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Predictors for progressive fibrosis in patients with connective tissue disease associated interstitial lung diseases

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ABSTRACT

Background: Connective tissue disease associated interstitial lung disease (CTD-ILD) is associated with decreased quality of life and high mortality risk. Outcome and treatment response is unpredictable. This study aimed to identify clinical predictors for CTD-ILD with poor outcome.

Methods: We performed a retrospective single centre cohort study in outpatients with CTD-ILD seen between 2004 and 2018. Clinical and biochemical data, pulmonary function tests (PFT) and high-resolution computed tomography (HRCT) results were analysed. Overall survival and progressive fibrosing ILD (PF-ILD, defined as a significant deterioration of PFT or HRCT) after two years of follow-up were assessed.

Results: In total, 150 patients with CTD-ILD were included. Thirty (20%) deaths occurred during a median follow-up of 40 months (IQR 27.3–60.8), which were attributed to pulmonary infection in six (4%), respiratory failure due to PF-ILD in ten (7%) and due to other causes in fourteen patients. PF-ILD occurred in 76 (50.7%) patients and was associated with poor overall survival (adjusted HR 5.73, 95%CI 1.17–28.11). Age, smoking, C-reactive protein, and steroid-use were independently associated with increased mortality risk as well. Furthermore, patients with diabetes mellitus (adjusted OR 4.52, 95%CI 1.10–18.51), steroid-use (adjusted OR 2.26, 95%CI 1.04–4.93), and a fibrotic HRCT pattern at baseline (adjusted OR 3.11, 95%CI 1.15–8.38) had a higher risk of PF-ILD.

Conclusion: PF-ILD is associated with increased mortality in patients with CTD-ILD. Patients with a fibrotic HRCT pattern at baseline, diabetes mellitus and steroid-use have a higher risk of developing PF-ILD.

1. Introduction

Interstitial lung disease (ILD) in patients with connective tissue disease (CTD) is a heterogeneous disease which negatively impacts quality of life and is associated with increased mortality [1,2]. Systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic inflammatory myopathy (IIM), primary Sjögren syndrome (PSS), systemic lupus erythematosus (SLE), and mixed CTD (MCTD) are CTDs with distinctive clinical features, yet ILD can occur in each condition. A subset of patients develops progressive fibrosis (PF-ILD), which is characterised by a rapid deterioration in symptoms, decline in lung function and/or progressive fibrosis on high-resolution computed tomography (HRCT) [3–5].

The management of CTD-ILD has improved in the last decades. Multidisciplinary collaboration and routine screening with HRCT and pulmonary function test (PFT) are now widely accepted and implemented [2,6,7]. Furthermore, the therapeutic armamentarium has expanded and includes immunosuppressants and more recently, anti-fibrotic therapy [3,8,9]. Moreover, autologous stem cell transplantation can be effective in carefully selected patients with SSc associated ILD [10–12]. Despite the advances in management and treatment, some patients with CTD-ILD still develop PF-ILD. To optimize management of CTD-ILD, predictors for progressive fibrosis early in the disease course are needed. This study aimed to identify clinical predictors for CTD-ILD with poor outcome.

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2. Methods

2.1. Design

A retrospective cohort study was performed at the University Medical Centre Utrecht, a tertiary referral hospital for CTDs.

2.2. Patients

All patients with an established diagnosis of CTD-ILD who were treated at the outpatient clinics of the Department of Rheumatology and Clinical Immunology and the Department of Pulmonology between 2004 and 2018 with a minimal follow-up of one year were included. All patients met the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for a CTD or fulfilled the proposed criteria for interstitial pneumonia with autoimmune features (IPAF), or ILD with undifferentiated connective tissue disease (UCTD) [13–18]. This study was conducted in accordance with the amended Declaration of Helsinki [19]. The institutional medical ethics committee of UMC Utrecht approved the study (study number 19/148).

2.3. Data collection

Demographical, clinical, radiological and pulmonary function data were retrieved from medical records. Data included age, sex, obesity (body mass index ≥35), disease duration, and smoking (pack-years). Treatment history and current therapies were registered.

2.4. Laboratory results

The following laboratory results were collected from medical records: erythrocyte sedimentation rate, C-reactive protein (CRP), creatine kinase, creatinine, rheumatoid factor, anti-CCP antibody, antineutrophil cytoplasmatic autoantibodies, antinuclear antibody and specific antinuclear antibodies, myositis-specific antibodies, carbohydrate antigen 15.3 (CA15.3) and soluble IL-2 receptor (sIL-2R).

2.5. Pulmonary function tests

PFT was performed in standard spirometry according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations [20,21]. The diffusing capacity for carbon monoxide (DLCO) was measured using the single-breath method (Masterlab, Jaeger, Wurzburg, Germany). Values were expressed as percentage of predicted. Data at baseline, six months, one year, two years, and last follow up were recorded. A significant and clinically relevant change in PFT was defined as ≥ 10% change in forced vital capacity (FVC) or ≥ 15% change in DLCO within 2 years [22]. A change in FVC of <10% or DLCO of <15% within 2 years was defined as stable.

2.6. Pulmonary imaging

HRCTs were evaluated at baseline, one year, and two years follow-up. HRCT patterns were classified according to the classification for idiopathic interstitial pneumonia [23], listing them as consistent with usual interstitial pneumonia (UIP), probable UIP or alternative diagnosis. The consistent UIP and probable UIP were summarised as UIP. The alternative diagnosis category was then classified as non-specific interstitial pneumonia (NSIP), lymphocytic interstitial pneumonia (LIP), desquamative interstitial pneumonia (DIP), nodular lymphocytic hyperplasia (NLH), organising pneumonia (OP) or pleuroparenchymal fibro-elastosis (PPFE). The NSIP pattern was categorized as fibrotic, cellular, or mixed [24]. The predominant HRCT patterns were categorized into fibrotic patterns (UIP, fibrotic NSIP, and PPFE) or inflammatory patterns (cellular and mixed NSIP, LIP, DIP, NLH, and OP) [25,26]. The percentage of lung involvement and changes of both inflammation and fibrosis on HRCT over time were evaluated independently by two radiologists, which were classified as progression, stable, or regression. Two experienced chest radiologists independently reviewed the HRCTs with blinding to clinical information or pathology diagnosis. In case of discrepancies, a third expert (pulmonologist) was consulted to reach consensus.

2.7. Progressive fibrosing interstitial lung disease

PF-ILD was defined when the following occurred: ≥ 10% decline in FVC, ≥ 15% decline in DLCO, and/or progressive fibrotic changes on HRCT (either in the fibrotic or inflammatory predominant group at baseline) within 2 years. The term PF-ILD has recently been popularised and refers to a subset of patients who develop rapid pulmonary function decline with subsequently high mortality rates [27]. However, different criteria for PF-ILD are used in literature. The INBUILD trial (nintedanib) set a two-year period for FVC decline of more than 10%, FVC decline between 5 and 10% and deterioration of respiratory symptoms, or deterioration of respiratory symptoms and progressive fibrotic changes on HRCT [4,8]. Meanwhile, the pirfenidone trial used a six months period for a decline in FVC of more than 5% or a significant symptomatic worsening [3], and the RELIEF trial used a period of at least six months with a maximum of 24 months for a decline in FVC of more than 5% [28]. The ILD guideline from the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society also suggested that a decline ≥10% in FVC or ≥15% in DLCO in the first 6–12 months is a mortality risk factor [22]; therefore, we combined these criteria in our study and defined PF-ILD as ≥ 10% decline in FVC, ≥ 15% decline in DLCO, or progressive fibrotic changes on HRCT within two years. Baseline HRCTs were classified as predominant inflammatory or predominant fibrotic pattern. HRCTs may contain both inflammatory and fibrotic components and change in inflammation and fibrosis was evaluated separately during follow-up. Only the progression of fibrosis on HRCT was included in our PF-ILD criteria. Patients with a predominantly inflammatory pattern on HRCT could, however, also show progression of their fibrotic component.

2.8. Statistical analysis

Descriptive statistics were used to describe patient characteristics. Survival was analysed using Kaplan-Meier survival analysis, and the difference between groups was examined in a log-rank test. The hazard ratios (HR) of clinical characteristics for death were calculated using Cox regression analysis. Correlations between biomarkers and the progression of PFT and HRCT were examined by logistic regression. Factors with a univariate p-value less than 0.2 were included in the multivariable regression [29]. Normality of the data was assessed with the Shapiro-Wilk test. Categorical variables were presented in frequencies, and the differences between groups were estimated with Fisher's exact test. The difference of continuous variables between groups was determined using the Mann-Whitney U or unpaired T-test test as appropriate. The interobserver agreement in the HRCT scores was tested using Cohen's kappa. The correlation between the variation of serum markers and PFT over-time was evaluated with Spearman's Rho. Missing data were excluded from the individual analysis. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using R 3.5.1.

3. Results

3.1. Patient characteristics

A total of 150 patients with CTD-ILD were identified and included (Table 1). The median follow-up duration was 40 months (IQR 27.3–60.8). In 117 (78%) patients, CTD was diagnosed before ILD onset. In these patients, median disease duration of CTD was fourteen months

Table 1
Baseline patient characteristics.

Characteristic	Patients N = 150
Female, n(%)	95 (63.3)
Age (years), median (IQR)	57 (48–68)
Disease Duration of CTD (months), median (IQR)	14 (2–73)
Systemic sclerosis, n(%)	53(35.3)
Sjögren's syndrome, n(%)	19(12.7)
Myositis, n(%)	29(19.3)
Rheumatoid arthritis, n(%)	24(16)
SLE, n(%)	5(3.3)
MCTD, n(%)	4(2,7)
UCTD, n(%)	16(10.7)
Comorbidities, n(%)	
Coronary artery disease	18 (12.0)
Congestive heart failure	15 (10)
Pulmonary hypertension	17 (11.3)
Diabetes mellitus	15 (10.0)
Cerebrovascular event	5 (3.3)
Obesity (BMI ≥35)	11 (7.3)
Smoking status, n(%)	
Current	9 (6.0)
Former	69 (46)
Never	71(47.3)
Immunosuppressants, n(%)	
Azathioprine	12 (8)
mycophenolate mofetil	48 (32)
cyclophosphamide	1 (0.7)
Rituximab	20 (13.3)
Methotrexate	16 (10.7)
Cyclosporine	5 (3.3)
Tacrolimus	1 (0.7)
Leflunomide	4 (2.7)
Adalimumab	3 (2)
Etanercept	1 (0.7)
Infliximab	1 (0.7)
Belimumab	1 (0.7)
Tocilizumab	1 (0.7)
Prednisolone	78 (52)
Immunomodulatory treatment, n(%)	
Hydroxychloroquine	22 (14.7)
IVIG	2 (1.3)
HSCT	3 (2)
Fibrotic CT patterns, n(%)	
UIP	12 (8)
Fibrotic NSIP	18 (12)
PPFE	1 (0.7)
OP/UIP	1 (0.7)
LIP/UIP	1 (0.7)
Inflammatory CT patterns, n(%)	
Cellular NSIP	55 (36.7)
Mix NSIP	36 (24)
OP	6 (4)
LIP	6 (4)
NSIP/OP	12 (8)
LIP/NSIP	2 (1.3)
Percentage of lung involvement, median (IQR)	17.5 (10.0–27.5)
Baseline FVC, median (IQR)	80.0 (65.0–94.6)
Baseline DLCO, median (IQR)	54.5 (43.3–66.0)

Abbreviations: CTD, connective tissue disease; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus; UCTD, undifferentiated connective tissue disease; IVIG, intravenous immunoglobulin; HSCT, hematopoietic stem-cell transplantation; TNFi, tumor necrosis factor alfa inhibitor; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; PPFE, pleuroparenchymal fibro-elastosis; OP, organising pneumonia; LIP, lymphocytic interstitial pneumonia; FVC, percentage of predicted forced vital capacity; DLCO, percentage of predicted single-breath diffusing capacity for carbon monoxide.

(IQR 2–73). CTDs included 53 (35%) SSc, 29 (19%) IIM, 24 (16%) RA, 19 (13%) PSS, sixteen (11%) UCTD, five (3%) SLE, and four (3%) MCTD. Immunosuppressants or immunomodulatory treatment for CTD and/or ILD was used in 128 (85%) patients (Table 1). In 72 (48%) patients, two or more immunosuppressants/immunomodulators were combined.

3.2. Radiology and pulmonary function test

At baseline, 33 (22%) patients had a predominant fibrotic pattern and 117 (78%) patients a predominant inflammatory pattern (Table 1). Of patients with predominant fibrotic patterns, eleven (33.3%) had SSc, seven (21.2%) RA, six (18.2%) PSS, five (15.2%) IIM, three (9.1%) UCTD, and one (3.0%) SLE. Of patients with predominant inflammatory patterns, 42 (35.9%) had SSc, 24 (20.5%) IIM, 17 (14.5%) RA, thirteen (11.1%) UCTD, thirteen (11.1%) PSS, four (3.4%) MCTD, and four (3.4%) SLE. No follow-up HRCT was done in 29 patients at one year and in 73 patients at two years of follow-up. Fibrosis on HRCT had progressed in 27 (22%) after one year of follow-up and six more patients progressed at two years. Inflammatory features on HRCT progressed in 32 (26%) patients, stabilized in 49 (41%), and improved in 40 (33%) after one year of follow-up; inflammatory features progressed in fourteen (18%), stabilized in 46 (60%), and improved in 17 (22%) patients at two years follow-up (Fig. 1). In 35 (47%) patients who did not develop PF-ILD, no HRCT was available at two years, yet PFT showed no significant decline at last follow-up. Three (4%) patients without PF-ILD did not follow-up HRCT at two years and PFT after two years. The kappa value for HRCT patterns was 0.4 among the radiologists. In addition, the kappa value for the progression of inflammation and fibrosis on HRCT was 0.6 and 0.5, respectively.

Median baseline FVC was 80.0% (IQR 65.0–94.6%) and DLCO 54.5% (IQR 43.3–66.0%). Baseline FVC and DLCO did not differ between patients with inflammatory and fibrotic HRCT patterns ($p = 0.051$ and 0.629, respectively). After two years of follow-up, FVC improved in 40 (28%), stabilized in 58 (41%), and declined in 45 (31%) patients. DLCO improved in 43 (33%), stabilized in 56 (42%), and declined in 33 (25%) patients after two years (Fig. 1). There was no follow-up of FVC in seven patients, and DLCO in 18 patients. PF-ILD occurred in 76 (50.7%) patients. The prevalence of PF-ILD did not differ between CTD, with fifteen (63%) RA, nine (56%) UCTD, 27 (51%) SSc, two (50%) MCTD, thirteen (45%) IIM, eight (42%) PSS, and two (40%) SLE. PF-ILD occurred in 51 (44%) patients with predominant inflammatory HRCT pattern at baseline and 25 (76%) patients with predominant fibrotic HRCT pattern at baseline. A trend of FVC improvement was seen in both the PF-ILD and non-PF-ILD group at six months and one year of follow-up. After two years of follow-up, deterioration of both FVC and DLCO was seen in the PF-ILD group. (Fig. 2).

3.3. Clinical features and the risk of progression

Correlations between clinical factors and change in lung function, HRCT, and occurrence of PF-ILD were examined. Changes in CA15.3 were negatively correlated with change in FVC (Rho −0.308, $p = 0.037$). Change in CRP was negatively correlated with change in FVC (Rho −0.302, $p = 0.006$) and DLCO (Rho −0.268, $p = 0.019$). Patients with inflammatory HRCT patterns at baseline had a lower risk of FVC decline than patients with a fibrotic pattern (adjusted OR 0.24, 95%CI 0.09–0.64). Patients with congestive heart failure had an increased risk of DLCO deterioration at two years follow-up (adjusted OR 27.41, 95% CI 1.79–419.2). Patients with diabetes mellitus (adjusted OR 4.52, 95% CI 1.10–18.51), steroid-use (adjusted OR 2.26, 95%CI 1.04–4.93), and fibrotic HRCT pattern at baseline (adjusted OR 3.11, 95%CI 1.15–8.38) had a higher risk of developing PF-ILD; conversely, patients with obesity (adjusted OR 0.16, 95%CI 0.03–0.85) and positive anti-dsDNA (adjusted OR 0.16, 95%CI 0.03–0.78) revealed a lower risk of developing PF-ILD (Table 2).

3.4. Survival analysis

During follow-up, 30 (20%) patients died. Eighteen patients died due to respiratory failure caused by PF-ILD (n = 10, 7%), pulmonary infection (n = 6, 4%), pulmonary hypertension (n = 1, 0.7%), and pulmonary flare of lupus (n = 1, 0.7%). After two years of follow-up, patients with

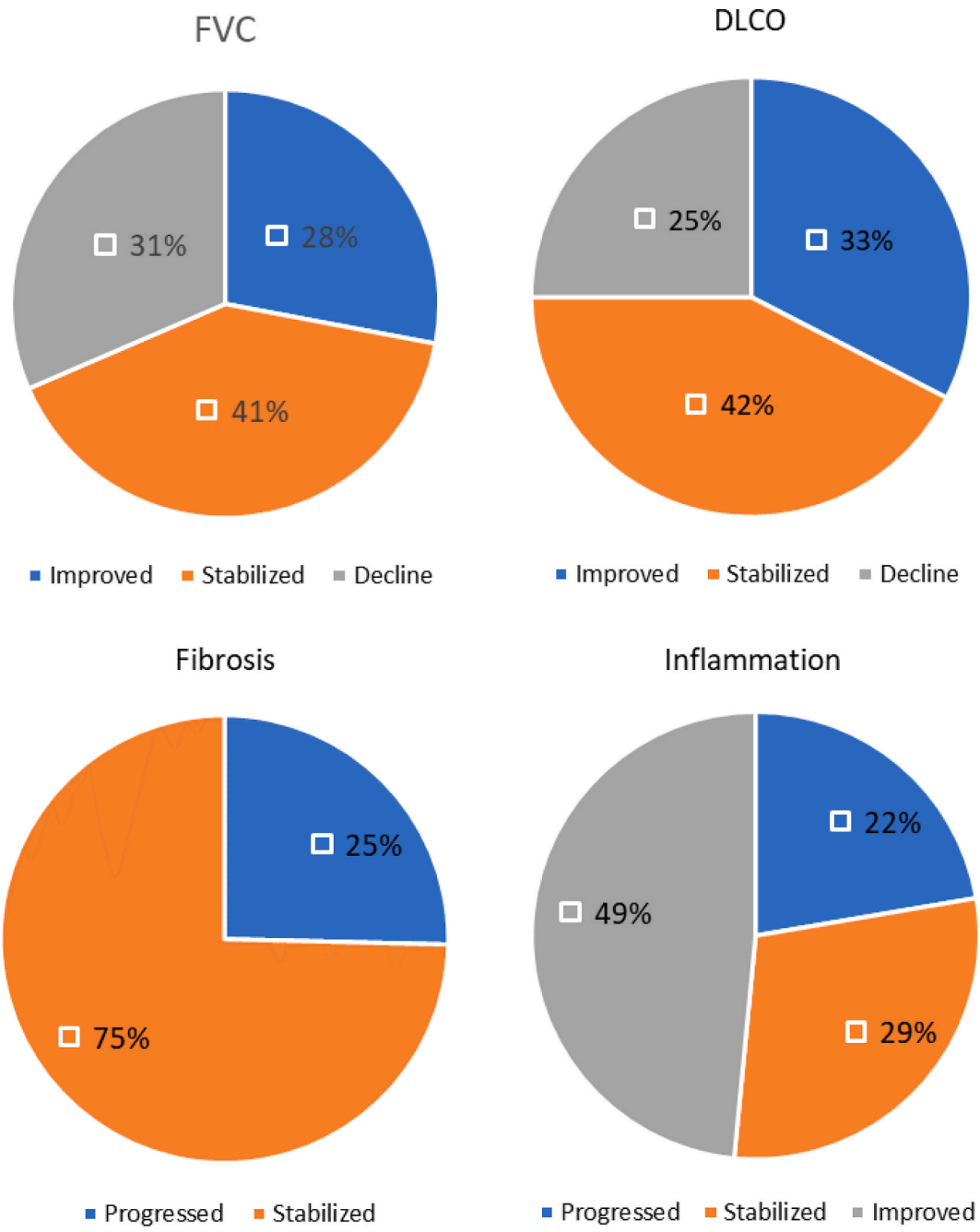

Fig. 1. The upper two pie charts illustrate the follow-up pulmonary function test. Fibrosis and inflammation on high-resolution computed tomography at one year and two years follow-up are combined in the lower two pie charts.

improved FVC and DLCO demonstrated better survival; PF-ILD was associated with poor prognosis (Fig. 3). There was no significant difference between the inflammatory HRCT at baseline with PF-ILD and the fibrotic HRCT at baseline with PF-ILD, HR 0.908 (95% CI 0.40–2.05, p = 0.817). The difference in mortality risk between patients with PF-ILD, baseline predominant inflammatory HRCT patterns and no progression of fibrosis on follow-up HRCT (n = 26) and patients with PF-ILD and progression of fibrosis on follow-up HRCT (n = 31) was also insignificant, HR 1.26 (95% CI 0.51–3.11, p = 0.617). A UIP pattern at baseline showed an insignificant increased mortality risk, HR 1.227 (95% CI 0.45–3.34, p = 0.689). The risk of FVC decline, DLCO decline or progressive fibrosis on HRCT were all insignificant too (Table S1). Age (adjusted HR 1.08, 95%CI 1.02–1.14, p = 0.009), smoking (adjusted HR 7.01, 95%CI 1.99–24.68, p = 0.002), steroid-use (adjusted HR 5.11, 95%CI 1.01–25.92, p = 0.049), CRP (adjusted HR 1.01, 95%CI 1.00–1.02, p = 0.022), and PF-ILD (adjusted HR 5.73, 95%CI 1.17–28.11, p = 0.031) were associated with increased mortality risk (Table 3). No dose-effect of smoking on mortality risk was observed. There was a dose-response effect of steroid use with a 10-year mortality rate of 2.4% (n = 41) for low dose (≤7.5 mg/day), 13.9% (n = 36) for medium dose (>7.5 and ≤ 30 mg/day) and 100% (n = 1) for high dose (>30 mg/day). Baseline FVC and DLCO were not correlated with steroid use (p value 0.051 and 0.181, respectively).

4. Discussion

PF-ILD describes a high-risk population in patients with ILD and manifests as deterioration in pulmonary symptoms, imaging and

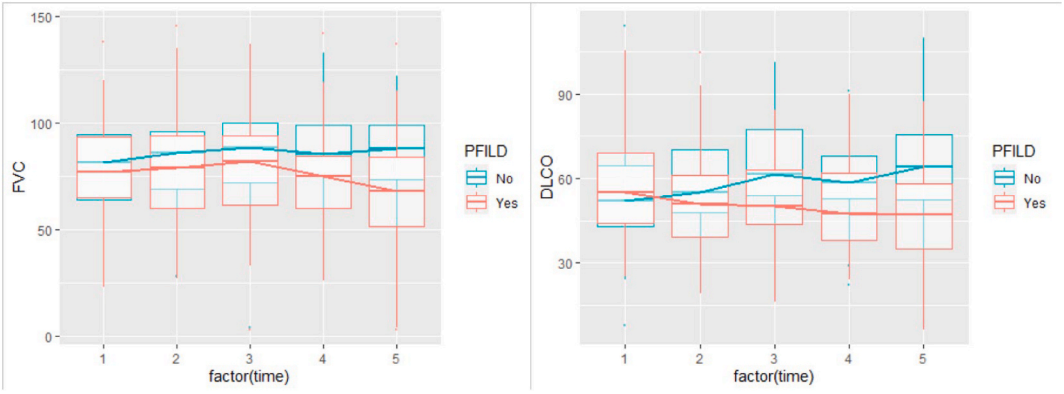

Fig. 2. Pulmonary function change over time between patients fulfilled progressive fibrosing interstitial lung diseases (PF-ILD) or not. Time-point: 1, baseline; 2, six months; 3, one year; 4, two years; 5, last follow up. FVC, percentage of predicted forced vital capacity; DLCO, percentage of predicted single-breath diffusing capacity for carbon monoxide.

Table 2
Predictors of PF-ILD with multivariable adjustment in logistic regression.

Risk factors	Crud OR (95% CI)	P	Adjusted OR (95% CI)	P
Coronary artery disease	2.13 (0.78–6.41)	0.155	1.09 (0.31–3.81)	0.898
Congestive heart failure	2.96 (0.96–11.11)	0.075	2.10 (0.50–8.78)	0.308
Pulmonary hypertension	2.59 (0.91–8.51)	0.089	1.47 (0.41–5.25)	0.552
Diabetes mellitus	2.96 (0.96–11.11)	0.075	4.52 (1.10–18.51)	0.036
Obesity	0.34 (0.07–1.23)	0.121	0.16 (0.03–0.85)	0.031
rituximab-use	0.48 (0.17–1.24)	0.138	0.39 (0.12–1.26)	0.115
steroid-use	2.01 (1.06–3.89)	0.035	2.26 (1.04–4.93)	0.040
Fibrotic HRCT pattern	4.04 (1.75–10.27)	0.002	3.11 (1.15–8.38)	0.025
Anti-Ro	0.61 (0.31–1.18)	0.144	0.61 (0.28–1.33)	0.217
Anti-CCP	2.56 (0.96–7.61)	0.070	1.45 (0.46–4.58)	0.522
Anti-dsDNA	0.30 (0.06–1.04)	0.078	0.16 (0.03–0.78)	0.024
Anti-Scl-PM	0.40 (0.10–1.30)	0.144	0.64 (0.16–2.48)	0.517

OR, odds ratio; 95%CI, 95% confidence interval; HRCT, high-resolution computed tomography.

function. We identified that having a fibrotic HRCT pattern at baseline, diabetes mellitus, and steroid use are clinical predictors for PF-ILD. In our study, approximately half of patients with CTD-ILD developed PF-ILD. Furthermore, ageing, smoking, high CRP at baseline, steroid-use and PF-ILD were associated with increased mortality in patients with CTD-ILD.

Our results are in line with previous SSc-ILD and non-IPF (idiopathic pulmonary fibrosis) ILD trials in which PF-ILD patients were identified as a high-risk group for poor outcome [3,4,30–32]. The early SSc-ILD trial also found that a rapid pulmonary function decline predicts mortality [33,34].

Other factors associated with increased mortality in our study were age, smoking, steroid-use, and CRP. Smoking is a known risk factor for mortality in many diseases and has also shown increased mortality in previous CTD studies [35]. The higher risk of PF-ILD on mortality in patients with steroids is partly because higher steroid dose was used in the more severely ill patients. However, we did not find a difference in baseline lung function and administration of steroids. In vitro steroids have mixed effects on fibroblast function and contradictory profibrotic and anti-fibrotic effect of steroids on fibroblasts are reported [36,37]. There are some clinical studies that evaluated the impact of steroids on CTD-ILD. Although the post-hoc analysis from INBUILD trial showed a non-significant influence of steroid use on the effects of nintedanib, steroid revealed an impact in placebo group. The mean rate of annual

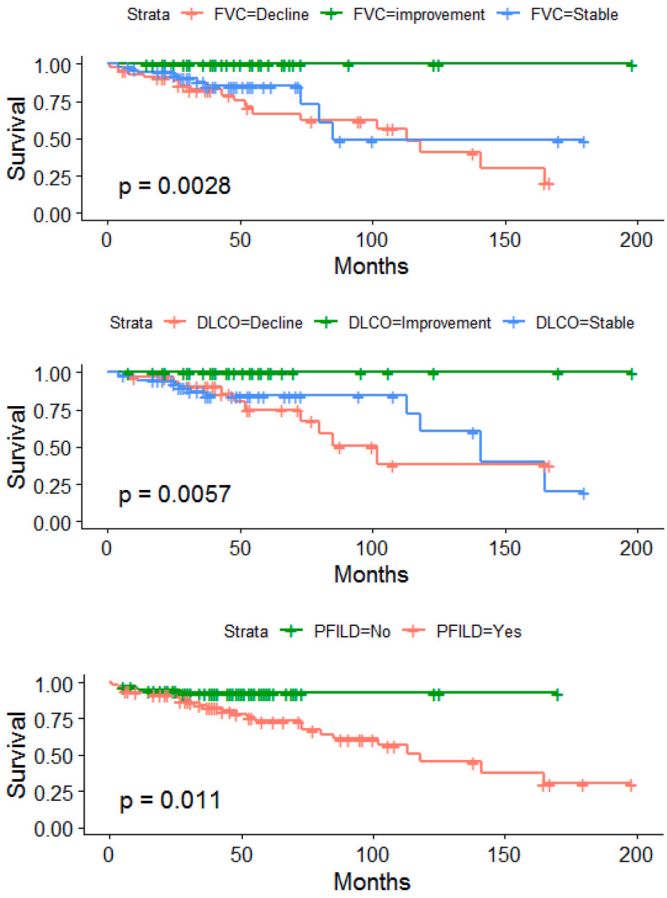

Fig. 3. The Kaplan-Meier plots for survival analysis among predicted forced vital capacity (FVC), predicted single-breath diffusing capacity for carbon monoxide (DLCO), and progressive fibrosing interstitial lung diseases (PFILD).

FVC decline in the placebo group was 206.4 ml/year in steroid users (n = 184) and 165.8 ml/year in non-steroid users (n = 147) [38]. Furthermore, development of irreversible organ damage was associated with steroid treatment independent of underlying CTD activity in patients with SLE [39]. These data suggest that steroid treatment could be detrimental in CTD-ILD. Also, steroids increased the risk of death and hospitalization in patients with IPF [40]. Therefore, it is essential that clinicians are aware of the risks associated with steroid use and minimise long-term steroid administration in patients with CTD-ILD, i.e. by combining steroids with other disease-modifying antirheumatic drugs at

Table 3
Predictors of mortality with multivariable adjustment in Cox regression.

Risk factor	Crud HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Age	1.11 (1.06–1.15)	<0.001	1.08 (1.02–1.14)	0.009
Smoking	1.64 (0.79–3.43)	0.187	7.01 (1.99–24.68)	0.002
Congestive heart failure	1.86 (0.75–4.58)	0.179	0.57 (0.16–2.05)	0.386
MMF-use	0.55 (0.23–1.35)	0.195	0.94 (0.24–3.63)	0.928
Steroid-use	4.37 (1.67–11.45)	0.003	5.11 (1.01–25.92)	0.049
CRP	1.01 (1.00–1.02)	0.028	1.01 (1.00–1.02)	0.022
PF-ILD	3.31 (1.24–8.82)	0.017	5.73 (1.17–28.11)	0.031
Anti-centromere	3.34 (1.14–9.79)	0.028	3.74 (0.88–15.94)	0.074
Anti-Ro	2.98 (1.42–6.23)	0.004	2.79 (0.77–10.12)	0.119
AMA	12.14 (2.69–54.89)	0.001	13.43 (0.64–282.81)	0.095

MMF, mycophenolate mofetil; HR, hazard ratio; 95%CI, 95% confidence interval; CRP, c-reactive protein; PF-ILD, progressive fibrosing interstitial lung diseases; AMA, Anti-mitochondrial antibody.

the onset of disease and thereafter proactively reduce steroid dosage.

Other immunosuppressants did not show a significant effect on mortality or progression to PF-ILD in our study. We did observe a trend towards improved survival in patients treated with mycophenolate mofetil (MMF), but possibly because of small sample size (48 patients) this did not reach significance. Benefits from immunosuppressants were reported in previous clinical studies, which observed preservation of pulmonary function in patients with SSc-ILD treated with MMF or cyclophosphamide [41], and benefits of tocilizumab, rituximab, and abatacept were seen in patients with ILD and SSc, RA, and IIM [6]. MMF is a key anchor drug for SSc-ILD [31], because of its' efficacy and safety profile and optional use combined with antifibrotic agents. MMF inhibits inosine monophosphate dehydrogenase for the de novo synthesis of guanosine purines, which majority suppress lymphocytes. Interestingly, MMF might also reduce pulmonary function decline in patients with IPF, suggesting potential anti-fibrotic effects [42]. The effects of the antifibrotic drug nintedanib have been evaluated in clinical trials and is a valuable addition to immunosuppressants. In the CTD-ILD subgroup analysis of INBUILD trial, the difference of annual FVC reduction rate between nintedanib and placebo was 104 ml/year (95%CI 21.1–186.9) [43]. Nintedanib may therefore reduce pulmonary function decline in CTD patients with PF-ILD. However, patients receiving immunosuppressants, including azathioprine, cyclosporine, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil or oral corticosteroids (>20 mg/day) at baseline were excluded from INBUILD trial. Consequently, the CTD-ILD patients in the INBUILD trial are different from our real-world cohort and studies are needed to determine the optimal timing of nintedanib and effects of combination therapy with immunosuppressants.

Another interesting finding was that patients with obesity and positive anti-dsDNA had a lower risk of developing PF-ILD. Although excess soft tissue in the abdominal cavity and chest is associated with reduction in total lung capacity and FVC [44], the role of obesity in PF-ILD has not been reported.

In our study, we also searched for serum biomarkers to predict lung function decline. We found CRP and CA15.3 were correlated with pulmonary function decline; for every units increased in CRP at baseline, the mortality hazard increased with one percent. CRP is a general biomarker which reflects the systemic inflammation and underline disease activity. The background autoimmunity not only plays a crucial role in pulmonary fibrosis but also contributes to systemic organ dysfunction. Control of CTD activity should always be part of pivotal therapy in patients with CTD-ILD. CA15.3, which is a mucin glycoprotein, has been used as a tumour marker for breast cancer. Another glycoprotein Krebs von den Lungen 6 (KL-6) has shown a high correlation with CA15.3 [45]. KL-6 is highly expressed on regenerated type II pneumocytes, and the serum KL-6 level has shown a diagnostic, prognostic, and monitoring value for progressive fibrosis in IPF and CTD-ILD [46–49]. Since KL-6 testing is not available worldwide, monitoring CA15.3 and CRP may be the best choice for clinicians in treating patients with CTD-ILD.

There are limitations in this cohort study. Firstly, it would have been interesting to include disease-specific activity scores in the analyses. However, comparison of disease activity between groups would have been difficult because the scores are disease-specific, and the groups would have been too small for comparison within groups. In addition, there might be confounding in the prediction model, therefore we adjusted for multiple variables in the regression analysis to minimise the risk of confounding. Also, in patients without HRCT at two years follow-up, we could have missed progression of fibrosis. Furthermore, the Cohen's kappa value for the different ILD patterns between the two pulmonary radiologists was not high in our study; a relatively low Cohen's kappa value was also seen in other ILD studies [50]. Clinical symptoms were not systematically scored in our cohort. A prospective study design combining physician global scores and patient report outcomes may provide more evidence on the risk stratification of clinical symptoms. Moreover, immunosuppressants/modulators used at inclusion were administered to treat the underlying CTD activity. In case of mild ILD without other major organ involvement, patients did not receive immunosuppressants. The median baseline HRCT involvement was 17.5% (Table 1) and 87 patients (58%) showed less than 20% lung involvement. Therefore, not all patients in our cohort were treated for ILD.

In conclusion, our study shows that a fibrotic HRCT pattern at baseline, diabetes mellitus, and steroid treatment increases the risk of developing PF-ILD, whereas positive anti-dsDNA and obesity revealed a lower risk of developing PF-ILD in patients with CTD-ILD. In addition, we found that PF-ILD, age, smoking, steroid use, and CRP are associated with increased mortality risk. These findings have important implications for clinical monitoring and confirm the central place of routine PFT and HRCT in follow-up in order to detect PF-ILD. Since antifibrotic treatment can be used in addition to intensive immunosuppressive treatment nowadays, it is important to closely monitor patients with CTD-ILD for PF-ILD. Furthermore, education on smoking cessation and minimising steroid use are also crucial in managing CTD-ILD.

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CRediT authorship contribution statement

Yu-Hsiang Chiu: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Julia Spierings:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – review & editing. **Pim A. de Jong:** Validation, Investigation, Writing – review & editing. **Firdaus Mohamed Hoesein:** Validation, Investigation, Writing – review & editing. **Jan C. Grutters:** Validation, Writing – review & editing. **Jacob M. van Laar:** Conceptualization, Validation, Resources, Writing – review & editing, Supervision. **Mareye Voortman:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

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Appendix A. Supplementary data

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