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Research article

Serum Krebs von den Lungen-6 as a potential biomarker for distinguishing combined pulmonary fibrosis and emphysema from chronic obstructive pulmonary disease: A retrospective study

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ABSTRACT

Background: The presence of fibrotic interstitial lung disease (ILD) is relatively common in patients with emphysema. This has been designated combined pulmonary fibrosis and emphysema (CPFE). CPFE had worse prognosis than emphysema alone. Krebs von den Lungen-6 (KL-6) levels as a biomarker of alveolar type 2 epithelial cell injury, which is widely used to identify the presence of ILD, whether it can differentiate CPFE from COPD remains unknown.

Methods: 259 patients from Xiangya Hospital with diagnosis of COPD, with or without ILD, and who had KL-6 tests were recruited for this retrospective analysis. Recorded data included demographic information, comorbidities, inflammatory biomarkers. Results of CT and pulmonary function tests were collected one week before or after KL-6 measurements.

Results: Among 259 patients, 52 patients were diagnosed with CPFE. The mean age was 67.39 ± 8.14 yeas. CPFE patients had higher ratio of rheumatic diseases (21.2 % vs 7.2 %, $P = 0.003$). CPFE patients exhibited higher values of FEV_1 (1.97 vs 1.57, $P = 0.002$) and FEV_1/FVC ratio (69.46 vs 57.64, $P < 0.001$) compared to COPD patients. CPFE patients had higher eosinophil counts, percentage of eosinophils, lactate dehydrogenase, total bilirubin levels and lower platelet counts. Serum KL-6 levels were higher in CPFE group compared to COPD group (574.95 vs 339.30 U/mL, $P < 0.001$). Multiple logistic regression showed that KL-6 level was an independent predictive factor for the presence of ILD among COPD patients. The AUC of serum KL-6 levels to differentiate CPFE was 0.711, with 95 % CI being 0.635 to 0.787. The cutoff point of KL-6 level was 550.95 U/mL with 57.7 % sensitivity and 79.7 % specificity for the discrimination of CPFE from COPD.

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Conclusion: CPFE patients show higher KL-6 levels compared to isolated COPD, suggesting the potential of KL-6 as a practical screening tool for interstitial lung disease, specifically CPFE. A KL-6 threshold of 550.95 U/mL in COPD patients may indicate a high need for high-resolution chest computed tomography to detect fibrosis.

1. Introduction

Tobacco smoke is one of the most important risk factors associated with the development of pulmonary diseases. Apart from chronic obstructive pulmonary disease (COPD), in some individuals, tobacco smoke can also trigger interstitial damage that results in pulmonary fibrosis, patients who had both emphysema and fibrosis were called combined pulmonary fibrosis and emphysema (CPFE) [1]. CPFE was first reported in 1948, the prevalence estimates of CPFE vary largely depending on the population recruited and the definition used, ranging from 8 to 67 %. Currently, there is a lack of comprehensive understanding of CPFE due to the absence of consensus on diagnostic criteria until 2022. As such, it is difficult to compare cohorts and draw consistent conclusions about the features, outcomes, and optimal management of these patients.

It is reported that patients with CPFE have worse survival than patients with emphysema alone [2]. Additionally, CPFE patients are more likely to have complications, including pulmonary artery hypertension and lung cancer [3–5], which may lead to worse outcomes. At present, high-resolution computed tomography (HRCT) is very important in differentiating fibrotic interstitial lung disease (fILD). However, it is challenging to perform routine screening among COPD patients due to the limitations of cost, radiation, and other considerations. Moreover, lung function tests were more frequently used in COPD management for motoring the disease progress, making it difficult to achieve early diagnosis of fILD. The identification of practical biomarkers for recognizing fibrotic ILD could help reduce economic costs and improve patient outcomes by enabling timely therapy.

Krebs von den Lungen-6 (KL-6) is classified as a polymorphic epithelial mucin (MUC1), representing a high molecular weight glycoprotein primarily secreted by injured bronchial epithelial cells or type II alveolar epithelial cells [6]. At present, KL-6 is widely used to screen early ILD, especially among patients with connective tissue disease(CTD) [7,8]. An optimal cutoff value of 500 U/mL has been established through comparisons between the interstitial pneumonia group and control groups consisting of other respiratory diseases, and is currently employed in certain countries as part of clinical practice [9]. COPD is a chronic inflammatory disease of the airways, epithelial damage plays a crucial role in its pathophysiology [10]. Given the elevated KL-6 levels found in ILD patients, more research is necessary to ascertain whether KL-6 can be useful in distinguishing CPFE patients from those with COPD. Additionally, with the new consensus on CPFE, more research is needed to explore its prevalence and clinical characteristics [1].

2. Methods

2.1. Study design and patient population

The present study obtained approval from the Ethics Committee of Xiangya Hospital, affiliated with Central South University, and was conducted in full compliance with the principles outlined in the Declaration of Helsinki and its subsequent revisions. The Ethics number assigned to this study is 202309183, and it was officially approved on September 6th, 2023. Detailed information pertaining to this study can be accessed at (https://ethics.tonoinfo.com/#/home/zndxxyyy). Informed consent was exempted due to the retrospective design of the study, and the analysis was performed using anonymized clinical data.

This study employed a retrospective design. The data were obtained from the database established by Xiangya Hospital, affiliated with Central South University, located in Hunan, China. The database included patients diagnosed with COPD who received medical care in the inpatient departments of Xiangya Hospital over a span of 20 years. Specifically, we focused on inpatients who had KL-6 measurements available in the comprehensive database. In cases where multiple KL-6 tests were conducted, we selected the first test administered upon admission. Subsequently, we performed a comprehensive search of the medical records using the keyword 'COPD' to verify that patients had a corresponding discharge diagnosis, and this diagnosis was further confirmed by two researchers. Following that, we proceed with the exclusion of specific infections that potentially impact KL6 levels, such as COVID-19, Pneumocystis jirovecii pneumonia (PJP), and tuberculosis. The CT images of these selected patients were meticulously reviewed by two pulmonologists and radiologists. Patients without CT data were excluded from the study. Based on the presence of pulmonary fibrosis, the recruited patients were categorized into two groups: the COPD group and the CPFE group. The diagnosis of emphysema was further validated by experienced radiologists and pulmonologists. The recorded data encompassed essential demographic information, such as age, gender, BMI, blood type, occupation, and smoking history. Additionally, regular blood biochemical tests, KL-6 levels, CT scans, and lung function parameters were collected. All data were documented upon admission, with CT scans and pulmonary function results obtained within one week of the KL-6 data.

2.2. KL-6 measurements

A 4 ml standardized blood sample was obtained from each patient according to established protocols. The serum was then separated via centrifugation at 3000 rpm for 10 min and stored at 4 °C until analysis. The KL-6 level (U/ml) was measured using the Nanopia® KL-6 kit (SEKISUI MEDICAL CO.LTD., Tokyo, Japan) through a latex particle-enhanced turbidimetric immunoassay

(LETIA), following the manufacturer's instructions. In summary, KL-6 in the samples forms agglutination with latex particles coated with mouse KL-6 monoclonal antibodies through the antigen-antibody reaction. The resulting change in absorbance is measured to determine the KL-6 level. The automated analyzer used for the KL-6 assay has a measurement range of 50–5000 U/ml ($r > 0.990$). If the KL-6 concentration in a sample exceeds this range, it is diluted with a specific buffer containing pH 7.6, 0.025 mol/L N2 hydroxyethylpiperazine-N′-2-ethanesulfonic acid buffer, and 20 % newborn calf serum. These samples are recommended to be diluted up to 5 times, and the obtained KL-6 concentration is multiplied by the dilution factor to determine the original sample's KL-6 concentration. The assay demonstrated high repeatability with a coefficient of variation (CV) below 10 % and a relative deviation (B) under 15 %.

2.3. Diagnostic criteria of CPFE

We applied the definition of CPFE as recommended in the latest expert consensus [1]. CPFE is characterized by the coexistence of emphysema and interstitial fibrosis, exhibiting a diverse range of manifestations on high-resolution chest computed tomography (HRCT). Emphysema is identified as areas of reduced attenuation (also referred to as density) without visible walls on CT scans. Emphysematous foci can be classified as centrilobular, paraseptal, or panacinar. Interstitial fibrosis is recognized as regions of increased lung tissue attenuation, presenting as reticulation and/or ground-glass opacities, often accompanied by honeycombing and/or traction bronchiectasis. To meet the HRCT criteria for CPFE, patients must fulfill the following conditions: 1) Presence of emphysema, regardless of subtype, on HRCT, characterized by well-defined areas of low attenuation delineated by a very thin wall (<1 mm) or no wall, involving a minimum of 5 % of the total lung volume; 2) Presence of lung fibrosis, regardless of subtype.

2.4. Pulmonary function test

The pulmonary function test was conducted by skilled technicians using a spirometer (MasterScreen-Body/Diff, CareFusion, Germany) in accordance with the guidelines set forth by the American Thoracic Society. The spirometry procedures were carried out by fully trained and certified technicians with expertise in spirometry techniques. Spirometry data were included in the analysis if subjects had a minimum of three acceptable forced expiratory maneuvers and the differences between the highest values of two FEV1 and FVC measurements were within 5 % or 150 mL, in accordance with the acceptability and repeatability criteria outlined by the ATS/ERS [11]. The lung function prediction equations utilized in this study were derived from the global lung function 2012 equations [12], which serve as a widely recognized reference. To ensure accurate interpretation of results within the Chinese population, these equations were further adjusted to align with their specific characteristics [13]. The detailed predicted value equations employed in our analysis have been meticulously documented and are provided in Supplementary Table 1 for comprehensive reference.

2.5. Imaging evaluation of CT scan

All patients underwent a standard chest computed tomography (CT) scan utilizing one of our three CT scanners: a 16-MDCT (Brilliance 16, Philipps), a 64-MDCT (SOMATOM Definition, Siemens), or a 320-MDCT (Aquilion ONE, Toshiba Medical Systems) scanner. The imaging parameters for thin-section CT scans across different multidetector devices were as follows: tube voltage of 120 kV, automatic tube current modulation, matrix size of 512 x 512, and a slice thickness ranging from 1 to 1.5 mm. A board-certified radiologist and pulmonologist, both of whom were blinded to the clinical information, assessed the extent of emphysema and fibrosis (grade 1, 5–25 %; grade 2, 26%–50 %; grade 3, 51%–75 %; grade 4, 76%–100 %). Additionally, they evaluated the specific type of emphysema and the characteristics of the fibrotic lesions.

2.6. Statistical analysis

Continuous variables were presented as the mean and standard deviation if the data followed a normal distribution, and as the median and interquartile range (IQR) if the data did not exhibit a normal distribution. Categorical variables were described in terms of frequency rates and percentages. To compare means of continuous variables with normally distributed data, we employed the *t*-test or analysis of variance (ANOVA). For non-normally distributed data, we utilized non-parametric tests. The proportions of categorical variables were analyzed using the $\chi 2$ test. The optimal cutoff point on the receiver operating characteristic (ROC) curve was determined through the maximization of the Youden index. Statistical analyses were performed using SPSS (version 26.0; SPSS Company, Chicago, IL, United States) and the Free Statistics analysis platform. A significance level of $P < 0.05$ was considered statistically significant. Graphs were generated using GraphPad Prism version 9.00 software and the Free Statistics analysis platform.

3. Results

3.1. Demographic of the study population

A retrospective review was undertaken on a total of 311 patients who were diagnosed with COPD, all of whom had KL-6 measurements accessible in the database. Nonetheless, 52 patients were excluded from the study due to specific infections or inadequate CT data. Consequently, a final cohort of 259 patients was included in the analysis. Among these patients, 207 were diagnosed with simple COPD, while the remaining 52 were diagnosed with CPFE (Supplementary Fig. 1).

The study participants had a mean age of 67.39 years (SD: 8.14), with the majority being male (90.7 %). The average body mass

index (BMI) was 22.63 kg/m^2 (SD: 3.26). The most prevalent occupations among the patients were farmers (35.5 %) and retirees (31.3 %). Regarding smoking history, patients were categorized as current smokers (42.9 %), former smokers (46.0 %), or never smokers (11.1 %). Among current and former smokers, the median duration of cigarette consumption was 45.00 years (IQR: 30.00–60.00).

Table 1
Baseline and clinical characteristics between subjects with COPD and CPFE.

Variable	Total (n = 259)	COPD (n = 207)	CPFE (n = 52)	*P* Value
Age, median (IQR), years	67.39 ± 8.14	67.29 ± 8.16	67.79 ± 8.16	0.694
Gender, n (%)				0.182
Female	24 (9.3)	22 (10.6)	2 (3.8)	
Male	235 (90.7)	185 (89.4)	50 (96.2)	
BMI	22.63 ± 3.26	22.71 ± 3.12	22.40 ± 3.68	0.644
Occupation, n (%)				0.894
Farmers	92 (35.5)	72 (34.8)	20 (38.5)	
Employees	30 (11.6)	26 (12.6)	4 (7.7)	
Freelancer	7 (2.7)	6 (2.9)	1 (1.9)	
Retired	81 (31.3)	64 (30.9)	17 (32.7)	
Unemployed	19 (7.3)	14 (6.8)	5 (9.6)	
Other	30 (11.6)	25 (12.1)	5 (9.6)	
Blood type (ABO), n (%)				0.844
A	56 (35.2)	47 (35.1)	9 (36.0)	
B	35 (22.0)	30 (22.4)	5 (20.0)	
O	55 (34.6)	47 (35.1)	8 (32.0)	
AB	13 (8.2)	10 (7.5)	3 (12.0)	
Smoking status, n (%)				0.202
Current smoker	108 (42.9)	85 (42.1)	23 (46.0)	
Former smoker	116 (46.0)	91 (45.0)	25 (50.0)	
Non-smoker	28 (11.1)	26 (12.9)	2 (4.0)	
Cigarette consumption-pack years	45.00 (30.00–60.00)	45.00 (30.00–60.00)	40.00 (30.00–72.75)	0.941
Comorbidities, n (%)				
Lung cancer	129 (52.7)	108 (55.1)	21 (42.9)	0.125
Pulmonary hypertension	53 (20.5)	45 (21.7)	8 (15.4)	0.310
Hypertension	98 (37.8)	79 (38.2)	19 (36.5)	0.829
Coronary heart disease	66 (25.5)	54 (26.1)	12 (23.1)	0.656
Cerebrovascular diseases	25 (9.7)	19 (9.2)	6 (11.5)	0.794
Diabetes	54 (20.8)	40 (19.3)	14 (26.9)	0.228
Tuberculosis	79 (30.5)	65 (31.4)	14 (26.9)	0.615
Chronic liver diseases	20 (7.7)	17 (8.2)	3 (5.8)	0.773
Rheumatic diseases	26 (10.0)	15 (7.2)	11 (21.2)	0.003
Rheumatoid arthritis	7 (2.7)	4 (1.9)	3 (5.8)	0.147
Systemic sclerosis	4 (1.5)	2 (1.0)	2 (3.8)	0.097
ANCA-associated vasculitis	5 (1.9)	2 (1.0)	3 (5.8)	0.057
Idiopathic inflammatory myositis	1 (0.4)	1 (0.5)	0 (0)	1.000
Gout	1 (0.4)	1 (0.5)	0 (0)	1.000
Systemic Lupus Erythematosus	2 (0.8)	2 (1.0)	0 (0)	1.000
Osteoarthritis	3 (1.2)	2 (1.0)	1 (1.9)	0.491
Mixed connective tissue disease	3 (1.2)	1 (0.5)	2 (3.8)	0.104
Clinical Manifestations, n (%)				
Fever	74 (28.7)	58 (28.0)	16 (31.4)	0.635
Cough	225 (87.2)	183 (88.4)	42 (82.4)	0.246
Expectoration	213 (82.6)	174 (84.1)	39 (76.5)	0.201
Hemoptysis	32 (12.4)	26 (12.6)	6 (11.8)	0.877
Dyspnea	176 (68.2)	142 (68.6)	34 (66.7)	0.791
Lung function				
FEV_1, L	1.67 ± 0.64	1.57 ± 0.62	1.97 ± 0.61	0.002
FEV_1, % predicted	66.00 ± 21.58	62.99 ± 21.48	74.24 ± 19.93	0.012
FVC, L	2.73 ± 0.70	2.68 ± 0.66	2.87 ± 0.82	0.169
FVC, % predicted	82.88 ± 18.27	82.48 ± 17.85	83.96 ± 19.64	0.702
FEV_1/FVC, %	60.62 ± 14.74	57.64 ± 14.24	69.46 ± 12.66	<0.001
DL_{CO}, mmol/min/kPa	3.95 ± 1.58	4.03 ± 1.73	3.73 ± 1.11	0.490
DL_{CO}, % predicted	51.19 ± 18.90	52.81 ± 20.01	46.95 ± 15.29	0.253
TLC, L	4.46 ± 0.89	4.40 ± 0.86	4.62 ± 0.98	0.384
Extent of emphysema lesion				0.695
0 %	14 (5.4)	14 (6.8)	0 (0.0)	
<5 %	40 (15.5)	35 (16.9)	5 (9.8)	
5%–25 %	80 (31.0)	59 (28.5)	21 (41.2)	
25%–50 %	32 (12.4)	24 (11.6)	8 (15.7)	
50%–75 %	43 (16.7)	31 (15.0)	12 (23.5)	
75%–100 %	49 (19.0)	44 (21.3)	5 (9.8)	

Data are presented as mean ± standard deviation (SD), medians (IQR) and n (%). *P* values were calculated by Student *t*-test, Mann–Whitney *U* test, Chi-square test or Fisher's exact test, as appropriate. *P* values indicate differences between COPD and CPFE.

There were no significant differences observed between the two groups in terms of age, gender, occupation, blood type and smoking status. Indeed, the prevalence of rheumatic diseases was found to be higher among CPFE patients in comparison to COPD patients (21.2 % vs. 7.2 %, P = 0.003). However, upon further subdivision of rheumatic diseases, no statistically significant difference was observed (Table 1).

3.2. Clinical characteristics and laboratory findings of the study population

The most common clinical symptoms reported were cough (87.2 %), expectoration (82.6 %), and dyspnea (68.2 %). In terms of lung function, CPFE patients exhibited relatively preserved pulmonary function, including higher values of forced expiratory volume in 1 s (FEV_1) (1.97 vs 1.57, $P = 0.002$), FEV_1% (74.24 vs 62.99, $P = 0.012$), and FEV_1/forced vital capacity (FEV_1/FVC) ratio (69.46 vs 57.64, $P < 0.001$) compared to COPD patients. Thoracic CT scans, which were accessible for all patients, detected the presence of emphysema in 245 cases, while the remaining 14 cases were diagnosed with COPD of the chronic bronchitis type. The distribution of emphysema extent was as follows: 0 % (5.4 %), <5 % (15.5 %), 5%–25 % (31.0 %), 25%–50 % (12.4 %), 50%–75 % (16.7 %), and 75%–100 % (19.0 %) (Table 1). CPFE patients exhibited elevated eosinophil counts (0.20 vs 0.10 × 10^9/L, $P = 0.033$), percentage of eosinophils (2.10 vs 1.40 %, $P = 0.028$), lactate dehydrogenase (226.50 vs 206.65 U/L, $P = 0.044$), total bilirubin levels (12.00 vs 9.75 μmol/L, $P = 0.045$), and KL-6 levels (574.95 vs 339.30 U/mL, $P < 0.001$; Fig. 1) compared to COPD patients. Conversely, COPD patients demonstrated higher levels of platelet counts (215.00 vs 185.50 × 10^9/L, $P = 0.025$) compared to CPFE patients, with both groups' values falling within the normal range. Both groups exhibited elevated levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Interleukin 6 (IL-6) and Tumor necrosis factor α (TNF-α) beyond the normal range; however, there was no significant difference observed between the COPD and CPFE groups (Table 2).

3.3. The imaging features of CPFE

According to the predefined inclusion criteria, the chest CT scans of 52 patients demonstrated the coexistence of emphysema and pulmonary fibrosis (Supplementary Table 2). The extent of emphysema and fibrotic lesions is summarized in Fig. 2A and B. The distribution of emphysema predominantly affected the upper lobes (94.2 %), while the fibrosis primarily localized to the lower lobes (63.5 %) (Fig. 2C). Regarding the classification of emphysema types, 25 patients (48.1 %) were categorized as mixed type, 8 patients (15.4 %) as centrilobular type, 11 patients (21.2 %) as panacinar type, and 8 patients (15.4 %) as paraseptal type (Fig. 2D). Ground-glass opacities, traction bronchiectasis, and reticular opacities were the most frequently observed findings, present in 96.2 %, 86.5 %, and 75.0 % of the cases, respectively (Fig. 2E). Based on high-resolution CT (HRCT) evaluations, the diagnoses were classified as usual interstitial pneumonia (UIP) in 37 patients (71.2 %) (Fig. 3A), nonspecific interstitial pneumonia (NSIP) in 13 patients (25.0 %) (Fig. 3B), and neither UIP nor NSIP in the remaining cases (Fig. 2F). Thick-walled large cysts, representing a distinctive imaging pattern of CPFE, were observed in 14 (26.9 %) of the patients (Fig. 3C and Supplementary Fig. 2).

3.4. Serum KL-6 levels are associated with the presence of CPFE

To enhance the clinical value of our data, we have rescaled the KL-6 values by dividing them by 100. Through logistic regression analysis, we investigated factors associated with CPFE and identified rheumatic diseases, platelet count, international normalized ratio (INR), high density lipoprotein cholesterol (HDL-C) and KL-6 as potential indicators of CPFE. Further analysis using multivariable regression demonstrated that KL-6 levels were independently associated with CPFE. Specifically, for every 100 U/mL increase in KL-6,

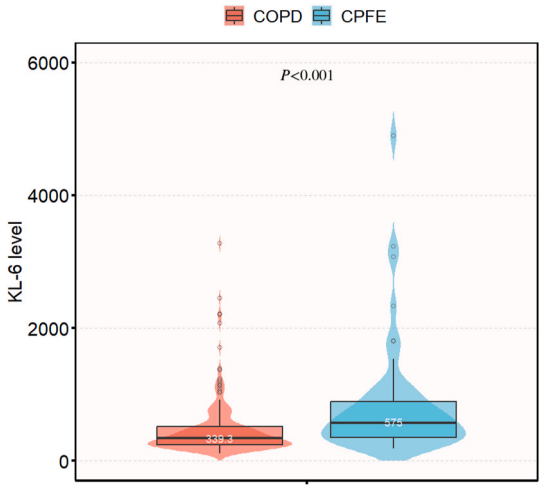

Fig. 1. Divergence in KL-6 levels between the COPD group and the CPFE group.

Table 2
Laboratory findings at admission between subjects with COPD and CPFE.

Laboratory findings	Normal Range	Total (n = 259)	COPD (n = 207)	CPFE (n = 52)	*P* Value
Blood Routine					
Red blood cell count, × 10^{12}/L	3.80–5.10	3.97 (3.54–4.40)	3.97 (3.56–4.40)	3.91 (3.44–4.44)	0.595
Hemoglobin, g/L	130–175	119.00 (103.00–131.00)	119.00 (103.00–131.00)	119.50 (106.00–132.00)	0.646
White blood cell count, × 10^9/L	3.5–9.5	7.40 (5.60–9.70)	7.60 (5.70–9.70)	6.85 (4.85–8.85)	0.168
Neutrophil count, × 10^9/L	1.8–6.3	5.30 (3.50–7.40)	5.40 (3.60–7.50)	4.70 (3.03–6.98)	0.245
Neut%	40.0–75.0	71.40 (61.80–82.60)	72.40 (62.20–83.10)	68.25 (59.93–91.35)	0.582
Lymphocyte count, × 10^9/L	1.1–3.2	1.20 (0.70–1.60)	1.20 (0.70–1.60)	1.10 (0.80–1.48)	0.595
Lymph%	20.0–50.0	16.80 (9.00–24.90)	16.60 (8.50–24.90)	17.45 (10.95–25.38)	0.522
Eosinophil count, × 10^9/L	0.02–0.52	0.10 (0.05–0.20)	0.10 (0.04–0.20)	0.20 (0.08–0.30)	0.033
Eos%	0.4–8.0	1.40 (0.60–3.40)	1.40 (0.50–3.00)	2.10 (0.90–5.00)	0.028
Platelet count, × 10^9/L	125–350	208.00 (158.00–273.00)	215.00 (165.00–279.00)	185.50 (136.50–232.00)	0.025
Blood Biochemistry					
Glucose, mmol/L	3.9–5.8	5.50 (4.73–7.45)	5.50 (4.78–7.45)	5.60 (4.47–7.61)	0.597
Aspartate aminotransferase, U/L	15.0–40.0	23.90 (18.60–32.15)	23.85 (18.60–31.25)	24.90 (18.20–34.60)	0.632
Alanine aminotransferase, U/L	9.0–50.0	17.70 (11.85–29.25)	17.85 (12.05–28.50)	16.70 (11.50–35.80)	0.640
Lactate dehydrogenase, U/L	120.0–250.0	210.00 (172.25–271.55)	206.65 (169.63–266.50)	226.50 (183.00–295.00)	0.044
Total bile acid, μmol/L	0–12.0	3.80 (2.20–6.00)	3.60 (2.00–5.90)	4.10 (2.50–7.80)	0.125
Total bilirubin, μmol/L	0–25.0	10.20 (7.40–14.40)	9.75 (7.10–14.00)	12.00 (8.50–14.50)	0.045
Albumin, g/L	40.0–55.0	34.50 (30.50–38.50)	34.50 (30.65–38.53)	34.30 (30.40–38.50)	0.742
Blood uric acid, μmol/L	208.0–428.0	315.89 ± 112.98	315.22 ± 116.61	318.55 ± 97.95	0.851
Blood urea, mmol/L	3.60–9.50	6.02 (4.63–7.66)	6.03 (4.69–7.83)	6.01 (4.28–7.54)	0.620
Serum creatinine, μmol/L	41.0–111.0	77.00 (64.25–90.00)	76.90 (64.08–90.78)	77.20 (65.00–87.00)	0.942
C-reactive protein, mg/L	0–8.00	21.70 (7.57–78.03)	18.95 (7.68–77.75)	28.00 (6.11–94.70)	0.621
Erythrocyte sedimentation rate, mm/h	0–21	59.50 (35.00–88.00)	60.00 (32.00–88.00)	56.00 (41.00–104.00)	0.105
Complement C3, mg/L	790.00–1520.00	922.44 ± 221.31	934.39 ± 220.30	877.96 ± 221.94	0.138
Complement C4, mg/L	100.00–400.00	254.14 ± 79.07	256.15 ± 77.74	246.61 ± 84.38	0.483
Interleukin 6, pg/mL	<5.9	10.90 (5.08–28.23)	11.30 (5.11–27.28)	10.08 (4.30–35.35)	0.917
Tumor necrosis factor α, pg/mL	<8.1	10.70 (7.79–14.38)	10.50 (7.67–13.70)	11.50 (8.06–17.40)	0.207
Krebs von den Lungen-6, U/mL	105.3–401.2	364.60 (253.10–606.80)	339.30 (239.70–514.40)	574.95 (344.48–941.60)	<0.001
Myocardial Injury Mediators					
Creatine kinase, U/L	50.0–310.0	50.40 (31.98–77.83)	52.85 (33.48–77.08)	44.90 (27.00–92.35)	0.495
Myoglobin, μg/mL	<70	38.10 (26.63–55.90)	36.45 (25.73–55.90)	43.30 (31.23–55.98)	0.214
Creatine kinase-MB, U/L	<24.0	12.20 (9.20–16.25)	12.30 (9.13–16.33)	12.05 (9.30–16.33)	0.871
N-Terminal pro-brain natriuretic peptide (NT-proBNP), pg/mL	0–450	309.49 (103.95–824.46)	311.00 (119.00–861.26)	287.67 (94.54–634.82)	0.799
Blood Coagulation					
D-dimer, μg/mL	0–0.5	0.32 (0.16–0.85)	0.31 (0.16–0.85)	0.39 (0.16–0.88)	0.706
Prothrombin time (PT), s	9.0–14.0	11.75 (11.00–12.60)	11.70 (11.00–12.60)	12.00 (11.00–13.20)	0.123
Activated partial thromboplastin time (APTT), s	22.3–32.5	28.25 (26.50–31.68)	28.15 (26.20–31.73)	29.65 (26.88–31.60)	0.229
Prothrombin Time - International Normalized Ratio (PT-INR)	0.8–1.2	0.99 (0.92–1.09)	0.99 (0.92–1.09)	1.02 (0.94–1.14)	0.063
Blood lipid					
Triglyceride, mmol/L	<1.70	1.14 (0.88–1.58)	1.17 (0.88–1.60)	1.12 (0.88–1.50)	0.613
Low density lipoprotein cholesterol, mmol/L	1.55–3.19	2.66 (2.09–3.28)	2.71 (2.09–3.33)	2.55 (2.15–3.03)	0.174
Total cholesterol, mmol/L	<5.18	4.11 (3.33–4.99)	4.22 (3.33–5.22)	3.85 (3.32–4.56)	0.136
High density lipoprotein cholesterol, mmol/L	1.04–1.55	0.94 (0.76–1.17)	0.97 (0.78–1.21)	0.86 (0.68–1.13)	0.051

Data are presented as mean ± standard deviation (SD), medians (IQR) and n (%). *P* values were calculated by Student *t*-test, Mann–Whitney *U* test, as appropriate. *P* values indicate differences of characteristics between subjects with COPD and CPFE.

the likelihood of CPFE incidence increased by 1.11 times (OR 1.11, 95 % CI 1.04–1.17, $P = 0.001$; Table 3). To assess the robustness of our adjusted model, we performed stratified analyses based on age, gender, rheumatic diseases, platelet count, INR and HDL-C. The forest plot revealed no significant interactions among these subgroups ($P > 0.05$, Fig. 4).

3.5. The role of KL-6 in distinguishing CPFE from COPD

To evaluate the diagnostic utility of serum KL-6 in distinguishing CPFE from COPD in clinical settings, we conducted receiver operating characteristic curve (ROC) analysis. The area under the curve (AUC) was calculated as 0.711, with a 95 % confidence interval (CI) of 0.635–0.787 ($P < 0.001$). The optimal cut-off point of KL-6 was possibly determined to be around 550.95 U/mL based on the maximum Youden index, indicating its potential value in discriminating CPFE among COPD patients. At this threshold, the corresponding sensitivity was found to be 57.7 %, while the specificity was 79.7 % (Fig. 5).

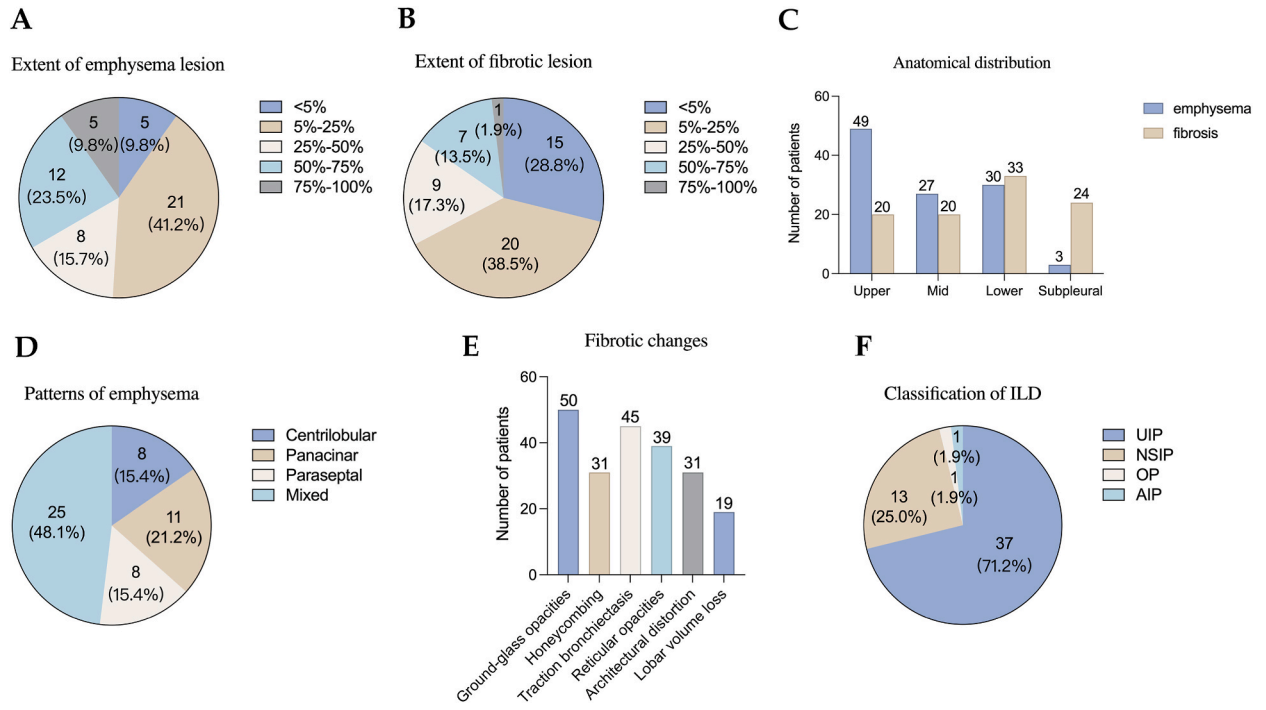

Fig. 2. The imaging features of CPFE. (A) Extent of emphysema lesion. (B) Extent of fibrotic lesion. (C) The anatomical distribution of emphysema and fibrosis. (D) Patterns of emphysema. (E) Fibrotic changes. (F) Classification of ILD.

4. Discussion

In this study, we conducted an initial statistical analysis of demographic data and selected biomarkers, which revealed significant associations between CPFE and various indicators. Subsequently, rheumatic diseases, platelet count, INR, HDL-C and KL-6 were subjected to multivariate logistic regression analysis to assess their predictive relevance for distinguishing between CPFE and COPD. The results demonstrated that rheumatic diseases and KL-6 exhibited statistical significance ($P < 0.05$). Furthermore, we employed ROC curve analysis to evaluate the diagnostic efficacy of KL-6. Our findings indicated that KL-6 could potentially serve as a biomarker for differentiating CPFE from COPD. The AUC was calculated as 0.711, with a 95 % CI of 0.635–0.787. Based on the maximum Youden index, the optimal cut-off point of KL-6 was estimated to be around 550.95 U/mL, with a sensitivity of 57.7 % and specificity of 79.7 %. Consequently, a KL-6 level higher than 550.95 U/mL in COPD patients suggests the potential requirement for HRCT to identify the presence of fibrosis.

KL-6 serves as a valuable serum biomarker for diagnosing various types of ILD and is closely associated with disease activity [14,15]. Additionally, elevated serum KL-6 levels are also associated with acute exacerbation and mortality in cases of CPFE [16]. In this study, we further validate that KL-6 can effectively differentiate individuals with CPFE within the COPD population. Therefore, in the presence of elevated KL-6 levels in patients with COPD, it is imperative for clinicians to perform HRCT to assess the potential presence of fibrosis. Furthermore, the identification of a critical value of 550.95 U/mL in the CPFE group, which surpasses the established cutoff value of 500 U/mL for interstitial pneumonia [9], potentially suggests a heightened severity of injury to bronchial epithelial cells or type II alveolar epithelial cells in CPFE when compared to cases of interstitial pneumonia.

In our study, platelet count exhibited a significant association with CPFE in the univariate regression analysis. This finding aligns with a systematic review that reported a significant increase in platelet count among individuals with COPD when compared to non-COPD controls [17], while another study demonstrated a statistically significant decrease in mean platelet count among patients with IPF in comparison to control subjects [18].

In the analysis of HRCT images, the coexistence of emphysema and interstitial fibrosis characterizes CPFE, resulting in a diverse range of manifestations. In our study involving 52 patients with CPFE, we observed that the distribution of emphysema was predominantly characterized by a mixed pattern, which aligns with findings from previous research [19]. Notably, the emphysema exhibited a predominant distribution within the upper lobes, whereas the fibrosis primarily localized to the lower lobes. Additionally, several cases showed concurrent spatial involvement of both emphysema and fibrosis. The association between fibrosis and emphysema exhibited variability, consistent with previous findings [20]. Ground-glass opacities, traction bronchiectasis, and reticular opacities were the most frequent findings. As previously mentioned, UIP is the most frequently identified pattern in ILD [21]. However, other types of ILD, such as NSIP, OP, and AIP have also been reported. Previous studies have indicated that admixed emphysema and thick-walled large cysts may represent characteristics of CPFE [22,23]. In our study, thick-walled large cysts were observed in 26.9 % of the patients, which closely aligns with the previously reported prevalence of 29 % [22]. This finding suggests that our study

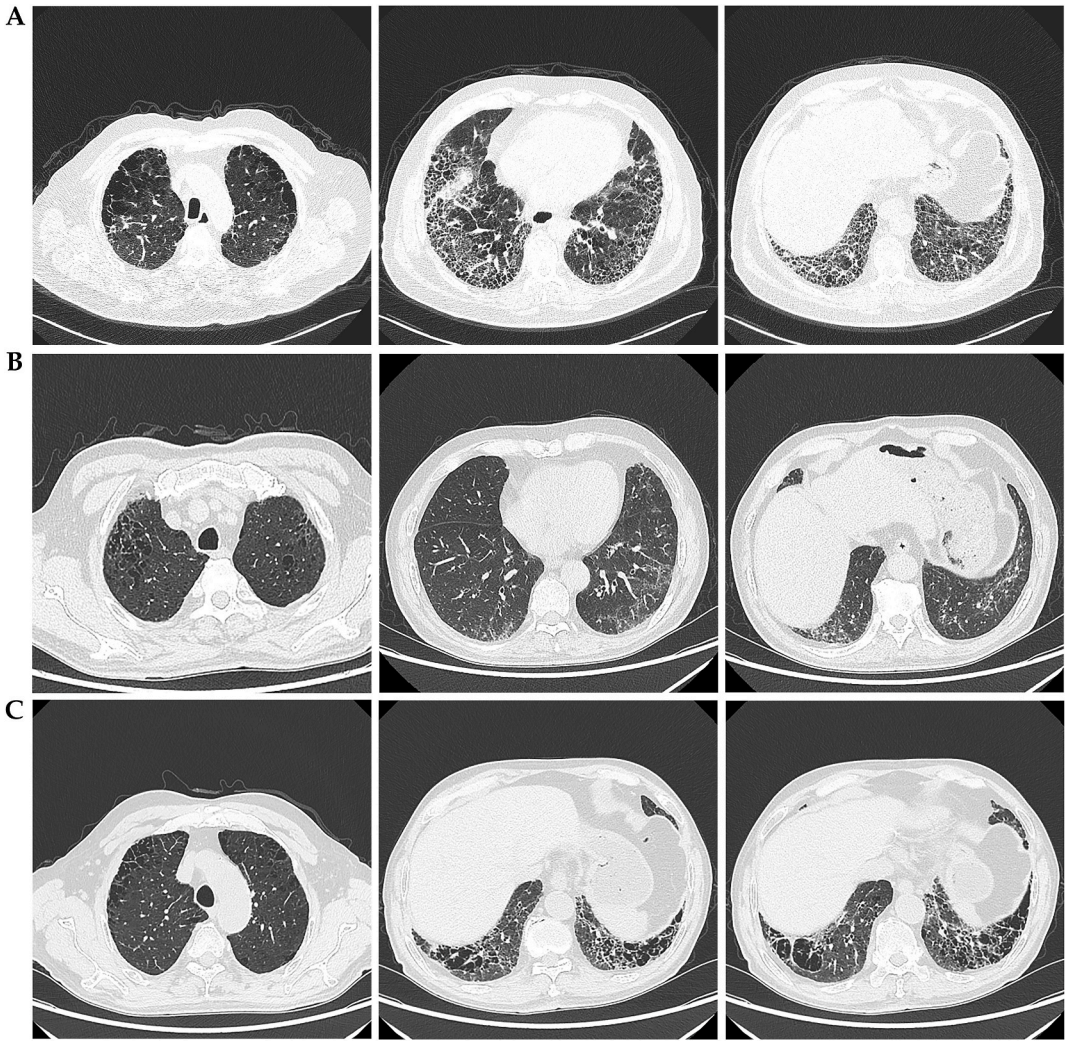

Fig. 3. High-resolution computed tomography showing a typical distribution of disease seen in combined pulmonary fibrosis and emphysema. (A) HRCT findings of a 75-year-old male with CPFE. Bilateral upper lung lobes exhibit central and paraseptal emphysema. Interstitial lesions in the right middle lobe, left upper lobe lingular segment, and bilateral lower lungs present as honeycombing. Traction bronchiectasis and decreased lung volumes are observed. Interstitial lesion pattern consistent with UIP. (B) HRCT findings of a 69-year-old male with CPFE. Bilateral upper lung lobes exhibit centrilobular and panlobular emphysema. Interstitial lesions in bilateral lower lungs appear as ground-glass opacities without honeycombing or traction bronchiectasis. Interstitial lesion pattern consistent with NSIP. (C) HRCT findings of a 69-year-old male with CPFE demonstrate admixed emphysema and fibrosis with thick-walled large cysts. There is central and peribronchiolar emphysema in the upper lung lobes, while the lower lobes exhibit interstitial lung disease characterized by honeycomb opacities accompanied by thick-walled large cysts.

potentially exhibits a promising level of representativeness in reflecting the characteristics of CPFE.

There were notable differences in lung function test results between patients with CPFE and those with COPD. As previously reported [24,25], parameters such as FEV_1, percent predicted FEV_1, and FEV_1/FVC showed significant variations, with higher values observed in the CPFE group compared to the COPD group. Additionally, a cohort study demonstrated a positive correlation between serum bilirubin levels and FEV_1, FVC, and $FEF_{25–75\ \%}$ [25], which further supports our conclusion that CPFE patients exhibit higher TBIL levels compared to COPD patients. Notably, our study revealed that although the CPFE group exhibited lower DL_{CO}, there was no statistically significant difference in DL_{CO} between the COPD and CPFE groups. Previous studies have reported a substantial decrease in DL_{CO} among CPFE patients [26], with the extent of fibrosis exerting a more pronounced impact on DL_{CO} than emphysema [20]. These findings may suggest a relatively higher proportion of patients with mild disease in our study population, as confirmed by the extent of fibrosis observed in the HRCT scans.

We have observed a significant correlation between CPFE syndrome and rheumatic diseases. This observation is consistent with several independent reports that have suggested the potential role of connective tissue diseases as a risk factor for the development of emphysema, regardless of smoking status [27–30]. Therefore, our findings provide further support for the notion that rheumatic diseases may indeed contribute significantly to the pathogenesis of CPFE. Considering the diverse nature of rheumatic diseases and

Table 3
Factors associated with CPFE.

Variables	OR (95%CI)	*P* value	Adjusted OR (95%CI)	*P* value
Age	1.01 (0.97–1.05)	0.693		
Gender (male)	2.97 (0.68–13.07)	0.149		
Smoking status (current smoker)	3.52 (0.78–15.93)	0.103		
Smoking status (former smoker)	3.57 (0.79–16.08)	0.097		
Pack years	1.00 (0.99–1.01)	0.919		
Comorbidities				
Lung cancer	0.61 (0.33–1.15)	0.127		
Rheumatic diseases	3.43 (1.47–8.02)	0.004	4.13 (1.22–13.94)	0.022
Pulmonary hypertension	0.66 (0.29–1.49)	0.313		
Hypertension	0.93 (0.50–1.75)	0.829		
Coronary heart disease	0.85 (0.42–1.74)	0.656		
Cerebrovascular diseases	1.29 (0.49–3.41)	0.607		
Diabetes	1.54 (0.76–3.11)	0.230		
Tuberculosis	0.81 (0.41–1.59)	0.531		
Chronic liver diseases	0.68 (0.19–2.43)	0.557		
Blood test				
Hb	1.01 (0.99–1.02)	0.506		
Neut	0.95 (0.86–1.05)	0.295		
Lymph	0.82 (0.51–1.32)	0.419		
Eos	2.83 (0.57–14.16)	0.205		
Plt	1.00 (0.99–1.00)	0.043	1.00 (0.99–1.00)	0.064
ALB	0.98 (0.93–1.04)	0.544		
LDH	1.00 (1.00–1.00)	0.436		
TBIL	1.01 (0.98–1.05)	0.459		
INR	10.27 (1.65–64.07)	0.013	4.18 (0.43–40.38)	0.216
CRP	1.00 (1.00–1.00)	0.387		
ESR	1.01 (1.00–1.02)	0.102		
C3	1.00 (1.00–1.00)	0.139		
C4	1.00 (0.99–1.00)	0.482		
TC	0.82 (0.64–1.06)	0.137		
HDL-C	0.35 (0.13–0.98)	0.045	0.42 (0.12–1.44)	0.582
KL-6/100 (U/mL)	1.11 (1.05–1.17)	<0.001	1.11 (1.04–1.17)	0.001

Abbreviations: Hb, hemoglobulin; Neut, neutrophil; Lymph, Lymphocyte; Eos, eosinophil; PLT, platelet; ALB, Albumin; LDH, Lactate dehydrogenase; TBIL, Total bilirubin; INR, International normalized ratio; CRP, C-reaction protein; ESR, erythrocyte sedimentation rate; C3, complement C3; C4, complement C4; TC, total cholesterol; HDL-C, High density lipoprotein cholesterol; KL-6, Krebs Von den Lungen-6.

their associated lesions, we conducted analysis based on disease classification. However, due to the sample size limitations, statistical differences were not observed between the groups. Conversely, previous studies consistently reported a higher incidence of pulmonary hypertension and lung cancer in the CPFE group compared to the emphysema group [1,24,31,32]. It is important to acknowledge that the divergent findings in our study may be influenced by potential biases in patient selection and limitations arising from a relatively small sample size. However, both the student t-test and multivariate logistic regression analysis did not reveal a significant difference in the prevalence of pulmonary hypertension and lung cancer between the CPFE and COPD groups. Additionally, the forest plot generated from stratified analyses indicated no significant interactions among the subgroups of rheumatic diseases. Based on these results, we can infer that even when considering the potential presence of selection bias, the presence of comorbidities does not impact the diagnostic value of KL-6 in identifying CPFE within the COPD population after appropriate adjustment for confounding factors.

The present study has several notable limitations that warrant acknowledgment. Firstly, it is important to recognize that this study is retrospective in nature. However, this retrospective design does not undermine the main findings of our study, which suggest that the KL-6 test may serve as a practical tool for differentiating CPFE from COPD. Secondly, as a single-center study, our findings may not fully capture the diverse spectrum of patients treated at local primary or secondary care centers. Nonetheless, our study likely provides insights into typical or real-world scenarios. Furthermore, we recognize that our dataset has missing values, particularly in relation to inadequate blood type data, however, it is crucial to emphasize that this parameter is not the principal research measures in our study, as such, it has no impact on the validity or interpretation of our main findings. Additionally, the limited sample size imposes constraints on our ability to accurately validate the calculated AUC. Thus, future research endeavors should prioritize larger prospective multi-center cohort studies to robustly validate our observations.

5. Conclusions

Our study findings indicate that patients with CPFE exhibit significantly higher KL-6 levels compared to those with isolated COPD. This suggests that KL-6 has the potential to serve as a practical screening tool for interstitial lung disease, specifically CPFE. Furthermore, a KL-6 threshold of 550.95 U/mL in COPD patients may indicate the necessity of high-resolution chest computed tomography for the detection of fibrosis.

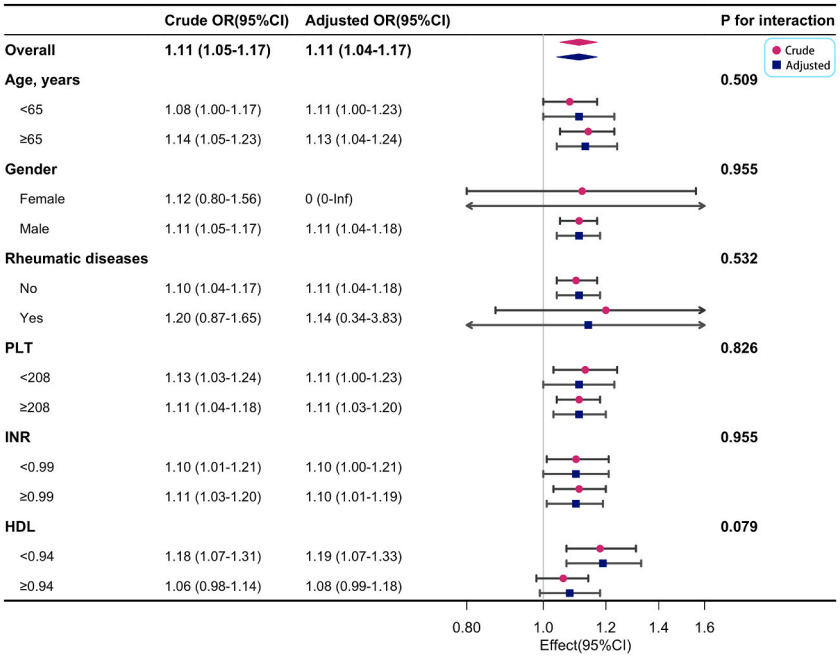

Fig. 4. Forest plot for the subgroup analysis of the presence of CPFE according to KL-6 levels. For each group of interest, the gray horizontal lines represent the 95 % confidence interval (CI).

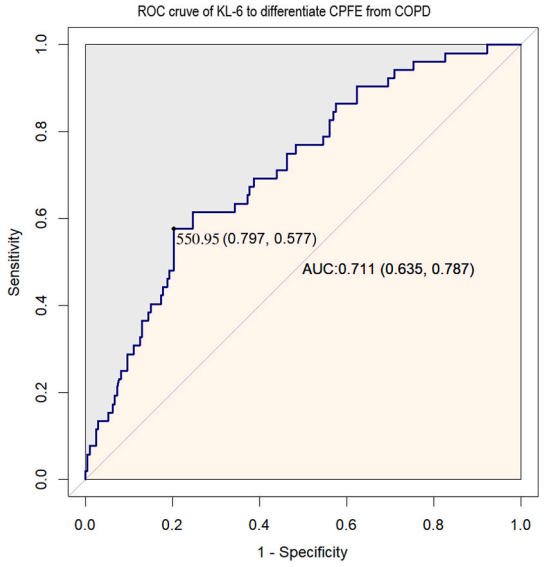

Fig. 5. ROC curve of KL-6 to differentiate CPFE from COPD.

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Ethical approval and consent to participate

This study was reviewed and approved by the local Ethics Committee of the Xiangya Hospital of Central South University with the approval number: No. 202309183, dated September 6th, 2023.

Data availability

Data will be made available on request.

CRediT authorship contribution statement

Aiyuan Zhou: Writing – original draft, Investigation, Formal analysis, Data curation. **Xiyan Zhang:** Writing – original draft, Investigation, Formal analysis, Data curation. **Rongli Lu:** Software, Investigation, Formal analysis. **Wenzhong Peng:** Investigation, Resources, Validation. **Yanan Wang:** Writing – review & editing, Resources. **Haiyun Tang:** Visualization, Supervision, Funding acquisition, Conceptualization. **Pinhua Pan:** Project administration, Funding acquisition, Conceptualization.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35099.

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