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ORIGINAL RESEARCH

The Diagnostic Value of Systemic Immune-Inflammatory Index (SII) and Lymphocyte–Albumin–Neutrophil Ratio (LANR) in Chronic Obstructive Pulmonary Disease with Lung Cancer

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Purpose: This study aims to explore the association of inflammatory markers such as the Systemic Immune-Inflammatory Index (SII) and LANR with the comorbidity of Chronic Obstructive Pulmonary Disease (COPD) and lung cancer.

Patients and Methods: A cross-sectional analysis was conducted on the clinical data of 309 patients with COPD only and 193 patients with COPD and lung cancer who attended the First Affiliated Hospital of Anhui Medical University. Additionally, we examined autonomous risk factors that contribute to the simultaneous development of COPD and lung cancer through univariate and multivariate logistic regression analyses. This analysis resulted in the development of a nomogram model for visual representation. The effectiveness of the model was assessed using a receiver operating characteristic (ROC) curve, calibration curve, and clinical decision analysis (DCA) curve, with internal validation conducted via repeated sampling methods.

Results: Multivariate analysis of clinical characteristics and inflammatory markers showed that smoking history of >60 pack-years, hemoptysis, emphysema, WBC count > 5.53 (×10^9/L), SII > 629.285, and LANR < 11.39 were significantly associated with the comorbidity of COPD and lung cancer. These factors were subsequently integrated into the nomogram model. The AUC of the model stood at 0.849 (95% CI: 0.815–0.882), demonstrating a notable improvement over the COPD-LUCSS scoring system (AUC: 0.716, 95% CI: 0.671–0.761). The DCA curve indicated a notable clinical advantage provided by the model. Additionally, patients with stage IV tumors exhibited elevated SII levels and reduced LANR levels compared to earlier stages, indicating potential prognostic significance for both markers.

Conclusion: Increased levels of the inflammatory markers SII and LANR are associated with the risk of comorbidity of COPD and lung cancer.

Keywords: lung cancer, inflammation, systemic immune-inflammation index, nomogram, LANR, chronic obstructive pulmonary disease

Introduction

Lung cancer is a type of malignancy that originates from respiratory epithelial cells located in the bronchi, bronchioles, and alveoli. It ranks among the top diseases globally in terms of both its incidence and mortality rates. The primary pathological subtypes of lung cancer encompass squamous cell carcinoma, adenocarcinoma, and small cell lung cancer. The development of lung cancer involves a complex pathogenesis, closely linked to chronic obstructive pulmonary disease (COPD). COPD is a chronic lung condition marked by persistent airflow limitation caused by ongoing inflammation of the airways, leading to obstructive bronchiolitis and emphysema. Due to demographic aging and

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environmental pollution, the incidence of COPD is on the rise.[1] Research findings indicate that the risk of lung cancer among COPD patients is significantly elevated, ranging from 4 to 6 times higher than in non-COPD.[2] This risk is notably linked to squamous cell carcinoma, as highlighted by recent studies.[3] Hence, it is of paramount importance to promptly identify high-risk individuals who exhibit an association between COPD and the progression of lung cancer. De-Torres et al[4] introduced the "COPD Lung Cancer Screening Score (COPD-LUCSS)" for COPD patient management, incorporating age, body mass index, smoking pack-years, and emphysema presence. However, multiple reports have highlighted its limited predictive efficacy.[5,6] For instance, in a study conducted by Gagnat among a community COPD population,[5] the COPD-LUCSS score exhibited a C-index of 0.63 and an area under the Receiver Operating Characteristic curve (ROC-AUC) of 0.61. Hence, it is essential to identify straightforward yet efficient biomarkers for COPD patients with lung cancer and create screening tools.

The mechanisms underlying the advancement of COPD to lung cancer mainly include genetic susceptibility, oxidative stress-antioxidant imbalance, formation of a tumor-promoting inflammatory microenvironment, epithelial-mesenchymal transition, among others.[7] Chronic airway inflammation significantly contributes to tumor development. By fostering a tumor microenvironment, it encourages gene mutations, aids immune evasion, and supports the creation of tumor blood vessels, thus contributing to the occurrence, development, and metastasis of lung cancer.[8]

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in inflammatory blood markers have been identified as independent risk factors for the development of lung cancer in COPD patients, based on current knowledge.[9,10] The systemic immune-inflammatory index (SII), prognostic nutritional index (PNI), and a novel inflammation marker comprising lymphocytes, albumin, and neutrophils (LANR)[11] are emerging inflammatory markers that effectively indicate the chronic inflammation and nutritional status of the body. Nevertheless, their value in diagnosing and treating COPD comorbid with lung cancer remains uncertain.

The main objective of this study is to explore the association between the aforementioned inflammatory markers and the risk of comorbidity of COPD and lung cancer. Moreover, the report aims to identify potential biomarkers and develop a novel clinical nomogram model for individuals with COPD and concomitant lung cancer.

Materials and Methods

Study Population

This study employed a cross-sectional design to identify an initial cohort of 1212 COPD outpatients who visited the First Affiliated Hospital of Anhui Medical University from June 1, 2020, to June 1, 2021. Some patients required continued inpatient treatment following their outpatient visits due to the severity of their condition.

Inclusion criteria: 1. COPD only group: Patients who satisfy the 2023 GOLD criteria for COPD diagnosis; 2. COPD with lung cancer group: Patients previously diagnosed with COPD who have now been diagnosed with lung cancer for the first time during this hospitalization, confirmed by definitive pathological evidence obtained through procedures such as lung puncture, surgical operation, or bronchoscopy biopsy; 3. Patients with comprehensive clinical data, encompassing age, gender, smoking history (pack-years), clinical symptoms, Body Mass Index (BMI), laboratory parameters, pulmonary function, chest CT scan results, and pertinent additional information; 4. Patients with adequate bone marrow reserve. Exclusion criteria include: 1. Presence of severe lung infections or other benign pulmonary diseases, such as pulmonary tuberculosis, bronchiectasis, interstitial lung disease, bronchial asthma, eg; 2. Patients with severe hematologic disorders, liver diseases, kidney diseases, or systemic diseases are excluded; 3. Patients with suspected lung nodules or lung shadows suggestive of malignant tumors but lacking pathological evidence are excluded;4. Patients with a history of primary malignant tumors in organs other than the lungs are excluded. The research protocol of this study has received approval from the Medical Ethics Committee of the First Affiliated Hospital of Anhui Medical University (Reference number: Quick-PJ 2024–04-67).

Data Collection

The demographic characteristics of enrolled patients were collected, including gender, age, smoking history (pack-years), alcohol consumption, BMI (Body Mass Index), laboratory parameters, pulmonary function tests, computed tomography (CT) scan results, tumor pathology types, and TNM staging. The procedures adhered to the principles outlined in the

Helsinki Declaration. Since this study was retrospective, the Ethics Committee waived the need for patient consent. We also declared that all patient data will be kept confidential and will not compromise the patients' interests.

Collect fasting peripheral venous blood samples from patients and perform laboratory analyses. Patient blood specimen information collected via the electronic medical record system during outpatient visits or before treatment or surgery during hospitalization, including the following parameters: white blood cell count (WBC), neutrophil count (N), lymphocyte count (L), eosinophil count (E), platelet count (PLT), serum albumin (ALB), and others. Additionally, it calculated SII, PNI, and LANR using the specific formulas outlined below: SII: $SII = PLT \times N/L$; PNI: $PNI = 10 \times ALB(g/dL) + 0.005 \times L(/mm3)$; LANR: $LANR = L \times ALB/N$.

The COPD-LUCSS score[4] was as follows: BMI < 25 kg/m^2 scored 1 point, smoking history > 60 pack-years scored 2 points, age > 60 years scored 3 points, presence of emphysema on radiological examination scored 4 points. The scoring system ranges from 0 to 10 points, categorizing the risk of lung cancer occurrence in COPD patients as either low risk (0–6 points) or high risk (7–10 points). Among high-risk patients, the risk of developing lung cancer was 4.5 times higher than that of low-risk patients.[4]

Statistical Analysis

The detailed process flowchart was depicted in Figure 1. Statistical analyses were performed using IBM SPSS Statistics (version 26.0) and R software (4.3.2). The Kolmogorov–Smirnov test was used to assess whether continuous data follows a normal distribution, thereby guiding the decision to use either parametric or non-parametric tests. Quantitative data conforming to a normal distribution were represented as "mean ± standard deviation (SD)" with an independent samples *t*-test utilized to assess variances between two groups. Non-normally distributed quantitative data were expressed as "median (interquartile range)" and then compared between two groups using the Mann–Whitney *U*-test, a nonparametric statistical method. The Kruskal-Walli's test was used to conduct multiple group comparisons. The quantitative data was converted into qualitative data using cutoff values derived from the ROC curve. Furthermore, we employed the $\chi 2$ test to compare the two groups. Univariate and multivariate logistic regression analyses were used to assess the association with the comorbidity of COPD and lung cancer. Assessing whether the variables are closely related through collinearity diagnosis. The "RMS" package in R software was employed to create a nomogram model, followed by internal model validation using bootstrap resampling (1000 iterations). We evaluated the model's discrimination and calibration through the creation of receiver operating characteristic (ROC) curves, calibration curves, and clinical decision analysis (DCA) curves. Using the DeLong test to assess the significance of the AUC. To better facilitate clinical use, a web-based interactive dynamic nomogram application was constructed using Shiny. A p-value (P) < 0.05 was used to denote statistically significant differences in this analysis.

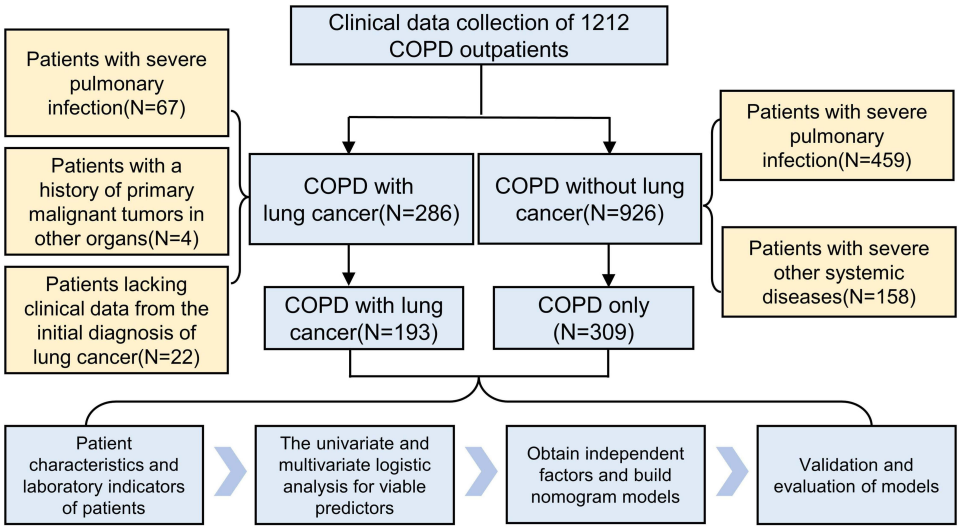

Figure 1 The overall flow of the study.
Notes: This is the flowchart of our study, including the inclusion and exclusion process of patients, as well as the construction and validation of the nomogram model.

Results

Patient Characteristics

In total, 502 patients met the eligibility criteria and were included in this study, comprising 309 individuals diagnosed with pure COPD and 193 patients with COPD comorbid with lung cancer. Detailed clinical data for all patients can be found in Table 1. Comparison of clinical data between COPD group and COPD group with lung cancer showed: The

Table 1 Comparison of Clinical Characteristics Between COPD with Lung Cancer Group and Pure COPD Group

Variable	COPD with Lung Cancer (N=193)	COPD Only (N=309)	χ2/U	P-Value
Gender			10.506	0.001
Female	26(13.47%)	79(25.57%)		
Male	167(86.53%)	230(74.43%)		
Age (years)			0.281	0.596
>60	94(48.7%)	143(46.28%)		
≤60	99(51.3%)	166(53.72%)		
Pack-years history>60			80.581	<0.001
Yes	178(92.23%)	167(54.05%)		
No	15(7.77%)	142(45.95%)		
Drinking			2.706	0.100
Yes	55(28.5%)	68(22.01%)		
No	138(71.5%)	241(77.99%)		
BMI (kg/m^3)			2.480	0.115
<25	156(80.83%)	231(74.76%)		
≥25	37(19.17%)	78(25.24%)		
Emphysema			38.382	<0.001
Yes	152(78.76%)	158(51.13%)		
No	41(21.24%)	151(48.87%)		
Chest pain			4.171	0.041
Yes	25(12.95%)	23(7.44%)		
No	168(87.05%)	286(92.56%)		
Hemoptysis			12.312	<0.001
Yes	35(18.13%)	24(7.77%)		
No	158(81.87%)	285(92.23%)		
Loss of weight			0.135	0.714
Yes	22(11.4%)	32(10.36%)		
No	171(88.6%)	277(89.64%)		
FEV1/FVC (%)	63.71(58.85, 67.03)	62.59(57.96, 66.22)	−1.844	0.065
GOLD			−8.465	<0.001
I	34(17.6%)	30(9.7%)		
II	122(63.2%)	87(28.2%)		
III	28(14.5%)	137(44.3%)		
IV	9(4.7%)	55(17.8%)		
Laboratory index				
WBC (×10^9/L)	6.94(5.79, 8.61)	5.84(4.74, 7.08)	−6.638	<0.001
Eosinophil (×10^9/L)	0.13(0.08, 0.24)	0.13(0.07, 0.22)	−1.332	0.183
PLT (×10^9/L)	212(167.5, 264)	207(173.5, 256)	−0.417	0.677
SII	759.03(504.02, 1153.42)	498.9(373.44, 666.42)	−7.870	<0.001
PNI	46.83(±6.79)	48.02(±5.34)	−2.071	<0.001
LANR	10.87(7.37, 15.82)	16.10(12.36, 22.33)	−8.951	<0.001

Notes: The clinical data of 502 COPD patients treated at the First Affiliated Hospital of Anhui Medical University and meeting the study criteria were collected. They were divided into the COPD only group and the COPD with lung cancer group based on whether they had lung cancer. Here are the clinical data and laboratory indicators of the two groups. Specifically, BMI, Pack-years history, and age were grouped according to COPD-LUSS scores.

male proportion, pack-years of smoking, emphysema ratio, proportions of chest pain and hemoptysis clinical symptoms, WBC, SII, and COPD-LUCSS score in the COPD group with lung cancer were higher than those in the pure COPD group (P<0.05), while PNI and LANR were the opposite (P<0.05). After classifying the two groups of patients according to the GOLD guidelines, the COPD with lung cancer group had more patients in GOLD stages I and II, totaling 156 cases (80.8%), while the COPD-only group had more patients in GOLD stages II and III, totaling 224 cases (72.5%). The difference between the two groups was statistically significant (P<0.001). Considering the potential selection bias, GOLD staging was not included in the subsequent logistic regression model.

Logistic Regression Analysis of COPD with Lung Cancer

As shown in Table 2, single-factor logistic regression analysis of the two groups indicated that 9 variables were significantly linked to the comorbidity of COPD and lung cancer (P<0.05). The variables exhibiting statistically significant associations with the odds of lung cancer, as determined through single-factor logistic regression analysis, are outlined below: Male (OR=2.206, 95% CI: 1.357–3.586); Smoking pack-years >60 pack-years (OR=10.09, 95% CI: 5.692–17.887); Emphysema (OR=4.534, 95% CI: 3.005–6.841); Chest pain (OR=1.85, 95% CI: 1.018–3.363); Hemoptysis (OR=2.631, 95% CI: 1.511–4.581); WBC>5.53 ($\times 10^9$/L) (OR=3.745, 95% CI: 2.398–5.849); SII >629.285 (OR=4.586, 95% CI: 3.121–6.738); PNI <41.85 (OR=2.592, 95% CI: 1.604–4.188); LANR <11.39 (OR=5.868, 95% CI: 3.905–8.816). Upon further multiple-factor logistic regression analysis, several independent risk factors for COPD combined with lung cancer were identified. These included smoking pack-years>60 pack-years (OR=8.737, 95% CI: 4.580–16.664), presence of hemoptysis (OR=2.356, 95% CI: 1.200–4.625), diagnosis of emphysema (OR=2.900, 95% CI: 1.759–4.782), WBC>5.53 ($\times 10^9$/L) (OR=2.882, 95% CI: 1.650–5.032), SII >629.285 (OR=1.794, 95% CI: 1.029–3.129), and LANR <11.39 (OR=3.161, 95% CI: 1.695–5.894) (P<0.05). The constant term of the multifactorial logistic regression model is shown in Supplementary Table 1. We performed collinearity diagnostics on the continuous variables WBC, SII, and LANR included in the multifactor logistic regression model, with results shown in Table 3: WBC (VIF: 1.317, Tolerance: 0.759), LANR (VIF: 1.42, Tolerance: 0.704), SII (VIF: 1.655, Tolerance: 0.604), indicating that there is no close correlation among them.

Construction of the Nomogram Model

We constructed a nomogram model using the 6 independent risk factors (smoking pack-years>60 pack-years, hemoptysis, emphysema, WBC>5.53 ($\times 10^9$/L), SII>629.285, and LANR<11.39) based on single-factor and multiple-factor logistic regression analyses. Please refer to Figure 2(a) for the nomogram model. To better facilitate clinical use, we developed a simple and user-friendly nomogram based on the six independent risk factors mentioned above, which is available

Table 2 The Logistic Regression Analysis Between COPD Only Group and COPD with Lung Cancer Group

Variate	Univariate Analyses		Multivariate Analyses			
	OR (95% CI)	P-Value	O (95% CI)	P-Value	Regression Coefficient	SE
Male	2.206(1.357, 3.586)	0.001	0.714(0.380, 1.339)	0.293	−0.338	0.321
Pack-years History>60	10.09(5.692, 17.887)	<0.001	8.737(4.580, 16.664)	<0.001	2.168	0.329
Emphysema	4.534(3.005, 6.841)	<0.001	2.900(1.759, 4.782)	<0.001	1.065	0.255
Chest pain	1.85(1.018, 3.363)	0.044	1.231(0.589, 2.573)	0.581	0.208	0.376
Hemoptysis	2.631(1.511, 4.581)	0.001	2.356(1.200, 4.625)	0.013	0.857	0.344
WBC>5.53 ($\times 10^9$/L)	3.745(2.398, 5.849)	<0.001	2.882(1.650, 5.032)	<0.001	1.058	0.284
SII >629.285	4.586(3.121, 6.738)	<0.001	1.794(1.029, 3.129)	0.039	0.585	0.284
PNI <41.85	2.592(1.604, 4.188)	<0.001	1.005(0.500, 2.020)	0.99	0.005	0.356
LANR <11.39	5.868(3.905, 8.816)	<0.001	3.161(1.695, 5.894)	<0.001	1.151	0.318

Notes: Through univariate logistic analysis of the two groups of data, we identified 9 variables significantly associated with the comorbidity of COPD and lung cancer (P < 0.05). Further multivariate analysis determined 6 independent risk factors associated with the comorbidity of COPD and lung cancer. The laboratory indicators in this study were categorized based on optimal cutoff values determined by ROC curves, converting continuous variables into categorical variables.

Table 3 Collinearity Diagnostics Among the Variables WBC, LANR, and SII

Variate	Collinearity Diagnosis	
	VIF	Tolerance
WBC	1.317	0.759
LANR	1.42	0.704
SII	1.655	0.604

Notes: VIF: Variance Inflation Factor.

online as shown in Figure 2(b) (https://xuyidan.shinyapps.io/DynNomapp/). The evaluation metrics of the model are provided in Supplementary Table 2.

Validation of the Nomogram Model

As depicted in Figure 3(a), the calibration curve exhibits minimal deviation from the theoretical line, as evidenced by a Hosmer-Leme show goodness-of-fit test statistic of 0.508 (P>0.05), suggesting a high degree of concordance between the predicted and observed outcomes within the nomogram model. As illustrated in Figure 3(b), the model was juxtaposed against the COPD-LUCSS score, and the ROC curve was depicted. The area under the ROC curve (AUC) for the nomogram model yielded a value of 0.849 (95% confidence interval [CI]: 0.815–0.882), while the AUC for the COPD-LUCSS score was 0.716 (95% CI: 0.671–0.761), and the difference between the two is significant (Z = 6.3553, $p = 2.08e^{-10}$). Based on the above, it is evident that the discriminative ability of the nomogram model is superior to the COPD-LUCSS score. Additionally, as shown in Figure 3(c) through the plotted DCA curve, the nomogram model provides more clinical benefit compared to the COPD-LUCSS score.

Correlation Analysis of LANR and SII with Clinical Features in COPD with Lung Cancer

The COPD combined with lung cancer group comprised 101 instances of squamous cell carcinoma (52.33%), 83 instances of adenocarcinoma (43.01%), 6 instances of small cell lung cancer (3.11%), and 3 instances of adenosquamous carcinoma (1.55%). Within this group, 72 cases were categorized as stage I (37.31%), 41 cases as stage II (21.24%), 41 cases as stage III (21.24%), and 39 cases as stage IV (20.21%).

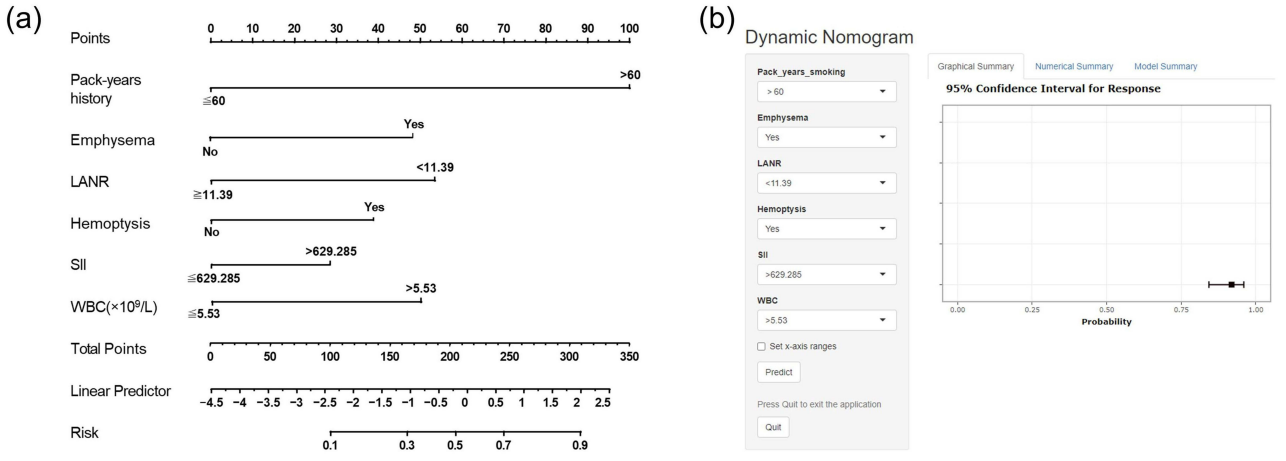

Figure 2 The nomogram models for predicting COPD with cancer.
Notes: (**a**) Here's nomogram with six elements. Each line indicates a factor; for example, pack-years history > 60 is scored as 100, while smoking pack-years ≤ 60 is scored as 0; (**b**) Online dynamic nomogram accessible at https://xuyidan.shinyapps.io/DynNomapp/.

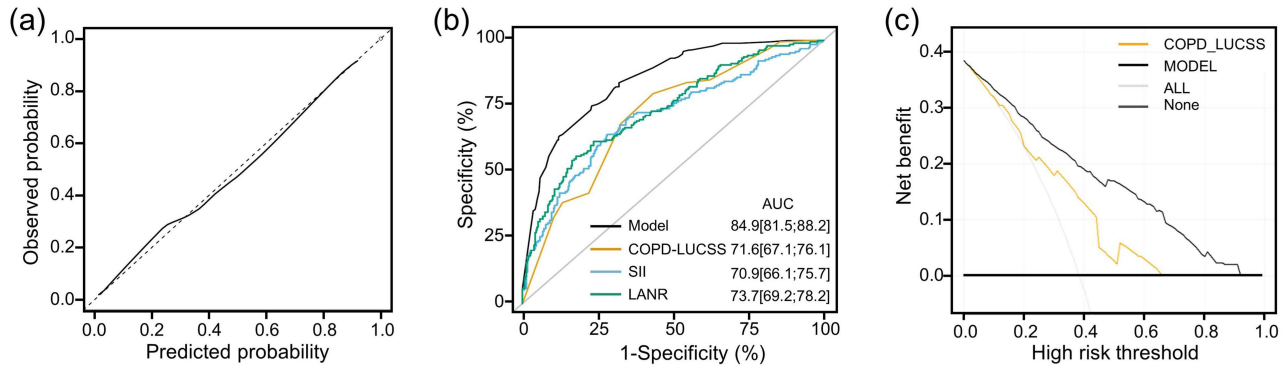

Figure 3 (**a**) The calibration curve of the nomogram (bootstrap 1000 repetitions); (**b**) The receiver operating characteristic (ROC) curve and the area under the ROC (AUC) of model, SII, LANR and COPD-LUCSS score; (**c**) The clinical decision curve analysis of nomogram of model and COPD-LUCSS score.

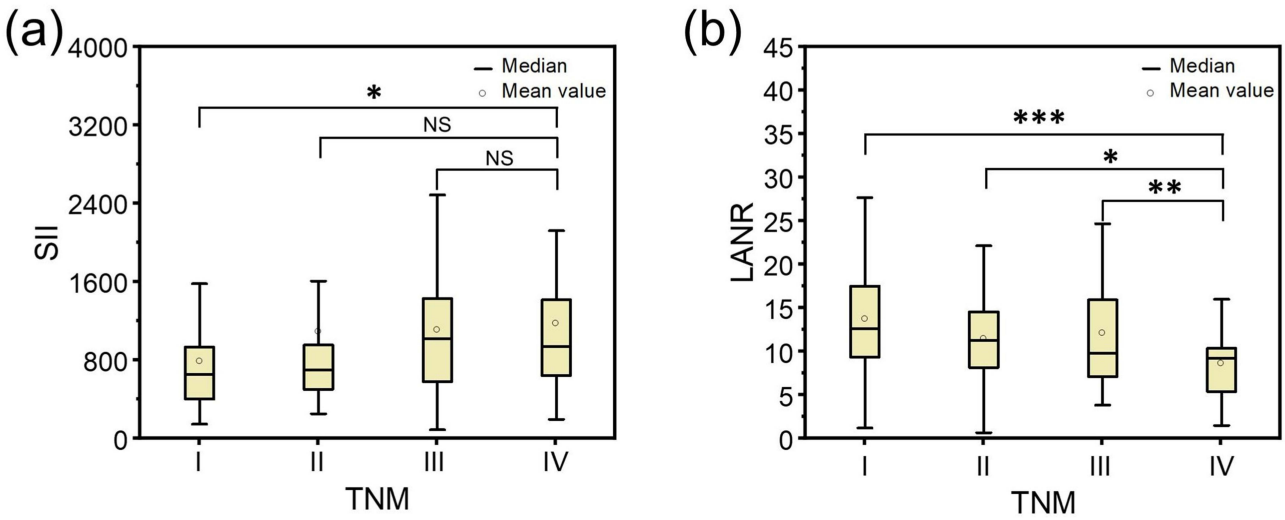

Figure 4 (**a**) SII level chart of patients with different TNM stages; (**b**) LANR level chart of patients with different TNM stages.
Notes: * (Single asterisk): Indicates statistical significance at the $p < 0.05$ level. ** (Double asterisks): Indicates statistical significance at the $p < 0.01$ level. *** (Triple asterisks): Indicates statistical significance at the $p < 0.001$ level.

There were differences in SII levels among patients with different TNM stages. Specifically, stage I had a SII level of 662.34 (406.74, 994.13), stage II had a SII level of 707.15 (501.35, 965.85), stage III had a SII level of 1029 (579.01, 1513.69), and stage IV had a SII level of 948.33 (650.62, 1421.54). As shown in Figure 4(a), the SII level exhibited a notable increase from stage I to stage IV, demonstrating a statistically significant difference ($P < 0.05$).

Moreover, there were differences in LANR levels among COPD with lung cancer patients in different TNM stages. Specifically, the LANR levels were as follows: in stage I, 12.69 (9.36, 17.6); in stage II, 11.37 (8.21, 14.99); in stage III, 9.89 (7.15, 16.46); and in stage IV, 9.28 (5.5, 10.45). As depicted in Figure 4(b), the levels of LANR were observed to be lower in patients with stage IV tumors compared to those in stages I, II, and III.

Discussion

According to forecasts by the World Health Organization (WHO), COPD was anticipated to ascend as the third most prevalent cause of mortality globally by the year 2030.[12] Notably, compromised lung functionality emerged as a significant contributing factor to the onset of lung cancer.[13] Moreover, the co-occurrence of COPD heightened the susceptibility of lung cancer patients to pulmonary infections, thereby impacting the effectiveness of treatments and the overall prognosis of survival.[14] This study investigates the correlation between 10 clinical indicators (gender, age, smoking history, alcohol history, BMI, emphysema, chest pain, hemoptysis, weight loss, lung function) and 5 laboratory

biomarkers (WBC, PLT, SII, PNI, LANR) with lung cancer comorbid with COPD. The results indicate that smoking pack-years exceeding 60, hemoptysis, emphysema, WBC > 5.53 (×10^9/L), SII > 629.285, and LANR < 11.39 are independent risk factors for lung cancer comorbid with COPD. Additionally, in COPD patients, we constructed a nomogram model associated with lung cancer, which demonstrated significant consistency and discriminative ability between the predicted and observed results.

Cigarette smoke represents a prevalent risk factor shared by both COPD and lung cancer. Numerous compounds present in tobacco exhibit toxicological properties, encompassing polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines, heavy metals (such as nickel, cadmium, chromium, and arsenic), alkaloids (notably nicotine and its principal metabolites), and aromatic amines, among various others. In the context of smoke exposure, obstructed lung tissue fosters a pro-tumorigenic inflammatory microenvironment characterized by activated lymphocytes. This inflammatory milieu exacerbates oxidative stress, precipitating genetic and epigenetic alterations that culminate in the progression of COPD to lung cancer.[7] Previous research has established that individuals with COPD who smoke are at a heightened risk, ranging from 2 to 4 times higher, of developing lung cancer when compared to smokers without COPD. Among these cases, squamous cell carcinoma emerges as the predominant pathological subtype.[2,15] In this investigation, a noteworthy association was established between smoking history and the heightened risk of developing COPD in conjunction with lung cancer. Notably, squamous cell carcinoma emerged as the predominant subtype among smokers afflicted with COPD concomitant with lung cancer, a finding that aligns with prior research.

Emphysema is considered a phenotype of COPD and is defined as the enlargement or destruction of alveolar walls leading to the dilation of distal air spaces in the terminal bronchioles.[16,17] A meta-analysis comprising 17 case-control studies revealed that individuals with a history of emphysema experience a 2.44-fold increased risk of developing lung cancer (95% Cl: 1.64, 3.62).[18] An additional cross-sectional study also demonstrated a statistically significant correlation between emphysema and lung cancer.[19] In our investigation, a noteworthy disparity was observed in the emphysema prevalence between the pure COPD group and the group characterized by COPD co-occurrence with lung cancer ($p < 0.05$), aligning with earlier scholarly findings. Multiple studies have found that FEV1/FVC (%) is a risk factor for lung cancer in COPD patients.[20–22] However, in our study, the COPD with lung cancer group had slightly higher FEV1/FVC (%) compared to the COPD-only group (p=0.065, approaching statistical significance). Additionally, the COPD with lung cancer group had relatively lower GOLD stages, consistent with the findings of de Torres et al.[23] Selection bias may have influenced our results to some extent. Some COPD patients with lung cancer included in our study were diagnosed with pulmonary nodules during health check-ups and presented at our outpatient clinic, often at an earlier stage of lung cancer. These patients might undergo more frequent medical examinations and monitoring, resulting in relatively higher FEV1/FVC (%) and lower GOLD stages. Conversely, some COPD patients with higher GOLD stages suspected of having lung cancer were not included in our study because their poor general condition prevented them from undergoing invasive procedures such as surgery or lung biopsy required for pathological diagnosis. Meanwhile, COPD patients with mild symptoms or slight lung function decline are less likely to visit the hospital. Additionally, survival bias is another factor to consider. COPD patients with poor lung function and lung cancer may have a shorter survival time, and thus were not observed in our study. Our study showed that hemoptysis occurred in 18.13% of COPD combined with lung cancer patients (vs 7.77% in the pure COPD group). Although the positivity rate was not high, it still has some reference value compared to the control group. However, Delage et al[24] reported only one lung cancer diagnosis among 39 COPD patients presenting with hemoptysis during a follow-up period of over one year, which differs from our study. The observed incongruity could potentially be ascribed to the limited sample size utilized in their investigation.

Rudolf Virchow[25] first proposed the relationship between inflammation-based biomarkers and tumor progression in 1909. Chronic inflammation and immune responses play important roles in tumor proliferation, infiltration, tumor angiogenesis, metastasis, and treatment resistance.[26,27] Neutrophils were the main circulating granulocytes in humans and reflect the host's inflammatory status.[28] High levels of neutrophils promoted tumor development by releasing large amounts of vascular endothelial growth factor, reactive oxygen species (ROS), reactive nitrogen species (RNS), or proteases,[29] thereby promoting tumor proliferation and metastasis by weakening the host immune system and inhibiting natural killer cell activity.[30,31] Lymphocytes were essential components of the human immune system, with T lymphocytes mediating cellular immunity in immune responses.[32] T lymphocytes played a crucial role in tumor

defense by effectively recognizing tumor cells, inducing cytotoxic cell death, and inhibiting tumor cell proliferation and migration.[33] However, platelets protected tumor cells from immune surveillance and responses by interacting with circulating tumor cells, aiding in tumor evasion and metastasis.[34] The SII is a biomarker that integrates neutrophils, lymphocytes, and platelets and could better reflect inflammatory responses and immune status.[35,36] Additionally, cancer-related malnutrition may activate systemic inflammation and lead to reduced immune function, resulting in poor prognosis.[37] Therefore, we also included the LANR, which combines lymphocytes, albumin, and neutrophils, in our study. The findings demonstrated that both SII and LANR independently contributed as risk factors in the development of COPD concomitant with lung cancer. Some studies have found that SII and LANR are associated with the prognosis of various cancers.[11,38,39] Through correlation analysis of LANR and SII levels with TNM staging in COPD combined with lung cancer patients, we found that late-stage patients had lower LANR levels and higher SII levels, suggesting an association with poor prognosis. Due to the lack of follow-up data, we are unable to comprehensively assess the long-term prognostic value of SII and LANR, including their ability to predict disease progression, treatment response, and overall survival. Additional prospective studies are warranted to substantiate and validate the aforementioned findings.

In summary, LANR and SII emerged as significant independent risk factors for the COPD with lung cancer. These findings were used as the basis for developing a nomogram-based risk prediction model specifically tailored for COPD and lung cancer comorbidity. Moreover, Bootstrap validation has underscored the robustness of this model across analogous populations, suggesting its potential efficacy in forthcoming scenarios. Furthermore, Decision Curve Analysis (DCA) has indicated promising clinical applicability, highlighting its prospective value in clinical practice. The AUC derived from the nomogram model developed in this investigation exhibited a superior performance compared to the COPD-LUCSS score (nomogram model AUC: 0.849, COPD-LUCSS score AUC: 0.716). This outcome suggests that the novel model could potentially offer enhanced predictive accuracy regarding the lung cancer risk in patients with COPD when contrasted with the COPD-LUCSS score. Hence, this model offers an efficient navigation tool for early tendency diagnosis, personalized treatment selection, and the design of clinical trials in managing patients with COPD. Finally, we found an association between low LANR levels and high SII levels with poor prognosis in cancer patients, which requires further exploration in future studies.

Our investigation is bound by several constraints. Primarily, it constitutes a single-center case-control study characterized by a limited sample size, potentially limiting its capacity to comprehensively encapsulate all aspects of COPD patient characteristics. Therefore, a large-scale multicenter case-control study with multiple data analyses is needed to further validate these results. Secondly, the cutoff values for most inflammation and nutritional indicators are not standardized. In this study, we determined the optimal cutoff values for these indices (such as SII, PNI, LANR, eg) through ROC curves. However, future large-sample prospective studies are needed to establish universal cutoff values and validate the results of this study.

Conclusion

This study aims to elucidate the association between the inflammatory markers SII and LANR and lung cancer comorbid with COPD, identify potential biomarkers, and develop a novel nomogram model for predicting lung cancer in patients with COPD by integrating clinical characteristics. The model exhibited excellent performance and discriminative ability, providing a theoretical basis for respiratory physicians in clinical decision-making and treatment planning.

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Disclosure

The authors report no conflicts of interest in this work.

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