

Evaluation of Predictive Values of Naples Prognostic Score in Patients with Unresectable Stage III Non-Small Cell Lung Cancer

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Background: Naples prognosis score (NPS) is a new prognostic score according to host inflammatory and nutritional state, and it could be useful for predicting tumor prognosis based on albumin level, total cholesterol level, neutrophil-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio. This study aimed to evaluate the clinical significance of Naples prognostic score (NPS) in stage III non-small cell lung cancer patients (NSCLC).

Patients and Methods: In this study, 206 patients diagnosed with locally advanced NSCLC receiving chemoradiotherapy were retrospectively reviewed from January 2013 to January 2017. The included patients were divided into 3 groups according to NPS (group 0, group 1, and group 2), and the associations of the NPS with clinical characteristics and outcomes were evaluated among the groups. Survival curves for the NPS were analyzed using the Kaplan–Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model to evaluate the prognostic value of overall survival (OS) and progression-free survival (PFS).

Results: The median follow-up time of this study was 37.0 (range, 13–59) months. The median OS was 27 months in group 0, 23 months in group 1, and 21 months in group 2, and median PFS was 15, 12 and 13 in group 0, group 1 and group 2, respectively. Age was significantly different among the 3 groups. The NPS was superior to other host inflammatory and nutritional indexes for prognostic risk stratification. In the multivariate analysis, NPS was identified as an independent prognostic indicator for OS and PFS (all $P < 0.05$).

Conclusion: The NPS system is considered to be a useful predictor of outcomes in patients with stage III NSCLC.

Keywords: Naples prognostic score, stage III NSCLC, predictive values

Introduction

Lung cancer is one of the most common malignant tumors and the leading cause of death among cancers worldwide.¹ Non-small cell lung cancer (NSCLC) comprises more than 80% of all lung cancers cases, whereby 30–40% of these patients are diagnosed with stage III NSCLC.² The majority of stage III NSCLC are not suitable for surgical resection due to serious internal medicine disease, poor excised completely or extensive lymph node metastases. Chemoradiotherapy is the standard of care for patients with unresectable stage III NSCLC tumors, which are generally treated with 40–50 days of definitive concurrent chemoradiotherapy, and the option of additional consolidation chemotherapy for patients with high tumor load.³ Despite advances in antineoplastic drugs and radiotherapy, stage III patients still

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have locoregional failure rates of 35–70%, and 5-overall survival (OS) rates are 10–20%,^{4–6} with median OS of 10–14 months.⁷ The clinical outcomes could be different for stage III NSCLC patients treated with the same therapy due to individual heterogeneity, which is the main clinical challenge in the management strategy of cancer patients. Therefore, identification of prognostic factors to categorize risk levels is crucial for individualized precision therapy.

Increasing evidence confirmed that systemic inflammation exerts a vital biological role during malignant tumors proliferation, metastasis, invasion, and angiogenesis.^{8–10} Systemic inflammation molecules affect biochemical mechanisms where tumor cells secrete inflammatory response cytokines, potentially reflecting degree of biological reactivity of tumor cells. The inflammation-related prognostic indicators, including neutrophil–lymphocyte ratio (NLR), lymphocyte–monocyte ratio (LMR) and platelet–lymphocyte ratio (PLR), could be used as predictors of the prognosis in NSCLC.^{11,12} However, these predictors also remained deficient for the fully reflecting prognosis and patients' whole condition by just one single inflammation-related indicator. Prognostic indicators reflecting host nutritional or immunological status, such as the prognostic nutritional index (PNI), systemic immune-inflammatory index (SII) and controlling nutritional status (CONUT), are associated with tumor prognosis.^{13–16} Therefore, an increasing number of clinical risk prognostic models, including inflammation-related and host nutritional status indicators, are urgently needed.

The Naples prognostic score (NPS), which is a new prognostic scoring system based on albumin, total cholesterol concentration, NLR, and LMR, comprehensively reflects the patient's inflammation and nutritional status. Researchers have shown its predictive value in endometrial cancer,¹⁷ colorectal cancer¹⁸ and esophageal squamous cell carcinoma.¹⁹ In addition, the predictive value of NPS is more accurate than that of other inflammatory-related and nutritional-related scoring systems.²⁰ NPS was evaluated in association with the cancer prognosis for both inflammation and nutritional status, and it has a better prognostic performance than either of them alone. However, the significance of NPS in the prognosis of patients with unresectable stage III NSCLC remains largely unknown. As a result, the present study had two aims: first, to evaluate the prognostic value of NPS among stage III NSCLC patients, second, to investigate the associations of the NPS with clinical characteristics.

Patients and Methods

Study Population

From January 2013 to January 2017, this study assessed the 206 patients undergoing chemoradiotherapy due to unresectable stage III NSCLC at Rizhao Center Hospital. The inclusion criteria were as follows: histologically or cytologically diagnosed with confirmed stage III NSCLC; Karnofsky performance score (KPS) 70–100; no prior anti-tumor treatment; availability of complete laboratory results; followed up for over 1 year. Patients who met the following criteria were excluded from the retrospective study: had inflammatory disorder or infectious disease; had malignant tumors at other sites or serious diseases affecting immune and the nutritional status. This retrospective cohort study was approved by the institutional review board of Rizhao Center Hospital institutions. All patients were provided with written informed consent. The study was performed in accordance with the International Conference on Harmonisation Guidelines on Good Clinical Practice and the Declaration of Helsinki.

Treatment Regimes

The standard chemoradiotherapy in our study consists of 6–7 weeks of intensity-modulated radiation therapy (IMRT) with cisplatin-based chemotherapy. All enrolled patients received chest computed tomography (CT) scans before radiation therapy. Individual radiotherapy target planning is implemented in conjunction with positron emission tomography-CT (PET-CT) and chest enhanced CT imaging results. The IMRT dose was 60 to 66 Gy in 1.8 to 2.0 Gy daily fractions, with 5 fractions a week. The radiotherapy plan was assessed and approved independently by 2 radiotherapy doctors (F.J and H.L.P). In this study, one hundred and twenty (120/206, 58.3%) patients received cisplatin/docetaxel and eighty-six (86/206, 41.7%) patients received cisplatin/etoposide.

NPS System

Routine laboratory blood test was performed, and the results were acquired from the Rizhao Center Hospital (Rizhao, China) within one week before IMRT. Based on the clinical information system, the following information was extracted from each study patient: gender, age, smoking status, pathological type, differentiation, tumor site, primary tumor size, TNM stage, serum albumin concentration, total cholesterol content, lymphocyte count, neutrophil count and monocytes count. As previously

reported by Galizia et al,¹⁸ NPS was calculated based on the serum albumin concentration, total cholesterol content, NLR and LMR. For patients with serum albumin ≥ 4 mg/dL, total cholesterol content >180 mg/dL, NLR < 2.96 , or LMR > 4.44 were scored as 0, while patients with serum albumin <4 mg/dL, total cholesterol content ≤ 180 mg/dL, NLR ≥ 2.96 , or LMR ≤ 4.44 was scored as 1. Patients were categorized into three groups based on NPS system: patients with a score of 0, 1 or 2, and 3 or 4 were assigned to groups 0, 1, and 2, respectively. And NPS were further analyzed in subgroups of stage IIIA or stage IIIB.

Follow-Up

Progression-free survival (PFS) was defined as the time from the date of starting radiotherapy to the date of disease progression recurrence, and OS was defined as the time between radiotherapy and death from any cause. Patients were followed up every 3 months for the first 3 years, then every 6 months for the following years and annually thereafter. Patient physical examination, laboratory test, CT or PET-CT were performed for evaluation of primary tumor and distant metastasis. Follow-up was conducted on 206 patients until August 2018.

Statistical Analysis

The IBM SPSS Statistics 23.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism software (version 5.0) were used to perform statistical analyses. *T*-tests or chi-square tests were applied to analyze the correlations between categorical variables and categorical data and NPS. Receiver operating characteristic (ROC) curves were generated to evaluate the recurrence prediction ability and differences of the scoring systems. The survival curves were performed by Kaplan–Meier method, and Log rank test was applied to compare prognostic survival differences among the NPS groups. The significant variables selected from univariate analysis were incorporated into multivariate analysis according to the Cox proportional hazards regression model. All the variables identified with a $P < 0.05$ were indicated to have statistical significance.

Results

Patient Characteristics

A total of 206 patients were diagnosed with NSCLC of unresectable stage IIIA or IIIB and received chemoradiotherapy in this study from January 2013 to January 2017 (Figure 1). The study population consisted of 86 females

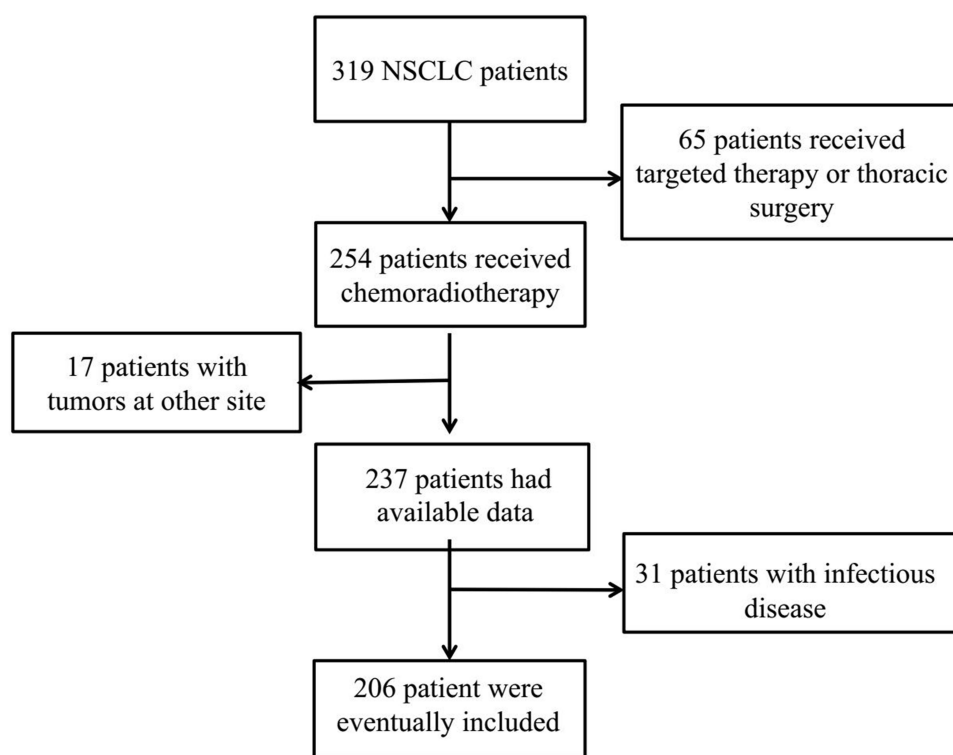


Figure 1 The flow chart of case screening.

(41.7%) and 120 male (58.3%), with the median age of 62 (range, 36–84) years. With regard to the tumor location, 96 (46.60%) tumors were located in the left and 110 (53.4%) tumors occurred in the right. Eighty-one (39.3%) patients had stage IIIA, and 125 (60.7%) had stage IIIB. One hundred and nineteen (57.8%) patients suffered recurrence and metastasis, and 138 (70.0%) patients died. In total, the median follow-up time was 37 months and ranged from 13 months to 59 months.

Associations of NPS System with Clinicopathologic Features

Based on the NPS system, the three groups were as follows: Group 0, 32 (15.5%) patients; Group 1, 135 (65.5%) patients; and Group 2, 39 (19.0%) patients (Table 1). Age ($P = 0.002$) was significantly different among the three NPS groups. However, there was no significant relation in patient, KPS, patient histology, differentiation, TNM status, serum CEA or CYFRA21-1 among the three groups.

NPS System Parameter and ROC Curves for Recurrence Prediction

All of the peripheral blood indicators are summarized in Table 2. The patients had a median serum albumin of 4.50 (95% confidence interval [CI]: 4.00–5.00), total cholesterol of 240 (95% CI: 230.00–261.99), NLR of 3.71 (95% CI: 3.55–3.85) and LMR of 2.97 (95% CI: 2.78–3.32). The scatter diagrams of serum albumin, total cholesterol, NLR and LMR were shown in Figure 2. NPS was found to have the largest area under the curve (AUC=0.715; 95% CI, 0.647–0.783; $P<0.001$). The AUCs were 0.589 ($P=0.029$), 0.623 ($P=0.003$), 0.630 ($P=0.001$), and 0.566 ($P=0.105$) for serum albumin, total cholesterol, NLR and LMR, respectively.

Univariate Analysis of OS and PFS

The univariate analysis results revealed that KPS ($P=0.001$), differentiation ($P=0.002$), primary tumor size ($P=0.012$), cTNM status ($P=0.001$), response rate ($P=0.022$) and NPS ($P<0.001$) were significantly correlated with OS. KPS ($P=0.005$), differentiation ($P=0.003$), cTNM status ($P=0.004$), response rate ($P=0.006$) and NPS ($P<0.001$) were significantly correlated with PFS (Table 3). We found no significant association between OS or PFS and age, patient histology, tumor site, serum CEA, and CYFRA21-1 (all $P>0.05$). Kaplan–Meier analyses were used to compare serum albumin, total

cholesterol, NLR, LMR and NPS. As shown in Figure 3, patients with serum albumin ≥ 4 mg/dL, total cholesterol >180 mg/dL and NLR ≤ 2.96 had significantly longer OS. Regarding PFS, the patients with serum albumin <4 mg/dL, total cholesterol ≤ 180 mg/dL and NLR > 2.96 had significantly worse PFS (Figure 4). The median OS in patients with group 0 was significantly higher than the OS in patients with group 1 and group 2 (27 vs 23 vs 21 months; $P<0.001$) (Figure 5A). Similarly, the median PFS were 15, 12, and 13 months for patients with group 0, 1, and 2, respectively ($P<0.001$) (Figure 5B). Further subgroup analysis revealed that patients with high NPS were more likely to have poorer outcomes in stage IIIA (OS, $P<0.001$; PFS, $P<0.001$) and stage IIIB (OS, $P=0.001$; PFS, $P=0.004$) (Figure 6).

Multivariate Analysis of OS and PFS

To future investigate the prediction value of NPS in stage III NSCLC, multivariate analysis results are shown in Table 4. Data confirmed that NPS was independent factor of OS (hazard ratio [HR], 1.988; 95% CI, 1.326–2.981; $P=0.001$) and that NPS (HR=1.793, 95% CI: 1.182–2.721, $P=0.006$) was significant prognostic factors of PFS. We also found that TNM status was as an independent predictor in OS ($P=0.031$).

Discussion

Establishment of a reliable prognostic prediction system is urgent in indicating risk stratification and tailoring appropriate treatment strategies for stage III NSCLC. The analysis of systemic inflammation and nutritional status can offer a method to evaluate the association between them and outcomes. The NPS as a new prognostic scoring system reflecting the patient's inflammation and nutritional status, to the best of our knowledge, the present study was the first to demonstrate the first association of NPS with outcomes and NPS serve better accuracy compared with other prognostic scoring systems.

In 1863, Virchow was the first researcher to report the relationship between inflammation and tumors.²¹ Then, many researchers investigate peripheral blood inflammation cells and explore the intrinsic relationship between inflammation and cancer. Inflammation is known to be an important factor in tumor progression and is one of the recognized hallmarks of tumor.²² In addition to, inflammatory cells are involved in tumor angiogenesis, immunosuppressive, resistance of radiation and chemotherapy drug by secreting inflammatory cytokines and immune negative

Table I Association of the Naples Prognostic Score and Clinical Characteristics

Characteristics	Naples Prognostic Score Group				P-value
	Values (N=206)	Group 0 (N=32)	Group 1 (N=135)	Group 2 (N=39)	
Age (years)					0.002
<60	87	13	48	26	
≥60	119	19	87	13	
Gender					0.524
Male	120	21	75	24	
Female	86	11	60	15	
Smoke					0.302
No	111	15	78	18	
Yes	95	17	57	21	
KPS					0.219
90–100	92	17	62	13	
70–80	114	15	73	26	
Patient histology					0.458
SCC	90	11	60	19	
AD	116	21	75	20	
Differentiation					0.076
Well/Moderate	79	15	55	9	
Poor	127	17	80	30	
Tumor site					0.182
Left	96	16	67	13	
Right	110	16	68	26	
Primary tumor size					0.050
≤ 4cm	104	16	75	13	
> 4cm	102	16	60	26	
cTNM status					0.256
IIIA	81	16	53	12	
IIIB	125	16	82	27	
Serum CEA(ng/mL)					0.280
Normal	130	23	80	27	
High	76	9	55	12	
CYFRA21-I(ng/mL)					0.585
Normal	123	18	84	21	
High	83	14	51	18	
Treatment modality					0.960
CCRT	93	15	60	18	
SCRT	113	17	75	21	
Response rate					0.251
CR+PR	79	11	57	11	
SD+PD	127	21	78	28	

Abbreviations: KPS, Karnofsky performance score; SCC, squamous cell carcinoma; AD, adenocarcinoma; BM, brain metastases; CEA, carcinoembryonic antigen; CYFRA21-I, cytokeratin 19 fragments; CCRT, concurrent chemoradiotherapy; SCRT, Sequential chemoradiotherapy; CR, complete response; PR, partial response; SD, Stable disease; PD, progressive disease.

Table 2 The Result of NPS System Parameter

Parameters	Median (Range)
Serum albumin (mg/dL)	4.50(3.10–5.70)
Total cholesterol (mg/dL)	240(114.25–895.00)
Neutrophil	6.19(2.16–12.19)
Lymphocyte	1.72(0.45–4.85)
Monocyte	0.54 (0.14–4.90)
NLR	3.71(0.74–14.34)
LMR	2.97(0.99–11.70)

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

regulation of cell infiltration.²³ Neutrophilia is an independent predictor of worse clinical outcome in malignant tumor patients.^{24,25} Lymphocytes act as the dominant anti-tumor cells. It has been demonstrated that lymphopenia is related to poor response and outcomes in several malignancies, including NSCLC.^{26–28} A high density of absolute monocyte counts is associated with shorter time to

response to immune checkpoint inhibitors.^{29,30} Basic research theories have been proposed to confirm this relationship. Neutrophils have several main functions: secreting growth factors to promote tumor formation; stimulating proliferation and metastasis by releasing inflammatory mediators; and protecting CTCs from immune cells attack.^{31,32} Lymphocytes participate in immune surveillance and kill tumor cells.^{33,34} Monocytes stimulate tumor angiogenesis, inflammatory response and improve tumor microenvironment by secreting oncostatin-M and VEGF.³⁵ NLR and LMR are more objective markers that reflect the inflammatory and immune status of the host. NLR was identified as predictive markers of clinical outcome in patients with various malignant tumors.^{36–38} There were also a number of clinical studies that investigated the prognostic significance of LMR, and the results confirmed that LMR was a significant prognostic predictor.^{39,40}

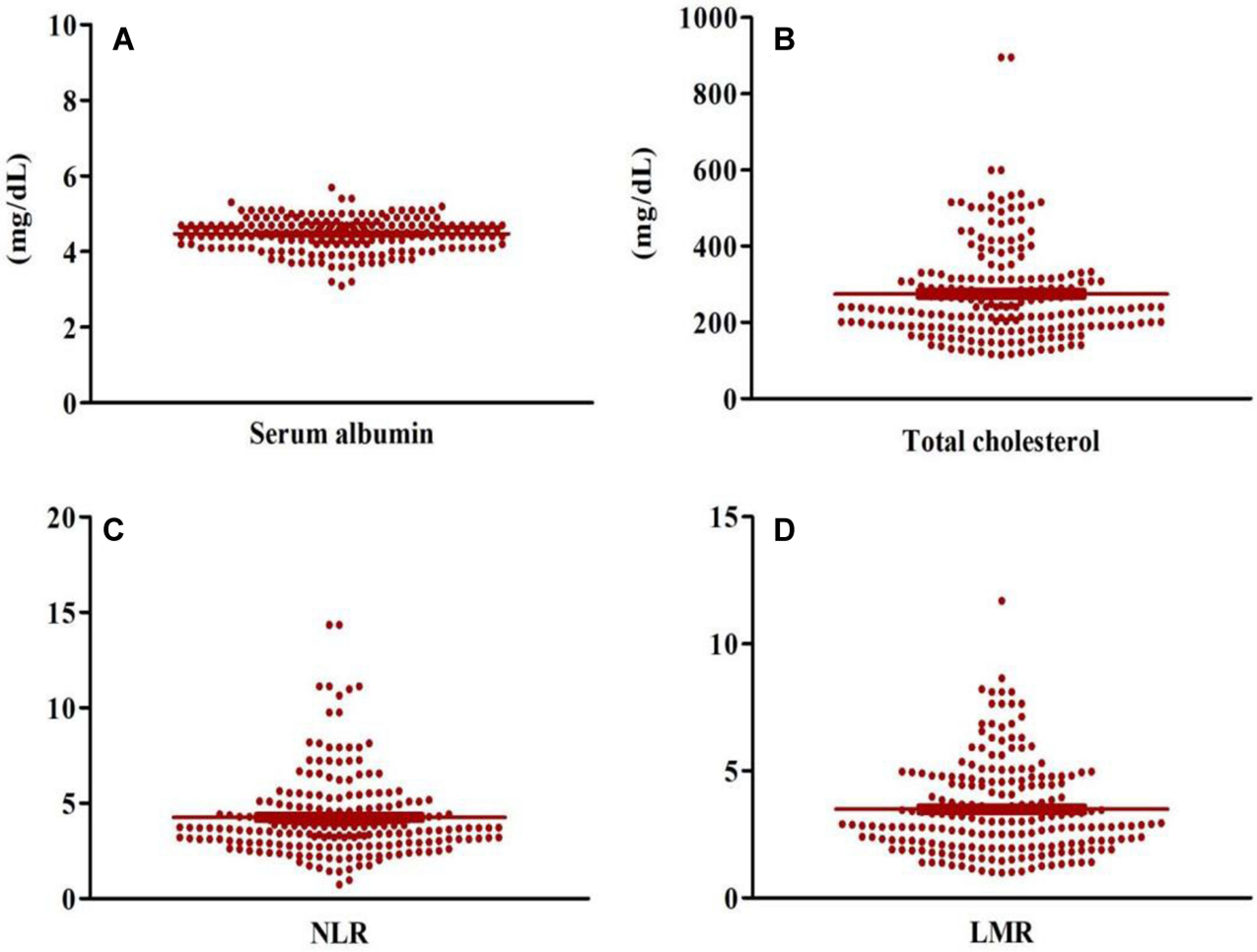


Figure 2 The expression levels of serum albumin (A), total cholesterol (B), NLR (C) and LMR (D) in scatter diagrams.

Table 3 Univariate Cox Regression Analysis of OS and PFS

Characteristics	OS			PFS		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (years)			0.096			0.481
<60	1.000			1.0000		
≥60	0.747	0.530–1.053		0.875	0.605–1.267	
Gender			0.809			0.994
Male	1.000	0.744–1.462		1.000	0.692–1.441	
Female	1.043			0.998		
Smoke			0.099			0.071
No	1.000	0.535–1.055		1.000	0.497–1.029	
Yes	0.751			0.715		
KPS			0.001			0.005
90–100	1.000	1.245–2.512		1.000	1.184–2.530	
70–80	1.768			1.731		
Patient histology			0.894			0.553
SCC	1.000	0.730–1.433		1.000	0.774–1.613	
AD	1.023			1.117		
Differentiation			0.002			0.003
Well/Moderate	1.000	1.252–2.647		1.000	1.235–2.784	
Poor	1.820			1.854		
Tumor site			0.111			0.248
Left	1.000	0.939–1.848		1.000	0.861–1.785	
Right	1.317			1.240		
Primary tumor size			0.012			0.179
≤ 4 cm	1.000	1.102–2.183		1.000	0.893–1.841	
> 4 cm	1.551			1.282		
cTNM status			0.001			0.004
IIIA	1.000	1.291–2.654		1.000	1.209–2.640	
IIIB	1.851			1.786		
Serum CEA(ng/mL)			0.660			0.979
Normal	1.000	0.765–1.526		1.000	0.691–1.462	
High	1.081			1.005		
CYFRA21-I(ng/mL)			0.20			0.08
Normal	1.000	0.560–1.129	0	1.000	0.493–1.042	1
High	0.795			0.717		
Treatment modality			0.11			0.13
CCRT	1.000	0.933–1.843	8	1.000	0.914–1.909	8
SCRT	1.311			1.321		
Response rate			0.022			0.006
CR+PR	1.000	1.064–2.190		1.000	1.174–2.607	
SD+PD	1.526			1.749		
NPS Group			<0.001			<0.001
0,1	1.000	1.845–		1.000	1.600–	
2	2.691	3.925		2.356	3.468	

Abbreviations: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance score; SCC, squamous cell carcinoma; AD, adenocarcinoma; CEA, carcinoembryonic antigen; CYFRA21-I, cytokeratin 19 fragments; CCRT, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

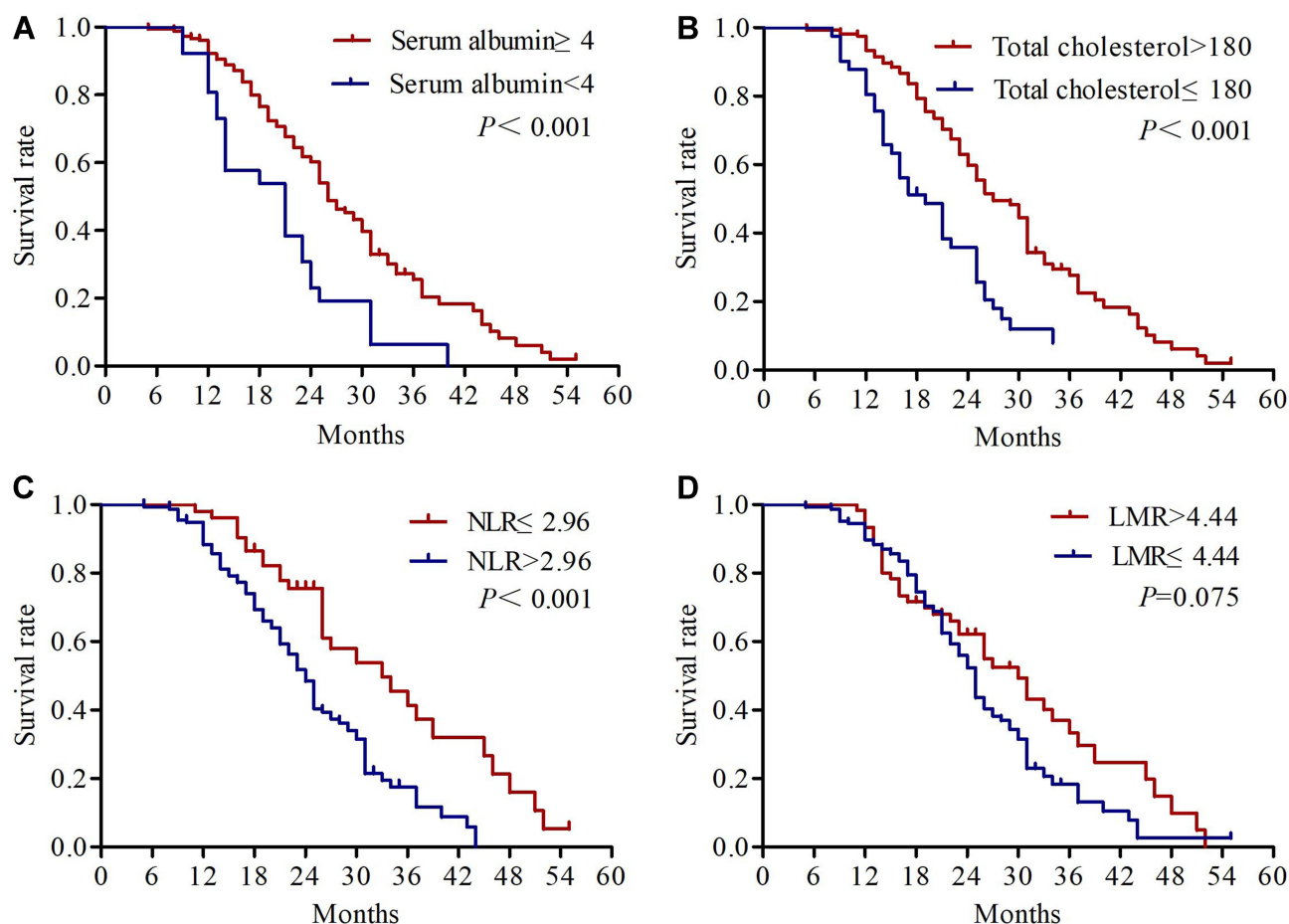


Figure 3 Kaplan-Meier survival curves of overall survival for serum albumin (A), total cholesterol (B), NLR (C) and LMR (D).

In addition to NLR and LMR, the biochemical mechanism by which NPS affects patient outcomes is also dependent on serum albumin, total cholesterol. Nutrition is closely associated with tumor growth, tumor angiogenesis and tumor progression and malnutrition is often the cause of these adverse factors. It is an urgent problem that we are faced with to search a prognostic evaluation system based on nutritional index. Serum albumin concentration is a marker for nutrition, and hypoalbuminemia has been proven to be a poor outcome in many nutritional scoring systems.^{41,42} Combined with the previous albumin-based prognostic evaluation system, we found that low albumin levels often represent highly malignant disease. In addition, total cholesterol content may be an important prognostic factor for overall survival in many human tumors, including NSCLC.^{43–45} The mechanism may be related to the following aspects: participating in the key malignant transformation of cellular signaling pathways via angiogenesis; inhibiting transmembrane signals

transmission; loss of immune surveillance and immune attack capability in immune cells.^{46,47}

Based on the above theoretical mechanism, NPS was based on four types of indicators, and NPS should be a more objective marker that reflects the patient's inflammation and nutritional status than all the other systemic inflammation scores. As previously analyzed, NPS had been confirmed as a predictive indicator for OS and had better predictive value than clinical prognostic parameters alone in patients with resected pancreatic cancer.⁴⁸ Kano et al found that NPS group had significant association with histopathological response to neoadjuvant treatments, and high NPS was associated with poor prognosis in locally advanced esophageal cancer patients.⁴⁹ In a similar study, Gennaro et al found that NPS is predictive of prognosis in colorectal cancer patients and may have important clinical guiding effects.¹⁸ Moreover, high NPS may be a significant contributing factor to poor prognosis in

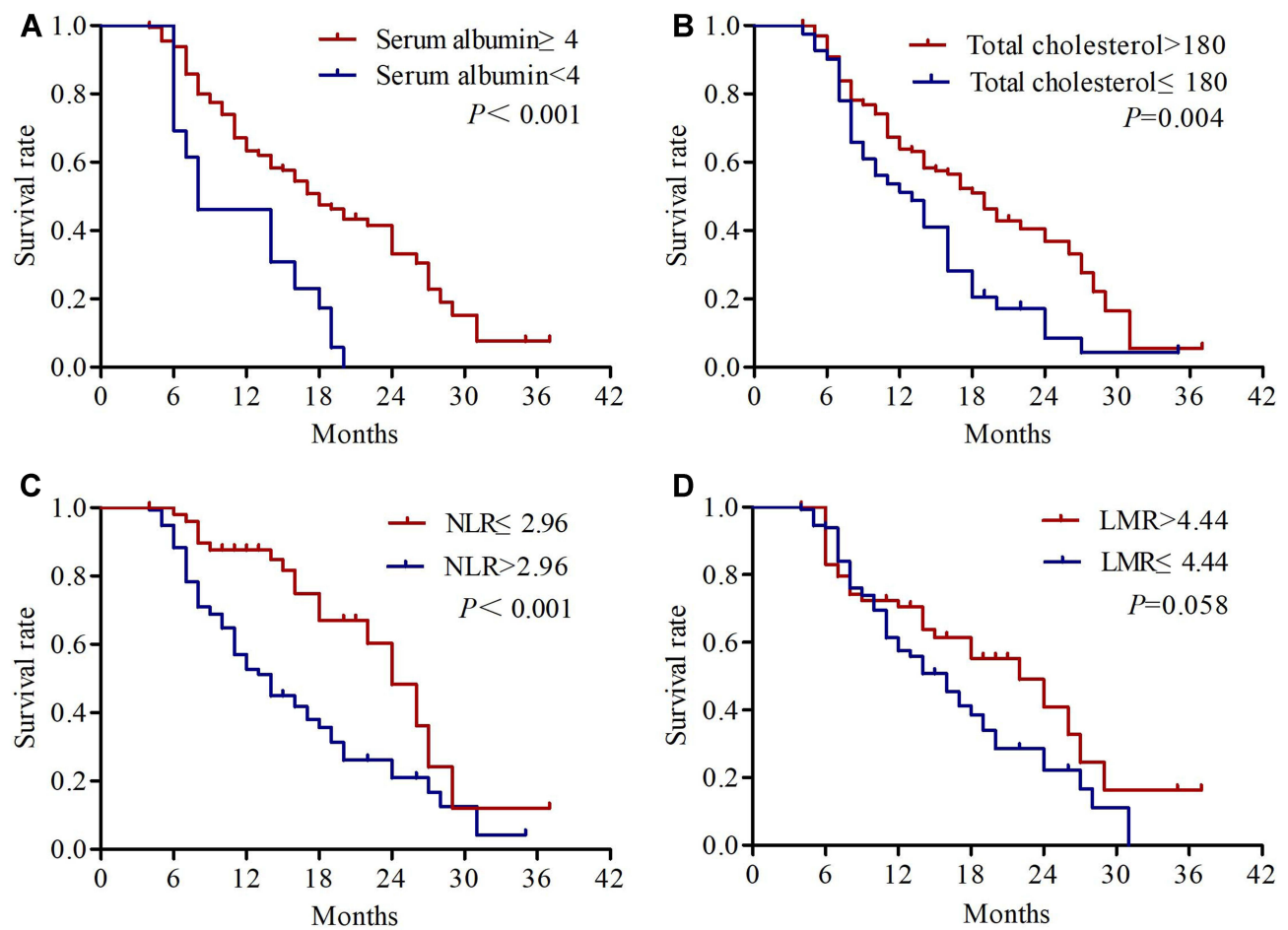


Figure 4 Kaplan-Meier survival curves of progression-free survival for serum albumin (A), total cholesterol (B), NLR (C) and LMR (D).

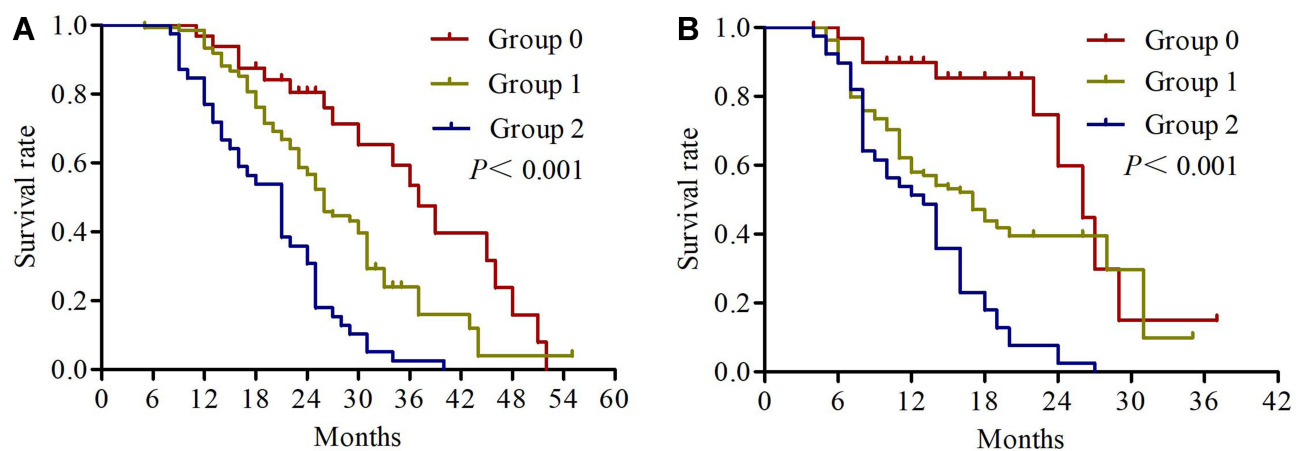


Figure 5 Kaplan-Meier survival curves of overall survival (A) and progression-free survival (B) for NPS group.

endometrial cancer, which is a valuable significantly independent prognostic factor.¹⁷ However, clinical data on NPS score system for NSCLC are still lacking, particularly in locally advanced NSCLC, which has not been reported so far. Li et al conducted a study involving 445 patients

with early-stage NSCLC in a single-center prospectively maintained database.⁵⁰ In this study, OS and DFS were significantly shortened in high NPS score group and pre-operative NPS could be an independent prognostic indicator. In addition, NPS held the better discriminative value

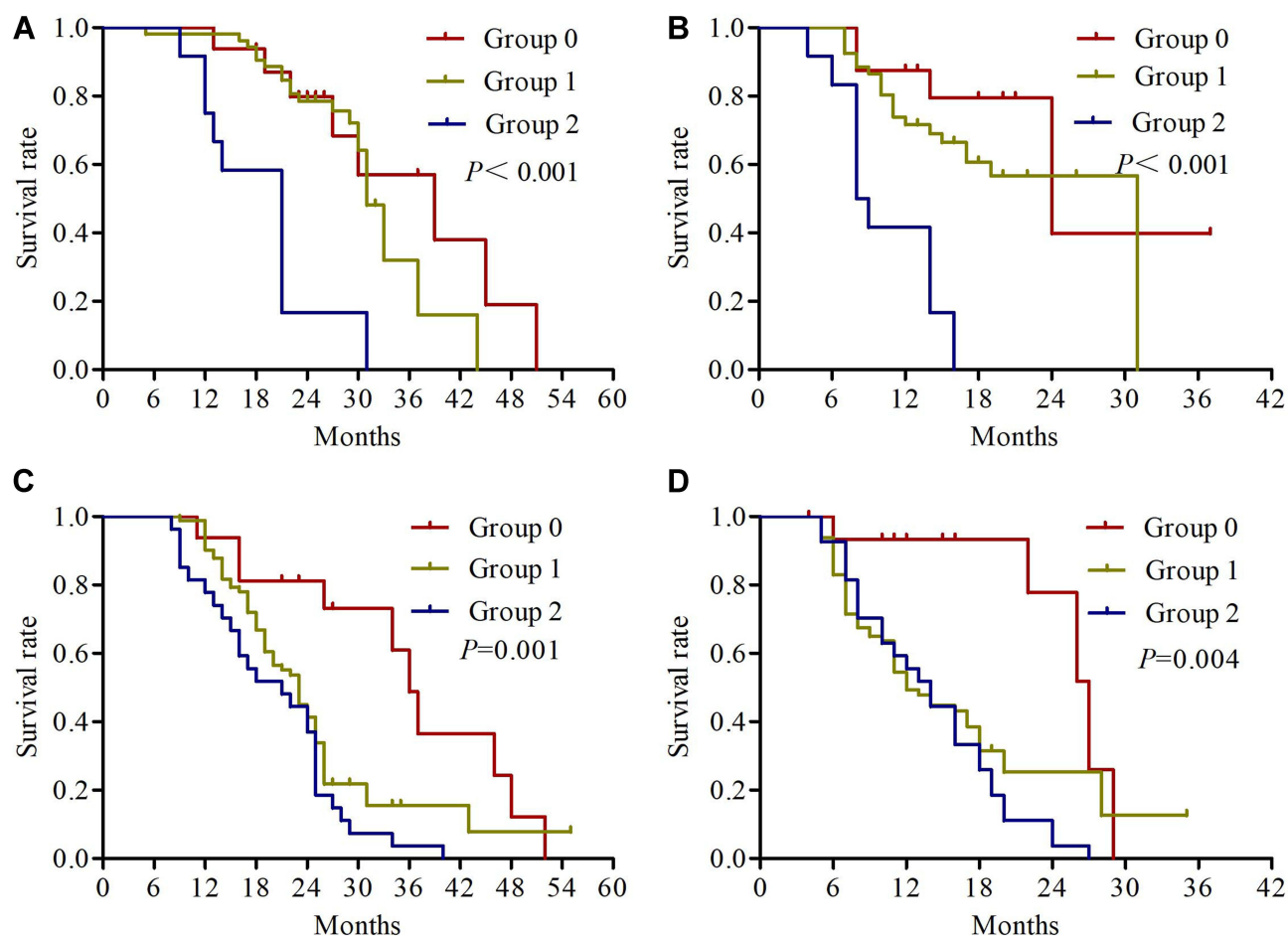


Figure 6 Kaplan-Meier survival curves of overall survival (A) and progression-free survival (B) for NPS group in stage IIIA NSCLC, and overall survival (C) and progression-free survival (D) for NPS group in stage IIIB NSCLC.

than other prognostic systems. By summarizing these research conclusions, NPS is an easily available and comprehensive predictive evaluation method, which represents a patient's whole-systemic inflammation and nutritional status in multidimensional aspects. As we have studied, our results revealed that NPS had the largest AUC compared with other indicators (Serum albumin, total cholesterol, NLR and LMR) according to the ROC analysis. We further proposed a new prediction model based on NPS, and results revealed that NPS was a strong independent prognostic factor. In this regard, its clinical application value was highlighted, which indicated its superiorities for identified patients with higher risk of recurrence or mortality.

Some limitations need to be addressed in this study. First, our study is a retrospective study, with a relatively small sample from a single center, which may reduce the generalizability of the study results. At the same time, selection bias is inevitable because of

study limitations. Second, laboratory indicators such as serum albumin, total cholesterol, neutrophils lymphocytes and monocytes may be influenced by various conditions, although we have strict inclusion criteria. Finally, the cutoff values of laboratory indicators were derived from the previous literature reports, which were not calculated by the highest Youden's index. This may not reflect differences in individual findings. Even so, the prognostic significance of NPS also presents considerable value in stage III NSCLC patients.

In this study, the NPS score system is an independent prognostic model affecting outcomes in stage III NSCLC patients. We found that the high NPS score is associated with poor OS and PFS. And the combination of laboratory indicators as NPS score system was superior to either indicator alone in terms of predicting ability. NPS score system can provide a more accurate assessment of outcomes and opinions on individualized hazard classification for stage III NSCLC patients.

Table 4 Multivariate Cox Regression Analysis of OS and PFS

Characteristics	OS			PFS		
	HR	95% CI	P-value	HR	95% CI	P-value
KPS 90–100 70–80	1.000 1.305	0.668–2.548	0.436	1.000 1.141	0.5690–2.288	0.710
Differentiation Well/Moderate Poor	1.000 1.130	0.548–2.331	0.74 0	1.000 1.235	0.578–2.638	0.58 6
Primary tumor size ≤ 4cm > 4cm	1.000 1.310	0.924–1.859	0.130			
cTNM status IIIA IIIB	1.000 1.512	1.038–2.204	0.03 1	1.000 1.446	0.958–2.181	0.07 9
Response rate CR+PR SD+PD	1.000 1.282	0.885–1.856	0.189	1.000 1.426	0.944–2.155	0.092
NPS Group 0/1 2	1.000 1.988	1.326–2.981	0.001	1.000 1.793	1.182–2.721	0.006

Abbreviations: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance score; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

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Disclosure

The authors report no conflicts of interest in this work.

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