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ORIGINAL RESEARCH

Naples Prognostic Score as an Independent Predictor of Survival Outcomes for Resected Locally Advanced Non-Small Cell Lung Cancer Patients After Neoadjuvant Treatment

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Background: The Naples Prognostic Score (NPS) can reflect patient's nutritional and inflammatory status, which is identified as a prognostic indicator for various malignant tumors. However, its significance in patients with resected locally advanced non-small cell lung cancer (LA-NSCLC) patients who receive neoadjuvant treatment remains unclear so far.

Methods: A total of 165 LA-NSCLC patients surgically treated from May 2012 to November 2017 were retrospectively investigated. The LA-NSCLC patients were divided into three groups according to NPS scores. The receiver operating curve (ROC) analysis was performed to reveal the discriminatory ability of NPS and other indicators for predicting the survival. The NPS and clinicopathological variables were further evaluated the prognostic value by univariate and multivariate Cox analysis.

Results: The NPS was related to age (P = 0.046), smoking history (P = 0.004), Eastern Cooperative Oncology Group (ECOG) score (P = 0.005), and adjuvant treatment (P = 0.017). Patients with high NPS scores had worse overall survival (OS) (group 1 vs 0, P = 0.006; group 2 vs 0, $P < 0.001$) and disease-free survival (DFS) (group 1 vs 0, $P < 0.001$; group 2 vs 0, $P < 0.001$). The ROC analysis demonstrated that NPS had better predictive ability than other prognostic indicators. Multivariate analysis revealed that NPS was independent prognostic indicator of OS (group 1 vs 0, hazard ratio [HR] =2.591, P = 0.023; group 2 vs 0, HR = 8.744, P = 0.001) and DFS (group 1 vs 0, HR =3.754, $P < 0.001$; group 2 vs 0, HR = 9.673, $P < 0.001$).

Conclusion: The NPS could be an independent prognostic indicator in patients with resected LA-NSCLC receiving neoadjuvant treatment and more reliable than the other nutritional and inflammatory indicators.

Keywords: surgery, locally advanced NSCLC, NPS, prognosis, neoadjuvant treatment

Introduction

The morbidity and mortality of lung cancer rank first in the world, which is a public problem worthy of our attention.[1,2] Non-small cell lung cancer (NSCLC) is the main pathological type of lung cancer, accounting for about 80–85% of all lung cancers.[3] The late clinical manifestations are the hidden symptoms of the NSCLC. Therefore, the outcome of NSCLC patients is extremely unfavorable compared with other solid malignancies.[4,5] Surgery is a reliable and effective treatment for resected locally advanced non-small cell lung cancer (LA-NSCLC) patients.[6,7] The 5-year survival rate of LA-NSCLC in the past few decades is about 30%, which is unsatisfactory.[8,9] In recent years, with the rapid development of programmed cell death receptor-1 (PD-1) and programmed cell death ligand-1 (PD-L1) checkpoints, the application of immune checkpoint inhibitors (ICIs)in the treatment of malignant tumors has shown a promising prospect.[10,11] Nevertheless, the value of ICIs is limited, and a considerable proportion of LA-NSCLC patients are resistant to ICIs.[12,13] Therefore, exploring the convenient, economical and reliable prognostic indicators to help to optimize the treatment options is necessary.

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According to previous reports, systemic inflammatory response is a hallmark that normal cells tend to malignant development, which is closely related to the occurrence and development of malignant tumors.[14–16] Systemic inflammatory can promote local tumor cells infiltration, distant metastasis and treatment resistance.[17,18] Systemic inflammatory related indicators have offered the utility value for predicting the tumor patient survival outcomes, such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and the C-reactive protein-to-albumin ratio (CAR).[19–23] Additionally, nutritional status as host related factor, has attracted researchers' interests in malignant tumors survival analysis.[24,25] The systemic inflammation score (SIS), Glasgow prognostic score (GPS), and prognostic nutritional index (PNI) are related to the prognosis of NSCLC.[26–28]

Recently, Naples Prognostic Score (NPS) has attracted extensive attention as a new indicator of combining inflammatory and nutritional status. The NPS, proposed by Galizia et al, consists of serum albumin concentration (Alb), total blood cholesterol (TC), NLR, and LMR. And the predictive value of NPS in malignant tumors was firstly validated in colorectal cancer patients undergoing surgery by a clinical trial (NCT03272646).[29] NPS has been reported to be significantly associated with survival outcomes in patients with ampullary carcinoma,[30] gastric cancer,[31] esophageal cancer,[32] pancreatic cancer,[33] stage I–II NSCLC[34] and endometrial cancer.[35] However, the relationship between NPS and long-term outcomes of resected LA-NSCLC patients after neoadjuvant treatment remains unclear.

The present study was designed to assess the predictive value of NPS in resected LA-NSCLC patients after neoadjuvant treatment. Meanwhile, based on the subgroup analysis, we also investigated the prognostic significance of NPS in stage IIIA and stage IIIB patients, respectively.

Materials and Methods

Patient Selection

We performed a retrospective study of 165 LA-NSCLC patients who underwent surgery in our hospital from May 2012 to November 2017. As shown in Figure 1, study flow diagram was identified. Clinicopathological variables including age, gender, smoking history, Eastern Cooperative Oncology Group (ECOG) score, pathological type, differentiation, TNM stage, surgery approach, adjuvant treatment, and postoperative complications were analyzed from the electronic medical record system of hospital.

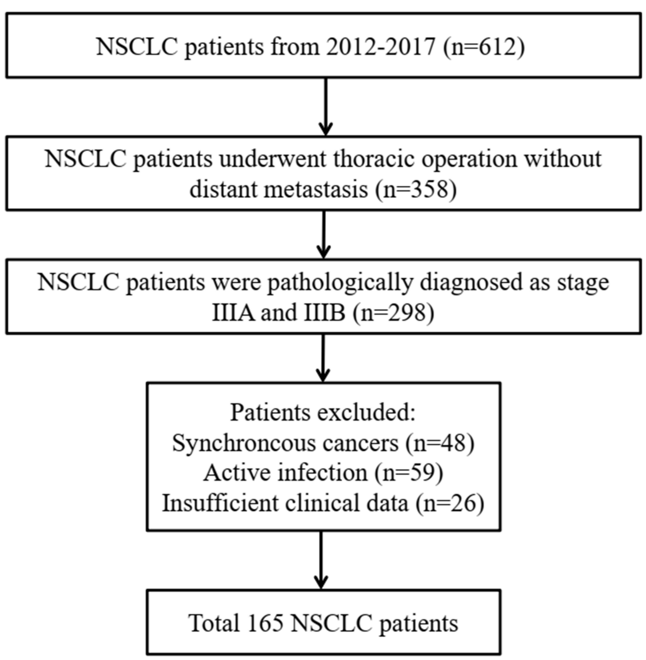

Figure 1 The flow chart of patient selection process.
Abbreviation: NSCLC, non-small cell lung cancer.

Evaluation of Inflammatory and Nutritional Indicators

The plasma laboratory examination was performed within seven days before neoadjuvant therapy. Laboratory examination included Alb, TC, absolute monocyte count, absolute neutrophil count, and absolute lymphocyte count. NLR was defined as absolute neutrophil count divided by absolute lymphocyte count. LMR was defined as absolute lymphocyte count divided by absolute monocyte count. The PNI was calculated as follows: 10 ×Alb value + 0.005 × total lymphocyte count.[36] Patients with Alb ≥ 4g/dL and LMR level ≥ 4.44 were assigned a SIS score of 0, patients with Alb < 4g/dL and LMR < 4.44 were allocated a SIS score of 2, and patients with Alb < 4g/dL or LMR < 4.44 were allocated a SIS score of 1.[37]

Establishment of NPS

As described previously, the NPS was calculated from Alb, TC, NLR, and LMR.[29] Alb <4 mg/dL, TC ≤ 180 mg/dL, NLR ≥ 2.96, or LMR ≤ 4.44 was scored as 1. Alb≥4 mg/dL, TC > 180 mg/dL, NLR < 2.96, or LMR > 4.44 was scored as 0. The NPS was evaluated as the sum of the above scores. Afterwards, these patients were divided into three groups based on respective NPS score: patients with a score of 0 were assigned to group 0; patients with a score of 1 or 2 were assigned to group 1; patients with a score of 3 or 4 were assigned to group 2.

Neoadjuvant Treatment and Surgery

All patients were treated with neoadjuvant platinum-based chemotherapy regimens or chemoradiotherapy. The thoracic surgeons analyzed the patient's condition and determined the surgical approaches, including thoracotomy or video-assisted thoracoscopic surgery (VATS) procedure.[38] Thoracotomy was chosen to ensure the safety of patient when the preoperative imaging examination showed large tumor scope, obvious tumor invasion or unclear anatomy with the surrounding important vascular structure. Elderly patients with poor physique and weak immunity were treated with VAST. Of course, patients' pain, economy and other factors were also taken into consideration when choosing surgical approaches. All patients were required to complete relevant pre-operative functional evaluation (blood examination, electrocardiograph test, heart Doppler ultrasound test, pulmonary function test). The specific scope of surgical resection included the complete lobectomy of the tumor and mediastinal lymph nodes dissection.[39] The intercostal muscles, thymus, or pleura were sutured after the surgical excision. Chest tubes were placed in the chest to facilitate lung fluid drainage. Pneumonia, atelectasis, secondary tracheal intubation, bronchopleural fistula, and pulmonary embolism within 1 month after lung cancer resection were defined as the postoperative complication.[40,41] The patients with respiratory failure post-surgery were excluded to ensure follow-up antitumor therapy.[42] The thoracic surgeons encouraged patients to perform the early rehabilitation exercises and nutritional support. Sequentially, patients received adjuvant chemotherapy or chemoradiotherapy after surgery.

Follow-Up

The follow-up information included the assessment of disease status, identification of survival outcomes or last lost follow-up. The patients were regularly followed up every 3 months in the first two years after treatment and every 6 months thereafter. Each hospital follow-up examination included physical examination, tumor markers, chest computed tomography, and other examinations. Overall survival (OS) was considered as the duration from the date of neoadjuvant treatment to death from any cause or last follow-up. Disease-free survival (DFS) was considered as the time from the date of neoadjuvant treatment to the date of disease progression or the death from any cause.

Statistical Analysis

The SPSS 21.0 software and GraphPad Prism 8.0 were used to perform data analysis. The association between NPS and clinicopathological variables was analyzed using chi-square tests. Spearman correlation analysis was used to identify the associations among inflammatory indicators and nutritional indicators. Receiver operating characteristic (ROC) curves were performed to determine the predictive abilities of the different scoring systems. The Kaplan-Meier (KM) method was applied in conducting OS and DFS differences analysis and visualized by survival curves. The clinicopathological variables in univariate analysis with P values < 0.05 were included into the multivariate prognostic analysis. The hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of variables were assessed for relative risk. $P < 0.05$ was considered to be statistically significant.

Results

Patient Characteristics

Among the NSCLC patients, 165 LA-NSNCL patients met the screening criteria who underwent neoadjuvant treatment and surgery, including 74 (44.8%) males and 91 (55.2%) females. A total of 82 (49.7%) patients were older than 60 years old, and 80 (48.5%) patients had smoking history. 79 (47.9%) patients received a VATS, 86 (52.1%) received a thoracotomy. The majority of the LA-NSNCL patients received neoadjuvant chemotherapy (66.1%). The median follow-up time was 34 (interquartile range: 29–61) months.

Relationships Between NPS and Clinicopathological Variables

The relationships between NPS and clinicopathological variables are shown in Table 1. Thirty-five patients in the NPS groups 0, 108 patients in the NPS groups 1, and 22 patients in the NPS groups 2 were further analyzed. NPS significantly increased among patients having smoking history ($P = 0.004$). Moreover, NPS significantly increased among cases having the ECOG score of 1 ($P = 0.005$), neoadjuvant chemoradiotherapy ($P = 0.017$). However, no significant difference was observed in gender, pathological type, differentiation, TNM stage, surgery approach, and postoperative complications.

Prognostic Value of the Inflammatory and Nutritional Indicators

Kaplan-Meier curves were used to perform the OS analysis based on the Alb, TC, NLR, LMR, PNI and SIS. Compared with patients in the low LMR group and high SIS score group, those in the high LMR group and low SIS score group had better OS (Figure 2). We next used the Kaplan-Meier curves to evaluate the DFS differences in Alb, TC, NLR, LMR, PNI and SIS. We found that the patients in the high Alb group, high TC group, high LMR group and low SIS score group had better DFS compare with the low Alb group, low TC group, low LMR group, and high SIS score group (Figure 3).

Prognostic Value of the NPS

We also explored the associations among inflammatory indicators and nutritional indicators. The results found that there were no significant correlations regarding Alb and NLR ($r = 0.006$, $P = 0.337$), Alb and LMR ($r = 0.016$, $P = 0.109$), TC and NLR ($r = 0.006$, $P = 0.311$), TC and LMR ($r = 0.001$, $P = 0.680$) (Figure 4). We used the ROC curves to determine the predictive abilities of the different scoring systems. As shown in Figure 5, the area under the curve (AUC) of NPS for predicting OS and DFS were 0.704 and 0.734, respectively. And the ROC results confirmed that the NPS had stronger discriminatory power for predicting the OS and DFS than Alb, TC, NLR, LMR, PNI and SIS (Table 2). OS analysis showed that the patients in NPS group 2 and group 1 had poorer survival benefits than those in NPS group 0 (group 1 vs 0, $P = 0.006$; group 2 vs 0, $P < 0.001$, Figure 6A). The Kaplan-Meier curves of DFS showed that patients in NPS group 2 and group 1 had significantly poorer DFS compared with those in NPS group 0 (group 1 vs 0, $P < 0.001$; group 2 vs 0, $P < 0.001$, Figure 6B).

We further performed subgroup analysis of TNM stage in LA-NSCLC patients (Figure 7). In the stage IIIA and stage IIIB, patients in NPS group 0 had significantly longer OS and DFS compared with those in NPS group 1 or 2 ($P < 0.001$; $P < 0.001$). In the stage IIIB, patients in NPS group 0 had significantly longer DFS compared with those in NPS group 1 or 2 ($P = 0.017$). However, no statistical significance was found between three groups in OS.

Cox Regression Analysis on Prognostic Factors

The univariate survival analysis of this study was shown in Table 3. Univariate Cox regression analysis was performed in age, gender, smoking history, ECOG score, body mass index (BMI), pathological type, differentiation, TNM stage, surgery approach, adjuvant treatment, CEA levels, postoperative complications, PNI, SIS and NPS. The results demonstrated that age, ECOG score, TNM stage, surgery approach, SIS, and NPS were closely associated with OS and DFS.

Table 1 Association of the NPS with LA-NSCLC Patient Clinicopathological Characteristics

Characteristics	NPS				P value
	Total (n=165)	Group 0 (n=35)	Group 1 (n=108)	Group 2 (n=22)	
Age (years)					0.046
<60	83(50.3%)	24(68.6%)	50(46.3%)	9(40.9%)	
≥60	82(49.7%)	11(30.4%)	58(53.7%)	13(59.1%)	
Gender					0.533
Female	91(55.2%)	17(48.6%)	60(55.6%)	14(63.6%)	
Male	74(44.8%)	18(51.4%)	48(44.4%)	8(36.4%)	
Smoking history					0.004
No	85(51.5%)	22(62.9%)	53(49.1%)	10(45.5%)	
Yes	80(48.5%)	13(37.1%)	55(50.9%)	12(54.5%)	
ECOG score					0.005
0	70(42.4%)	23(65.7%)	41(38.0%)	6(27.3%)	
1	95(57.6%)	12(34.3%)	67(62.0%)	16(72.7%)	
BMI (kg/m2)					0.805
≥18.5	83(49.7%)	19(54.3%)	54(50.0%)	10(45.5%)	
<18.5	82(50.3%)	16(45.7%)	54(50.0%)	12(54.5%)	
Pathological type					0.451
AD	100(60.6%)	21(60.0%)	63(58.3%)	16(72.7%)	
SCC	65(39.4%)	14(40.0%)	45(41.7%)	6(27.3%)	
Differentiation					0.367
Well / Moderate	72(43.6%)	14(40.0%)	51(47.2%)	7(31.8%)	
Poor	93(56.4%)	21(60.0%)	57(52.8%)	15(68.2%)	
TNM stage					0.169
IIIA	130(78.8%)	31(88.6%)	84(77.8%)	15(68.2%)	
IIIB	35(21.2%)	4(11.4%)	24(22.2%)	7(31.8%)	
Surgery approach					0.788
Thoracotomy	86(52.1%)	19(54.3%)	57(52.8%)	10(45.5%)	
VAST	79(47.9%)	16(45.7%)	51(47.2%)	12(54.5%)	
Neoadjuvant treatment					0.017
Chemotherapy	109(66.1%)	30(85.7%)	67(62.0%)	12(54.5%)	
Chemoradiotherapy	56(33.9%)	5(14.3%)	41(38.0%)	10(45.5%)	
CEA Levels					0.844
≤5 ng/mL	57(34.5%)	11(31.4%)	39(36.1%)	7(28.0%)	
>5 ng/mL	108(65.5%)	24(68.6%)	69(63.9%)	15(72.0%)	
Postoperative complications					0.360
Yes	87(52.7%)	15(42.9%)	61(56.5%)	11(50.0%)	
No	78(47.3%)	20(57.1%)	47(43.5%)	11(50.0%)	

Abbreviations: NPS, Naples Prognostic Score; LA-NSCLC, locally advanced non-small cell lung cancer; Group 0, patients with a NPS score of 0; Group 1, patients with a NPS score of 1 or 2; Group 2, patients with a score of 3 or 4; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; SCC, squamous cell carcinoma; AD, adenocarcinoma; VATS, video-assisted thoracoscopic surgery; CEA, carcinoembryonic antigen.

Based on above results of univariate Cox regression analysis, multivariate analysis demonstrated that NPS was independent prognostic factor of poor OS (group 1 vs 0, hazard ratio [HR] =2.591, P = 0.023; group 2 vs 0, HR = 8.744, P = 0.001) and DFS (group 1 vs 0, HR =3.754, P < 0.001; group 2 vs 0, HR = 9.673, P < 0.001) (Table 4).

Discussion

Though people's awareness of cancer prevention is increasing year by year, the incidence rate of NSCLC was gradually increasing in China.[43] TNM staging is often used by clinicians to evaluate the prognosis of NSCLC patients and guide treatment decisions. However, TNM staging is not so accurate and reliable for NSCLC patients in clinical practice. Even if NSCLC patients are in the same stage, their survival outcomes are different. Scholars generally believe that the

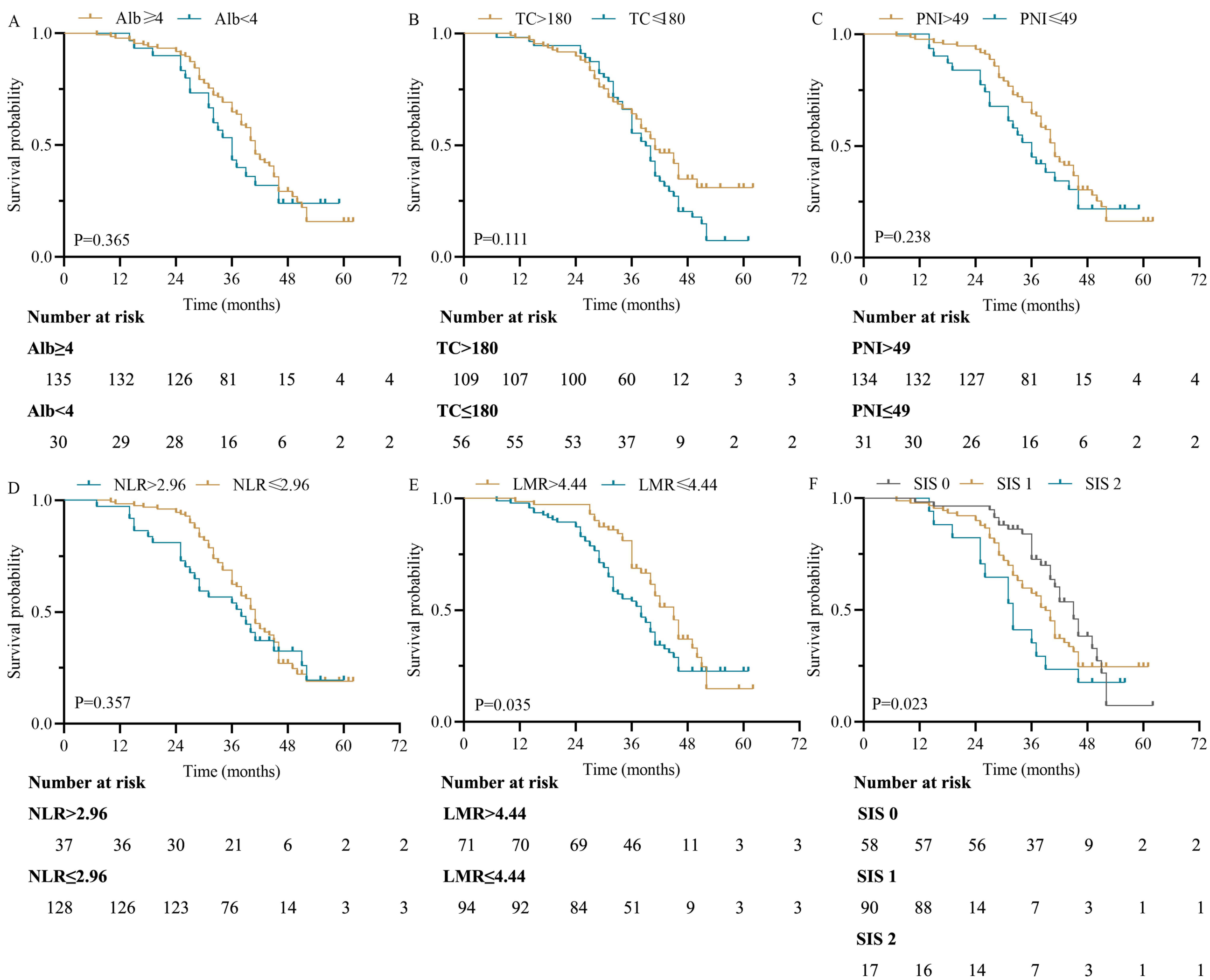

Figure 2 Kaplan-Meier curves for OS in patients with LA-NSCLC according to Alb (**A**), TC (**B**), PNI (**C**), NLR (**D**), LMR (**E**) and SIS (**F**).
Abbreviations: OS, overall survival; LA-NSCLC, locally advanced non-small cell lung cancer; Alb, serum albumin concentration; TC, total blood cholesterol; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SIS, the systemic inflammation score.

occurrence of tumor is a complicated biological process,[44,45] and a single prognostic index is easily influenced by the arbitrary cut-off value. Therefore, we should focus on the clinical application of multidimensional prognostic evaluation systems, such as the NPS. This present study firstly assessed the prognostic value of NPS in resected LA-NSCLC patients after neoadjuvant treatment. Our results demonstrated that the NPS can accurately predict survival outcomes for resected LA-NSCLC patients after neoadjuvant treatment, and high NPS score implied a poor OS and DFS.

Increasing evidences have revealed that the malignant tumor cells formation is associated with inflammatory mediators.[46] Systemic inflammation is the characteristic of tumor microenvironment, which can promote tumor cells invasion, metastasis, and weaken the host antitumor immunity. Researchers have made adequate work on the effect of inflammation on tumors, and have obtained the theoretical consensus.[47,48] Systemic inflammation-related blood cells include neutrophils, platelets, monocytes and so on. Only by fully grasping the mechanism of inflammatory cells acting on tumor, can we better comprehend the systemic inflammation-related prognostic indicators.

First, we analyze these mechanisms from the perspective of neutrophils. Neutrophils play stable roles not only in anti-infection but also in promoting role of cancer.[49] Specifically, neutrophils specifically release the matrix metalloproteinase (MMPs) and vascular endothelial growth factor (VEGF), which induce tumor metastasis and tumor-associated angiogenesis.[50] In terms of body immunity, neutrophils suppress the immune T-cell activation to weaken anti-tumor

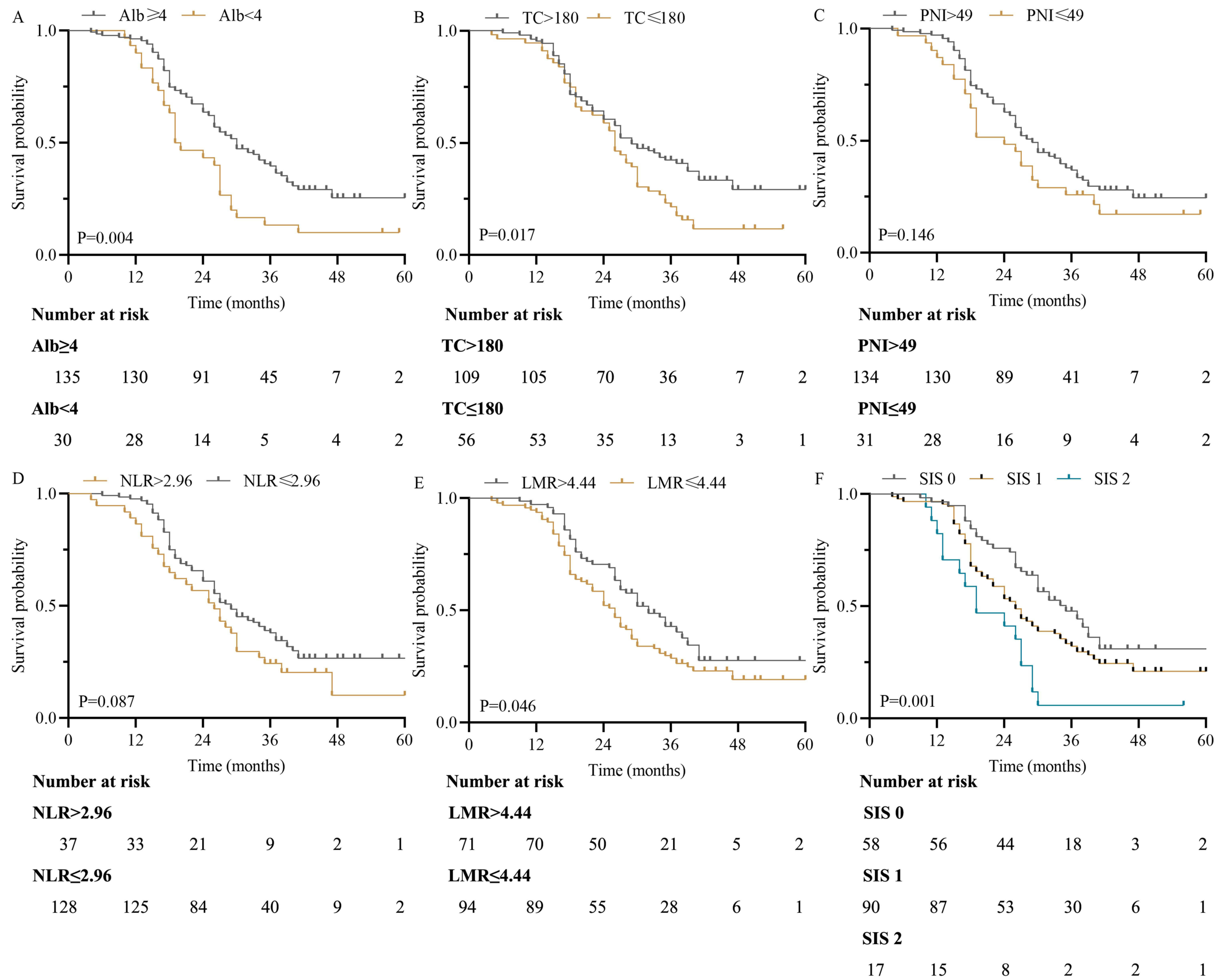

Figure 3 Kaplan-Meier curves for PFS in patients with LA-NSCLC according to Alb (**A**), TC (**B**), PNI (**C**), NLR (**D**), LMR (**E**) and SIS (**F**).
Abbreviations: DFS, disease-free survival difference; LA-NSCLC, locally advanced non-small cell lung cancer; Alb, serum albumin concentration; TC, total blood cholesterol; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SIS, the systemic inflammation score.

immune effect, which destroy the immune balance of the body, resulting in the tumorigenesis.[51] Secord, the potential of monocytes to differentiate into tumor-associated macrophages (TAMs) has attracted much attention. TAMs are found as key controlling factors in tumor microenvironment, and enhance cancer rapidly multiplying in size and cancer cells migration.[52] More interestingly, monocytes can promote the blood circulation of tumor cells, thus increasing the risk of distant metastasis.[53] Considering these, the elevated monocytes may represent a high tumor burden status. Last, lymphocytes are the essential cornerstone of the immune system, which effectively reduce the risk of tumor cell invasion and metastasis. Given the above findings, elevated NLR and decreased LMR reveal the pro-inflammatory and weak immune status.

Additionally, Alb and TC were incorporated into NPS scoring systems. Alb and TC serve as nutritional indicators, their mechanisms of action on tumor are also gradually clear.[54] Previous reports indicated that patients with hypoalbuminemia had poorer outcomes in advanced gastrointestinal cancer.[55] More importantly, Alb is also an indicator of systemic inflammation, because some pro-inflammatory cytokines can reduce the concentration of Alb.[56] TC has been identified to correlate with tumorigenesis and survival in gastric cancer patients.[57]

Given the significance of neutrophils, monocytes, lymphocytes, Alb and TC in cancer, we have sufficient evidences to believe that NPS is a reliable prognostic evaluation system in clinical practice. Galizia et al firstly proposed the NPS as

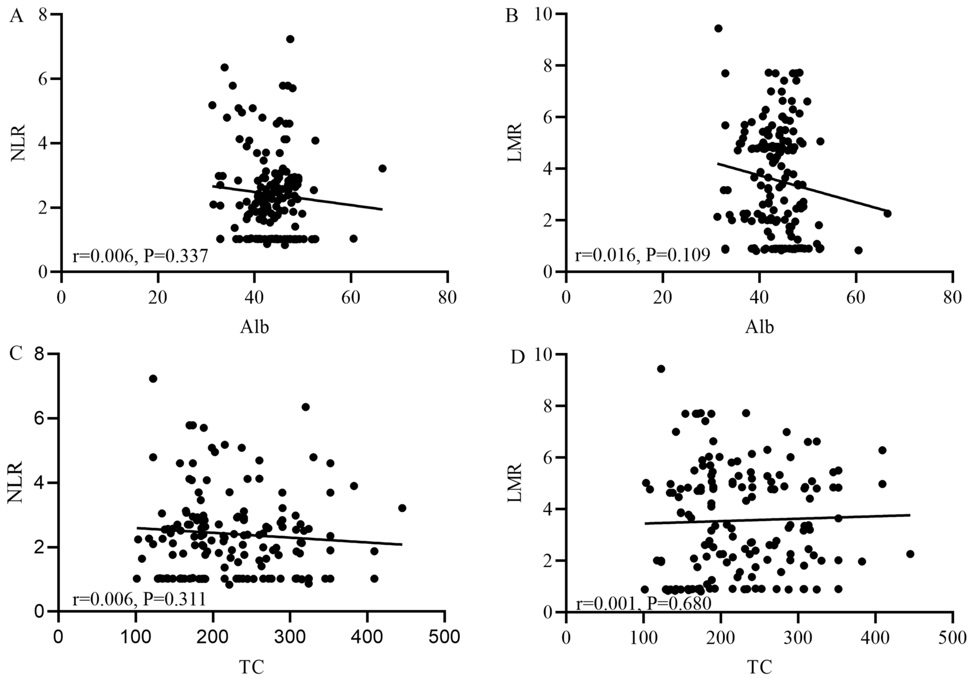

Figure 4 Correlation analysis between Alb and NLR (**A**), Alb and LMR (**B**), TC and NLR (**C**), TC and LMR (**D**).
Abbreviations: Alb, serum albumin concentration; TC, total blood cholesterol; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

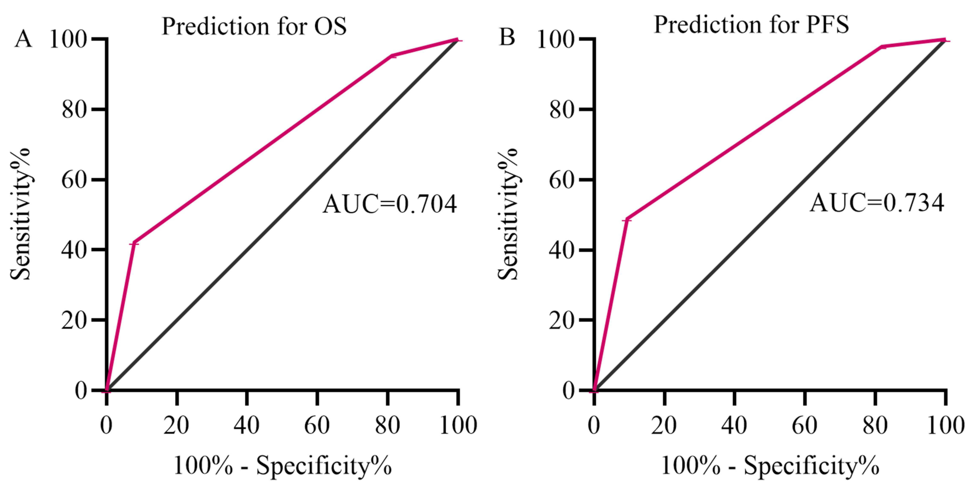

Figure 5 ROC curves of NPS for predicting OS (**A**) and DFS (**B**).
Abbreviations: ROC, receiver operator characteristic curve; OS, overall survival; DFS, disease-free survival.

a prognostic indicator, and found that preoperative NPS was closely associated with long-term outcomes in colorectal cancer patients.[29] Importantly, Galizia et al's conclusion has also been confirmed in cancers other than colon cancer. Jin and colleagues found that NPS can independently predict the incidence of postoperative complications after pancreatoduodenectomy, and demonstrated the predictive value of NPS for short- and long-term outcomes in ampullary carcinoma patients.[30] Similarly, Lieto et al found the predictive value of NPS in gastric cancer with a retrospective study in Italy. NPS mirrored the immune-nutritional conditions, and showed a trustworthy power in predicting tumor regression grade and survival.[58] Besides, a relevant study about gastrointestinal stromal tumors also revealed that NPS was associated with tumor progression and long-term survival.[59]

The application of incorporating multimodal prognostic indicators in the management of cancers is still challenging. As we have seen, we are trying our best to explore the predictive value of NPS in resected LA-NSCLC patients after

Table 2 ROC Analysis of Inflammatory or Nutritional-Related Indicators

Variables	OS			PFS		
	AUC	95% CI	P value	AUC	95% CI	P value
Alb	0.546	0.457–0.635	0.316	0.586	0.495–0.676	0.082
TC	0.637	0.552–0.722	0.003	0.625	0.536–0.714	0.011
NLR	0.530	0.440–0.620	0.516	0.558	0.465–0.651	0.241
LMR	0.582	0.493–0.672	0.075	0.586	0.490–0.682	0.082
BMI	0.510	0.420–0.601	0.824	0.505	0.408–0.602	0.918
PNI	0.551	0.463–0.640	0.267	0.547	0.453–0.640	0.346
SIS	0.604	0.516–0.692	0.024	0.639	0.549–0.730	0.005
NPS	0.704	0.621–0.787	<0.001	0.734	0.649–0.820	<0.001

Abbreviations: OS, overall survival; PFS, progression-free survival; Alb, albumin; TC, total cholesterol; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; BMI, body mass index; PNI, prognostic nutritional index; SIS, the systemic inflammation score; NPS, Naples Prognostic Score.

neoadjuvant treatment. The optimal cut-off values of NLR, LMR, Alb and TC were determined according to Galizia's study, which did not reflect the heterogeneity of individual research. However, this does not affect our conclusions. In terms of the correlation between NPS and clinicopathological variables, we found that NPS was significantly associated to the age (P = 0.046), smoking history (P = 0.004), ECOG score (P = 0.005), and neoadjuvant treatment (P = 0.017). Although the number of group 0 and group 2 patients who were included in this study was small, we still obtained the positive results. In addition, the OS and DFS of LA-NSCLC patients in NPS 0 group was significantly longer than that in NPS 1 group and 2 group. In the present study, univariate analysis confirmed that age, ECOG score, TNM stage, surgery approach, SIS, and NPS were prognostic risk factors for the LA-NSCLC patients. As we expected, the results of multivariate analysis showed that NPS was independent risk factors for the OS (group 1 vs 0, HR =2.591, P = 0.023; group 2 vs 0, HR = 8.744, P = 0.001) and DFS (group 1 vs 0, HR =3.754, P < 0.001; group 2 vs 0, HR = 9.673, P < 0.001) of LA-NSCLC patients. In addition, age and surgery approach were independent risk factors for the OS and DFS of LA-NSCLC patients. These findings are consistent with those previously reported, and further verified the clinical application value of NPS in tumors. We firmly believe that the NPS can be served as a reliable index for recurrence

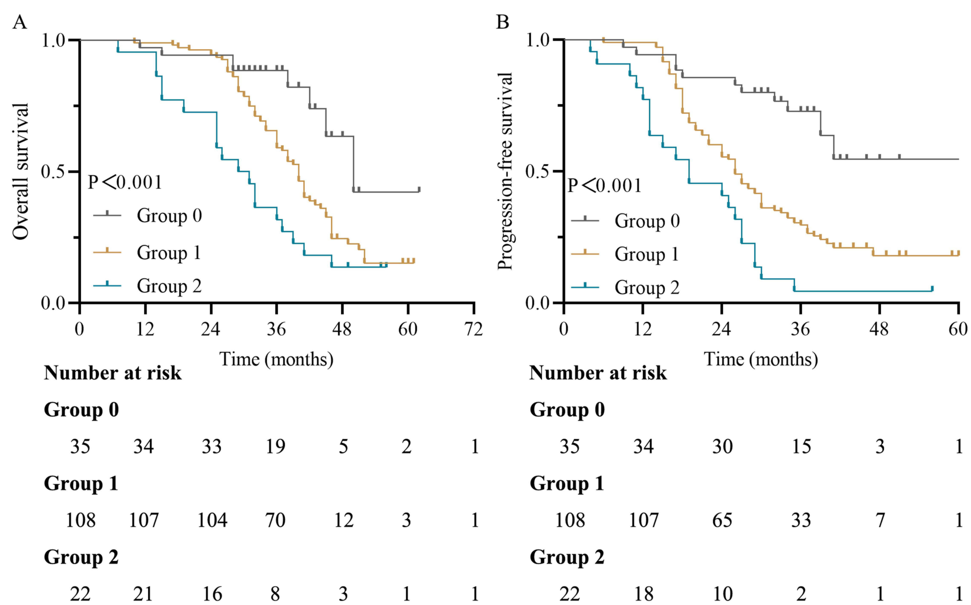

Figure 6 Kaplan-Meier survival curves in patients with LA-NSCLC. (**A**) OS based on NPS groups; (**B**) DFS based on NPS groups.
Abbreviations: OS, overall survival; DFS, disease-free survival.

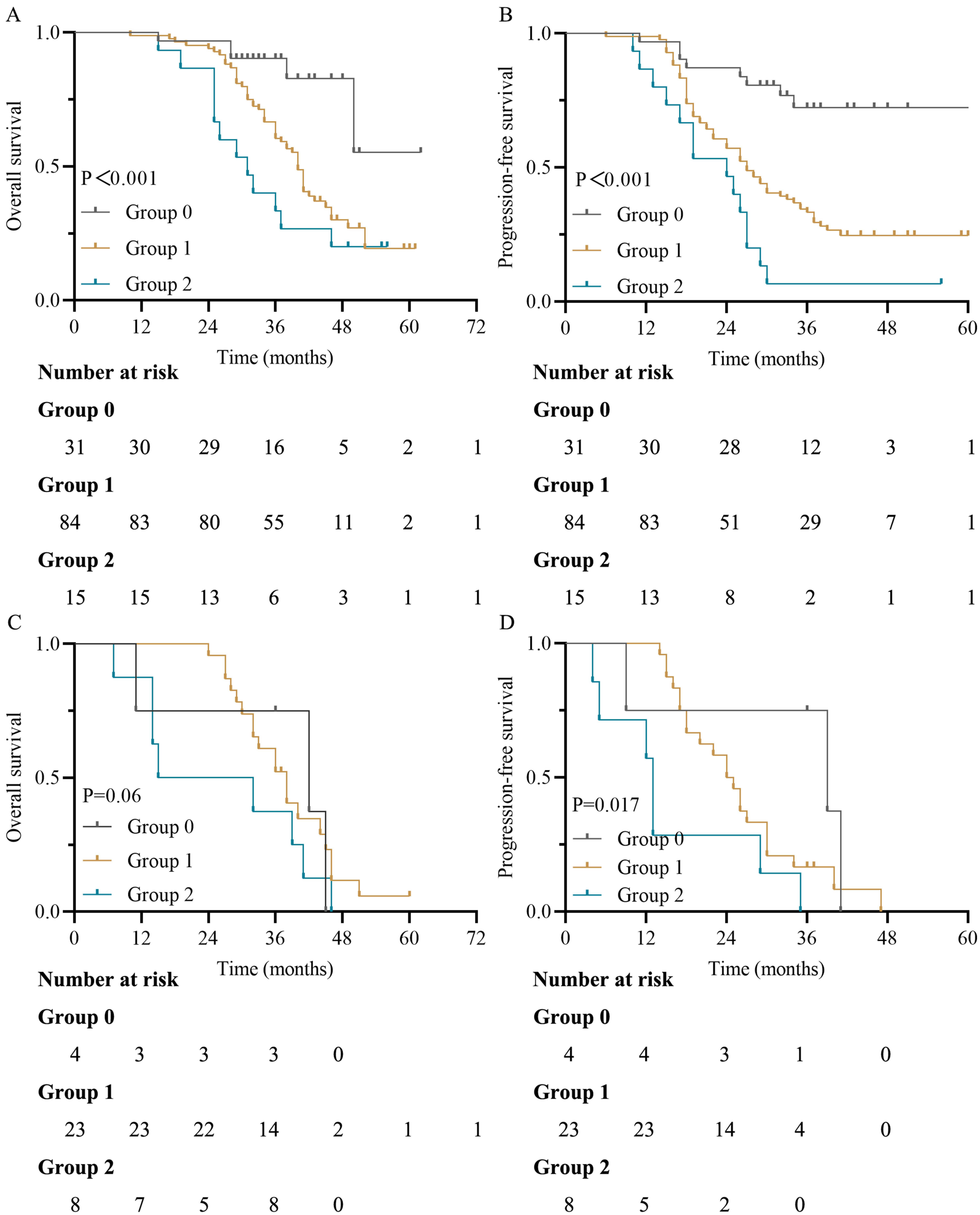

Figure 7 Kaplan-Meier survival curves in patients with LA-NSCLC according to the TNM stage. (**A** and **B**) OS and DFS based on NPS groups in stage IIIA; (**C** and **D**) OS and DFS based on NPS groups in stage IIIB.

Abbreviations: OS, overall survival; DFS, disease-free survival.

Table 3 Univariate and Multivariate Analyses of OS

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age (years)		0.033		0.004
<60	Reference		Reference	
≥60	1.542(1.036–2.294)		2.007(1.256–3.208)	
Gender		0.753		
Female	Reference			
Male	0.939(0.633–1.392)			
Smoking history		0.161		
No	Reference			
Yes	1.323(0.894–1.958)			
ECOG score		0.012		0.103
0	Reference		Reference	
1	1.722(1.128–2.629)		1.457(0.927–2.291)	
BMI (kg/m2)		0.283		
≥18.5	Reference			
<18.5	1.239(1.838–1.832)			
Pathological type		0.982		
AD	Reference			
SCC	1.004(0.674–1.496)			
Differentiation		0.308		
Well/Moderate	Reference			
Poor	1.228(0.828–1.821)			
TNM stage		0.007		0.278
IIIA	Reference		Reference	
IIIB	1.797(1.172–2.756)		1.276(0.821–1.986)	
Surgery approach		0.044		0.001
Thoracotomy	Reference		Reference	
VAST	0.668(0.451–0.989)		0.455(0.287–0.723)	
Neoadjuvant treatment		0.086		
Chemotherapy	Reference			
Chemoradiotherapy	1.420(0.951–2.120)			
CEA Levels		0.489		
≤5 ng/mL	Reference			
>5 ng/mL	0.866(0.577–1.300)			
Postoperative complications		0.338		
Yes	Reference			
No	0.825(0.557–1.222)			
PNI		0.238		
>49	Reference			
≤49	1.325(0.830–2.114)			
SIS				
0	Reference		Reference	
1	1.420(0.909–2.219)	0.123	0.946(0.565–1.585)	0.834
2	2.051(1.081–3.891)	0.028	0.428(0.134–1.363)	0.151
NPS				
Group 0	Reference		Reference	
Group 1	2.771(1.335–5.749)	0.006	2.591(1.141–5.881)	0.023
Group 2	5.025(2.196–11.501)	<0.001	8.744(2.505–30.517)	0.001

Note: The variables in univariate analysis (*P* values <0.05) were entered into the multivariate analysis.

Abbreviations: OS, overall survival; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; SCC, squamous cell carcinoma; AD, adenocarcinoma; VATS, video-assisted thoracoscopic surgery; CEA, carcinoembryonic antigen; PNI, prognostic nutritional index; SIS, the systemic inflammation score; NPS, Naples Prognostic Score.

Table 4 Univariate and Multivariate Analyses of DFS

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)		0.025		0.002
<60	Reference		Reference	
≥60	1.523(1.053–2.201)		1.958(1.282–2.990)	
Gender		0.999		
Female	Reference			
Male	1.000(0.693–1.442)			
Smoking history		0.375		
No	Reference			
Yes	1.179(0.819–1.698)			
ECOG score		0.001		0.028
0	Reference		Reference	
1	1.875(1.274–2.759)		1.621(1.054–2.493)	
BMI (kg/m2)		0.508		
≥18.5	Reference			
<18.5	1.131(10.785–1.629)			
Pathological type		0.470		
AD	Reference			
SCC	1.146(0.791–1.660)			
Differentiation		0.619		
Well /Moderate	Reference			
Poor	1.098(0.760–1.585)			
TNM stage		0.002		0.150
IIIA	Reference		Reference	
IIIB	1.878(1.249–2.825)		1.340(0.900–1.998)	
Surgery approach		0.007		<0.001
Thoracotomy	Reference		Reference	
VAST	0.607(0.421–0.875)		0.410(0.268–0.629)	
Neoadjuvant treatment		0.258		
Chemotherapy	Reference			
Chemoradiotherapy	1.244(0.852–1.818)			
CEA Levels		0.992		
≤5 ng/mL	Reference			
>5 ng/mL	1.002(0.682–1.470)			
Postoperative complications		0.653		
Yes	Reference			
No	0.920(0.638–1.325)			
PNI		0.146		
>49	Reference			
≤49	1.389(0.892–2.165)			
SIS				
0	Reference		Reference	
1	1.519(1.000–2.308)	0.050	0.718(0.437–1.178)	0.189
2	2.992(1.639–5.462)	<0.001	0.617(0.200–1.900)	0.400
NPS				
Group 0	Reference		Reference	
Group 1	3.278(1.746–6.153)	<0.001	3.754(1.804–7.811)	<0.001
Group 2	6.819(3.270–14.222)	<0.001	9.673(2.973–31.474)	<0.001

Note: The variables in univariate analysis (*P* values <0.05) were entered into the multivariate analysis.
Abbreviations: DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; SCC, squamous cell carcinoma; AD, adenocarcinoma; VATS, video-assisted thoracoscopic surgery; CEA, carcinoembryonic antigen; PNI, prognostic nutritional index; SIS, the systemic inflammation score; NPS, Naples Prognostic Score.

surveillance and prognosis evaluation for LA-NSCLC. The poorer the nutritional status and physical inflammation, the higher the risk of disease progression will be.

Our study has several limitations. First, due to the nature of single-center and retrospective study with limited cohort size, the findings might be inevitably affected by selection bias. Second, the cutoff value for NLR, LMR, Alb and TC were determined through Galizia et al's method,[29] which makes these findings lack certain specificity. Third, although all patients received neoadjuvant and surgical treatment, patients had different postoperative adjuvant treatment, which may affect the long-term survival. Therefore, a larger, multicenter and prospective study is needed to verify our findings.

Conclusion

This study indicated that NPS is a superior predictor of survival outcomes compared with Alb, TC, NLR, LMR, BMI, PNI, and SIS. Besides, NPS could be utilized to guide the individualized treatment in resected LA-NSCLC patients after neoadjuvant treatment.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of the affiliated Suzhou Hospital of Nanjing Medical University. All authors confirmed that this study complied with the Declaration of Helsinki. And all individuals participating in this study signed written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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