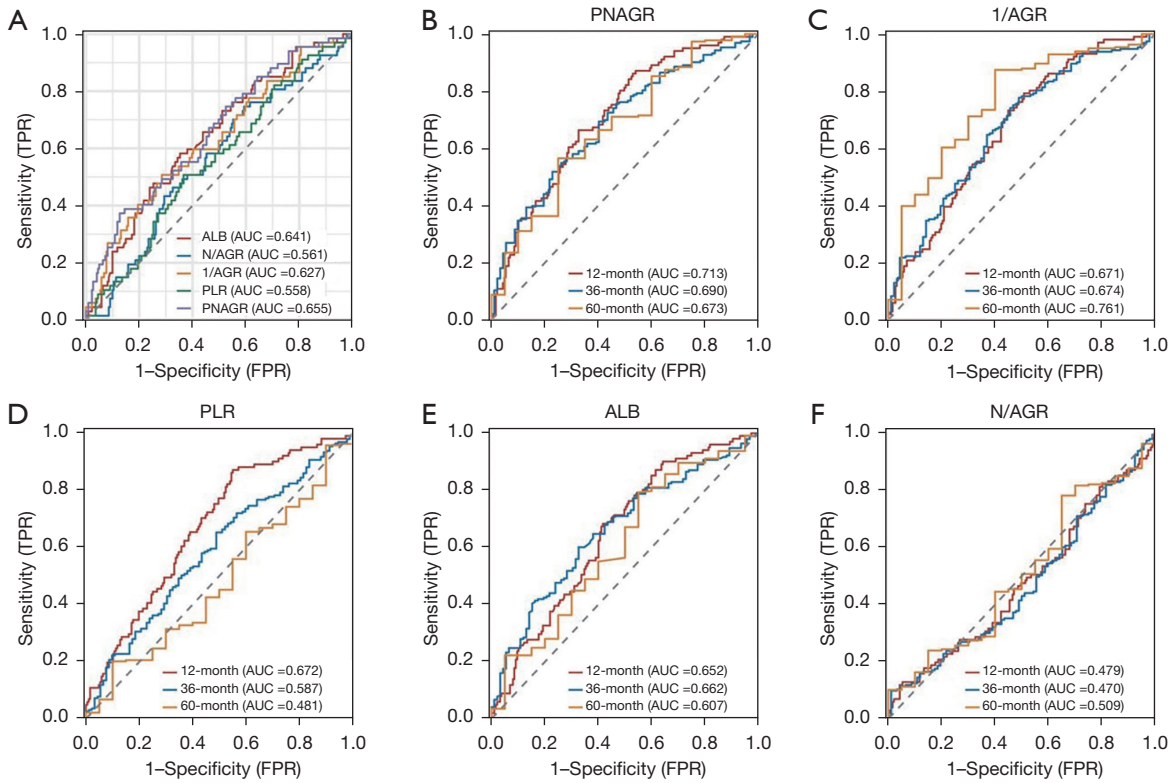

Figure 6 ROC curves for diagnostic and prognostic indicators of NSCLC stage III and IV patients. (A) Diagnostic ROC curves. (B-F) PNAGR, 1/AGR, PLR, ALB, and N/AGR and time-dependent ROC curves. TPR, true positive rate; FPR, false positive rate; ALB, albumin; 1/AGR, 1/albumin-to-globulin ratio; PLR, platelet-to-lymphocyte ratio; N/AGR, neutrophil/albumin-to-globulin ratio; AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; NSCLC, non-small cell lung cancer.

can drive the oncogenic transformation of lung cancer (24). Disorders of preoperative nutrition are more prevalent in patients with NSCLC than in patients with other malignancies, on account of inadequate food intake, weight loss, and muscle wasting (25). Trestini *et al.* showed that the AGR can be a potential prognostic indicator of survival and a predictive marker of treatment-related toxicity in patients with NSCLC (26). AGR has been extensively applied for the evaluation of preoperative nutritional status and in prognosis prediction of various types of human cancers (27). Research has found that higher preoperative AGR values are linked to improved OS in NSCLC patients, establishing AGR as an independent prognostic factor (28). Furthermore, there is increasing evidence to suggest that serum ALB can be used to assess cancer cachexia, which is caused by the systemic inflammatory response induced by the tumor or the host response (16). Therefore, identifying malnourished patients preoperatively and initiating nutritional support in a timely and early manner can facilitate postoperative recovery, reduce postoperative complications, and enhance long-term prognosis. However, since these biomarkers reflect different pathological conditions in cancer patients, it is necessary to integrate and evaluate them to improve the accuracy of cancer prognosis prediction. Thus, the LASSO method was introduced to analyze the relative impact of 20 indicators that contributed to endpoint events; coefficients were assigned to variables, and those with that contributed the least were eliminated. Herein, a composite blood index (PANGR) was established on the basis of PLR, ALB, and AGR, which has improved predictive power as a prognostic indicator. Also, we found that patients with high levels of PNAGR had later clinical staging and poorer OS. In addition, multivariate analysis identified PNAGR, N/AGR is an independent prognostic predictor of OS. Importantly, PNAGR showed better prognostic survival prediction compared to single metrics (including PLR, ALB, and N/AGR) with an AUC value of 0.753. Similarly, the PNAGR predicted the prognosis of patients with stage III and

IV better than any other indicator. Furthermore, it was discovered that the PNAGR high level was linked to a lower OS rate, indicating that PNAGR is a dependable prognostic indicator for the systemic inflammatory response and can accurately evaluate nutritional status, which supports the more comprehensive survival assessment of NSCLC patients.

This study has some limitations. This was a retrospective, single-center study, which leaves the possibility of selection bias and recall bias in the study population and clinical data. There is no clear consensus on the construction of the PNAGR, and the efficacy of the PNAGR in the assessment of long-term prognosis still needs to be investigated. Thus, controlled studies that cover prospective, large-sample, multicenter, randomized characteristics are needed to the clinical predictive value of PNAGR validated in NSCLC.

Conclusions

This study found that PNAGR is a new prognostic predictor, which has good predictive diagnostic value for NSCLC patients.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-91/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-91/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-91/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Qingdao Municipal Hospital (No. 2022yxy077) and the requirement for individual consent for this retrospective analysis was waived.

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