

RESEARCH

Open Access



Multidisciplinary-derived clinical score for accurate prediction of long-term mortality in fibrotic lung disease patients

Yu-Wan Liao^{1,2}, Yi-Ming Chen³, Ming-Cheng Liu⁴, Yu-Cheng Wu^{1,5}, Chiann-Yi Hsu⁶, Pin-Kuei Fu^{1,7,9*†}, Wen-Nan Huang^{1†} and Yi-Hsing Chen^{1,8†}

Abstract

Background Idiopathic pulmonary fibrosis (IPF) stands out as one of the most aggressive forms of interstitial lung diseases (ILDs), currently without a definitive cure. Multidisciplinary discussion (MDD) is now considered a cornerstone in diagnosing and differentiating ILD subtypes. The Gender-Age-Physiology (GAP) score, developed to assess IPF prognosis based on sex, age, forced vital capacity, and diffusion capacity for carbon monoxide (DLCO), is limited in not considering dyspnea and functional impairment during the walking test. We proposed a MDD-based clinical score for mortality prediction among those patients.

Methods From December 2018 to December 2019, we enrolled ILD patients with IPF and non-IPF and followed-up them till December 2020. Based on DLCO, modified Medical Research Council (mMRC) Dyspnea Scale, and six-minute walking test (6MWT) distance, a functional score was developed for mortality prediction.

Results We enrolled 104 ILD patients, 12 (11.5%) died by the one-year follow-up. In receiver operating characteristic (ROC) curve analysis, DLCO (% predicted) was the most accurate variable predicting one-year mortality with an area under curve (AUC) of 0.88 (95% confidence interval [CI]=0.80–0.94), followed by mMRC Dyspnea Score (AUC=0.82 [95% CI=0.73–0.89]), 6MWT distance (AUC=0.80 [95% CI=0.71–0.88]), and GAP score (AUC=0.77 [95% CI=0.67–0.84]). Only the GAP score (hazard ratio [HR]=1.55, 95% CI=1.03–2.34, $p=0.037$) and functional score (HR=3.45, 95% CI=1.11–10.73, $p=0.032$) were significantly associated with one-year mortality in multivariable analysis.

Conclusion The clinical score composite of DLCO, mMRC Dyspnea Scale, and 6MWT distance could provide an accurate prediction for long-term mortality in ILD patients, laying out a helpful tool for managing and following these patients.

Keywords Idiopathic pulmonary fibrosis, Interstitial lung disease, Multidisciplinary discussion, 6-min walk test

[†]Pin-Kuei Fu, Wen-Nan Huang and Yi-Hsing Chen contributed equally.

*Correspondence:

Pin-Kuei Fu

yetquen@gmail.com

Full list of author information is available at the end of the article



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Background

Idiopathic pulmonary fibrosis (IPF) stands out as one of the most aggressive forms of interstitial lung diseases (ILDs), currently without a definitive cure [1]. IPF manifests as an undue proliferation of fibroblasts, which in turn produce an excessive amount of extracellular proteins, notably collagen [2]. This overproduction facilitates recurrent tissue scarring and fibrosis within the lung parenchyma, culminating in increased rigidity of the lungs. Consequently, this rigidity impairs oxygen absorption and gas exchange capabilities [2]. Post-diagnosis, the prognosis for IPF is grim, often resulting in fatality within 2–3 years [3]. The etiology remains elusive, and there are no established treatments that offer significant improvement in patient outcomes [4]. Furthermore, even the term IPF itself is still debatable. While some researchers urge “splitting” it into distinct subcategories that respond uniquely to specific treatments, others suggest “lumping” IPF together with other types of advancing fibrotic lung diseases that have common underlying causes and exhibit similar disease progression [5].

Recent advancements in the field have underscored the importance of novel predictors of outcomes in fibrotic lung diseases. Notably, emerging studies and review articles have highlighted the significance of the PD-1/PD-L1 axis and mediastinal lymphadenopathy as novel markers in the progression and prognosis of these diseases [6, 7]. These developments indicate a shift towards more precision-based approaches in understanding and managing ILD.

Owing to the wide pathological and prognostic diversity of ILD disorders with a paradoxical clinical and radiological mimicry, a multidisciplinary discussion (MDD) among experts, including pulmonologists, chest radiologists, pathologists, and rheumatologists, is pivotal in making an accurate ILD diagnosis. This pivotal role was highlighted by the European Respiratory Society (ERS) and American Thoracic Society (ATS) since 2001 [8], and the published practice guidelines and epidemiologic studies over the recent years emphasized the necessity and importance of MDDs in managing ILDs [9, 10]. When compared to diagnoses made by individual physicians, this technique boosts diagnostic confidence and interobserver agreement among ILD specialists [11, 12].

Several prospective registries for ILDs have been created in North America and Europe [13–15]. Studies based on well-designed and well-performed patient registries can provide a real-world perspective on clinical practice, patient outcomes, safety, and clinical comparative and support cost-effectiveness analyses. They study the disease course in compliance with current diagnostic and treatment guidelines and can serve as important tools for decision-making [16–18]. However, there have

been few published epidemiological studies on ILD, particularly in Asia [19]. In addition, many registries have focused only on IPF with limited data for other fibrotic ILD subtypes (CTD-ILD or non-IPF populations) [20]. The Gender-Age-Physiology (GAP) score, modified Medical Research Council (mMRC) Dyspnea Scale, ventilatory efficiency slope, six-minute walking test (6MWT) distance, DLCO, and CO₂ partial pressure in the arterial blood at maximal exercise could be important predictors for mortality [21–23]. Since the landmark SENSICIS [24] and INBUILD [25] trials demonstrated that systemic sclerosis-associated ILD, CTD-ILD, and other non-IPF progressive fibrosing ILDs could benefit from the same antifibrotic treatment as IPF, registries of patients with and without IPF are warranted. Moreover, identifying prognosis factors among all fibrotic lung diseases is critical for patients and clinicians to introduce antifibrotic agents and start the rehabilitation program in the early stage of fibrotic lung disease [26, 27].

The Registry of Interstitial Lung Disease (REGILD) is a prospective, single-center registry study enrolling IPF and non-IPF populations in central Taiwan. Every patient enrolled in the REGILD registry is evaluated by MDD experts, including pulmonologists, rheumatologists, radiologists, and pathologists. This study aimed to identify associated prognostic factors in the REGILD cohort and develop a new clinical score for predicting long-term prognosis in real world. Moreover, it compared the overall mortality prediction power of the newly developed score to the standard GAP score, based on factors estimated during the first year of follow-up.

Methods

Study design, patient enrollment, and ethics

The REGILD is a prospective, single-center registry study enrolling IPF and non-IPF populations in the Integrated Care Center of Interstitial Lung Disease of Taichung Veterans General Hospital, a tertiary referral center in Taiwan. Between December 2018 and December 2019, we enrolled patients with documented fibrotic lung diseases on high-resolution computed tomography (HRCT) that were confirmed by an MDD team comprising expert pulmonologists, rheumatologists, radiologists, and pathologists. Patients enrolled into analyzed were followed-up at least 1-year till December 2020. IPF patients were categorized as “definite,” “probable,” or “indeterminate” with IPF according to the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines. ILD patients with established diagnoses of connective tissue diseases were classified as CTD-ILD. Patients classified as having interstitial pneumonia of autoimmune features (IPAF) must meet the IPAF classification criteria [14]. The

exclusion criteria were age < 20 years and HIV infection. All enrolled patients provided written informed consent. This study was conducted in compliance with the Declaration of Helsinki and approved by the Ethics Committee of Taichung Veterans General Hospital (IRB number: CE18325B; date of approval: December 18, 2018).

ILD assessment protocol in the REGILD registry cohort

The index day was defined as the day the patient signed the informed consent form. The participants completed the mMRC Dyspnea Scale Dyspnea Questionnaire on the index day. Within one week of enrolment, the participants were administered the pulmonary function test (PFT), 6MWT, and cardiopulmonary exercise test. Baseline demographic data, including age, Gender, and ethnicity, were recorded. Clinical data comprised presenting symptoms, physical examination, environmental and occupational exposures, smoking history, and comorbidities. The GAP score was calculated for each patient.

PFT and 6MWT procedure

Forced vital capacity (FVC) and DLCO were obtained from spirometry results according to the recommendations of the American Thoracic Society [28]. The 6MWT was performed according to the guidelines of the American Thoracic Society [29]. The patients were instructed to walk as far as possible in six minutes in a corridor between two orange traffic cones placed 30 m apart. Data on oxygen saturation and the distance walked in six minutes were obtained.

Statistical analysis

Descriptive analysis was performed with categorical data presented as absolute numbers and relative frequencies. Continuous variables are presented as median (interquartile range [IQR]) for non-parametric data. The Mann–Whitney U test was used to compare continuous variables. The Chi-square and Fisher's exact tests were used to compare categorical variables. P-value was adjusted using Benjamini–Hochberg correction when comparing survival and non-survival group to control the false discovery rate [30]. A Cox proportional regression was used to examine possible factors for mortality with univariate and multivariate models. The area under the receiver operating characteristic (ROC) curve (AUC) indicates the predictive value. Better predictive power was acknowledged when the AUC was > 0.70. Kaplan–Meier estimates and log-rank tests were used to calculate mortality based on the following three variables: DLCO, mMRC Dyspnea Scale, and 6MWT distance. Statistical analyses were performed using SPSS Statistics (version 22; IBM Corporation, Armonk, NY, USA). A p -value < 0.05 was considered statistically significant.

Results

Baseline characteristics and pulmonary physiology

Table 1 shows patient characteristics in this registry. One hundred and four participants were enrolled: 33 with (31.7%) and 71 without (68.3%) IPF. Compared with patients without IPF, patients with IPF were older and more often male. In our registry, among patients without IPF, the most common CTD was idiopathic inflammatory myositis (35.5%), followed by primary systemic sclerosis (29.0%) and IPAF (12.7%). The proportion with definite usual interstitial pneumonia (UIP) patterns on HRCT scans was higher in the IPF (81.8%) than in the non-IPF (47.9%) group. The median GAP score was 3 in the IPF group (IQR = 2–4.5), compared to 2 in the non-IPF group (IQR = 1–3). mMRC dyspnea scale were higher in the IPF group than in the non-IPF group. The proportion of patients receiving antifibrotic agents was higher in the IPF group.

In this cohort, baseline FVC, FEV1, and DLCO (% predicted) data did not differ significantly between groups. Nevertheless, IPF patients had a higher FEV1/FVC (84.0%, $p = 0.033$). On the contrary, the non-IPF group had greater 6MWT distances than the IPF group (461 m vs 403.5 m, $p = 0.007$). Oxygen saturations (SpO₂) before and after the 6MWT did not differ significantly between the IPF and non-IPF groups ($p = 0.365$). More than half of the participants in both groups had a nadir SpO₂ of < 90% (Table 1).

Primary outcome of one-year mortality

Of the 104 patients, 12 died before the cutoff in December 2020. Eight of them died from pneumonia and respiratory failure, three succumbed to malignancies (two to lung cancer and one to colon cancer), and one patient died from an ischemic stroke. Five deceased patients had IPF, and seven had non-IPF (Table 2). Patients in the mortality group had significantly higher GAP and mMRC Dyspnea Scores (all $p < 0.01$). In addition, patients in the mortality group had a lower % predicted FEV1 (56.0% vs 78.5%, $p = 0.031$), lower % predicted DLCO (39.5% vs 71.5%, $p < 0.001$), and lower initial SpO₂ (92 [IQR = 90.8–96] vs 96 [IQR = 95–97], $p = 0.007$). In contrast, patients in the survival group could walk further in the 6MWT (451.5 m vs 307.5 m, $p = 0.014$) and were less desaturated afterward (89.5% vs 78.5%, $p = 0.020$; Table 2).

Predictive factors for one-year mortality

ROC curve analysis was performed to evaluate the efficacy of DLCO (% predicted), mMRC Dyspnea Score, and 6MWT distance, in addition to GAP score for predicting one-year mortality in this cohort (Fig. 1). The AUCs, optimal cutoff values, and other statistical indicators are

Table 1 Study characteristics among IPF and CTD-ILD patients. One hundred and four participants were enrolled in the study, with 33 (31.7%) having idiopathic pulmonary fibrosis (IPF) and 71 (68.3%) without. Patients with IPF were typically older, more often male, and had higher definite usual interstitial pneumonia (UIP) patterns on HRCT scans compared to those without IPF. Additionally, the IPF group had higher median GAP scores and Modified Medical Research Council (mMRC) dyspnea scale readings, and a greater proportion were receiving antifibrotic agents

	IPF (n = 33) ^a	Non-IPF (n = 71) ^a	p-value ^b
Age	69 (62–74)	61 (51–66)	<0.001
Male	24 (72.7%)	16 (22.5%)	<0.001
Smoking status			
No	13 (39.4%)	57 (80.3%)	<0.001
Current smoker	2 (6.1%)	3 (4.2%)	
Ex-smoker	18 (54.5%)	11 (15.5%)	
Smoking index	42.5 (21.3–77.5)	30 (18.8–65)	0.381
Charlson Comorbidity Index (CCI)	3.0 (1–4)	2.00 (2–4)	0.749
Pattern in HRCT			
NSIP	0 (%)	37 (52.1%)	<0.001
UIP pattern (Probable UIP)	6 (18.2%)	24 (33.8%)	
UIP pattern (Definite UIP)	27 (81.8%)	10 (14.1%)	
GAP score	3 (2–4.5)	2 (1–3)	<0.001
mMRC Dyspnea Scale	1 (1–3)	1 (0–1)	0.014
Anti-fibrotic agents	20 (60.6%)	12 (16.9%)	<0.001
Pulmonary function test			
FVC (L)	2.2 (1.8–2.8)	2.0 (1.7–2.6)	0.451
FVC (% predicted)	80.0 (61–96)	74.0 (60–88)	0.550
FEV1 (% predicted)	81.0 (64–91.5)	77.0 (59–87)	0.287
FEV1/FVC (%)	84.0 (78.5–89.5)	82.0 (78–85)	0.033
DL _{CO} (% predicted)	64.0 (39–79)	71.0 (53.5–82.5)	0.112
6MWT			
Distance (m)	403.5 (345–462)	461 (399–516.75)	0.007
Initial SpO ₂	96.0 (93.8–97)	96.0 (95–97)	0.168
SpO ₂ after 6MWT	88.0 (83.3–92)	89.5 (85–92)	0.365
Nadir SpO ₂ < 90%	18.0 (60.0%)	32.0 (50.0%)	0.494
One- year Mortality	4 (12.1%)	8 (11.3%)	1.000

^a Median (IQR); n (%)

^b Mann-Whitney *U* test, Chi-Square test, Fisher's exact test

IPF idiopathic pulmonary fibrosis UIP usual interstitial pneumonia, HRCT high-resolution computed tomography, NSIP non-specific interstitial pneumonia, GAP gender, age, physiology, mMRC modified Medical Research Council, FVC forced vital capacity, FEV1 forced expiratory volume in one second, DLCO diffusion capacity for carbon monoxide, 6MWT 6-min walking test, SpO₂ oxygen saturation

presented in Additional file 1: Table S1. DLCO (% predicted) was the most accurate variable with an AUC of 0.88 (95% confidence interval [CI]=0.80–0.94), followed by mMRC Dyspnea Score (AUC=0.82 [95% CI=0.73–0.89]), 6MWT distance (AUC=0.80 [95% CI=0.71–0.88]), and GAP score (AUC=0.77 [95% CI=0.67–0.84]). The cutoffs were 63 for DLCO (% predicted), 1 for mMRC Dyspnea Score, 392 m for 6MWT distance, and 2 for GAP score (Additional file 1: Table S1).

We proposed a clinical scoring system based on DLCO (% predicted), mMRC Dyspnea score and

6MWT distance, where One point is scored if any of the following variables are fulfilled: (1) DLCO < 63% predicted, (2) mMRC Dyspnea Score > 1, (3) or 6MWT distance < 392 m, with a minimum score of 0 and maximum score of 3. Figure 2 delineates Kaplan–Meier curves for GAP score and the proposed composite score. Patients with GAP score ≤ 2 had a significantly higher survival rate compared to those with GAP score > 2 (98.04% vs 79.25%, *p* = 0.003; Fig. 2a). Likewise, patients with composite score < 2 had significantly higher survival rate than those with composite score ≥ 2 (100% vs 75%, *p* < 0.001; Fig. 2b).

Table 2 Study characteristics among survival and non-survival groups. Out of the 104 patients, 12 died before the December 2020 cutoff, with eight succumbing to pneumonia and respiratory failure, three to malignancies, and one to an ischemic stroke. Of the deceased, five had idiopathic pulmonary fibrosis (IPF) and seven did not. The mortality group had significantly higher GAP and mMRC Dyspnea Scores, along with lower predicted FEV1, DLCO percentages, and initial SpO₂, compared to the survival group

	Survival (n = 92) ^a	Mortality (n = 12) ^a	p-value ^{b,c}
Age	62 (57.3–69.8)	67.5 (61.3–70.5)	0.301
Male	32 (34.8%)	8 (66.7%)	0.055
Classification of ILD			
IPF	28 (30.4%)	5 (41.7%)	0.513
Non-IPF	64 (69.6%)	7 (58.3%)	
Pattern in HRCT			
NSIP	41 (44.6%)	2 (16.7%)	0.048
UIP pattern (Probable UIP)	41 (44.6%)	10 (83.3%)	
UIP pattern (Definite UIP)	10 (10.9%)	0 (0.0%)	
GAP score	2 (1–3)	3 (3–5)	0.002
mMRC Dyspnea Scale	1 (0–1)	3 (2–3)	<0.001
Antifibrotic agents	29 (31.5%)	3 (25.0%)	0.751
Pulmonary function test			
FVC (L)	2.2 (1.8–2.7)	1.5 (1.3–2.5)	0.087
FVC (% predicted)	77.0 (64.3–88.8)	57.0 (47.8–88.8)	0.127
FEV1 (% predicted)	78.5 (66.0–89.0)	56 (49.0–79.8)	0.031
FEV1/FVC (%)	83.0 (78.3–86.0)	82 (71.8–90.0)	0.636
DLCO (% predicted)	71.5 (56.0–82.8)	39.5 (31.0–53.5)	<0.001
6MWT			
Distance (m)	451.5 (386.3–507.0)	307.5 (159.5–409.5)	0.014
Initial SpO ₂	96. (95.0–97.0)	92.0 (90.8–96.0)	0.007
SpO ₂ after 6MWT	89.5 (85.3–92.0)	78.5 (73.5–86.3)	0.002
Nadir SpO ₂ < 90%	44 (50.0%)	6 (100%)	0.028

^a Median (IQR); n (%)

^b Mann-Whitney U test, Chi-Square test, Fisher's exact test

^c Adjusted p-value using Benjamini–Hochberg correction to control the false discovery rate

ILD Interstitial lung disease, IPF idiopathic pulmonary fibrosis, UIP usual interstitial pneumonia, HRCT high-resolution computed tomography, NSIP non-specific interstitial pneumonia, GAP gender, age, physiology, mMRC modified Medical Research Council, FVC forced vital capacity, DLCO diffusion capacity for carbon monoxide, 6MWT 6-min walking test, SpO₂ oxygen saturation

Univariate and multivariate analyses of factors associated with one-year mortality

Univariate and multivariate Cox analyses for one-year mortality are shown in Table 3. Higher GAP scores were associated with decreased survival in the univariate (HR = 1.55, 95% CI = 1.19–2.01, $p = 0.001$) and multivariate (HR = 1.55 [95% CI = 1.03–2.34], $p = 0.037$) models. Likewise, the clinical composite score (DLCO + mMRC score + 6MWT distance) was associated with higher risk of mortality in the univariate (HR = 4.46 [95% CI = 1.72–11.58], $p = 0.002$) and multivariate (HR = 3.45 [95% CI = 1.11–10.73], $p = 0.032$) models. Other factors including age, gender, UIP pattern, antifibrotic agents, and pulmonary function were not significant predictors of mortality in the univariate analysis.

Discussion

In the Oldham et al. cohort, approximately 70% of patients who met IPAF criteria had HRCT or pathological UIP, whereas the Chartrand et al. [31], Ahmad et al. [32] and Kelly et al. [33] cohorts had HRCT or pathological NSIP/OP/NSIP with OP patterns in more than 60% of patients. In this prospective cohort study, IPAF patients had a higher proportion of UIP. However, this is not the case for all IPAF patients. This variability underscores the need for individualized diagnostic pathways and the importance of a thorough clinical, radiological, and histopathological assessment to accurately classify and treat each case.

In this study, we established the predictive value of DLCO, mMRC Dyspnea Scale, and 6MWT distance for one-year mortality in patients with newly diagnosed

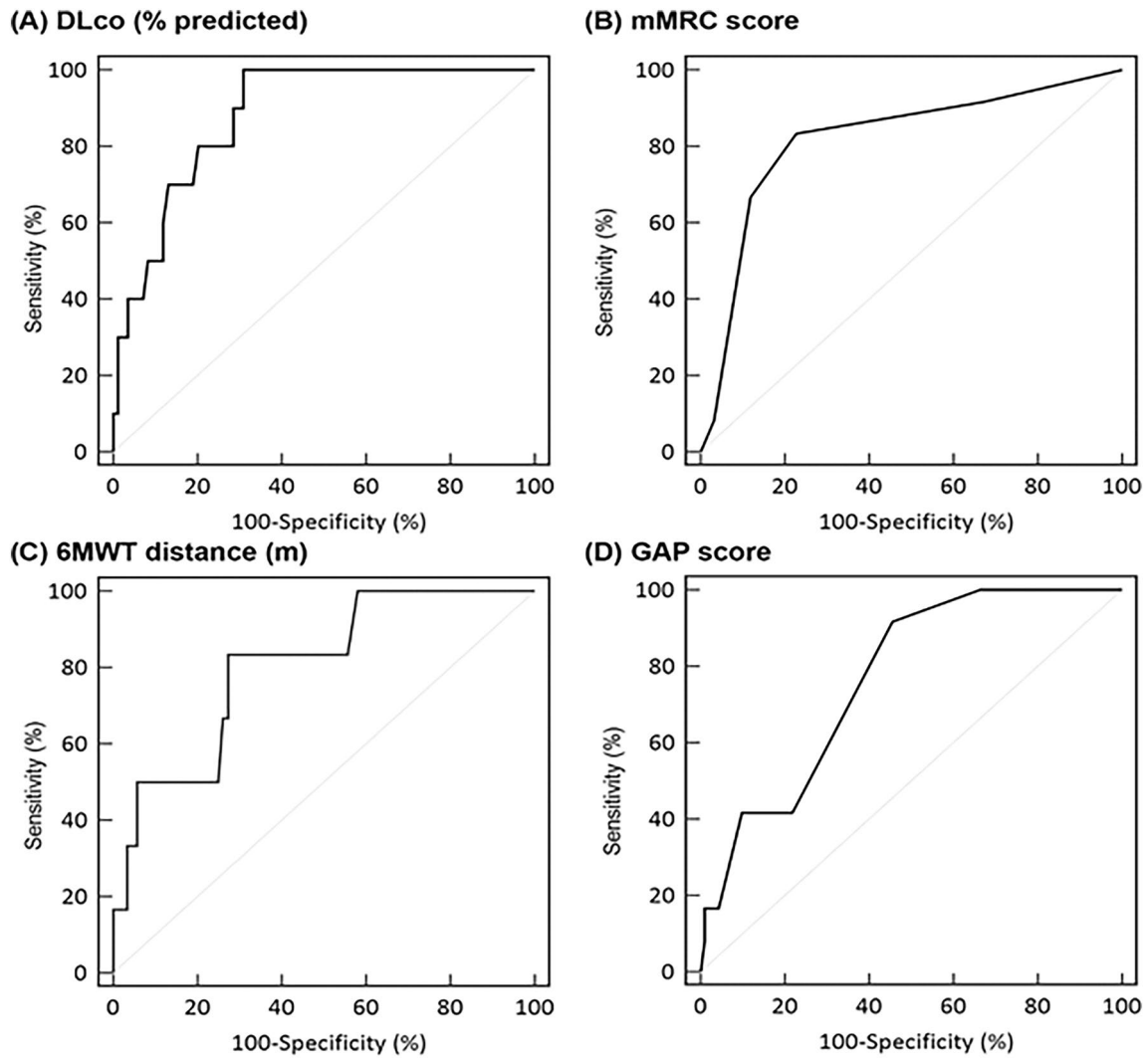


Fig. 1 ROC curves: **A** DLCO (%predicted); **B** mMRC score; **C** 6MWT distance (m); **D** GAP score

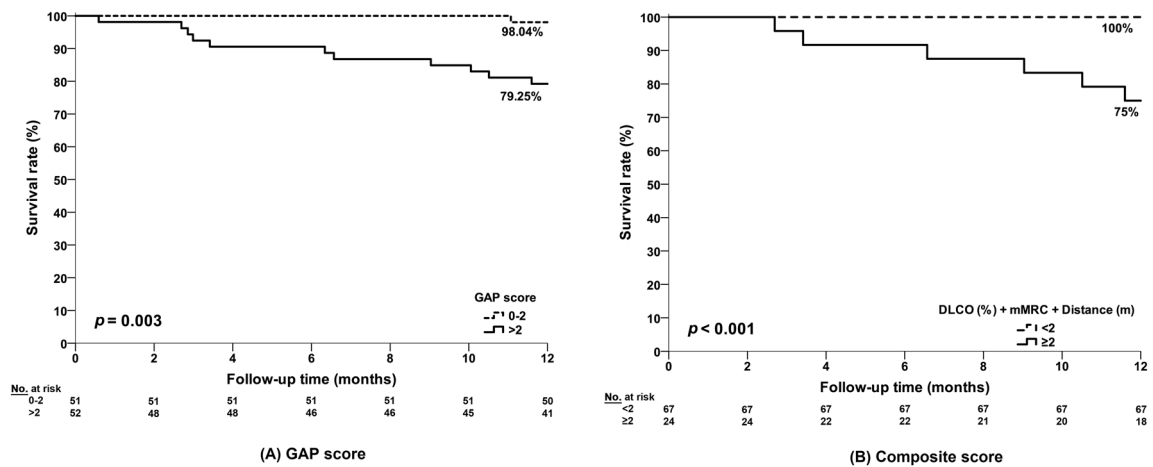


Fig. 2 Kaplan–Meier Survival curves: **A** According to the GAP score (score 0–2 vs score >2); **B** According to the composite score (score <2 vs score ≥2)

Table 3 Univariate and multivariate analyses of factors associated with one-year mortality. Higher GAP scores were linked to reduced survival in both univariate and multivariate models, with respective hazard ratios (HR) of 1.55 ($p = 0.001$) and 1.55 ($p = 0.037$). Similarly, a clinical composite score combining DLCO, mMRC score, and 6MWT distance was associated with an increased mortality risk in both univariate and multivariate analyses. Other factors such as age, gender, UIP pattern, antifibrotic agents, and pulmonary function did not significantly predict mortality in the univariate analysis

	Simple model		Adjusted for GAP score	
	HR (95%CI) ^a	p-value	HR (95%CI) ^a	p-value
Demographics				
Age	1.02 (0.97–1.07)	0.495		
Male	3.28 (0.99–10.91)	0.052		
CTD-ILD	0.66 (0.21–2.07)	0.475		
Antifibrotic agents	0.73 (0.20–2.71)	0.643		
Pulmonary function				
FVC (% predicted)	0.99 (0.96–1.02)	0.439		
FEV1 (%)	0.99 (0.96–1.02)	0.547		
FEV1/FVC (%)	0.97 (0.90–1.06)	0.498		
GAP score	1.55 (1.19–2.01)	0.001	1.55 (1.03–2.34)	0.037
DLCO (%) + mMRC score + 6MWT distance (m)	4.46 (1.72–11.58)	0.002	3.45 (1.11–10.73)	0.032

^a HR (95% CI) from the Cox regression

fibrotic lung disease, including both IPF and non-IPF populations, in a tertiary referral center in Taiwan. Utilizing an MDD approach, we further categorized patients into IPF or non-IPF groups after a comprehensive evaluation using these tests. Significantly, the composite score from these assessments emerged as a crucial tool in identifying the specific type of lung disease in each patient. This level of diagnostic precision is vital for guiding physicians in selecting the most appropriate preventative and therapeutic interventions, thereby optimizing treatment outcomes. The findings from this study underscore the importance of a holistic, multidisciplinary assessment in effectively managing fibrotic lung diseases and underscore the value of these specific measures in predicting patient outcomes and informing clinical decision-making.

The 2022 ATS/ERS/JRS/ALAT official guidelines recommend a one-year interval for assessing the progression of Interstitial Lung Disease (ILD), highlighting its importance in identifying progressive pulmonary fibrosis (PPF) phenotypes. Our study, while not specifically focused on PPF, proposes that mortality within one year of an ILD diagnosis indicates a more severe progression, leading us to select one-year mortality as our primary endpoint [34].

Significantly, in our cohort, the one-year mortality rate was 12%, with no discernible difference between IPF and non-IPF groups. This observation differs from a study conducted by Moor CC et al., 2021, which identified a one-year all-cause mortality rate of 20% among IPF patients, notably higher than the rate observed in

our cohort [35]. The variance in mortality rates may be attributed to the inclusion of patients in more advanced stages of IPF with elevated GAP stages and significantly diminished lung function (FVC < 20% of predicted value) in the study by Moor CC et al. [35]. In contrast, our study primarily involved newly diagnosed ILD patients who exhibited relatively better-preserved lung function. This study thus provides a real-world insight into the one-year survival of patients with newly diagnosed ILD, emphasizing the importance of early-stage identification and intervention.

The findings of this study are particularly relevant in the context of evolving research that underscores the significance of novel predictors of outcomes in fibrotic lung diseases. Recent studies and review articles have emphasized the emerging role of the PD-1/PD-L1 axis and mediastinal lymphadenopathy as novel markers, offering potential insights into the progression and prognosis of these conditions [6, 7]. This highlights the growing importance of precision medicine approaches in understanding and managing ILD.

Our findings reveal a notable correlation between DLCO and the 6MWT distance, suggesting a comprehensive approach to assessing both pulmonary function and physical capability. This correlation is crucial as it provides a broader perspective on patient health, extending beyond basic pulmonary function tests. Patients with advanced fibrosis often exhibit a reduced DLCO and cover shorter distances in the 6-min walk test (6MWT). A study on diffuse systemic

sclerosis-associated ILD, which included 121 patients, demonstrated a notable correlation between SpO₂ levels during the 6MWT and DLCO [36]. Additionally, we came across a study examining the correlation between the 6-min walk distance (6MWD) and DLCO in patients with COPD. This study identified a correlation coefficient of 0.39 ($p < 0.05$) between 6MWD and DLCO [37]. Furthermore, a 2017 study investigated the relationship between 6MWD and DLCO in ILD patients [38]. Their results showed a positive correlation, with a Pearson correlation coefficient of 0.272 ($p = 0.001$).

In our cohort, the classification of IPAF within CTD-ILD aligns with current diagnostic understanding. While IPAF represents a unique subset, its inclusion in CTD-ILD reflects the complexities and overlaps within ILD classifications. We also explored the HRCT imaging characteristics of non-IPF patients, noting significant variability among different ethnic groups. This diversity highlights the importance of personalized approaches in diagnosing and managing ILD, particularly in diverse populations.

On the univariate and multivariate analysis of factors associated with one-year mortality, we found that the GAP score and the newly established predictor composite of DLCO, mMRC Dyspnea Scale, and 6MWT distance were the only significant predictors for one-year mortality. This aligns with the most recent ATS/ERS/JRS/ALAT clinical practice guideline, which defines a clinically suspected case of IPF as a patient with unexplained patterns of bilateral pulmonary fibrosis on chest radiography or chest computed tomography, bibasilar inspiratory crackles, and age > 60 years [34]. The guideline also emphasizes the role of MDD in diagnosing IPF, highlighting the importance of multidisciplinary approaches in accurate diagnosis and management.

Our study's findings resonate with those of Shou et al., who demonstrated that static DLCO and changes in DLCO are predictive of mortality (95% CI = 0.08–0.90) [39]. Similarly, Goh et al. found that DLCO alone or in combination with FVC predicts mortality in Interstitial Lung Disease [40], and Walsh et al. reported an association of DLCO with increased mortality in patients with connective tissue disease-related fibrotic lung disease (CTD-FLD; $p = 0.013$, 95% CI = 0.95–0.99) [41].

Furthermore, we observed that the mMRC Dyspnea Scale (AUC = 0.82) can predict one-year mortality in fibrotic lung disease patients. This finding is consistent with Cheng et al.'s study, where the mMRC Dyspnea Scale (AUC = 0.87) was used to predict mortality in IPF patients [21]. Nishiyama et al. also found it to be a reliable predictor of survival in IPF patients (HR = 2.402, 95% CI = 1.495–3.858, $p = 0.0003$) [42].

The 6MWT distance (AUC = 0.80) also predicted one-year mortality in fibrotic lung disease patients, with a cutoff point at 392 m. This is in line with the findings of Cheng et al., where non-survivors experienced more oxygen desaturation during the test [21], and Mancuzo et al.'s report that a 6MWD of < 330 m or < 70% of the predicted value is linked to a substantially decreased survival rate in IPF patients [22].

Patients in the mortality group had significantly higher GAP scores. The median GAP score was 3 in the IPF group, compared with 2 in the non-IPF group, paralleling the findings of Cheng et al., where a GAP score ≥ 4 was associated with 1-year mortality in IPF patients [21]. Notably, the HR of our new predictor composite of DLCO, mMRC Dyspnea Scale, and 6MWT distance was higher than that of the GAP score (HR = 3.45 [1.11–10.73] vs HR = 1.55 [1.03–2.34]), indicating its potential utility in clinical practice. Furthermore, the effectiveness of the GAP score and the potential for enhanced accuracy with modified GAP scores tailored for specific populations are areas warranting further exploration [43].

Conclusion

In this study, we focused on confirming the mortality predictive role of a multidisciplinary discussion (MDD) clinical score, comprising DLCO, mMRC Dyspnea Scale, and 6MWT distance, among newly diagnosed fibrotic lung disease patients within Asian populations. Our findings, demonstrating an adjusted hazard ratio (HR) comparable to that of the GAP score in the multivariate analysis, underscore the potential utility of this composite score in clinical practice. While we successfully identified significant predictors for one-year mortality, it's important to acknowledge the limitation of our relatively small sample size. Despite this, our study contributes valuable insights, particularly for managing both IPF and non-IPF patients and highlights the need for further research in diverse populations to refine and validate our findings. This effort to develop and validate novel predictive tools reflects an ongoing commitment to improving patient care and outcomes in the field of interstitial lung disease.

Abbreviations

6MWT	Six-minute walking test
6MWD	Six-minute walking distance
ATS	American Thoracic Society
CI	Confidence interval
CTD-ILD	Connective tissue disease-associated interstitial lung disease
DLCO	Diffusion capacity for carbon monoxide
ERS	European Respiratory Society
FVC	Forced vital capacity
GAP	Gender-Age-Physiology
HR	Hazard ratio
IPAF	Interstitial pneumonia of autoimmune features
IPF	Idiopathic pulmonary fibrosis
IQR	Interquartile range

MDD	Multidisciplinary discussion
mMRC	Modified Medical Research Council
PFT	Pulmonary function test
REGILD	Registry of Interstitial Lung Disease
ROC	Receiver operating characteristic

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s40001-024-01644-7>.

Additional file 1. Table S1. The AUC and cutoff for different predictors. DLCO (% predicted) was the most accurate variable for predicting outcomes, with an Area Under the Curve (AUC) of 0.88, followed by mMRC Dyspnea Score (AUC = 0.82), 6MWT distance (AUC = 0.80), and GAP score (AUC = 0.77). The respective cutoffs for these variables were 63% for DLCO, 1 for mMRC Dyspnea Score, 392 meters for 6MWT distance, and 2 for GAP score.

Acknowledgements

The editorial assistance was provided to the authors by Nova Journal Experts.

Author contributions

YWL conceived and designed the study, analyzed and interpreted the data, and drafted the manuscript. YMC analyzed and interpreted the data. MCL conceived and designed the study, analyzed and interpreted the data, and drafted the manuscript. YCW and CYH acquired the data. PKF conceived and designed the study, analyzed and interpreted the data, drafted the manuscript, revised the manuscript, validated the data, and supervised the study. WNH analyzed and interpreted the data. YHC analyzed and interpreted the data. All authors read and approved the final manuscript.

Funding

This study was supported by Taichung Veterans General Hospital (TCVGH-1127307D; TCVGH-1123104D; TCVGH-1128303D; TCVGH-1123510C & TCVGH-1123511C).

Availability of data and materials

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

Declarations

Ethics approval and consent to participate

This study was conducted in compliance with the Declaration of Helsinki and approved by the Ethics Committee of Taichung Veterans General Hospital (IRB number: CE18325B; date of approval: December 18, 2018). All patients signed an informed consent form.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Integrated Care Center of Interstitial Lung Disease, Taichung Veterans General Hospital, Taichung 40705, Taiwan. ²Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Division of Allergy, Taichung Veterans General Hospital, Taichung 40705, Taiwan. ³Division of Translation Medicine, Department of Medical Research, Taichung Veterans General Hospital, Taichung 40705, Taiwan. ⁴Department of Radiology, Taichung Veterans General Hospital, Taichung 40705, Taiwan. ⁵Department of Critical Care Medicine, Taichung Veterans General Hospital, Taichung 40705, Taiwan. ⁶Biostatistics Task Force, Department of Medical Research, Taichung Veterans General Hospital, Taichung 40705, Taiwan. ⁷Division of Clinical Research, Department of Medical Research, Taichung Veterans General Hospital, Taichung 40705, Taiwan. ⁸Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung 40200, Taiwan. ⁹Department

of Medical Research, Taichung Veterans General Hospital, 1650 Taiwan Boulevard Sect. 4, Taichung 407219, Taiwan.

Received: 8 November 2023 Accepted: 6 January 2024

Published online: 20 January 2024

References

- Barratt SL, Creamer A, Hayton C, Chaudhuri N. Idiopathic Pulmonary Fibrosis (IPF): an overview. *J Clin Med*. 2018;7:201.
- Mei Q, Liu Z, Zuo H, Yang Z, Qu J. Idiopathic Pulmonary Fibrosis: an update on pathogenesis. *Front Pharmacol*. 2021;12: 797292.
- Sauleda J, Núñez B, Sala E, Soriano JB. Idiopathic pulmonary fibrosis: epidemiology, natural history, phenotypes. *Med Sci*. 2018;6:110.
- Spagnolo P, Kropski JA, Jones MG, Lee JS, Rossi G, Karamitsakos T, et al. Idiopathic pulmonary fibrosis: disease mechanisms and drug development. *Pharmacol Ther*. 2021;222: 107798.
- Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ. What's in a name? That which we call IPF, by any other name would act the same. *Eur Respir J*. 2018;51:1800692.
- Adegunsoye A, Oldham JM, Bonham C, Hrusch C, Nolan P, Klejch W, et al. Prognosticating outcomes in interstitial lung disease by Mediastinal Lymph Node Assessment. An Observational Cohort Study with independent validation. *Am J Respir Crit Care Med*. 2019;199:747–59.
- Karamitsakos T, Galaris A, Chrysikos S, Papaioannou O, Vamvakaris I, Barbayianni I, et al. Expression of PD-1/PD-L1 axis in mediastinal lymph nodes and lung tissue of human and experimental lung fibrosis indicates a potential therapeutic target for idiopathic pulmonary fibrosis. *Respir Res*. 2023;24:279.
- American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med*. 2002;165:277–304.
- Sharif R. Overview of idiopathic pulmonary fibrosis (IPF) and evidence-based guidelines. *Am J Manag Care*. 2017;23:S176–82.
- Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2013;188:733–48.
- Flaherty KR, King TE Jr, Raghu G, Lynch JP 3rd, Colby TV, Travis WD, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med*. 2004;170:904–10.
- Sanduzzi Zamparelli S, Sanduzzi Zamparelli A, Bocchino M. The evolving concept of the multidisciplinary approach in the diagnosis and management of interstitial lung diseases. *Diagnostics*. 2023;13:2437.
- Kaul B, Cottin V, Collard HR, Valenzuela C. Variability in global prevalence of interstitial lung disease. *Front Med*. 2021;8: 751181.
- Fischer A, Antoniou KM, Brown KK, Cadranet J, Corte TJ, du Bois RM, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Respir J*. 2015;46:976–87.
- Hambly N, Farooqi MM, Dvorkin-Gheva A, Donohoe K, Garlick K, Scallan C, et al. Prevalence and characteristics of progressive fibrosing interstitial lung disease in a prospective registry. *Eur Respir J*. 2022;60:2102571.
- Gliklich RE, Dreyer NA, Leavy MB, editors. *Registries for Evaluating Patient Outcomes: A User's Guide*. 3rd ed. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014.
- Barczy E, Starobinski L, Kolonics-Farkas A, Eszes N, Bohacs A, Vasakova M, et al. Long-term effects and adverse events of nintedanib therapy in idiopathic pulmonary fibrosis patients with functionally advanced disease. *Adv Ther*. 2019;36:1221–32.
- Guler SA, Zumstein P, Berezowska SA, Pöllinger A, Geiser T, Funke-Chambour M. Idiopathic pulmonary fibrosis in a Swiss interstitial lung disease reference centre. *Swiss Med Wkly*. 2018;148: w14577.
- Ye Y, Hubbard R, Li GH, Ho SC, Sing CW, Cheung CL, et al. Validation of diagnostic coding for interstitial lung diseases in an electronic

- health record system in Hong Kong. *Pharmacoepidemiol Drug Saf.* 2022;31:519–23.
20. Fisher J, Kolb M, Algami M, Morisset J, Johansson K, Shapera S, et al. Baseline characteristics and comorbidities in the Canadian REgistry for Pulmonary Fibrosis. *BMC Pulm Med.* 2019;19:1–9.
 21. Cheng Y-Y, Lin S-Y, Chang S-T, Lin C-H, Fu P-K. Cardiopulmonary Exercise Test, mMRC and GAP score Can Predict 1-year Mortality in patients with idiopathic pulmonary fibrosis: a prospective Study; 2021 (preprint).
 22. Mancuzo EV, Soares MR, Pereira CA. Six-minute walk distance and survival time in patients with idiopathic pulmonary fibrosis in Brazil. *J Bras Pneumol.* 2018;44:267–72.
 23. Mena-Vázquez N, Rojas-Gimenez M, Romero-Barco CM, Manrique-Arija S, Francisco E, Aguilar-Hurtado MC, et al. Predictors of progression and mortality in patients with prevalent rheumatoid arthritis and interstitial lung disease: a prospective cohort study. *J Clin Med.* 2021;10:874.
 24. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med.* 2019;380:2518–28.
 25. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SL, Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med.* 2019;381:1718–27.
 26. Matsuo S, Okamoto M, Ikeuchi T, Zaizen Y, Inomoto A, Haraguchi R, et al. Early intervention of pulmonary rehabilitation for fibrotic interstitial lung disease is a favorable factor for short-term improvement in health-related quality of life. *J Clin Med.* 2021;10:3153.
 27. Sugino K, Ono H, Watanabe N, Ando M, Tsuboi E, Homma S, et al. Efficacy of early antifibrotic treatment for idiopathic pulmonary fibrosis. *BMC Pulm Med.* 2021;21:1–10.
 28. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med.* 2007;175:1304–45.
 29. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* 2002;166:111–7.
 30. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol.* 1995;57:289–300.
 31. Chartrand S, Swigris JJ, Stanchev L, Lee JS, Brown KK, Fischer A. Clinical features and natural history of interstitial pneumonia with autoimmune features: A single center experience. *Respir Med.* 2016;119:150–4.
 32. Ahmad K, Barba T, Gamondes D, Ginoux M, Khouatra C, Spagnolo P, et al. Interstitial pneumonia with autoimmune features: clinical, radiologic, and histological characteristics and outcome in a series of 57 patients. *Respir Med.* 2017;123:56–62.
 33. Kelly BT, Moua T. Overlap of interstitial pneumonia with autoimmune features with undifferentiated connective tissue disease and contribution of UIP to mortality. *Respirology.* 2018;23:600–5.
 34. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic Pulmonary Fibrosis (an Update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med.* 2022;205:e18–47.
 35. Moor CC, Tak van Jaarsveld NC, Owusuaa C, Miedema JR, Baart S, van der Rijt CCD, et al. The value of the surprise question to predict one-year mortality in idiopathic pulmonary fibrosis: a prospective cohort study. *Respiration.* 2021;100:780–5.
 36. Rizzi M, Sarzi-Puttini P, Airoldi A, Antivalle M, Battellino M, Atzeni F. Performance capacity evaluated using the 6-minute walk test: 5-year results in patients with diffuse systemic sclerosis and initial interstitial lung disease. *Clin Exp Rheumatol.* 2015;33:S142–7.
 37. Kochetova E. Six minute walk distance (6MWD) and pulmonary diffusing capacity (DL_{CO}) in patients with COPD. *Eur Resp J.* 2015;46:PA4798.
 38. Hu Z, Que C. Six-Minute-Walk Test (6MWT) and Pulmonary Function in Interstitial Lung Disease (ILD) Patients. A24 IPF: Clinical Studies, Therapeutics, and More I. p. A1121-A.
 39. Shou AY, Salvatore MM. CT predictors of outcomes in patients with connective tissue disease and progressive lung fibrosis. *Clin Imaging.* 2023;94:42–9.
 40. Goh NS, Hoyles RK, Denton CP, Hansell DM, Renzoni EA, Maher TM, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol.* 2017;69:1670–8.
 41. Walsh SL, Sverzellati N, Devaraj A, Keir GJ, Wells AU, Hansell DM. Connective tissue disease related fibrotic lung disease: high resolution computed tomographic and pulmonary function indices as prognostic determinants. *Thorax.* 2014;69:216–22.
 42. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Kato K, Kataoka K, et al. A simple assessment of dyspnoea as a prognostic indicator in idiopathic pulmonary fibrosis. *Eur Resp J.* 2010;36:1067–72.
 43. Nishikiori H, Chiba H, Lee SH, Kondoh S, Kamo KI, Nakamura K, et al. A modified GAP model for East-Asian populations with idiopathic pulmonary fibrosis. *Respir Investig.* 2020;58:395–402.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.