

## Research Article

# Prognostic Value of Combination of Controlling Nutritional Status and Tumor Marker in Patients with Radical Non-Small-Cell Lung Cancer

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**Background.** Controlling nutritional status (CONUT) and tumor markers are associated with prognosis in patients with non-small-cell lung cancer (NSCLC). This study is aimed at exploring the potential usefulness of T-CONUT, constructed by combining CONUT and tumor markers, for NSCLC patients undergoing radical surgery. **Methods.** A total of 483 patients with NSCLC underwent radical surgical resection. The receiver characteristic operating curve (ROC) was used to select the tumor marker with the highest predictive performance, and CONUT was combined with this marker to construct the T-CONUT. The Kaplan–Meier method and log-rank test were used to analyze the overall survival (OS), and chi-square analysis was used to analyze the association between T-CONUT and clinicopathological characteristics. The independent risk factors were analyzed by Cox regression. A nomogram was constructed by R studio. Calibration plots, the *c*-index, and decision curves were evaluated for the performance of the nomogram. **Results.** ROC analysis showed that the predictive performance of CYFRA21–1 was better than that of CEA, NSE, and SCC. CYFRA21–1 was selected for combining with CONUT to construct T-CONUT. Elevated T-CONUT indicates poor prognosis of patients. Histological type, pTNM, and T-CONUT are independent risk factors associated with patient prognosis. The areas under the curve of the nomogram for predicting 3- and 5-year OS were 0.760 and 0.761, respectively. **Conclusion.** T-CONUT comprising CYFRA21–1 and CONUT can effectively predict the prognosis of NSCLC patients.

## 1. Introduction

Lung cancer (LC) has the second highest incidence of all cancers and is the leading cause of cancer death [1]. The pathological subtypes of LC are classified into non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), of which NSCLC is the most common pathological type, accounting for 85% of LCs [2]. Despite significant improvements in treatment in recent years, the prognosis for NSCLC remains poor, with a median survival time of only 30.5 months [3]. Accurately predicting the prognosis of NSCLC patients still faces great challenges, and there are even some differences in the prognosis of patients at the same stage [4].

LC is a malignant tumor with a high incidence of malnutrition and cachexia. Malnutrition has been reported in 26%

of NSCLC patients, while 46% of patients are at risk [5]. Malnutrition is not only a common problem faced by NSCLC patients at diagnosis but also a frequent sign during chemotherapy and adjuvant therapy. Esophagitis or anorexia caused by chemoradiotherapy may affect the treatment plan and increase the nutritional burden [6, 7]. Malnutrition can adversely affect the prognosis of patients with NSCLC, such as affected quality of life, treatment-resistant, and increased mortality [8, 9]. Therefore, it is necessary to develop fast, simple, and accurate markers to accurately identify the nutritional status of NSCLC patients before surgery, which is of great value for guiding clinical treatment and predicting prognosis.

Controlling nutritional status (CONUT) is calculated from serum albumin (Alb), total cholesterol (TC), and

peripheral lymphocyte count (TLC) [10], which relate to a variety of nutritional indicators that can enable quick assessment of nutritional status and allow the prognosis of NSCLC patients to be accurately predicted [11–13]. In addition to directly reflecting nutritional status, CONUT indirectly reflects the activity of tumor lesions. Elevated CONUT is often accompanied by higher levels of tumor markers [14] that help monitor tumor recurrence and metastasis [15, 16]. Increasing evidence confirms that the T-CONUT score, as jointly constructed from CONUT and tumor marker values, can not only provide a comprehensive preoperative nutritional assessment but also be a natural monitor of tumor activity. Researchers have shown its predictive value in colorectal cancer [17]. In addition, the nomogram constructed by tumor markers can effectively predict the prognosis of NSCLC patients [18]. However, there are few studies on T-CONUT in NSCLC, and the decision of whether to construct a nomogram with T-CONUT for better evaluation of the prognosis of NSCLC still needs to be further explored.

As a result, this study compared the predictive value of different tumor markers for the prognosis of NSCLC patients and selected the tumor marker with the highest predictive performance when combined with CONUT to construct T-CONUT. A nomogram was constructed based on the clinicopathological features of the patients.

## 2. Materials and Methods

**2.1. Patients.** This study retrospectively analyzed NSCLC patients who underwent radical surgical resection at the Department of Thoracic Surgery, Cancer Hospital Affiliated to Harbin Medical University, from December 2011 to May 2016. The diagnosis of NSCLC was based on the intraoperative pathological tissue obtained and confirmed by two pathologists. The patients received routine preoperative examinations during hospitalization, including CT, bone scan, electrocardiogram, routine hematology, and tumor markers. The clinicopathological information of patients was stored in the case system of the Cancer Hospital Affiliated to Harbin Medical University, including gender, age, tumor size, tumor location, and pTNM staging. The above content is in line with the eighth edition of the AJCC Staging Manual [19].

The inclusion criteria were as follows: (1) pathologically diagnosed patients with NSCLC; (2) undergo radical surgery; (3) patients without other malignancies.

The exclusion criteria were as follows: (1) preoperative radiotherapy or chemotherapy; (2) treatment with steroids; (3) autoimmune diseases; (4) serious infection; (5) hematological malignancies.

All patients underwent routine review after surgery, including chest CT, abdominal ultrasound, blood tumor markers, superficial lymph node ultrasound, and head MRI.

**2.2. Hematology Parameters.** Patients underwent routine hematology tests one week before surgery. Prognostic nutritional index (PNI) is calculated as peripheral blood lymphocyte count ( $\times 10^9/\text{ml}$ )  $\times 5$  + serum albumin value (g/l) [20]. Systemic inflammation score (SIS) was calculated as

TABLE 1: Patient characteristics.

Clinicopathological features	Patients 483(%)
Sex	
Male	281 (58.2)
Female	202 (41.8)
Age (years)	
$\leq 60$	284 (58.8)
$> 60$	199 (41.2)
BMI ( $\text{kg}/\text{m}^2$ ), median, range	23.39 (14.69-32.1)
SCC (ng/ml)	
$\leq 1.5$	409 (84.7)
$> 1.5$	74 (15.3)
CEA (ng/ml)	
$\leq 5$	327 (67.7)
$> 5$	156 (32.3)
NSE (ng/ml)	
$\leq 15.2$	369 (76.4)
$> 15.2$	114 (23.6)
CYFRA21-1 (ng/ml)	
$\leq 3.3$	259 (53.6)
$> 3.3$	224 (46.4)
Smoking history	
No	227 (47.0)
Yes	256 (53.0)
Tumor location	
Left lung	192 (39.8)
Right lung	291 (60.2)
Histological type	
Squamous cell carcinoma	157 (32.5)
Adenocarcinoma	301 (62.3)
Others	25 (5.2)
pTNM	
I	269 (55.7)
II	81 (16.8)
III	133 (27.5)
CONUT	
$< 2$	330 (68.3)
$\geq 2$	153 (31.7)
PNI	
$\geq 52.48$	203 (42.0)
$< 52.48$	280 (58.0)
SIS	
0	175 (36.2)
1	215 (44.5)
2	93 (19.3)

follows: Alb  $< 40$  g/l and LMR  $< 4.44$  scored 2; Alb  $\geq 40$  g/l or LMR  $\geq 4.44$  scored 1; Alb  $\geq 40$  g/l and LMR  $\geq 4.44$  scored 0 [21]. CONUT was calculated by Alb and TLC, which was divided into normal (0-1), mild (2-4), moderate (5-8), and severe (9-12, 14).

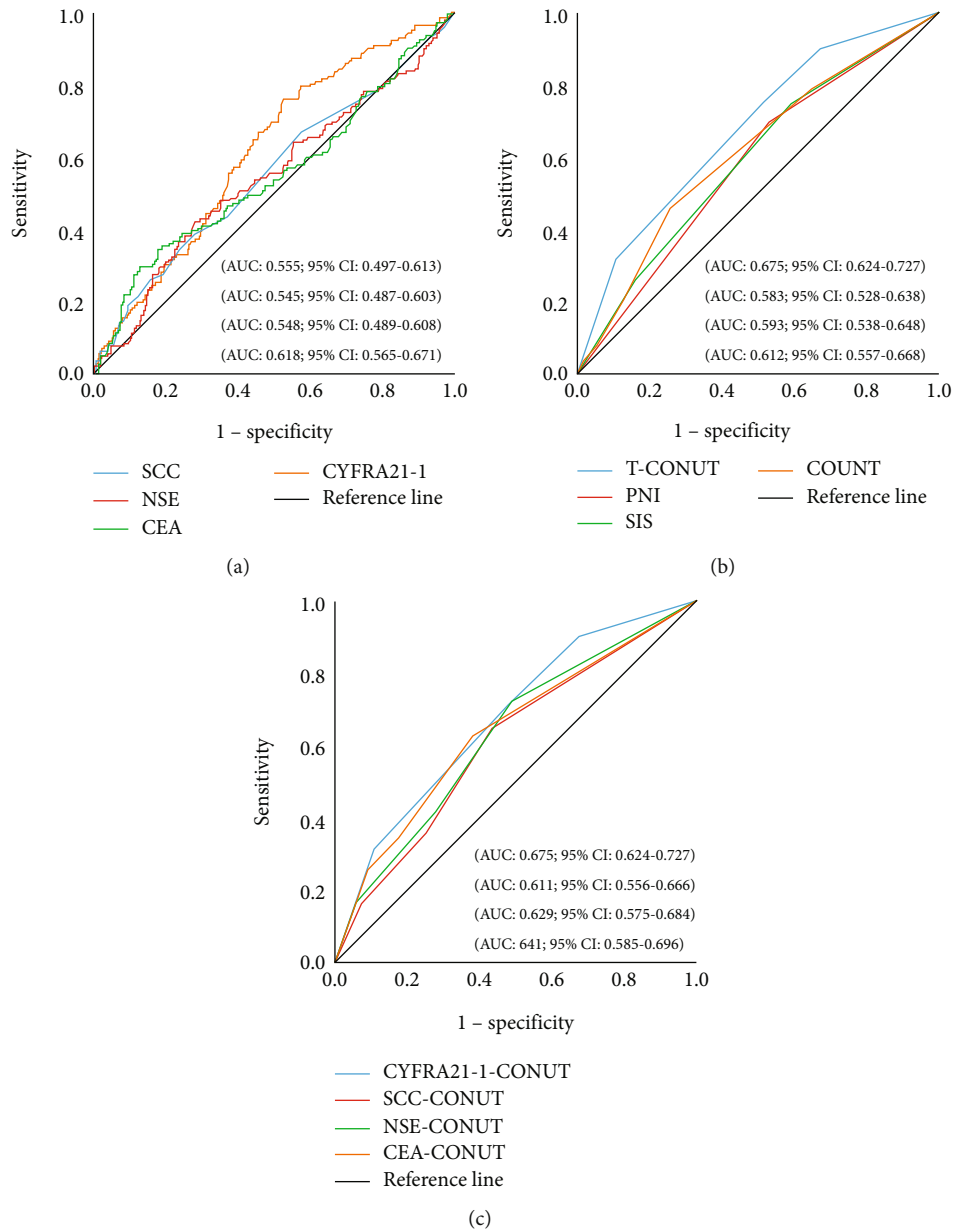


FIGURE 1: ROC of tumor markers and nutritional markers among total patients. (a) Comparison of predictive performance of different tumor markers. (b) Comparison of predictive performance of T-CONUT with nutritional markers. (c) Comparison of predictive performance of different tumor markers combined with CONUT.

**2.3. Construction of T-CONUT.** At first, a receiver characteristic operating curve (ROC) of carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1), neuron specific enolase (NSE), and squamous cell associated antigen (SCC) was established individually for the NSCLC patients. Then, the area under the curve (AUC) was calculated to determine the optimal cutoff values. The values above the cutoff were considered high, otherwise were considered to be low. Based on the tumor markers and the CONUT values, the patients were divided into four groups: group 1—tumor markers and CONUT both below the cutoff point; group 2—tumor markers below but CONUT above the cutoff point; group 3—tumor markers above while CONUT below

the cutoff point; and group 4—tumor markers and CONUT both above the cutoff point.

**2.4. Statistical Analysis.** Overall survival (OS) was defined as the follow-up time from the time of operation to the time of death or the last survival. If the patients were alive at the last follow-up, they were included in this study. ROC was used to calculate the AUC. The optimal cut-off value was calculated using the “Youden index.” Kaplan-Meier method with Long-rank was used to analyze survival curves. Cox regression models were used to analyze the calculation of hazard ratios (HRs) and 95% confidence intervals (CIs) and to identify independent risk factors. T-ROC and nomogram

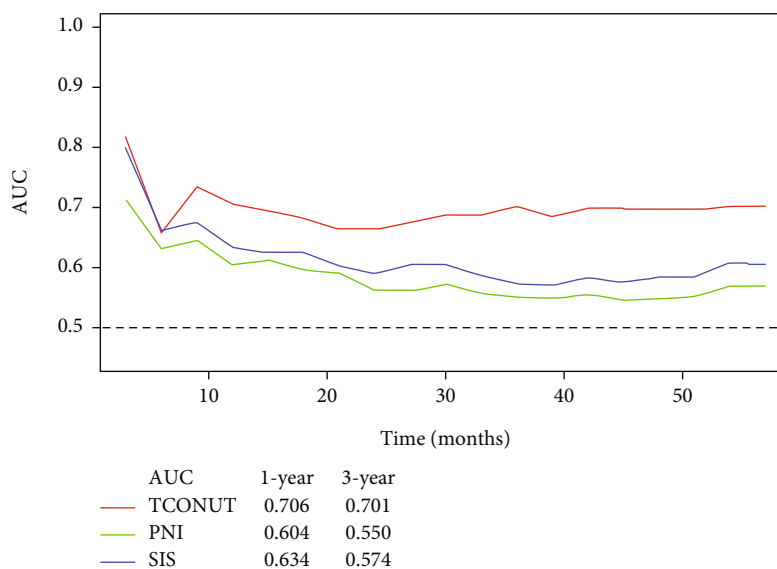


FIGURE 2: Time-dependent ROC curves for the T-CONUT, PNI, and SIS. The horizontal axis represents month after surgery, and the vertical axis represents the estimated AUC for survival at the time of interest. Red, green, and blue solid lines represent the estimated AUCs for the T-CONUT, PNI, and SIS, respectively.

were performed by R studio. Calibration plots, decision curve, and  $c$ -index were used to validate the performance of nomogram. All analyses were performed using SPSS for Windows version 25.0 and R software version 4.1.2 for statistical analysis,  $P < 0.05$  was considered statistically significant.

### 3. Results

**3.1. Patient Characteristics.** The study included 483 patients, 281 males and 202 females, with a median age of 58 (range 25-78) and BMI at 23.39 (range 14.69-32.1). Among them, there were 269 at stage I, 81 at stage II, and 133 at stage III, according to the pTNM definition (Table 1).

**3.2. Accuracy Comparison of Different Prognostic Markers.** To select tumor markers suitable for evaluating NSCLC according to ROC, CYFRA21-1 and CONUT had the highest AUC (Figures 1(a) and 1(b)), and the cutoff values of CYFRA21-1, CONUT, and PNI are 2.75, 2, and 52.48.

After finding that CYFRA21-1 and CONUT have the highest AUC, we construct T-CONUT according to the cutoff values of CYFRA21-1 and CONUT. The patients in group 1-group 4 were 125 (25.9%), 71 (14.7%), 205 (42.4%), and 82 (17%), respectively. The prognostic accuracy of T-CONUT, PNI, and SIS was compared by ROC and T-ROC. The results showed that T-CONUT had the highest AUC, which indicated that T-CONUT had high accuracy in predicting OS (Figures 1(b) and 2).

Furthermore, we combine different tumor markers with CONUT and ROC showed that the cutoff values of SCC, NSE, and CEA are 1.15, 14.18, and 6.63. Then, we combine different tumor markers with CONUT, respectively. The AUC of CYFRA21-1-CONUT was higher than that of SCC-CONUT, NSE-CONUT, and CEA-CONUT (Figure 1(c)).

**3.3. T-CONUT and Patient Survival.** Chi-square analysis showed that T-CONUT was associated with sex, SCC, NSE ( $P < 0.001$ ), smoking history, histological type, and pTNM stage and was significantly correlated (Table 2).

The survival curve showed that the 5-year OS rate of  $\text{CONUT} \geq 2$  was significantly lower than that of  $\text{CONUT} < 2$  (54.5% vs. 74.8%) (Figure 3(a)); the 5-year OS rate of  $\text{CYFRA21-1} > 2.75$  was significantly lower than that of  $\text{CYFRA21-1} \leq 2.75$  (59.0% vs. 81.4%) (Figure 3(b)); for T-CONUT, the 5-year OS rates of group 1-group 4 were 87.6%, 70.7%, 66.8%, and 38.6% (Figure 3(c)). Obviously, elevated T-CONUT indicates poor prognosis of patients.

According to pTNM, for stage I, the 5-year OS rates of T-CONUT group 1-4 were 97.4%, 82.7%, 74.3%, and 60.1%. For stage II, the 5-year OS rates of T-CONUT groups 1-4 were 72.4%, 66.7%, 60.8%, and 42.0%. For stage III, the 5-year survival rates of T-CONUT groups 1-4 were 63.8%, 27.3%, 57.2%, and 23.3% (Figures 4(a)-4(c)).

The Cox found that histological type, pTNM, and T-CONUT were independent risk factors (Table 3).

**3.4. Construction of a Nomogram.** Histological type, pTNM, and T-CONUT were independent risk factors; we combined these factors to construct a nomogram (Figure 5(a)). ROC showed that nomogram had the highest AUC in 3-year and 5-year OS, the sensitivity were 75.5% and 64.6%, and the specificity were 85.2% and 52.5% (Figures 5(b) and 5(d)). The  $c$ -index was 0.725. Calibration plots and decision curve showed good predictive performance of nomogram (Figures 5(c), 5(f), and 6).

### 4. Discussion

Preoperative nutritional status is crucial for lung cancer patients, and malnutrition adversely affects lung cancer patients, whether for treatment, quality of life, or predicting

TABLE 2: Chi-square analysis of T-CONUT and patient characteristics.

Clinicopathological features	Group 1 (125)	Group 2 (71)	Group 3 (205)	Group 4 (82)	P
Sex					<b>0.001</b>
Male	56 (44.8)	41 (57.7)	126 (61.5)	58 (70.7)	
Female	69 (55.2)	30 (42.3)	79 (38.5)	24 (29.3)	
Age (years)					0.209
≤60	78 (62.4)	47 (66.2)	110 (53.7)	49 (59.8)	
>60	47 (37.6)	24 (33.8)	95 (46.3)	33 (40.2)	
BMI (kg/m <sup>2</sup> )					0.093
≤23.39	58 (46.4)	34 (47.9)	96 (46.8)	51 (62.2)	
>23.39	67 (53.6)	37 (52.1)	109 (53.2)	31 (37.8)	
SCC (ng/ml)					<b>&lt;0.001</b>
≤1.5	120 (96.0)	65 (91.5)	166 (81.0)	58 (70.7)	
>1.5	5 (4.0)	6 (8.5)	39 (19.0)	24 (29.3)	
CEA (ng/ml)					0.275
≤5	86 (68.8)	49 (69.0)	144 (70.2)	48 (58.5)	
>5	39 (31.2)	22 (31.0)	61 (29.8)	34 (41.5)	
NSE (ng/ml)					<b>&lt;0.001</b>
≤15.2	111 (88.8)	67 (94.4)	137 (66.8)	54 (65.9)	
>15.2	14 (11.2)	4 (5.6)	68 (33.2)	28 (34.1)	
Smoking history					<b>0.003</b>
No	73 (58.4)	39 (54.9)	80 (39.0)	35 (42.7)	
Yes	52 (41.6)	32 (45.1)	125 (61.0)	47 (57.3)	
Tumor location					0.302
Left lung	51 (40.8)	29 (40.8)	73 (35.6)	39 (47.6)	
Right lung	74 (59.2)	42 (59.2)	132 (64.4)	43 (52.4)	
Histological type					<b>&lt;0.001</b>
Squamous cell carcinoma	17 (13.6)	21 (29.6)	88 (42.9)	31 (37.8)	
Adenocarcinoma	105 (84.0)	46 (64.8)	108 (52.7)	42 (51.2)	
Others	3 (2.4)	4 (5.6)	9 (4.4)	9 (11.0)	
pTNM					<b>&lt;0.001</b>
I	84 (67.2)	48 (67.6)	110 (53.7)	27 (32.9)	
II	17 (13.6)	12 (16.9)	32 (15.6)	20 (24.4)	
III	24 (19.2)	11 (15.5)	63 (30.7)	35 (42.7)	

prognosis. Malnutrition in lung cancer patients may be caused by insufficient intake, impaired function, and complications of adjuvant therapy [22, 23]. A previous study reported that 42.8% of lung cancer patients had malnutrition, a proportion which is significantly higher than for some digestive system tumors such as gastric cancer and colorectal cancer [23]. Therefore, accurately assessing the nutritional status of LC patients is of great significance for better tolerance of adjuvant therapy, nutritional intervention guidance, and prognosis.

In this study, we found that the CONUT score could effectively predict the prognosis of NSCLC patients undergoing radical surgery. CONUT had the highest AUC, which was consistent with previous studies [24]. Part of the reason is that CONUT contains total cholesterol levels, which can reflect inflammation in the body, liver function, changes in body fluids and energy reserves. However, the calculation methods of PNI and SIS do not include total cholesterol.

Hikage et al. showed that CONUT has high sensitivity in patients with hypocholesterolemia [25], and changes in total cholesterol levels can effectively judge postoperative recovery and tumor aggressiveness. Total cholesterol levels tend to decrease when tumors recur, suggesting that CONUT can more comprehensively and accurately reflect the nutritional status of NSCLC [26]. In addition, there are certain differences in the nutritional status of ethnic groups in different regions. For example, the obesity rate in Western countries is higher than in Eastern countries, and the obesity rate in economically developed regions is higher than in low-income regions [27–29]. Therefore, some specific nutritional scores help better predict prognosis [30, 31]. Our institution is a high-capacity center in Northeast China, and the results also have certain applicable value. Although our results may have limited clinical applicability, this does not prevent us from making recommendations for LC experts: for LC patients with a high incidence of malnutrition, variations

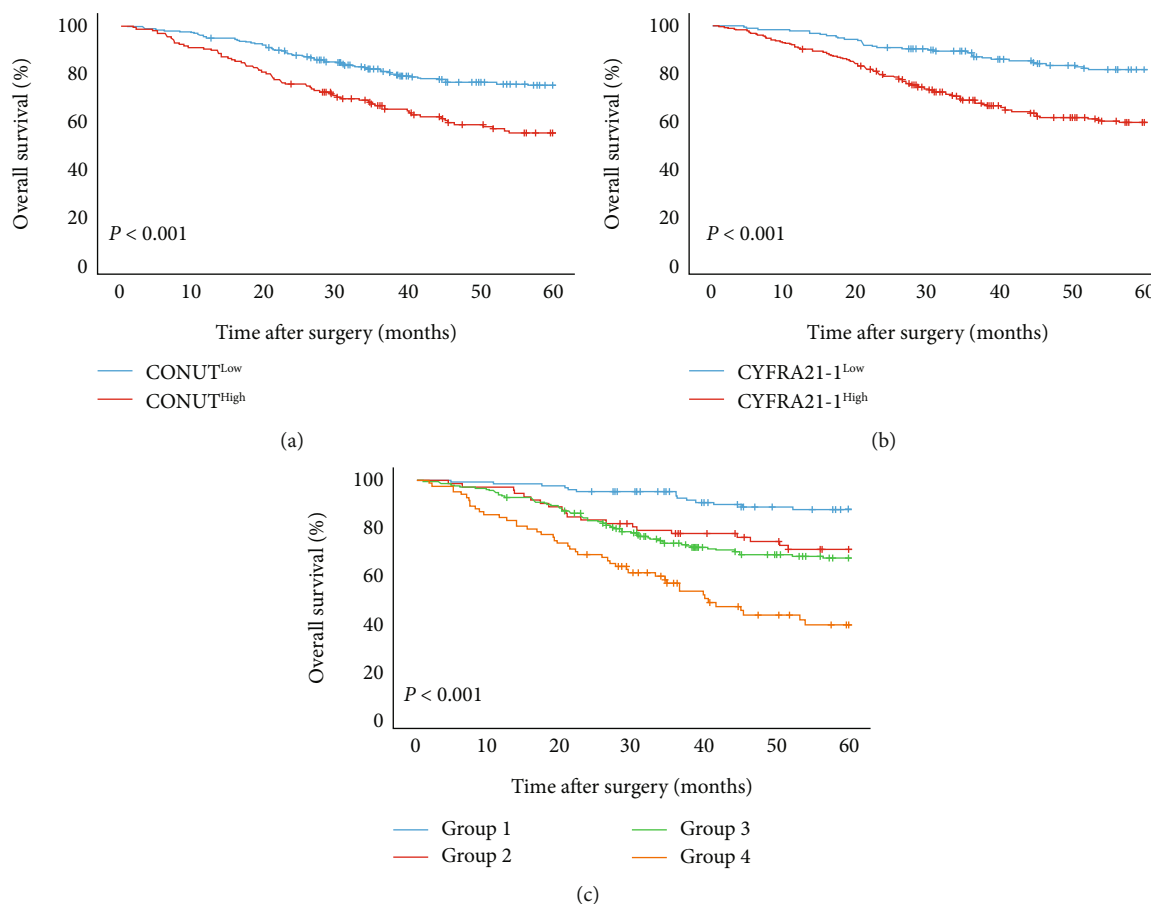


FIGURE 3: Kaplan–Meier analysis of OS of overall NSCLC patients. (a) Association of the CONUT with the OS of overall patients. (b) Association of the CYFRA21-1 with the OS of overall patients. (c) Association of the T-CONUT with the OS of overall patients.

in the nutritional status of lung cancer patients with different physiques in different regions needs to be recognized. At the same time, we also call for multicenter and large-sample studies to use region and ethnicity as independent evaluation factors for nutritional indicators, which will help to more accurately assess the nutritional status of patients before surgery.

We found that elevated CONUT was associated with poor prognosis, suggesting that poor nutritional status will lead to poor prognosis. This finding indicates that different nutritional indicators play different roles in NSCLC patients. Albumin is synthesized by the liver and has antitumor oxidative properties [32]. Decreased albumin reflects a loss of body defenses and reduced responsiveness to antitumor therapy [33]. Guner et al. showed that albumin was more prognostic than NLR and PLR [34], and the score weight of albumin in the CONUT score was twice that of other indicators, which also shows that albumin has importance for the prognosis of patients. Cholesterol participates in the basic structure of cell membranes and maintains cell physiological functions through intracellular signal transduction. Decreased cholesterol levels suggest both a lack of energy storage and metabolic imbalances that contribute to the development and progression of cancer [35]. As an important part of the immune system, lymphocytes inhibit tumor

cell growth, invasion, and migration by exerting cytotoxic functions, and their decreased levels suggest a poor prognosis for patients [36]. These mechanisms explain why elevated CONUT is associated with poor patient outcomes.

Notably, some studies have found that CONUT is significantly associated with tumor marker levels, and when CONUT is elevated, it is often accompanied by higher tumor marker levels [14, 37]. Selecting specific tumor markers according to different tumor tissues helps to accurately determine the biological behavior of tumors. The T-CONUT constructed by Yamamoto et al. combines CEA and CONUT and can effectively predict the prognosis of colorectal cancer patients [17]. T-CONUT constructed by Wang et al. as a combination of CA19-9 and CONUT can well predict the prognosis of patients with pancreatic ductal adenocarcinoma [38]. These studies suggest that the combined score can provide more comprehensive prognostic information and better serve patients. They also provide a good theoretical basis for us to combine tumor markers with CONUT as T-CONUT may have better predictive performance for NSCLC.

ROC showed that CYFRA21-1 was more accurate in predicting prognosis than CEA, SCC, and NSE, which was consistent with previous studies [39]. Although the sensitivity of tumor markers depends on tumor tissue classification,

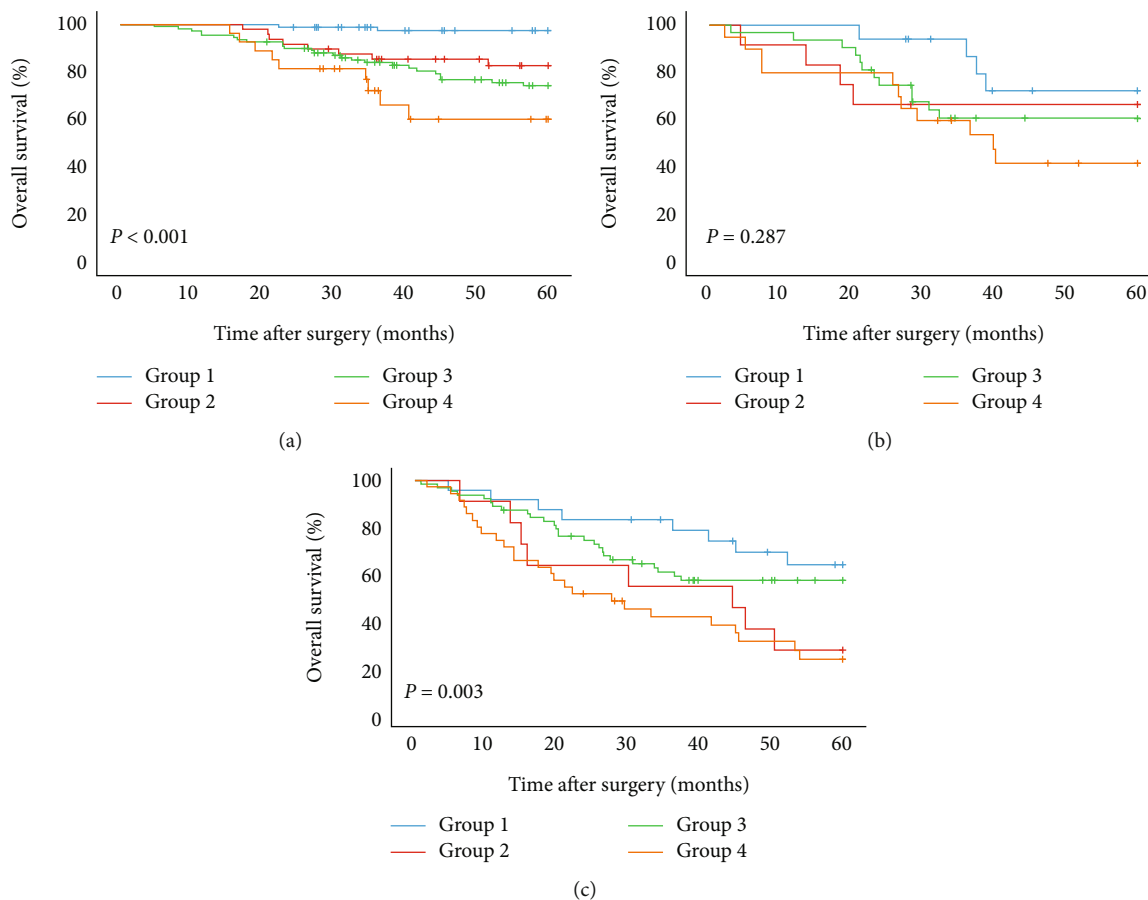


FIGURE 4: Kaplan–Meier analysis of OS of NSCLC patients at each pTNM stage according to the T-CONUT. (a) Association of the T-CONUT with the OS of patients with stage I NSCLC. (b) Association of the T-CONUT with the OS of patients with stage II NSCLC. (c) Association of the T-CONUT with the OS of patients with stage III NSCLC.

different studies have shown that CYFRA21-1 can effectively assess the prognosis of NSCLC patients. Zhang et al. found that CYFRA21-1 was an independent risk factor associated with the prognosis of lung adenocarcinoma whose predictive power was better than that of CEA and CSE [16]. Reinmuth et al. showed that CYFRA21-1 was more sensitive to lung squamous cell carcinoma than CEA, NSE, and SCC [40]. These results suggest that CYFRA21-1 still has good applicability, even for different histological types. In addition, we combined different tumor markers with CONUT and still found that T-CONUT, constructed with CYFRA21-1 and CONUT, had the highest AUC. This indicates that CYFRA21-1-CONUT is more suitable for predicting the prognosis of NSCLC patients; it can provide simple, accurate, and rapid preoperative evaluation and has definite applicable value.

After constructing T-CONUT from CYFRA21-1 and CONUT, we found that strong tumor aggression was associated with increased T-CONUT, suggesting that greater aggression would lead to lower nutritional status. In addition, we also found that when T-CONUT scores were higher, there was a significantly increased proportion of patients who smoked. Smoking is one of the causes of LC. Smoking may suppress appetite and affect eating [41] while anorexia can lead to insufficient nutritional intake and

weight loss. As anorexia progresses, lung cancer patients may eventually develop refractory cachexia [42]. Smoking can also lead to more aggressive lung cancer, acquisition of drug resistance, and ultimately, poor prognosis [43, 44]. Therefore, smoking cessation will not only reduce the incidence of LC but also help improve nutritional status.

Clinically, pTNM staging can accurately assess the biological behavior of NSCLC and predict prognosis. However, nutritional status gradually decreases with increasing pTNM staging, and pTNM staging based on macroscopic anatomy cannot provide microscopic blood prognostic information. Some blood nutritional markers, such as albumin serum and total cholesterol, have the advantages of being cheap and easy to apply and can allow rapid preoperative assessment. More importantly, these blood nutritional markers can accurately predict the prognosis of patients with NSCLC. Li et al. constructed a nomogram based on pTNM staging and the albumin-fibrin ratio to accurately predict the prognosis of NSCLC [45]. Guo et al. constructed a combination of N stage and serum albumin to globulin ratio as a nomogram to accurately predict long-term survival in NSCLC [46]. Zeng et al. constructed C-reactive protein and TNM staging as a nomogram which can accurately predict the prognosis of NSCLC patients undergoing radical surgery [47]. These studies demonstrate that predictive

TABLE 3: The Cox regression of overall patients.

Clinicopathological features	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Sex		0.111		
Male	1			
Female	0.757 (0.537-1.066)			
Age	0.994 (0.976-1.014)	0.566		
BMI	0.954 (0.907-1.002)	0.061		
SCC	1.059 (1.004-1.117)	<b>0.034</b>	1.015 (0.952-1.081)	0.655
CEA	1.000 (0.997-1.004)	0.811		
NSE	0.999 (0.995-1.004)	0.786		
Smoking history		0.513		
No	1			
Yes	1.117 (0.802-1.555)			
Tumor location		0.484		
Left lung	1			
Right lung	1.130 (0.803-1.589)			
Histological type		<b>0.014</b>		<b>0.004</b>
Squamous cell carcinoma	1		1	
Adenocarcinoma	1.230 (0.845-1.791)	0.280	1.856 (1.211-2.843)	<b>0.005</b>
Others	2.558 (1.364-4.797)	<b>0.003</b>	2.513 (1.316-4.801)	<b>0.005</b>
pTNM		<b>&lt;0.001</b>		<b>&lt;0.001</b>
I	1		1	
II	2.806 (1.771-4.445)	<b>&lt;0.001</b>	2.614 (1.619-4.222)	<b>&lt;0.001</b>
III	4.036 (2.757-5.907)	<b>&lt;0.001</b>	3.248 (2.183-4.834)	<b>&lt;0.001</b>
T-CONUT		<b>&lt;0.001</b>		<b>&lt;0.001</b>
0	1		1	
1	2.749 (1.389-5.443)	<b>0.004</b>	2.720 (1.352-5.471)	<b>0.005</b>
2	3.254 (1.823-5.808)	<b>&lt;0.001</b>	3.252 (1.800-5.874)	<b>&lt;0.001</b>
3	7.204 (3.948-13.145)	<b>&lt;0.001</b>	4.716 (2.470-9.003)	<b>&lt;0.001</b>
PNI		<b>0.002</b>		0.336
≥52.48	1		1	
<52.48	1.744 (1.219-2.495)		1.243 (0.798-1.938)	
SIS		<b>0.003</b>		0.466
0	1		1	
1	1.746 (1.167-2.612)	<b>0.007</b>	1.315 (0.840-2.057)	0.231
2	2.175 (1.374-3.442)	<b>0.001</b>	1.338 (0.761-2.353)	0.311

models constructed from anatomical staging and nutritional markers can personalize patient risk stratification, reduce prognostic bias, and serve patients better. Notably, we combined different tumor markers with CONUT and ROC and showed that CYFRA21-1-CONUT had the highest AUC. Moreover, Cox analysis showed that T-CONUT constructed from CYFRA21-1 and CONUT, histological type, and pTNM stage were independent risk factors associated with patient prognosis. Afterward, we integrated the above parameters to construct a nomogram model. However, although a nomogram built with CYFRA21-1-CONUT had the highest AUC, the AUC values for ROCs in this study were not as high as expected. We think this may be due to the small sample size, also recognizing that a larger sample

will be required for validation. Nevertheless, the AUC of the nomogram in predicting the patient's OS at both 3 and 5 years was higher than that of pTNM staging. This indicates that T-CONUT can supplement pTNM staging with more comprehensive prognostic information. This study suggests that the nomogram constructed with T-CONUT can provide clinicians with more comprehensive tumor prognostic information, which is helpful for comprehensively grasping the biological behavior of the tumor, and its prognostic performance is higher than that of traditional pTNM staging. The calibration plot showed that the nomogram performed well in predicting the status of patients at 3 and 5 years. The advantages of the nomogram also show that both nutritional status and pTNM staging play an important role in



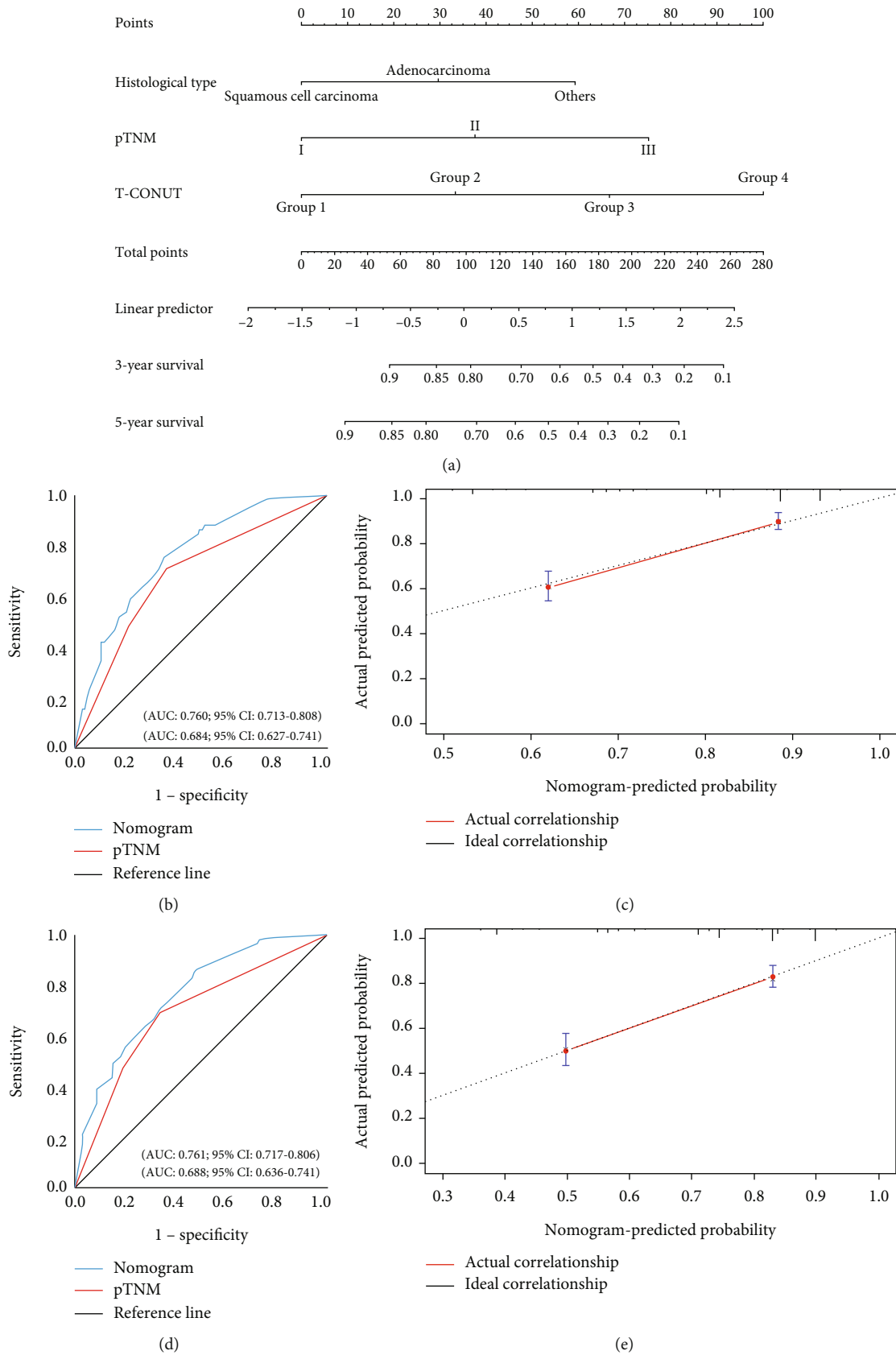


FIGURE 5: (a) Nomogram model predicting the 3- and 5-year OS of all patients. (b) ROC curve of the nomogram model predicting the 3-year OS of all patients. (c) Calibration curve for 3-year nomogram predictions. (d) ROC curve of the nomogram model predicting the 5-year OS of all patients. (e) Calibration curve for 3-year nomogram predictions.

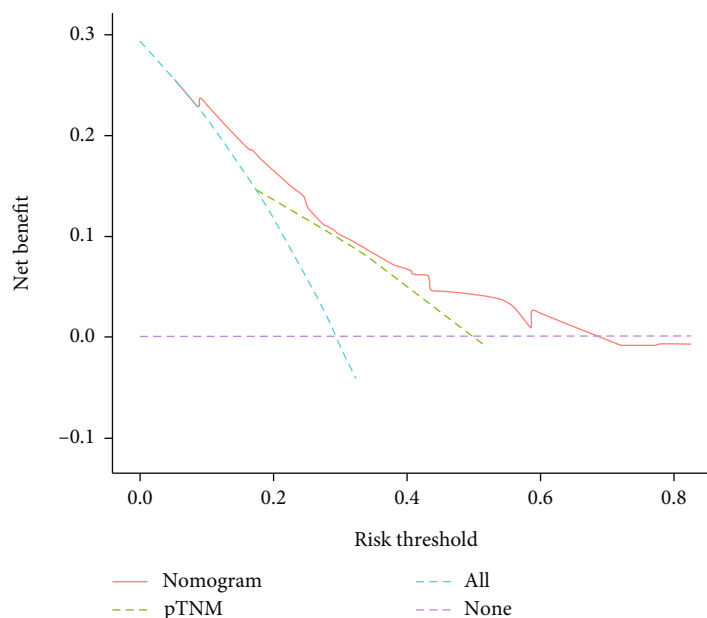


FIGURE 6: Decision curve analysis for the 5-year survival predictions. In the decision curve analysis, the  $y$ -axis indicates net benefit, calculated by summing the benefits (true positives) and subtracting the harms (false positives). The nomogram model (red dotted line) had the highest net benefit compared with the pTNM staging system (green dotted line). The straight line represents the assumption that all the patients will die, and the horizontal line represents the assumption that none of the patients will die.

predicting the prognosis of NSCLC. Some nutritional markers supplement pTNM staging with more comprehensive prognostic information. The nomogram combined with staging can better serve NSCLC patients and is worthy of clinical application.

**4.1. Research Limitations.** There are some limitations to this retrospective study. First, the results of this study require multicenter validation. Second, we only collected the information of tumor markers and nutritional markers of patients before surgery, and dynamic monitoring of these indicators can help predict prognosis more accurately.

## 5. Conclusion

The T-CONUT constructed by the combination of CYFRA21-1 and CONUT can effectively predict the prognosis of NSCLC patients. An elevated T-CONUT group suggested a poor prognosis. Furthermore, the nomogram constructed by T-CONUT combined with the clinicopathological features of the patients helps to better serve NSCLC patients.

## Data Availability

The data used to support the findings of the manuscript are available by contacting the corresponding author upon reasonable request.

## Ethical Approval

All procedures followed were in accordance with the ethical standards of the Human Subjects Responsibility Committee

(institutional and national) and the 1964 Declaration of Helsinki and subsequent editions. This study was approved by the Ethics Committee of the Cancer Hospital Affiliated to Harbin Medical University (ChiECRCT20210277).

## Conflicts of Interest

The authors declare that they have no conflict of interest.

## Authors' Contributions

Keru Ma and Hao Wang designed and conceived this project, and they contributed equally to this work. Keru Ma, Hao Wang, and Xiangyu Jiang interpreted and analyzed the data. Jianqun Ma revised the manuscript for important intellectual content, and Keru Ma, Hao Wang, Xiangyu Jiang, and Chengyuan Fang participated in the patient information collection. Keru Ma and Hao Wang contributed equally to the work as first authors.

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## References

- [1] H. Sung, J. Ferlay, R. L. Siegel et al., "Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA: a Cancer Journal for Clinicians*, vol. 71, no. 3, pp. 209–249, 2021.
- [2] D. Planchard, S. Popat, K. Kerr et al., "Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for

- diagnosis, treatment and follow-up<sup>†</sup>,” *Annals of Oncology*, vol. 29, p. iv192, 2018.
- [3] M. Maemondo, A. Inoue, K. Kobayashi et al., “Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR,” *The New England Journal of Medicine*, vol. 362, no. 25, pp. 2380–2388, 2010.
  - [4] R. Govindan, J. Bogart, and E. E. Vokes, “Locally advanced non-small cell lung cancer: the past, present, and future,” *Journal of Thoracic Oncology*, vol. 3, no. 8, pp. 917–928, 2008.
  - [5] M. Kovarik, M. Hronek, and Z. Zadak, “Clinically relevant determinants of body composition, function and nutritional status as mortality predictors in lung cancer patients,” *Lung Cancer*, vol. 84, no. 1, pp. 1–6, 2014.
  - [6] N. Kiss and A. Curtis, “Current insights in nutrition assessment and intervention for malnutrition or muscle loss in people with lung cancer: a narrative review,” *Advances in Nutrition*, vol. 13, 2022.
  - [7] M. E. Cooley, “Symptoms in adults with lung cancer: a systematic research review,” *Journal of Pain and Symptom Management*, vol. 19, no. 2, pp. 137–153, 2000.
  - [8] J. Polański, B. Jankowska-Polańska, and G. Mazur, “Relationship between nutritional status and quality of life in patients with lung cancer,” *Cancer Management and Research*, vol. 13, pp. 1407–1416, 2021.
  - [9] J. Polański, B. Jankowska-Polańska, I. Uchmanowicz et al., “Malnutrition and quality of life in patients with non-small-cell lung cancer,” *Advances in Experimental Medicine and Biology*, vol. 1021, pp. 15–26, 2017.
  - [10] J. Ignacio de Ulíbarri, A. González-Madroño, N. G. de Villar et al., “CONUT: a tool for controlling nutritional status. First validation in a hospital population,” *Nutrición Hospitalaria*, vol. 20, no. 1, pp. 38–45, 2005.
  - [11] S. Takamori, G. Toyokawa, M. Shimokawa et al., “A novel prognostic marker in patients with non-small cell lung cancer: musculo-immuno-nutritional score calculated by controlling nutritional status and creatine kinase,” *Journal of Thoracic Disease*, vol. 11, no. 3, pp. 927–935, 2019.
  - [12] T. Ohba, S. Takamori, R. Toyozawa et al., “Prognostic impact of the controlling nutritional status score in patients with non-small cell lung cancer treated with pembrolizumab,” *Journal of Thoracic Disease*, vol. 11, no. 9, pp. 3757–3768, 2019.
  - [13] G. Toyokawa, Y. Kozuma, T. Matsubara et al., “Prognostic impact of controlling nutritional status score in resected lung squamous cell carcinoma,” *Journal of Thoracic Disease*, vol. 9, no. 9, pp. 2942–2951, 2017.
  - [14] D. Kuroda, H. Sawayama, J. Kurashige et al., “Controlling nutritional status (CONUT) score is a prognostic marker for gastric cancer patients after curative resection,” *Gastric Cancer*, vol. 21, no. 2, pp. 204–212, 2018.
  - [15] H. Chen, F. Fu, Y. Zhao et al., “The prognostic value of preoperative serum tumor markers in non-small cell lung cancer varies with radiological features and histological types,” *Frontiers in Oncology*, vol. 11, article 645159, 2021.
  - [16] L. Zhang, D. Liu, L. Li et al., “The important role of circulating CYFRA21-1 in metastasis diagnosis and prognostic value compared with carcinoembryonic antigen and neuron-specific enolase in lung cancer patients,” *BMC Cancer*, vol. 17, no. 1, p. 96, 2017.
  - [17] M. Yamamoto, H. Saito, C. Uejima et al., “Prognostic value of combined tumor marker and controlling nutritional status (CONUT) score in colorectal cancer patients,” *Yonago Acta Medica*, vol. 62, no. 1, pp. 124–130, 2019.
  - [18] X. Lv, Z. Wu, J. Cao et al., “A nomogram for predicting the risk of lymph node metastasis in T1-2 non-small-cell lung cancer based on PET/CT and clinical characteristics,” *Translational Lung Cancer Research*, vol. 10, no. 1, pp. 430–438, 2021.
  - [19] A. G. Nicholson, K. Chansky, J. Crowley et al., “The International Association for the Study of Lung Cancer lung cancer staging project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer,” *Journal of Thoracic Oncology*, vol. 11, no. 3, pp. 300–311, 2016.
  - [20] J. Y. Liu, H. M. Dong, W. L. Wang et al., “The effect of the prognostic nutritional index on the toxic side effects of radiochemotherapy and prognosis after radical surgery for gastric cancer,” *Cancer Management and Research*, vol. 13, pp. 3385–3392, 2021.
  - [21] S. Li, Z. Wang, W. Zhang, J. Li, K. Zhou, and G. Che, “Systemic inflammation score: a novel risk stratification tool for postoperative outcomes after video-assisted thoracoscopic surgery lobectomy for early-stage non-small-cell lung cancer,” *Cancer Management and Research*, vol. 11, pp. 5613–5628, 2019.
  - [22] D. De Ruyscher, C. Faivre-Finn, K. Nackaerts et al., “Recommendation for supportive care in patients receiving concurrent chemotherapy and radiotherapy for lung cancer,” *Annals of Oncology*, vol. 31, no. 1, pp. 41–49, 2020.
  - [23] B. G. Na, S. S. Han, Y. A. Cho et al., “Nutritional status of patients with cancer: a prospective cohort study of 1, 588 hospitalized patients,” *Nutrition and Cancer*, vol. 70, no. 8, pp. 1228–1236, 2018.
  - [24] S. C. Lee, J. G. Lee, S. H. Lee et al., “Prediction of postoperative pulmonary complications using preoperative controlling nutritional status (CONUT) score in patients with resectable non-small cell lung cancer,” *Scientific Reports*, vol. 10, no. 1, p. 12385, 2020.
  - [25] M. Hikage, Y. Taniyama, T. Sakurai et al., “The influence of the perioperative nutritional status on the survival outcomes for esophageal cancer patients with neoadjuvant chemotherapy,” *Annals of Surgical Oncology*, vol. 26, no. 13, pp. 4744–4753, 2019.
  - [26] A. Niendorf, H. Nägele, D. Gerding, U. Meyer-Pannwitt, and A. Gebhardt, “Increased LDL receptor mRNA expression in colon cancer is correlated with a rise in plasma cholesterol levels after curative surgery,” *International Journal of Cancer*, vol. 61, no. 4, pp. 461–464, 1995.
  - [27] X. Li, C. Wu, J. Lu et al., “Cardiovascular risk factors in China: a nationwide population-based cohort study,” *The Lancet Public Health*, vol. 5, no. 12, pp. e672–e681, 2020.
  - [28] B. A. Swinburn, G. Sacks, K. D. Hall et al., “The global obesity pandemic: shaped by global drivers and local environments,” *Lancet*, vol. 378, no. 9793, pp. 804–814, 2011.
  - [29] J. C. Brown, S. Yang, E. F. Mire et al., “Obesity and cancer risk in white and black adults: a prospective cohort study,” *Obesity (Silver Spring)*, vol. 29, no. 6, pp. 960–965, 2021.
  - [30] O. Bouillanne, G. Morineau, C. Dupont et al., “Geriatric nutritional risk index: a new index for evaluating at-risk elderly medical patients,” *The American Journal of Clinical Nutrition*, vol. 82, no. 4, pp. 777–783, 2005.
  - [31] R. C. Thirlby and J. Randall, “A genetic “obesity risk index” for patients with morbid obesity,” *Obesity Surgery*, vol. 12, no. 1, pp. 25–29, 2002.

- [32] V. Arroyo, R. García-Martínez, and X. Salvatella, "Human serum albumin, systemic inflammation, and cirrhosis," *Journal of Hepatology*, vol. 61, no. 2, pp. 396–407, 2014.
- [33] J. P. Xiong, J. Y. Long, W. Y. Xu et al., "Albumin-to-alkaline phosphatase ratio: a novel prognostic index of overall survival in cholangiocarcinoma patients after surgery," *World journal of gastrointestinal oncology*, vol. 11, no. 1, pp. 39–47, 2019.
- [34] A. Guner, S. Y. Kim, J. E. Yu et al., "Parameters for predicting surgical outcomes for gastric cancer patients: simple is better than complex," *Annals of Surgical Oncology*, vol. 25, no. 11, pp. 3239–3247, 2018.
- [35] S. A. Törnberg, L. E. Holm, J. M. Carstensen, and G. A. Eklund, "Cancer incidence and cancer mortality in relation to serum cholesterol," *Journal of the National Cancer Institute*, vol. 81, no. 24, pp. 1917–1921, 1989.
- [36] B. Z. Qian, "Inflammation fires up cancer metastasis," *Seminars in Cancer Biology*, vol. 47, pp. 170–176, 2017.
- [37] M. Shiihara, R. Higuchi, W. Izumo et al., "Impact of the controlling nutritional status score on severe postoperative complications of pancreaticoduodenectomy for pancreatic cancer," *Langenbeck's Archives of Surgery*, vol. 406, no. 5, pp. 1491–1498, 2021.
- [38] A. Wang, B. Sun, M. Wang et al., "Predictive value of CONUT score combined with serum CA199 levels in postoperative survival of patients with pancreatic ductal adenocarcinoma: a retrospective study," *Peer J*, vol. 8, p. e8811, 2020.
- [39] M. J. Edelman, L. Hodgson, P. Y. Rosenblatt et al., "CYFRA 21-1 as a prognostic and predictive marker in advanced non-small-cell lung cancer in a prospective trial: CALGB 150304," *Journal of Thoracic Oncology*, vol. 7, no. 4, pp. 649–654, 2012.
- [40] N. Reinmuth, B. Brandt, M. Semik et al., "Prognostic impact of Cyfra21-1 and other serum markers in completely resected non-small cell lung cancer," *Lung Cancer*, vol. 36, no. 3, pp. 265–270, 2002.
- [41] Y. H. Jo, D. A. Talmage, and L. W. Role, "Nicotinic receptor-mediated effects on appetite and food intake," *Journal of Neurobiology*, vol. 53, no. 4, pp. 618–632, 2002.
- [42] K. Fearon, F. Strasser, S. D. Anker et al., "Definition and classification of cancer cachexia: an international consensus," *The Lancet Oncology*, vol. 12, no. 5, pp. 489–495, 2011.
- [43] L. Zhang, J. Li, J. Hu et al., "Cigarette smoke extract induces EGFR-TKI resistance via promoting EGFR signaling pathway and ROS generation in NSCLC cell lines," *Lung Cancer*, vol. 109, pp. 109–116, 2017.
- [44] O. Arrieta, A. D. Campos-Parra, C. Zuloaga et al., "Clinical and pathological characteristics, outcome and mutational profiles regarding non-small-cell lung cancer related to wood-smoke exposure," *Journal of Thoracic Oncology*, vol. 7, no. 8, pp. 1228–1234, 2012.
- [45] S. Q. Li, Y. H. Jiang, J. Lin et al., "Albumin-to-fibrinogen ratio as a promising biomarker to predict clinical outcome of non-small cell lung cancer individuals," *Cancer Medicine*, vol. 7, no. 4, pp. 1221–1231, 2018.
- [46] X. Guo, J. Shao, B. Zhai et al., "Relationship and prognostic significance between preoperative serum albumin to globulin ratio and CT features of non-small cell lung cancer," *European Journal of Radiology*, vol. 128, article 109039, 2020.
- [47] Q. Zeng, N. Xue, D. Dai et al., "A nomogram based on inflammatory factors C-reactive protein and fibrinogen to predict the prognostic value in patients with resected non-small cell lung cancer," *Journal of Cancer*, vol. 8, no. 5, pp. 744–753, 2017.