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Impact of COPD pulmonary structural remodeling on the prognosis of patients with advanced lung squamous cell carcinoma

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ABSTRACT

Background: By observing the changes of lung imaging airway structure in patients with advanced lung squamous cell carcinoma (ALUSC) , the relationship between the different types of COPD pulmonary structural remodeling and the prognosis of patients with ALUSC was analyzed.
Methods: We reviewed the medical records of 278 patients with ALUSC. The degree of emphysema and the percentage of bronchial wall thickness (WT%) on chest HRCT were calculated by Synapse3D software, Lung structural remodeling can be divided into there types: airway remodeling dominated, emphysema dominated, and mixed types.
Results: Compared with the diagnosis, the Goddard score increased, the proportion of airway remodeling dominated type decreased and the proportion of mixed type increased during the progression of ALUSC. In Kaplan-Meier analysis, whether with or without COPD, the mPFS and mOS of patients with mixed type were the shortest, and the difference was statistically significant. Univariate and multivariate Cox proportional hazard regression analysis showed that mixed type was an independent risk factor for poor PFS and OS in patients with ALUSC.
Conclusion: Patients with ALUSC all have varying degrees of lung structural remodeling, and patients with mixed lung structural remodeling have the worst prognosis. In addition, the aggravation of emphysema during tumor progression is more pronounced than the thickening of the airway wall, and the changes of emphysema was more powerful in predicting the progression of ALUSC.Clinicians must pay more attention to the changes of COPD (especially emphysema) in the process of diagnosis and treatment of ALUSC.

1. Introduction

According to data from the National Cancer Center in 2022, lung cancer is still the malignant tumor with the highest morbidity and mortality in China [1]. Nevertheless, in view of the heterogeneity of lung cancer and the diversity of prognostic factors, the overall 5-year survival rate of it is still only 7 %–25 % [2].

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease caused by airway structural remodeling caused by chronic inflammatory stimulation, resulting in incomplete reversible airflow limitation [3]. COPD is one of the most common underlying

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diseases in patients with lung cancer, 40%–70 % of lung cancer patients suffer from COPD, which is higher in lung squamous cell carcinoma (LUSC) due to common risk factors such as smoking and environmental exposure [4,5]. Previous studies have confirmed that the prognosis of LUSC patients with COPD is negatively correlated with pulmonary function grade [6–8], and active treatment of COPD can improve the quality of life and prognosis of such patients [9,10]. However, pulmonary function test can not directly reflect the relationship between the different characteristics of pulmonary structural remodeling and airflow limitation, and its accuracy is easily affected by the general condition of patients, degree of fit, quality control and so on, and these defect can be made up by imaging examination [11].

High resolution computer tomography (HRCT) is not only an effective method to evaluate airway remodeling in COPD, but also an important basis for the diagnosis and evaluation of advanced LUSC (ALUSC) . The development of image examination equipment and image post-processing technology makes it possible to evaluate the changes of COPD from the point of view of tissue structure remodeling and even to diagnose COPD early [12–14]. Some studies have shown that the pulmonary structural remodeling is associated with the incidence of lung cancer and is a risk factor for poor prognosis of lung cancer, especially LUSC [11,15,16]. This effect may be related to the long-term chronic airway inflammation and oxidative stress caused by COPD and emphysema, for example, they can significantly increase the methylation level of Anti-oncogenic microRNA-7, which will promotes the development of lung cancer [17]. Of course, some studies have found that non-small cell lung cancer patients with COPD can benefit more from immune checkpoint inhibitors [18,19]. The effect of COPD on the prognosis of lung cancer still needs further study.

In this study, from the perspective of the prognostic impact of lung structural remodeling caused by the occurrence and development of COPD on ALUSC, the Goddard score and airway wall thickness percentage (WT%) index calculated based on imaging image post-processing techniques were selected to classify COPD lung structural remodeling into three categories: airway remodeling-dominant (Type A) , emphysema-dominant (Type E) , and mixed types (Type M) [20–22], in order to explore the correlation between imaging characteristics of lung structural remodeling and poor prognosis of ALUSC. The purpose of this study is to provide a basis for strengthening the whole-course management of chronic airway diseases in the treatment of patients with ALUSC, and to improve the prognosis of patients with ALUSC.

2. Materials and methods

2.1. Patients

A total of 278 patients with ALUSC who were hospitalized in the Department of Respiratory and Critical Care Medicine at Shanghai Changhai Hospital for ≥2 courses between January 1, 2017 and December 31, 2021 were included in the study. The follow-up deadline was October 31, 2022.

Inclusion criteria : (1) Age ≥18 years old; (2) The diagnosis of locally advanced or advanced LUSC was made by two pathologists with deputy senior professional titles or above according to the Chinese Medical Association's Clinical Guidelines for Lung Cancer (2021 Edition) [5]; (3) The patient receives ≥2 courses of treatment and can evaluate the treatment effect; (4) The diagnosis of COPD is based on the "Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (Revised 2021)" [23].

Exclusion criteria : (1) Patients with metastatic lung squamous cell carcinoma; (2) Individuals with a history of other malignancies; (3) Data related to laboratory and imaging examinations cannot be accessed; (4) Individuals with other diseases related to lung structural remodeling; (5) Those who have lost follow-up.

2.2. Clinical data information

Clinical data was collected through hospital information management system, electronic case management system, laboratory information system, and telephone follow-up, mainly including age, gender, smoking index, Body Mass Index (BMI), Performance Status (PS), TNM staging, treatment plan, histopathology, nucleus related antigen (Ki-67), cardiovascular antigen (CEA), Squamous cell carcinoma antigen (SCC), cytokeratin fragment antigen 21-1 (CYFRA21-1), D-dimer, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), survival status data.

2.3. Pulmonary function tests

Using the MasterScreen lung function instrument (Jaeger, Germany), professional examination technicians trained patients in human-machine cooperation and measured their lung function before and after inhaling bronchodilators. Collect 2 indicators: FEV_1%, FEV_1/FVC.

2.4. Evaluation and classification of lung structural remodeling indicators

Scan parameter Settings : The tube voltage was 120 kV, the tube current was automatic and intelligent selection, the pitch was 0.915, the FOV was 350 mm × 350 mm, the speed of scanning bed was 146.4 mm/s, and the rotation time was 0.5s. Low KV images were scanned with a slice thickness of 3–5 mm and image reconstruction with a slice thickness and slice distance of 1 mm. Before scanning, the subjects were trained to hold their breath at the end of deep inspiration, and then they were trained to complete the end-inspiration scan in the supine position.

Import the original HRCT images into Synapse3D software (FUJIFILM, Japan), reconstruct the lung parenchyma and bronchial

tree, select and measure lung structural remodeling indicators, and classify them, as shown in Fig. 1 and Table 1.

(1) Goddard score: automatically select CT images 1 cm above the upper edge of the aortic arch, 1 cm below the protuberance, and 3 cm above the septal muscle. Define a CT value less than −950Hu as an area of decreased lung density, and calculate the percentage of low attenuation area (LAA%) of the lung as the Goddard score for that plane. LAA%≤5 % is 0 point, 5 %<LAA%≤25 % is 1 point, 25 %<LAA%≤50 % is 2 points, 50 %<LAA%≤75 % is 3 points, and LAA%>75 % is 4 points. The total score is 24 points.

The Goddard score is divided into 5 levels, with 0 level: the total score is 0 points; Level 1: 1–6 points; Level 2: 7–12 points; Level 3: 13–18 points; Level 4: 19–24 points.

(2) WT%: Select the apical segment of the right upper lobe bronchus as the measurement target, and take 5 cross-sectional images perpendicular to the long axis of the airway at 2 mm intervals, with the midpoint of the bronchus as the center. Use graphic cutting method to extract the inner and outer contours of the airway, automatically calculate WT%, and take the average value as the final result.

The WT% score is divided into 4 levels, with 0 level: WT%≤20 %; Level 1: 20 % < WT%≤30 %; Level 2: 30 % < WT%≤40 %; Level 3: WT%>40 %.

2.5. Statistical analysis

PASS 15 software was used for sample size calculation.Accepting an alpha risk of 0.05 and a beta risk of 0.1 in a two-sided test and the event rate was 0.8,the sample size was 291.After strict screening of relevant cases, 278 cases were finally included in this study.

SPSS 26 software was used for statistical analysis, and GraphPad Prism 8.0 software was used for graphics.Kolmogorov-Smirnov test was used to analyze the normality of measurement data. The measurement data of skewed distribution in the data were expressed as Median (Q1, Q3), and Mann Whitney *U* test and Kruskal wallis H test were used; The counting data was expressed as a percentage (%), using $\chi 2$ test or Fisher exact probability method. Kaplan-Meier survival curve was used to evaluate PFS and OS, and Log-rank test was used to assess differences. The application of COX proportional risk regression model to evaluate the impact of lung structural remodeling indicators and other factors on PFS and OS. ($P < 0.05$ was considered statistically significant).

2.6. Ethics approval and consent to participate

The study was approved by the Shanghai Changhai Hospital Ethics Committee (No.CHEC2023-227). This study is a retrospective study, which will not cause additional harm to patients and will not affect the treatment and prognosis of patients. Written informed consent is not necessary according to the Shanghai Changhai Hospital Ethics Committee.

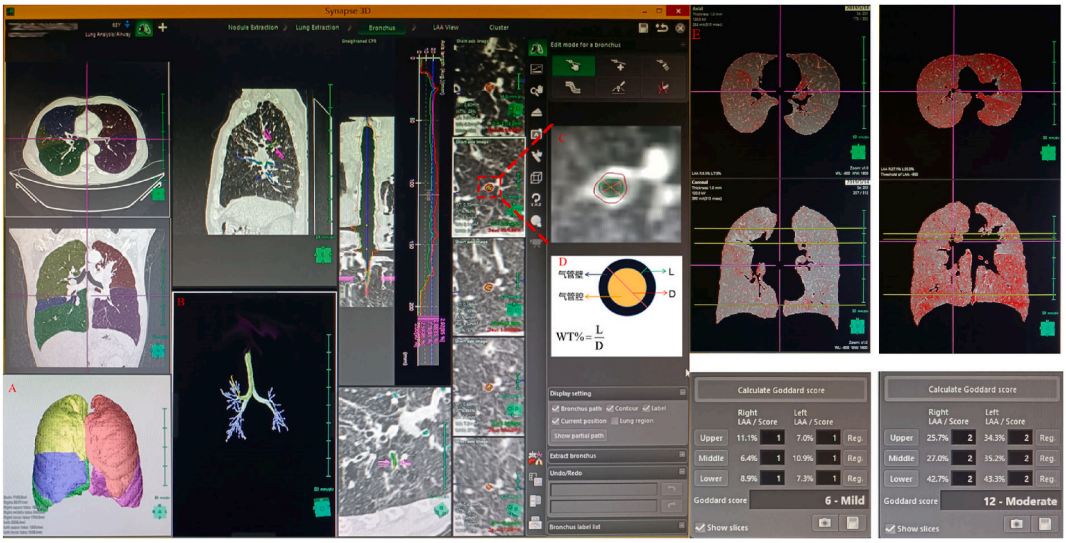

Fig. 1. Interface diagram of Synapse 3D software.
Note: A: 3D reconstruction of lung parenchyma; B: three-dimensional reconstruction of bronchial tree; C: airway contour extraction; D:Schematic diagram of the calculation method of the percentage of airway wall thickness (L: airway wall thickness; D: extra-tracheal diameter; WT%: percentage of airway wall thickness); E: measurement of Goddard score.

Table 1
Classification of lung structural remodeling.

Type	Goddard score	WT% score
Type A	≤1 level	≥1 level
Type E	≥1 level	0 level
Type M	≥2 level	≥1 level

3. Result

3.1. Comparison of general clinical data

The with COPD group had a larger proportion of male and elderly patients, a higher smoking index and received fewer treatment plans. The mPFS and mOS between the two groups were 6 vs 8 months (P = 0.014) and 13.5 vs 18.5 months (P = 0.001), as shown in Table 2.

In the group with COPD, the levels of CRP, ESR and D-dimer tended to decrease, while SCC and CYFRA21-1 increased, but the differences were not statistically significant. The level of CEA was significantly higher than that in control group (P < 0.05), as shown in Table 3.

The comparison between the lung remodeling groups showed that only FEV_1/FVC (%) was statistically different, as shown in Table 4.

3.2. Comparison of lung structural remodeling indicators and subtypes

Compared with the group without COPD, the Goddard score and WT% in the group with COPD increased, but the difference was not statistically significant (Fig. 2-A/B), while the proportion of Type M was statistically different (Fig. 2-C).

Table 2
Comparison of general clinical data.

	All Subjects (n = 278)	without COPD (n = 84)	with COPD (n = 194)	*p*
Gender #				<0.001
female	29 (10.43)	17 (20.24)	12 (6.19)	
male	249 (89.57)	67 (79.76)	182 (93.81)	
Age (years) #				0.009
≤65	67 (24.1)	29 (34.5)	38 (19.6)	
> 65	211 (75.9)	55 (65.5)	156 (80.4)	
BMI (Kg/m^2) #				0.697
< 24	189 (67.99)	59 (70.24)	130 (67.01)	
≥24	89 (32.01)	25 (29.76)	64 (32.99)	
Smoking index (pack-years) *	40 (20, 60)	20 (0, 40)	45 (30, 72.6)	<0.001
Clinical stage #				0.772
IIIB	67 (24.1)	18 (21.43)	49 (25.26)	
IIIC	28 (10.07)	7 (8.33)	21 (10.82)	
IVA	119 (42.81)	39 (46.43)	80 (41.24)	
IVB	64 (23.02)	20 (23.81)	44 (22.68)	
Tumor size (cm) *	5.05 (3.575,6.80)	5.25 (3.75,7.40)	4.95 (3.525,6.5)	0.467
Tumor location #				0.178
Left upper lung	97 (34.9)	24 (28.6)	73 (37.6)	
Left lower lung	34 (12.2)	11 (13.1)	23 (11.9)	
Right upper lung	72 (25.9)	22 (26.2)	50 (25.8)	
Right middle lung	14 (5)	8 (9.5)	6 (3.1)	
Right lower lung	61 (21.9)	19 (22.6)	42 (21.6)	
Ki-67 (%)*	70 (50, 80)	70 (40, 80)	70 (50, 85)	0.145
PS score (point) #				0.149
0	23 (8.27)	11 (13.1)	12 (6.19)	
1	232 (83.45)	67 (79.76)	165 (85.05)	
2	19 (6.83)	4 (4.76)	15 (7.73)	
3	4 (1.44)	2 (2.38)	2 (1.03)	
Treatment plan #				0.034
chemotherapy	75 (26.98)	18 (21.43)	57 (29.38)	
chemotherapy + radiation therapy	46 (16.55)	9 (10.71)	37 (19.07)	
chemotherapy + anti angiogenesis	25 (8.99)	6 (7.14)	19 (9.79)	
chemotherapy + immunotherapy	76 (27.34)	26 (30.95)	50 (25.77)	
≥3-line treatment	56 (20.14)	25 (29.76)	31 (15.98)	
PFS (months)*	6.5 (3.5,11)	8 (5,13)	6 (3,10)	0.014
OS (months)*	15 (9,26)	18.5 (12.75,28)	13.5 (8,23.75)	0.001

Note:*: Values are given as median(Q1 , Q3);#: Values are given as n(%).

Table 3
Comparison of peripheral blood results.

	All Subjects (n = 278)	without COPD (n = 84)	with COPD (n = 194)	*p*
CRP (mg/L)	14.15 (5.84, 34.05)	14.7 (4.72, 28.75)	13.8 (6.02, 37.38)	0.249
ESR (mm/H)	29 (16, 53)	30 (16.75, 56.25)	29 (16, 52)	0.814
D-dimer (mg/L)	0.5 (0.36, 0.75)	0.5 (0.37, 0.81)	0.49 (0.36, 0.74)	0.506
SCC (μg/L)	2.75 (1.3, 6.7)	2.25 (1.1, 5.8)	2.95 (1.3, 7.3)	0.296
CYFRA21-1 (ng/ml)	8.64 (3.59, 22.41)	6.66 (3.63, 18.52)	10.13 (3.54, 23.62)	0.317
CEA (μg/L)	4.2 (2.59, 7.56)	3.28 (2.17, 7.21)	4.34 (2.82, 7.83)	0.046

Note:Values are given as median(Q1 , Q3).

Table 4
Comparison of general data between groups with pulmonary structural remodeling.

	All Subjects (n = 278)	Type A (n = 187)	Type E (n = 25)	Type M (n = 66)	*p*
Gender #					0.902
female	29 (10.4)	20 (10.7)	3 (12)	6 (9.1)	
male	249 (89.6)	167 (89.3)	22 (88)	60 (90.9)	
Age (years) #					0.184
≤65	135 (48.6)	96 (51.3)	8 (32)	31 (47)	
>65	143 (51.4)	91 (48.7)	17 (68)	35 (53)	
BMI (Kg/m^2) #					0.170
≤24	189 (68)	121 (64.7)	17 (68)	51 (77.3)	
>24	89 (32)	66 (35.3)	8 (32)	15 (22.7)	
Smoking index (pack-years) *	40 (20,60)	40 (20,60)	30 (0,50)	40 (20.62,50.75)	0.161
COPD #					0.102
No	84 (30.2)	63 (33.7)	8 (32)	13 (19.7)	
Yes	194 (69.8)	124 (66.3)	17 (68)	53 (80.3)	
Clinical stage #					0.595
IIIB	67 (24.1)	48 (25.7)	8 (32)	11 (16.7)	
IIIC	28 (10.1)	20 (10.7)	1 (4)	7 (10.6)	
IVA	119 (42.8)	79 (42.2)	9 (36)	31 (47)	
IVB	64 (23)	40 (21.4)	7 (28)	17 (25.8)	
Tumor size (cm) *	5.05 (3.575,6.8)	5.2 (3.7,6.9)	5.1 (3.8,6.5)	4.65 (3.2,6.5)	0.264
Tumor location #					0.611
Left upper lung	97 (34.9)	68 (36.4)	9 (36.0)	20 (30.3)	
Left lower lung	34 (12.2)	18 (9.6)	5 (20.0)	11 (16.7)	
Right upper lung	72 (25.9)	53 (28.3)	4 (16.0)	15 (22.7)	
Right middle lung	14 (5)	10 (5.3)	1 (4.0)	3 (4.5)	
Right lower lung	61 (21.9)	38 (20.3)	6 (24.0)	17 (25.8)	
Ki-67 (%)*	70 (50 , 80)	70 (40 , 80)	60 (50 , 80)	70 (55.25 , 80)	0.692
PS score (point) #					0.363
0	23 (8.3)	20 (10.7)	1 (4)	2 (3)	
1	232 (83.5)	153 (81.8)	23 (92)	56 (84.8)	
2	19 (6.8)	11 (5.9)	1 (4)	7 (10.6)	
3	4 (1.4)	3 (1.6)	0 (0)	1 (1.5)	
Treatment plan #					0.133
chemotherapy	75 (27)	53 (28.3)	4 (16)	18 (27.3)	
chemotherapy + radiation therapy	46 (16.5)	33 (17.6)	2 (8)	11 (16.7)	
chemotherapy + anti angiogenesis	25 (9)	12 (6.4)	4 (16)	9 (13.6)	
chemotherapy + immunotherapy	76 (27.3)	50 (26.7)	6 (24)	20 (30.3)	
≥3-line treatment	56 (20.1)	39 (20.9)	9 (36)	8 (12.1)	
FEV_1% *	77.5 (66.18 , 87.73)	81 (70.13 , 89)	78.1 (65 , 81.85)	70.85 (61.53 , 86.35)	0.075
FEV_1/FVC(%) *	66.56 (61.95 , 69.5)	67.9 (63.2 , 72.63)	64.7 (62.88 , 67.1)	63.38 (55.48 , 67.7)	0.007

Note:*: Values are given as median(Q1 , Q3);**#:** Values are given as n(%).

3.3. Comparison of pulmonary structural remodeling indexes and subtypes between diagnosis and progression of ALUSC

Goddard score and WT% increased in the progression of ALUSC, but there was no significant difference in the latter (Fig. 3-A/B). When the disease progressed, the proportion of Type M increased and that of type A decreased, and the difference was statistically significant, as shown Table 5.

3.4. The effect of pulmonary structural remodeling classification on the prognosis of patients with ALUSC

In all Subjects, the mPFS of type A, E and M were 7, 9 and 4 months, respectively. The differences between type A, type E and type M were significant ($P < 0.001$ and $P = 0.004$)(Fig. 4-A). The mOS of type A, E and M were 20,20 and 10 months, respectively. There was only significant difference between type A and M groups ($P < 0.001$)(Fig. 4-B).

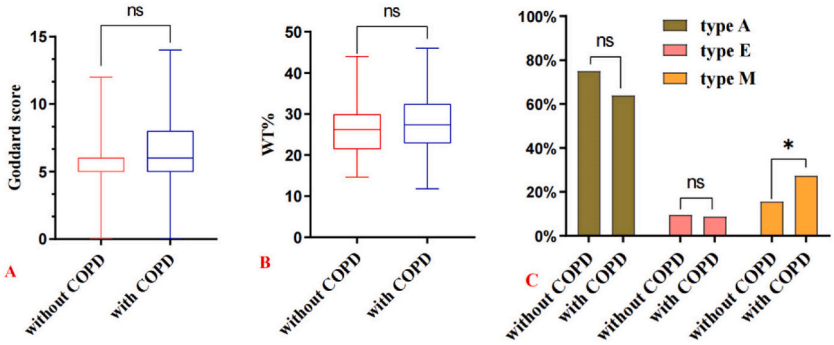

Fig. 2. comparison of pulmonary structural remodeling indexes and subtypes between with COPD group and without COPD group. Note: A: comparison of Goddard score; B: comparison of percentage of airway wall thickness (WT%); C: comparison of pulmonary structural remodeling classification. ns:P > 0.05; *:P < 0.05.

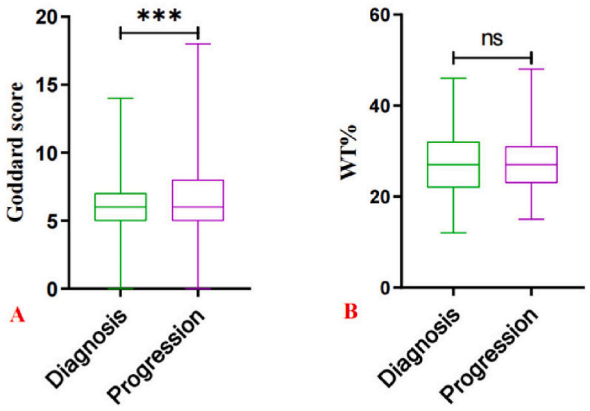

Fig. 3. comparison of lung structural remodeling indexes between diagnosis and progression of ALUSC. Note: A and B are the comparison of Goddard score and percentage of tracheal wall thickness (WT%) between progression and diagnosis. ns:P > 0.05; ***:P < 0.001..

Table 5
changes of pulmonary structural remodeling typing during the progression of ALUSC.

		Progression			$\chi 2$	*p*
		Type A	Type E	Type M		
Diagnosis	Type A	115	12	42	79.209	<0.001
	Type E	6	8	9		
	Type M	7	7	49		

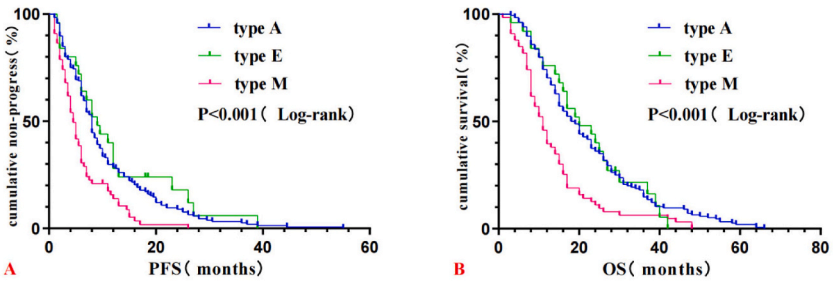

Fig. 4. A is the Kaplan-Meier curve comparison of PFS for the three groups of pulmonary structural remodeling classification, and B is the comparison of OS.

In the group with COPD, the mPFS of type A, E and M were 6.5, 9.5 and 4.5months,respectively. The differences between type M and type A, type E were significant ($P < 0.001$ and $P = 0.001$)(Fig. 5-A). The mOS of patients with type A, E and M were 17, 19 and 9 months, respectively. The differences between type M and type A, type E were significant ($P < 0.001$ and $P = 0.017$) (Fig. 5-B).

3.5. Univariate and multivariate analysis of prognosis of ALUSC

3.5.1. Univariate and multivariate analysis of PFS

Univariate analysis showed that PS score, COPD, diagnosis stage, first-line treatment regimen, Goddard score, WT%, structural remodeling type, Ki-67 and CEA were risk factors for the progression. The above factors were included in the multivariate analysis, suggesting that the increase of CEA and Ki-67 were independent risk factors for the progression. Compared with IIIB, the risk of progression in patients with stage IIIC, IVA and IVB at diagnosis was increased by 0.786 times, 0.431 times and 0.552 times, respectively; in first-line treatment, the risk of progression in patients with chemotherapy + immunotherapy was 0.476 times lower than that in patients with chemotherapy alone; and the risk of tumor progression in patients with type M was 1.789 times higher than that in patients with type A. See Table 6.

3.5.2. Univariate and multivariate analysis of OS

Univariate analysis showed that PS score, COPD, diagnosis stage, treatment plan, Goddard score, WT%, structural remodeling type, Ki-67, SCC, CEA, CYFRA21-1, CRP, ESR and D-dimer were risk factors for death. The above factors were included in the multivariate analysis, suggesting that higher PS score, WT%, Ki-67, CYFRA21-1, ESR and COPD were independent risk factors for death. In addition, the risk of death of patients with chemotherapy + immunotherapy, $\geq$ 3-line therapy and chemotherapy + radiotherapy decreased by 0.61,0.445 and 0.372 times respectively compared with those who only received chemotherapy. The risk of death of patients with type M and E was 2.416 and 1.95 times higher than that of patients with type A, respectively, as shown in Table 7.

4. Discussion

COPD is not only an independent risk factor for LUSC, but also the most common underlying disease. In recent years, the effects of COPD on the treatment and prognosis of LUSC have been reported. WANG [24] and ZHAI [25] found that the respiratory symptoms of patients with LUSC with COPD were more obvious, and the OS was significantly shorter than those without COPD. This study also concluded that the prognosis of patients with COPD and poor pulmonary function was significantly worse, which was consistent with previous studies. Standardized treatment of COPD can prolong the median OS of ALUSC, which can not only inhibit the progression of tumor through anti-inflammatory effect, but also avoid the influence of acute aggravation of COPD or other serious complications on the overall condition of patients, so as to strive for more treatment opportunities for patients [9,10].

The essential reason for the decline of pulmonary function in patients with COPD is the pathological remodeling of lung tissue structure. In recent years, with the development of CT imaging technology and the development and clinical use of image post-processing software, it is possible to accurately obtain the morphological and structural characteristics of lung tissue. Through the quantitative analysis of HRCT, clinicians can more intuitively understand the structural remodeling changes in the disease state, and analyze and evaluate the occurrence and development of lung disease from the perspective of imaging [26].

Studies have shown that there is a strong correlation between pulmonary function and chest HRCT quantitative pulmonary structural indexes in patients with COPD [27]. Changes in pulmonary structure mediate the relationship between genetic susceptibility to COPD and changes in pulmonary function [28]. However, this correlation is not absolute, LABAKI [29]found in their study that some smokers with airflow obstruction diagnosed by pulmonary function tests had only mild imaging emphysema, while some smokers without airflow obstruction had a severe burden of emphysema. It suggested that chest CT imaging and pulmonary function test can predict and evaluate the disease risk from different dimensions. In this study, it was observed that there was no difference in the index of pulmonary structural remodeling between the patients with COPD and the control group, which may be due to the fact that most of the patients with GOLD1 and 2 grade had the same level of changes in lung structure as those in the control group, which was consistent with the fact that structural changes preceded functional changes. In the group with COPD, the remodeling of lung structure was aggravated gradually with the increase of GOLD grade, which was consistent with the change of lung function.

In recent years, studies on the relationship between lung structural remodeling and the pathogenesis and prognosis of lung cancer have also been reported. Studies have shown that higher CT emphysema index and mixed phenotype are associated with more clinical symptoms, worse lung function and worse prognosis in patients with ALUSC [16,30]. However, after analyzing the data of two national lung cancer screening trials, it was found that the quantitative chest CT Emphysema index could not predict the morbidity and mortality of lung cancer, and the progress of Emphysema index could not predict the increase of lung cancer mortality [29,31].The differences between the results of various studies may be related to the heterogeneity of patients in different regions or races, the different CT examination standards used for imaging, and the failure to control the harmful exposure of the participants in the lung cancer screening program.

The Goddard score and WT% index collected in this study are obtained automatically by image post-processing software, which largely avoids the influence of subjective consciousness on the accuracy of the data. As the application of image post-processing software in clinical work is not yet popular, we use vision + manual measurement to obtain approximate data of lung structural remodeling in our daily work. Under this premise, Goddard score and WT% data are relatively accurate, so the results of this study have a certain guiding significance for clinical work.

Previous studies have confirmed that the activation of various signaling pathways caused by epithelial mesenchymal

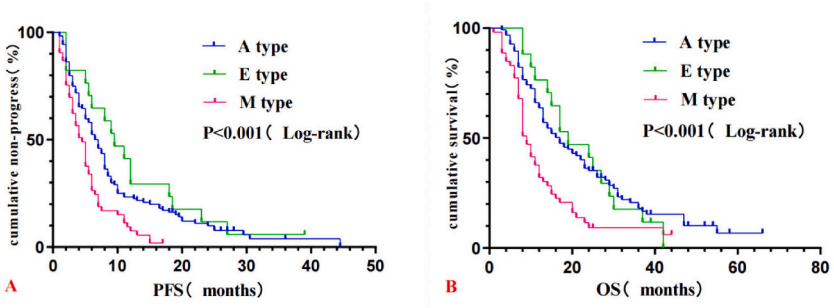

Fig. 5. A is the Kaplan-Meier curve comparison of PFS for the three groups of pulmonary structural remodeling classification in the group with COPD, and B is the comparison of OS.

Table 6
univariate and multivariate analysis of PFS in patients with ALUSC.

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*	HR	95%CI	*p*
PS score	1.363	1.053–1.766	0.019	1.174	0.886–1.557	0.264
COPD						
No	1					
Yes	1.348	1.027–1.770	0.031	1.173	0.885–1.554	0.267
Diagnosis stage						
IIIB	1					
IIIC	1.584	1.000–2.510	0.050	1.786	1.110–2.874	0.017
IVA	1.264	0.920–1.736	0.149	1.431	1.019–2.009	0.039
IVB	1.281	0.891–1.841	0.181	1.522	1.047–2.212	0.028
First-line treatment regimen						
chemotherapy	1					
chemotherapy + immunotherapy	0.560	0.405–0.775	<0.001	0.524	0.376–0.730	<0.001
immunotherapy	1.017	0.590–1.752	0.951	0.779	0.445–1.362	0.380
other	0.917	0.227–3.703	0.903	1.089	0.261–4.546	0.907
Goddard score	1.080	1.028–1.135	0.002	1.030	0.961–1.103	0.400
WT%	1.036	1.018–1.054	<0.001	1.044	1.022–1.066	<0.001
Structural remodeling type						
Type A	1					
Type E	0.856	0.553–1.324	0.485	1.480	0.890–2.459	0.131
Type M	1.745	1.300–2.342	<0.001	1.789	1.324–2.417	<0.001
Ki-67	1.010	1.004–1.015	0.001	1.009	1.003–1.015	0.002
CEA	1.003	1.000–1.006	0.032	1.003	1.000–1.006	0.027

transformation, chronic inflammation, oxidative stress and changes in extracellular matrix components are the pathological mechanisms of lung remodeling in COPD [32]. Since the above factors are also the common pathogenesis of COPD and lung cancer, we believe that this is the reason why there are also lung structural remodeling in patients without diagnosis of COPD.Alternatively, these patients already have COPD-like changes but do not meet the lung-function criteria for the diagnosis of COPD.On the other hand, in this study, there was no statistically significant difference in CRP, ESR, D-dimer, SCC and CYFRA21-1 levels between the COPD group and the simple LUSC group, which may be related to the majority of COPD cases included in the study were GOLD 1–2 grade and the symptoms were well controlled, and the combination of COPD could not cause sufficient changes. In addition, the small sample size may also be an important reason.

At the same time, we found that the Goddard score increased with tumor progression, but the WT% had no significant change. In the classification of pulmonary structural remodeling, the proportion of type A decreased and that of type M increased. The results showed that there were significant changes in the pathological degree and phenotype of lung structural remodeling during the progression of ALUSC, suggesting that the change of emphysema index plays a more significant role in predicting the progression of ALUSC, which has not been reported in previous studies.

We should further strengthen the health education of chronic disease knowledge, advocate smoking cessation, reduce environmental exposure and other healthy lifestyles, actively prevent and control the occurrence and development of COPD to reduce the incidence of LUSC, maintain good lung function, and provide more treatment opportunities for patients with advanced lung squamous cell carcinoma, so as to further improve the prognosis of ALUSC.

The limitation of this study:1. Our analysis does not include regional quantitative emphysema data, which may further improve the risk prediction model of clinical outcomes; 2. In this retrospective study, we were unable to obtain sufficient data to assess the effect of pulmonary remodeling on oxygenation because blood gas analysis and oxygen saturation testing are not routinely performed on

Table 7
univariate and multivariate analysis of OS in patients with ALUSC.

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*	HR	95%CI	*p*
PS score	1.699	1.294–2.231	<0.001	1.436	1.049–1.966	0.024
COPD						
No	1					
Yes	1.484	1.108–1.988	0.008	1.357	1.001–1.839	0.049
Diagnosis stage						
IIIB	1					
IIIC	0.803	0.474–1.363	0.417	0.691	0.402–1.188	0.181
IVA	1.009	0.717–1.420	0.958	0.971	0.679–1.387	0.871
IVB	1.392	0.949–2.042	0.091	1.341	0.896–2.007	0.153
Treatment plan						
chemotherapy	1					
chemotherapy + radiation therapy	0.610	0.409–0.910	0.015	0.628	0.414–0.951	0.028
chemotherapy + anti angiogenesis	0.994	0.625–1.583	0.981	0.802	0.484–1.332	0.394
chemotherapy + immunotherapy	0.501	0.343–0.732	<0.001	0.390	0.260–0.585	<0.001
≥3-line treatment	0.597	0.413–0.862	0.006	0.555	0.377–0.816	0.003
Goddard score	1.124	1.062–1.188	<0.001	1.051	0.969–1.140	0.232
WT%	1.043	1.024–1.064	<0.001	1.051	1.028–1.075	<0.001
Structural remodeling type						
Type A	1					
Type E	1.167	0.750–1.817	0.494	1.950	1.137–3.344	0.015
Type M	2.060	1.513–2.805	<0.001	2.416	1.731–3.372	<0.001
Ki-67	1.011	1.004–1.017	0.001	1.010	1.004–1.017	0.002
CEA	1.003	1.000–1.007	0.027	1.003	0.999–1.007	0.153
SCC	1.009	1.000–1.019	0.046	1.001	0.989–1.013	0.829
CYFRA21-1	1.008	1.003–1.012	0.002	1.008	1.003–1.013	0.004
CRP	1.005	1.002–1.008	0.002	1.002	0.998–1.006	0.350
ESR	1.006	1.001–1.011	0.023	1.010	1.005–1.015	<0.001
D-dimer	1.145	1.007–1.301	0.038	0.970	0.822–1.143	0.713

admission in patients in acceptable condition; 3.This was a single-center retrospective study investigating a relatively small sample size, especially the original data of pulmonary function test was not available for some patients, which further reduced the sample size and statistical power when comparing the patients with COPD.The results observed in the current study should be validated prospectively.

Further research directions:1. PET-CT can perform functional and structural synchronous imaging, and the measurement of 18F-FDG uptake in lung tissue can be used to study the airway lesions of COPD and the relationship between airway and systemic inflammation. Whether we can quantitatively process PET-CT images and explore its relationship with the prognosis of advanced lung cancer; 2. Tumor growth has a strong dependence on the changes of blood supply and microenvironment, then whether the pulmonary vascular remodeling caused by COPD has an impact on the prognosis of lung cancer.

5. Conclusion

In short, the prognosis of patients with ALUSC confirmed by retrospective analysis of COPD is even worse, and this effect can be evaluated by pulmonary structural remodeling such as emphysema and airway stenosis on chest HRCT. Mixed pulmonary structural remodeling is an independent risk factor for poor PFS and OS in ALUSC. The aggravation of emphysema may play a more important role in the progression of ALUSC, suggesting that clinicians should pay attention to the remodeling of lung structure shown by chest HRCT in the treatment of ALUSC, and try to slow down this change as much as possible, so as to improve the prognosis of patients.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Xuefeng Gao: Conceptualization, Formal analysis, Writing – original draft. **Zhenlei Wang:** Investigation, Writing – original draft. **Jian Liu:** Methodology, Writing – review & editing. **Jian Fan:** Visualization. **Kai Huang:** Visualization. **Yiping Han:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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