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Factors associated with rapid progression in fibrotic interstitial lung disease

Xianqiu Chen [a,1], Qiuliang Ji [a,1], Qian Yao [b], Ying Zhou [b,*]

[a] Department of Respiratory Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China
[b] Department of Respiratory Medicine and Clinical Research Center, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

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ABSTRACT

Background: Early identification of fibrotic interstitial lung disease (F-ILD) patients with high risk of progression will help initiate early therapeutic intervention and potential improvement of outcomes. This study was designed to assess the predictors of progression in patients with F-ILD.
Methods: Patients with F-ILD in Shanghai Pulmonary Hospital between January 1, 2019 and July 31, 2021 were retrospectively analyzed. The patients enrolled were divided into progressive group and non-progressive group according to the specified criteria. Baseline characteristics were collected and a multivariate regression was conducted to identify independent predictors of progression.
Results: Of the 177 F-ILD cases, 87 were enrolled in the progressive group and 90 were in the non-progressive group. The cohort included 11 types of F-ILD, primarily were connective tissue disease-associated interstitial lung disease (CTD-ILD) (43, 24.3 %), idiopathic pulmonary fibrosis (IPF) (39, 22.0 %), interstitial pneumonia with autoimmune features (IPAF) (32, 18.1 %), and unclassifiable (23, 13.0 %). The highest proportion of progression was seen in nonspecific interstitial pneumonia (NSIP) subgroup (66.7 %), followed by IPF (59.0 %) and HP (57.1 %). After adjusting for gender and age, a course of disease longer than 9.5 months (OR: 2.633; 95 % CI: 1.190–5.826, $P = 0.017$), lymphocyte in peripheral blood more than 2.24 (10^9/L) (OR: 2.670; 95 % CI: 1.095–6.510, $P = 0.031$), and emphysema in high-resolution computed tomography (HRCT) (OR: 2.387; 95 % CI: 1.017–5.640, $P = 0.046$) were independent predictors of progression in F-ILD patients.
Conclusions: This study suggested that in patients with F-ILD, long course of disease, elevated blood lymphocyte and emphysema on HRCT were independent predictors of progression, which may suggest utility in early therapeutic intervention.

1. Introduction

Many patients with interstitial lung disease (ILD) develop pulmonary fibrosis [1], of which a proportion may develop a progressive-fibrosing phenotype. There has been increasing awareness of fibrotic interstitial lung disease (F-ILD) since 2018. Cottin et al. [2] firstly proposed the concept of progressive fibrosing interstitial lung disease (PF-ILD) who may develop a

* Corresponding author. 507 Zheng Min Road, Shanghai, 200433, China.
E-mail address: happyying79550@sina.com (Y. Zhou).
[1] Xianqiu Chen and Qiuliang Ji contributed equally to this work.

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progressive-fibrosing phenotype in patients with ILDs. A complete statement of the concept was described in the study of INBUILD published in 2019 [3]. In 2020, George et al. proposed the suggested definition of PF-ILD in clinical practice to meet one of the following criteria: relative decline of ≥10 % in forced vital capacity (FVC) over 24 months despite treatment; relative decline in FVC of ≥5 % with decline in diffusing capacity of the lung for carbon monoxide (DLCO) of ≥15 % over 24 months despite treatment; relative decline in FVC of ≥5 % with increased fibrosis on high-resolution computed tomography (HRCT) over 24 months despite treatment; relative decline in FVC of ≥5 % with progressive symptoms over 24 months despite treatment; progressive symptoms along with increased fibrosis on HRCT over 24 months despite treatment [4]. Based on this, the American Thoracic Society (ATS) proposed the standard of progression of pulmonary fibrosis (PPF) in 2022 [5], which was defined as at least two of three criteria (worsening symptoms, radiological progression, and physiological progression) occurring within the past year with no alternative explanation in a patient with an ILD other than idiopathic pulmonary fibrosis (IPF).

As the phenotype of F-ILD is associated with worsening respiratory symptoms, lung function decline, limited response to immunomodulatory therapies, decreased quality of life and early death [2], early identification of F-ILD patients with high risk of progression will help to get early therapeutic intervention and potential improvement of outcomes. Research is needed to identify distinguishing clinical features that may predict which individuals are more likely to develop progressive fibrosis [6]. However, there is limited published research on the progression predictors of non-IPF F-ILD. The aim of the present study was to identify predictors of disease progression of those with F-ILD beyond IPF from their demographic information, clinical features, imaging data and blood biomarkers being managed in a single center in China.

2. Methods

Patients enrolled in the study required a follow-up of at least one year. We reviewed the data in July 2022, so the latest case to be selected was from July 2021. Moreover, in order to ensure a sufficient number of cases, cases were selected two and a half years ahead. Therefore, the screened cases included in this study were consecutive cases from January 2019 to July 2021. Consecutive patients diagnosed with ILD between January 1, 2019 and July 31, 2021 at the Shanghai Pulmonary Hospital, and having complete lung function data available, were screened for this study, and the electronic medical records of these patients were retrospectively reviewed. After excluding lung cancer, lung transplantation, tuberculosis and non-fibrotic ILD, the patients were divided into progressive group and non-progressive group according to the following criteria developed for the purposes of this project. Those who met at least one of the following criteria were defined as progressive group: an annual decline of more than 10 % in FVC; an annual decline of more than 10 % in DLCO; an increased extent of fibrosis on HRCT in one year, according to the previous studies [7–10].

There were two researchers participated in the screening of cases. First, successive cases diagnosed with ILD were screened by XQC, then verified by Dr. YZ. The researchers selected successive cases and grouped them strictly according to the inclusion and exclusion criteria, but were not blinded. At time of enrollment, information of age, gender, body mass index (BMI), smoking history, course of disease, diagnosis, baseline pulmonary function (including FVC, FVC % predicted, DLCO % predicted), physiologic variables (GAP) stage [11], complete blood counts, systolic pulmonary artery pressure (SPAP) estimated by echocardiography, and tumor markers in peripheral blood were recorded.

XQC and QY were in charge of the objective data review in electronic medical record system, who were both independent to the clinical management of the patients. In addition, each subject's HRCT was independently reviewed by two expert thoracic radiologists who were blinded to the subjects' clinical status and demographics. All disagreements were resolved through consensus. The HRCT scans were classified as showing an usual interstitial pneumonia (UIP) pattern or not [12], having the presence of emphysema or not, and showing tractive bronchiectasis or not. The extent of fibrosis was further calculated using a 4-point scale: 0 = no involvement, 1 = 1–25 % involvement, 2 = 26–50 % involvement, 3 = 51–75 % involvement, and 4 = 76–100 % involvement [13].

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Shanghai Pulmonary Hospital (No. k22-238). This retrospective study followed STROBE reporting guidelines (supplementary materials).

GraphPad Prism (Version 8.0 for Windows, GraphPad Software, Boston, Massachusetts USA, www.graphpad.com) and SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) were used for figure drawing and statistical analysis. Quantitative data were presented as mean ± standard deviation (SD). The independent sample Student's t-test was used for comparisons between the progressive and non-progressive group. Multiple groups were compared by One-way ANOVA method. The chi-square test was used for constituent ratio comparisons. If the theoretical frequency was greater than or equal to one and less than five, the continuous correction chi-square test was used. If the theoretical frequency was less than one, Fisher's exact test was used. Receiver operating characteristic (ROC) curves were used to identify cut-off values. The study involved more than two independent variables to explore the independent risk factors for disease progression, multiple regression analysis was used for statistical analysis, and was adjusted for confounding factors such as age and gender to be more reliable. Those with $P < 0.1$ were included in the multivariate regression with forward selection method, to determine the independent predictors for progression in F-ILD patients. Values of $P < 0.05$ (two-sided) were considered statistically significant.

3. Results

3.1. Clinical characteristics

A total of 354 consecutive diagnosed ILD patients in Shanghai Pulmonary Hospital were screened. After excluding lung cancer, lung

transplantation and tuberculosis cases, 324 ILD cases were included in the analysis. Further, after excluding 147 non-fibrotic ILD cases, a total of 177 F-ILD cases were included finally. According to the definition of progression in the methods section, 87 cases were enrolled in progressive group and 90 cases were enrolled in non-progressive group. The participant flow chart is shown as Fig. 1.

Baseline demographics of included participants is given in Table 1. There were no significant differences in age and gender between the two groups. There were also no significant differences in BMI, the proportion of smoker, baseline lung function, and SPAP between the two groups. The average courses of disease of the two groups were 25.9 (±23.6) versus 23.5 (±31.2) months, but the percentage of patients with a course of disease longer than 9.5 months was much more in the progressive group than the non-progressive group (78.2 % vs. 54.4 %, $P = 0.001$) (Table 1).

There was no significant difference in white blood cell (WBC), lymphocyte, neutrophil and neutrophil/lymphocyte between the two groups. However, in the progressive group, the patients with neutrophil greater than 3.43 (10^9/L) and lymphocyte greater than 2.24 (10^9/L) were both more than that in non-progressive group, with *P* values of 0.016 and 0.042, respectively. There was no obvious difference in HRCT score, the proportions of UIP pattern and traction bronchiectasis, but the proportion of emphysema was significantly higher than that in non-progressive group (35.6 % vs. 20.0 %, $P = 0.020$). In the statistics of tumor markers, the proportions of patients with a level of carbohydrate antigen 199 (CA199) (more than 7.47 U/ml) and CA50 (more than 4.69 U/ml) were both significantly higher in the progressive group ($P = 0.047$ and 0.006, respectively) (Table 1).

3.2. Classifications of F-ILD in the study

Among the 177 cases of F-ILD included in this study, connective tissue disease-associated interstitial lung disease (CTD-ILD) accounted for the largest number of cases (43, 24.3 %), followed by IPF (39, 22.0 %), interstitial pneumonia with autoimmune features (IPAF) (32, 18.1 %), unclassifiable (23, 13.0 %), sarcoidosis (8, 4.5 %), hypersensitivity pneumonitis (HP) (7, 4.0 %), nonspecific interstitial pneumonia (NSIP) (6, 3.4 %), cryptogenic organizing pneumonia (COP) (6, 3.4 %), pulmonary alveolar proteinosis (PAP) (5, 2.8 %), combined pulmonary fibrosis and emphysema (CPFE) (5, 2.8 %) and pneumoconiosis (3, 1.7 %) (Fig. 2A). The proportions of progressive patients were calculated in the subgroups with more than 5 cases of patients. The highest proportion of progression was in NSIP subgroup (66.7 %), followed by IPF subgroup (59.0 %) and HP subgroup (57.1 %) (Fig. 2B). While the proportions of progression in the unclassifiable subgroup and COP subgroup were both lower, were 30.4 % and 16.7 %, respectively.

3.3. Predictors of progression in F-ILD patients

After adjusting for gender and age, a course of disease longer than 9.5 months (OR: 2.633; 95 % CI: 1.190–5.826, $P = 0.017$), lymphocyte in peripheral blood more than 2.24 (10^9/L) (OR: 2.670; 95 % CI: 1.095–6.510, $P = 0.031$), and emphysema in HRCT (OR: 2.387; 95 % CI: 1.017–5.640, $P = 0.046$) were independent predictors of progression in F-ILD patients, determined by multivariate logistic regression, as shown in Fig. 3. A combination of the three factors yielded a ROC curve to predict progression in F-ILD patients, with a sensitivity and specificity of 46.5 % and 82.0 %, respectively. The area under the curve (AUC) is 0.682, $P < 0.001$ (Fig. 4).

4. Discussion

This retrospective study assessed the predictors of progression in patients with F-ILD at a single-center in China. Combined the standards of PF-ILD [2] and PPF [5], and in order to minimize the influence of subjective factors and ensure the reliability of a retrospective study, we put forward the inclusion criteria in this study as mentioned minutely in methods.

A total of 354 patients with ILD were screened in this study, and 177 patients with F-ILD were retrospectively reviewed. The category included CTD-ILD, IPF, IPAF, unclassifiable ILD, sarcoidosis, HP, NSIP, COP, PAP, CPFE, and pneumoconiosis. Statistical

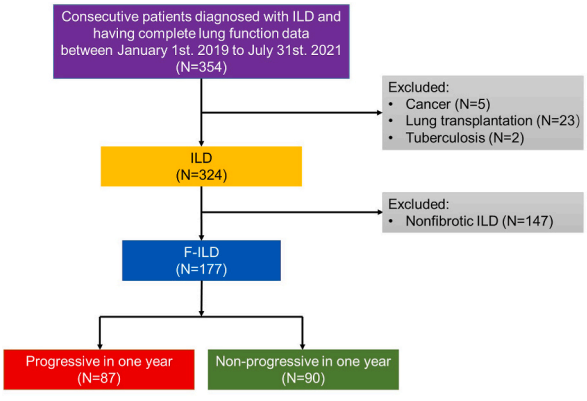

Fig. 1. Flow chart of enrollment.
Abbreviations: ILD, interstitial lung disease; F-ILD, fibrotic interstitial lung disease.

Table 1
Baseline characteristics of patients at onset of disease.

Characteristics	Progressive group (N = 87)	Non-progressive group (N = 90)	*P* value
Age at diagnosis, mean ± SD (year)	62.1 ± 9.3	59.8 ± 9.9	0.111
Male, %	63.2	50.0	0.076
GAP (I/II/III)	61/18/8	61/21/8	/
Baseline pulmonary function, mean ± SD			
FVC (L)	2.33 ± 0.73	2.27 ± 0.75	0.591
FVC (% predicted)	73.8 ± 17.7	71.4 ± 19.2	0.385
DLCO (ml/min/mmHg)	12.48 ± 5.12	11.99 ± 3.76	0.499
DLCO (% predicted)	66.4 ± 23.6	62.4 ± 19.8	0.247
BMI ($kg{\cdot}m^{-2}$)	25.49 ± 3.12	25.86 ± 3.37	0.451
Smoking history, %	37.9	33.3	0.523
Course of disease, mean ± SD (month)	25.9 ± 23.6	23.5 ± 31.2	0.569
Course of disease >9.5 (month), %	78.2	54.4	**0.001**
Blood count examination:			
White blood cell >6.40 (10^9/L), %	60.5	47.2	0.078
Neutrophil >3.43 (10^9/L), %	67.4	49.4	**0.016**
Lymphocyte >2.24 (10^9/L), %	32.6	19.1	**0.042**
Monocyte <0.375 (10^9/L), %	32.6	25.8	0.328
Neutrophil/Lymphocyte	2.60 ± 1.45	2.75 ± 2.07	0.564
HRCT manifestation:			
HRCT scores (1/2/3/4)	15/36/32/4	18/45/20/7	0.378
UIP pattern, %	27.6	20.0	0.236
Emphysema, %	35.6	20.0	**0.020**
Traction bronchiectasis, %	48.3	54.4	0.412
SPAP >33.5 (mmHg), %	28.8	18.3	0.116
CA199 > 7.47 (U/ml), %	63.0	47.7	**0.047**
CA50 > 4.69 (U/ml), %	67.5	46.5	**0.006**
CA153 > 27.28 (U/ml), %	25.9	19.4	0.077

Data were presented in the forms of mean ± SD or percentage of cases, except for GAP and HRCT scores. Independent-samples *t*-test or Chi-square test was used for statistical analysis between the two groups. Receiver operating characteristic curves were used to identify cut-off values. *P* values with statistical differences were shown in bold.

Abbreviations: ILD, interstitial lung disease; SD, standard deviation; GAP, gender, age, and physiologic variables; BMI, body mass index; HRCT: high-resolution computed tomography; UIP, usual interstitial pneumonitis; FVC: forced vital capacity; DLCO: diffusion capacity for carbon monoxide; SPAP, systolic pulmonary artery pressure; CA, carbohydrate antigen.

analysis showed that in addition to the well-known IPF subgroup, NSIP and HP were also the subgroups most prone to disease progression, consistent with the previous report carried out in the United States [14].

After adjusting for gender and age, a course of disease longer than 9.5 months, lymphocyte in peripheral blood more than 2.24 (10^9/L), and emphysema in HRCT were found three independent predictors of progression in F-ILD patients. It shows that when the disease course of a F-ILD patient exceeds 9.5 months, it is necessary to pay more attention to the disease situation and adjust the treatment as appropriate. Current study results are somewhat different from previous studies. Andrew et al. and Mikolasch et al. both reported that neutrophil lymphocyte ratio was an indicator for disease progression in IPF patients (HR 1.3; 95%CI 1.16–1.48; $P = 0.00002$ and HR 2.04, 95 % CI 1.09–3.81, n = 71, $P = 0.025$) [15,16], and also reported in Nathan et al.' s study [17]. However, the above studies were all carried out in cohort of IPF patients, not all F-ILD patients. In another study, it was reported that only increased blood monocyte level was a risk factor for radiological progression in patients with early fibrotic interstitial lung abnormality (HR 1.79, 95 % CI 1.05–2.86; $P = 0.030$) [18]. However, a significant difference was not found in either neutrophil lymphocyte ratio or monocyte in this present study. These findings showing associations between certain WBC and IPF outcomes suggest a systemic inflammatory state. Neutrophils, monocytes and lymphocytes have all been linked with the pathogenesis of IPF. However, the relationship between local and systemic inflammation may not always be clear, and the mechanism by which systemic inflammation may arise and how this might reflect disease progression in patients with IPF or F-ILD are not yet well understood [17].

Previous studies have reported that compared with patients with IPF alone, patients with CPFE were reported to have worse survival [19–21]. It suggests that the phenotype of emphysema may be a predictor of poorer prognosis. However, most of these studies were aimed at IPF, there are also some different opinions about emphysema worldwide [22–25]. There's not much research on all types of patients with F-ILD in a large cohort. This present study is one of the rare studies to conduct a statistical analysis of all types of F-ILD including IPF, and first proposed that the elevation of peripheral blood lymphocytes and the emphysema phenotype on HRCT were closely related to disease progression, which may be further verified in a larger cohort and more research centers in the future. Meanwhile, it was found in this present study that when the three conditions are met at the same time, the ROC for predicting disease progression reached at 0.682. Particularly, the three indicators could be easily and quickly obtained from inpatient or outpatient. It could have certain guiding significance for the management of patients with F-ILD and the timing of anti-fibrosis treatment.

Several limitations associated with retrospective and monocentric design in this study. It was a single-center study with a relatively small sample size, which may cause some biases. Authors plan to further expand the cohort and set up a validation cohort to verify findings. Secondly, due to the absence of lung function data, not all consecutive cases patients with F-ILD were included in the study, which may have some influence on the results. Thirdly, some patients with unclassifiable type of F-ILD, due to the low percentage of

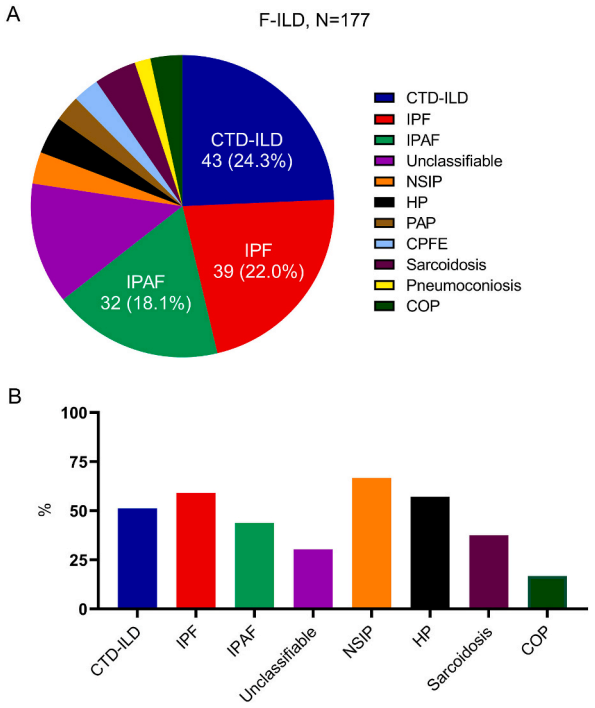

Fig. 2. Classifications of F-ILD in this study and proportion of progression in different categories
(A) Classifications of F-ILD in this study. (B) Proportion of progression in different categories of F-ILD
Abbreviations: F-ILD, fibrotic interstitial lung disease; CTD-ILD, connective tissue disease-associated interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IPAF, interstitial pneumonia with autoimmune features; NSIP, nonspecific interstitial pneumonia; HP, hypersensitivity pneumonitis; PAP, pulmonary alveolar proteinosis; CPFE, combined pulmonary fibrosis and emphysema; COP, cryptogenic organizing pneumonia.
Number and proportion of cases in each category: CTD-ILD, 43 (24.3 %); IPF, 39 (22.0 %); IPAF, 32 (18.1 %); Unclassifiable ILD, 23 (13.0 %); sarcoidosis, 8 (4.5 %); HP, 7 (4.0 %); NSIP, 6 (3.4 %); COP, 6 (3.4 %); PAP, 5 (2.8 %); CPFE, 5 (2.8 %); Pneumoconiosis, 3 (1.7 %).
Number and proportion of progressive cases in each category: CTD-ILD, 22 (51.2 %); IPF, 23 (59.0 %); IPAF, 14 (43.8 %); Unclassifiable ILD, 7 (30.4 %); NSIP, 4 (66.7 %); HP, 4 (57.1 %); sarcoidosis, 3 (37.5 %); COP, 1 (16.7 %). The proportion of progressive patients was calculated in the groups with more than 5 cases of patients.

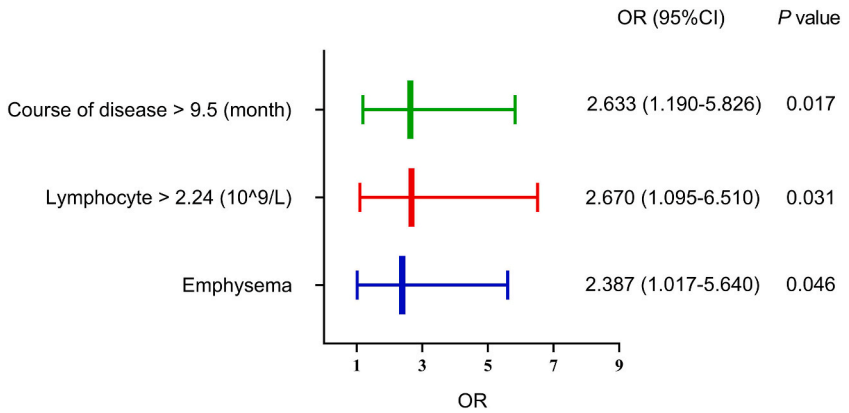

Fig. 3. Predictors of progression in F-ILD patients
After adjusting for gender and age, course of disease >9.5 (month) (OR: 2.633; 95 % CI: 1.190–5.826), lymphocyte in peripheral blood >2.24 (10^9/L) (OR: 2.670; 95 % CI: 1.095–6.510), and emphysema in HRCT (OR: 2.387; 95 % CI: 1.017–5.640) were independent predictors of progression in F-ILD patients as determined by logistic regression.
Abbreviations: F-ILD, fibrotic interstitial lung disease; OR, odds ratio; HRCT, high-resolution computed tomography.

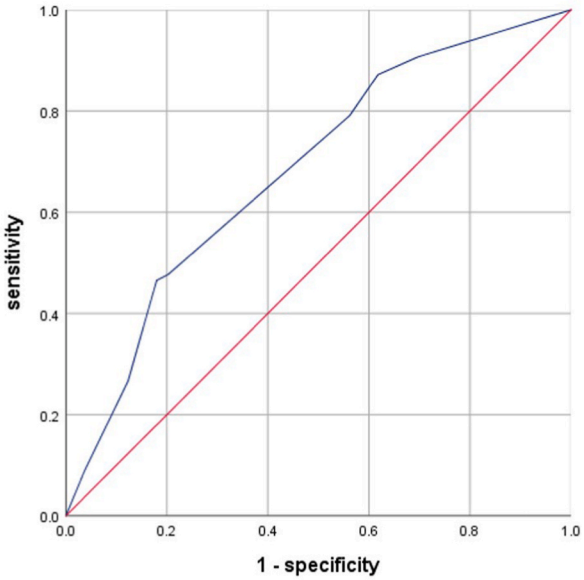

Fig. 4. A ROC curve to predict progression in F-ILD patients.
A combination of course of disease >9.5 months, lymphocyte in peripheral blood >2.24*10^9/L, and emphysema in HRCT yielded a ROC curve to predict progression in F-ILD patients, with a sensitivity and specificity of 46.5 % and 82.0 %, respectively. The area under the curve (AUC) is 0.682, $P < 0.001$.
Abbreviations: F-ILD, fibrotic interstitial lung disease; ROC, receiver operating characteristic.

surgical biopsies, may have resulted in an imprecise classification.

5. Conclusions

In conclusion, this study demonstrates that long course of disease, elevated blood lymphocyte and emphysema on HRCT were promising predictors of progression in patients with F-ILD. Patients who meet with these features may suggest an early therapeutic intervention and ultimately to improve the prognosis.

Ethics statement

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Shanghai Pulmonary Hospital (No. k22-238).

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Xianqiu Chen: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Qiuliang Ji:** Writing – original draft. **Qian Yao:** Writing – original draft, Formal analysis. **Ying Zhou:** Writing – review & editing, Funding acquisition, Data curation, 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.2023.e22565.

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