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Air trapping in patients with idiopathic pulmonary fibrosis: a retrospective case—control study

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Idiopathic pulmonary fibrosis (IPF) is characterised by progressive worsening of lung function. In some cases, IPF is accompanied by air-trapping and emphysema. This study aimed to evaluate air trapping quantified with RV/TLC in patients with IPF. This retrospective study included 122 patients diagnosed with IPF in South Korea between January 2011 and December 2020. Air trapping was defined as RV/TLC ≥ 0.40. Increased RV/TLC was found in 34.4% of all patients. The RV/TLC negatively correlated with lung function (forced expiratory volume in 1 s and functional vital capacity [FVC]) and showed consistent results after 1 year of follow-up. After propensity score matching, FVC and diffusion capacity between the groups showed no statistical difference. No difference in lung function decline was found between the increased and not increased RV/TLC groups. Regarding univariable analysis, the patients in the increased RV/TLC group had a lower risk of all-cause mortality (hazard ratio 1.753, P = 0.034). Using multivariable analysis, age, pirfenidone treatment, and FVC were significant factors for survival but not increased RV/TLC. Increased RV/TLC was related to emphysema and demonstrated a negative relationship with lung function. Although increased RV/TLC might relate to poor clinical outcome, it was not independent prognostic factor for IPF.

Keywords Idiopathic pulmonary fibrosis, Mortality, Pirfenidone, Air trapping, Pulmonary function tests, RV/TLC ratio

Abbreviations

IPF	Idiopathic pulmonary fibrosis
ILD	Interstitial lung disease
FVC	Forced vital capacities
DL_{CO}	Diffusion capacity of the lung for carbon monoxide
FEV1	Forced expiratory volume in 1 s
RV/TLC	Residual volume/total lung capacities ratio
CT	Computed tomography
PFT	Pulmonary function test
UIP	Usual interstitial pneumonia
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease (ILD) characterised by chronic and progressive scarring of the lungs, decreased lung function, and poor prognosis[1]. The course of progression of IPF varies between patients; median survival from the time of diagnosis in untreated patients has been reported to be approximately three years[2]. Most deaths in patients with IPF occur due to IPF itself and acute exacerbations of the disease[3]. Prognostic factors for disease progression include comorbidities, age, smoking, decreased lung function, gender-age-physiology (GAP) score, exercise capacity, and body weight loss in patients with IPF[4–6]. The impact of forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DL_{CO}) has been studied and validated in several reports; however, other parameters in pulmonary function tests have been less studied. Forced expiratory volume in 1 s (FEV1) and air trapping quantified by residual volume/total lung capacity (RV/TLC) ratio have been related to worsening of lung function and chest computed tomography (CT) parameters in patients with airway diseases such as chronic obstructive pulmonary disease (COPD)[7–9]. A previous study showed that air trapping is common in patients with ILD, not only in those with obstructive

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lung diseases. Air trapping defined by quantitative CT measurements reportedly relates to slightly worse event-free survival, without statistical significance[10]. Only a few studies have evaluated the impact of air trapping on restrictive lung diseases, such as ILDs including IPF.

Therefore, this study aimed to evaluate air trapping quantified by RV/TLC in patients with IPF. The relationships of air trapping with clinical outcomes were assessed, along with analyses of other parameters of pulmonary function test (PFT) with chest CT features such as emphysema findings.

Results

Participants and baseline characteristics

A total of 122 patients were included in this study. The mean age of the participants was 70.0 (± 7.9) years. The study population comprised 92 (75.4%) male patients and 53 (43.4%) ever-smokers. In the increased RV/TLC group, there were more emphysema findings on CT with decreased baseline FVC (Table 1). Fifty-five (45.1%) patients were treated with antifibrotic agent (pirfenidone) (Supplementary Table 1). The pirfenidone-treated group comprised younger patients (P = 0.012) than did the group administered no antifibrotic medications. The mean lung function of all included patients was: baseline FVC (% of predicted), 78.3%; DL_{CO} (% of predicted), 65.9%; TLC (% of predicted), 83.2%; and RV (% of predicted), 75.1%. None of the patients were prescribed inhalers, including long-acting beta-agonists, long-acting muscarinic antagonists, or inhaled corticosteroids.

Characteristics according to air trapping

After propensity score matching, increased RV/TLC group had numerically lower FVC without showing statistical significance. Twenty-one (51.2%) patients exhibited radiological emphysema in the increased RV/TLC group compared with 11 (28.9%) in the not increased RV/TLC group (P = 0.044) (Table 2). RV/TLC negatively correlated with FEV1 (% of predicted) (Pearson coefficient, − 0.306; P = 0.001), FVC (% of predicted) (Pearson coefficient, − 0.387; P < 0.001) and forced expiratory flow between 25 and 75% of vital capacity (FEF25–75%) (% of predicted) (Pearson coefficient, − 0.078; P = 0.393). However, RV/TLC positively correlated with follow-up RV/TLC after 1 year (Pearson correlation, 0.546; P-value < 0.001) (Supplementary Table 2, Fig. 1A–D). Air trapping according to baseline RV/TLC was significantly related to 1 year follow-up RV/TLC (Supplementary Table 3).

Survival outcomes

After propensity score matching, elevated RV/TLC was associated with a higher risk of all-cause mortality (log-rank, P = 0.031) (Fig. 2). Using survival analysis, the antifibrotic agent treatment group had a lower risk of all-cause mortality (log-rank, P = 0.020) (Fig. 3). Using Cox proportional hazard regression and univariate analysis, age (Hazard ratio [HR], 1.052; P = 0.033), without pirfenidone treatment (HR 0.443; P = 0.021), low FVC (HR 0.955; P < 0.001), low DL_{CO} (HR 0.976; P = 0.002), and increased RV/TLC ratio (%) (HR 1.753; P = 0.034) were significant factors for mortality. Using multivariable analysis, age (HR 1.083; P = 0.013), pirfenidone treatment (HR 0.385; P = 0.016), and FVC (HR 0.949; P < 0.001) were significant factors for mortality, whereas DL_{CO} (HR 0.993; P = 0.453) and increased TLC/RV ratio (%) (HR 1.393; P = 0.415) were not (Table 3).

Characteristics	All patients (N = 122)	Patients with increased RV/TLC (≥ 0.4) (n = 42)	Patients without increased RV/TLC (< 0.4) (n = 80)	P-value
Age (years)	70 (± 7.9)	71.7 (± 7.3)	70.0 (± 8.0)	0.071
Male sex	92 (75.4%)	26 (61.9%)	65 (81.3%)	0.701
BMI, kg/m^2	24.0 (± 3.7)	22.6 (± 4.0)	24.7 (± 3.2)	0.002
Ever-smoker	53 (43.4%)	20 (47.6%)	33 (41.3%)	0.701
UIP on CT	122 (100.0%)	42 (100.0%)	80 (100.0%)	
Emphysema on CT	42 (34.4%)	22 (52.4%)	20 (25.0%)	0.004
Hypertension	40 (32.8%)	13 (30.1%)	27(33.8)	0.930
Diabetes mellitus	20 (16.4%)	6 (14.3%)	14 (17.5%)	0.688
Malignancy	21 (17.2%)	7 (16.7%)	14 (17.5%)	0.821
FEV1/FVC	83.0 (± 7.1)	84.2 (± 6.3)	82.4 (± 6.3)	0.212
FVC (% of predicted)	78.3 (± 19.0)	72.0 (± 20.3)	81.7 (± 17.5)	0.007
DL_{CO} (% of predicted)	65.9 (± 24.9)	66.9 (± 27.8)	65.0 (± 23.4)	0.855
Δ[a] FVC (L/year)	− 0.113 (± 0.344)	− 0.087 (± 0.360)	− 0.126 (± 0.334)	0.615
Δ FVC (% of predicted/year)	− 2.5 (± 11.0)	− 2.5 (± 10.7)	− 2.5 (± 12.0)	1.000
Δ DL_{CO} (% of predicted/year)	− 6.1 (± 19.2)	− 9.7 (± 27.8)	− 4.3 (± 13.1)	0.210

Table 1. Characteristics according to residual volume/total lung capacity ratio. Data are expressed as mean (± standard deviation) or n (%). [a]Δ was defined as lung function after 1 year—baseline lung function. *BMI* Body mass index, *UIP* Usual interstitial pneumonia, *CT* Computed tomography, *FEV1* Forced expiratory volume in 1 s, *FVC* Forced vital capacity, *DL_{CO}* Diffusion capacity of carbon monoxide.

Characteristics	All patients (N = 79)	Patients with increased RV/TLC (≥ 0.4) (n = 41)	Patients not increased RV/TLC (< 0.4) (n = 38)	P-value
Age (years)	71.2 (± 8.1)	71.7 (± 7.4)	70.7 (± 8.8)	0.567
Male sex	58 (73.4%)	26 (63.4%)	32 (84.2%)	0.037
BMI, kg/m^2	23.3 (± 3.7)	22.6 (± 4.0)	24.1 (± 3.2)	0.062
Ever-smoker	35 (44.3%)	20 (48.8%)	15 (39.5%)	0.874
UIP on CT	79 (100.0%)	41 (100.0%)	38 (100.0%)	
Emphysema on CT	32 (40.5%)	21 (51.2%)	11 (28.9%)	0.044
Hypertension	28 (35.4%)	13 (31.7%)	15 (39.5%)	0.471
Diabetes mellitus	13 (16.5%)	6 (14.6%)	7 (18.4%)	0.650
Malignancy	15 (19.0%)	7 (17.1%)	8 (21.1%)	0.652
Pirfenidone use	30 (38.0%)	18 (43.9%)	12 (31.6%)	0.259
FEV1/FVC	82.8 (± 7.6)	84.2 (± 8.8)	81.4 (± 5.9)	0.113
FVC (% of predicted)	76.5 (± 21.1)	72.0 (± 20.3)	81.3 (± 21.0)	0.051
DL_{CO} (% of predicted)	65.8 (± 26.2)	66.9 (± 27.8)	64.8 (± 24.9)	0.729
Δ FVC (% of predicted/year)	− 2.5 (± 10.5)	− 2.5 (± 12.0)	− 2.5 (± 8.8)	0.497

Table 2. Characteristics according to residual volume/total lung capacity ratio after propensity score matching. Data are expressed as mean (± standard deviation) or n (%). [a]Δ was defined as lung function after 1 year—baseline lung function. *BMI* Body mass index, *UIP* Usual interstitial pneumonia, *CT* Computed tomography, *FEV1* Forced expiratory volume in 1 s, *FVC* Forced vital capacity, DL_{CO} Diffusion capacity of carbon monoxide.

Discussion

The findings of this study showed that in patients with IPF, 34.4% showed increased RV/TLC with decreased TLC and RV due to restrictive lung defects. Increased RV/TLC might relate to emphysema finding on CT, without significant lung function decline. After propensity score matching, although univariable survival analysis showed that increased RV/TLC might be a risk factor of survival in patients with IPF, it was not analysed as an independent risk factor.

In the patients with IPF, TLC and functional residual capacity did not decrease in those with mild IPF but decreased in moderate-to-severe IPF cases[11]. Air trapping and pulmonary hyperinflation are usually accompanied by airway diseases such as COPD. A recent study has suggested that static hyper-trapping might be related to poor clinical course in patients with airway diseases[12,13]. However, only a few studies have evaluated the effects of air trapping in patients with ILD. Compared with IPF, chronic hypersensitivity pneumonitis shows worse airway resistance and increased RV, TLC, and RV/TLC[14]. In this study, regarding IPF, increased RV/TLC could account for 34.4%, which could not be ignored. It can be an indicator that should be checked to understand and manage patients' lung condition.

Recent studies on IPF have shown that older age, male sex, low baseline PFT results, and weight loss are related to poor prognosis of IPF[4,15,16]. Antifibrotic treatment with pirfenidone or nintedanib has been shown to improve survival outcomes through reduced lung function decline and acute exacerbation[17–19]. Currently, the main treatment strategy is early detection of IPF and maintenance of antifibrotic agent treatment regimens[20]. In the context of antifibrotic agents, a previous study reported that 34.5% of patients underwent dose adjustments during treatment period[4]. In our study, the maintenance duration was 1–58 months. Twenty-two of 55 (45.5%) patients were maintained on a full dose of pirfenidone (600 mg; three times a day), whereas 43 of 55 (78.2%) experienced dose reduction or withdrawal.

Acute exacerbation of IPF is fatal; patients with airway diseases such as asthma or COPD also experience acute exacerbation. However, patients with asthma or COPD experiencing acute exacerbations require fewer intensive treatments[21]. Although lung function tests are usually categorised into obstructive and restrictive lung defects, mixed lung defects have both obstructive and restrictive physiologies in the real world[22]. However limited data was evaluated in patients with IPF. In this study, air trapping quantified by RV/TLC was negatively related to baseline lung function, including FEV1, FVC, and 1-year follow-up RV/TLC in patients with IPF. It can be elicited that air trapping might affect parameters of the lung function test.

Old age and airflow limitation have been reported to correlate with resting pulmonary hyperinflation[13]. However, in our study, FEV1/FVC and age did not differ significantly between the RV/TLC groups. Our findings showed that static air trapping negatively correlated with lung function in patients with IPF. However, similar to a previous study[20], older age and baseline low lung function test results were significant risk factors for mortality; antifibrotic agents reduced mortality. However, RV/TLC was not an independent factor for survival.

This study has limitations that need consideration. First, this was a single-centre, retrospective study. Further large-scale studies and prospective validations are warranted to evaluate the impact of air trapping in patients with IPF. Second, since this was a retrospective study that retrieved information from electronic medical records (EMR), work-ups including serologic bio-markers and 6-min walking tests were not evaluated concurrently. Third, none of the patients in our study were treated with bronchodilators. Therefore, to evaluate whether hyperinflation in patients with IPF could be a treatable trait, additional longitudinal follow-ups with interventions are needed.

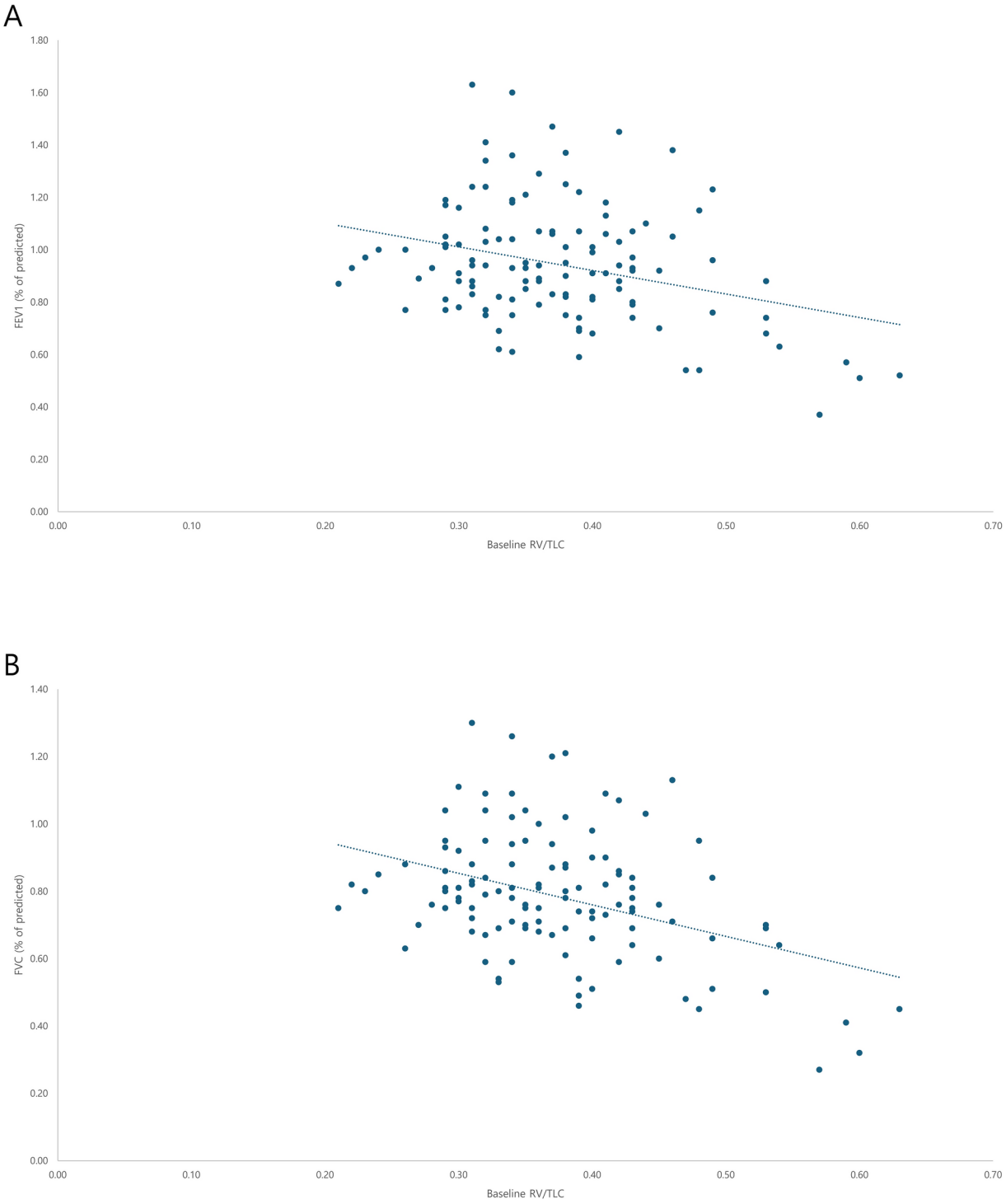

Fig. 1. Dot plot between various parameters. (**A**) between baseline RV/TLC ratio FEV1. (**B**) between RV/TLC ratio and FVC. (**C**) between RV/TLC ratio and FEF 25–75%. (**D**) between baseline RV/TLC ratio and follow-up RV/TLC after 1 year. *FEF* Forced expiratory flow, *FEV1* Forced expiratory volume in 1 s, *FVC* Forced vital capacities, *RV/TLC* Residual volume/total lung capacities ratio.

However, our study is valuable as it is the first to assess increased RV/TLC in patients with IPF. In addition, we analysed clinical course including CT image, lung functions, and mortality according to RV/TLC in patients with IPF.

In summary, emphysema observed on CT might be related to air trapping on the PFT of patients with IPF. FVC and RV/TVC might be negatively correlated. Moreover, elevated RV/TLC might also be related to poor prognosis in patients with IPF.

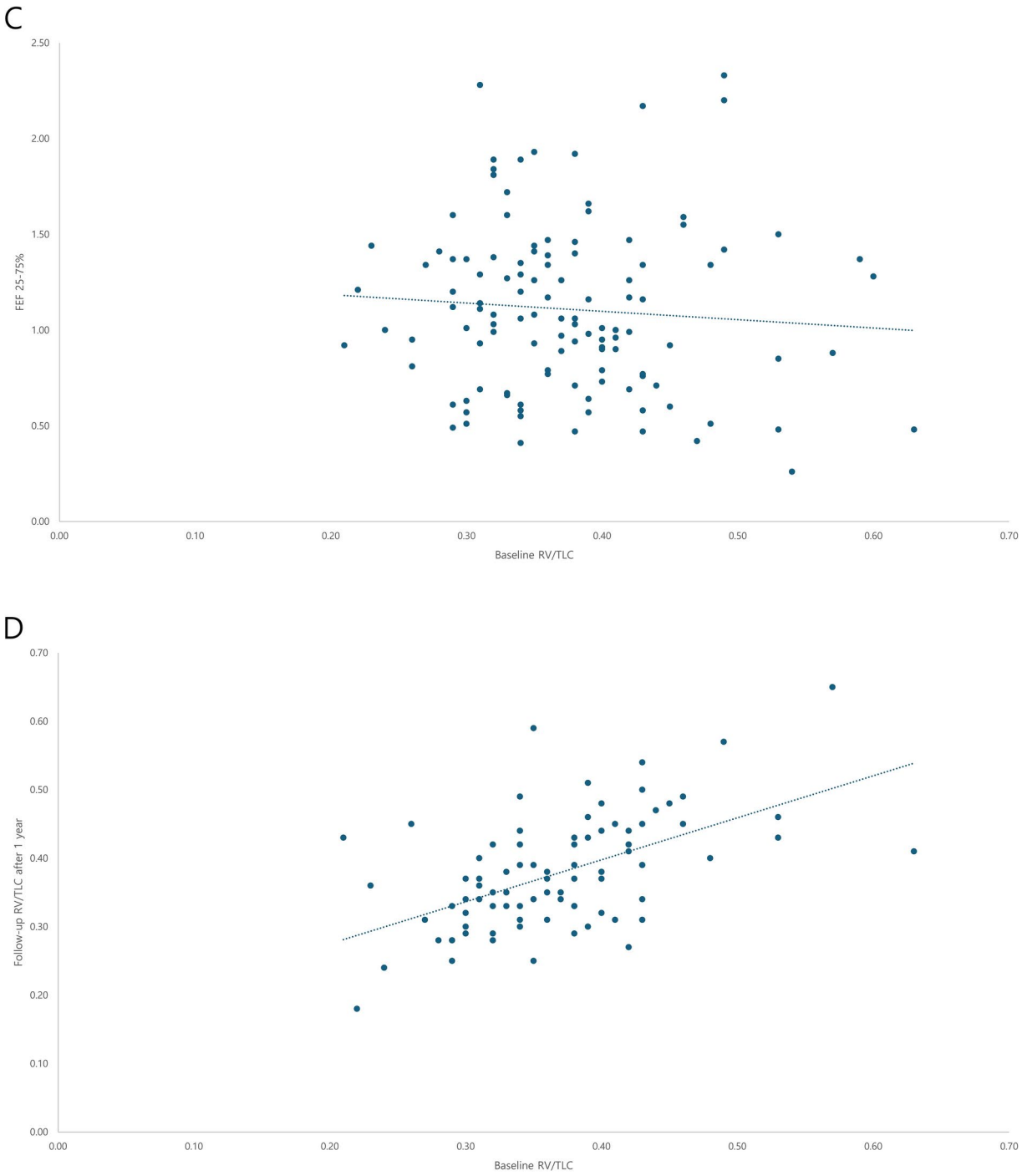

Figure 1. (continued)

Methods

Study design and patients

This retrospective study analysed the clinical data of 257 patients diagnosed with IPF at a tertiary medical centre in South Korea between January 2011 and December 2020. This study analysed the prognostic factors of IPF using a case–control design. Patients were excluded from the study based on the following exclusion criteria: (1) 46 patients who did not show usual interstitial pneumonia (UIP) patterns that met the Society consensus definition of the official American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/ and Latin American Thoracic Society statement[23]; and (2) 89 patients with confirmed connective tissue-related ILD or follow-up loss without evaluation or incomplete medical records (Fig. 4). A total of 122 patients were included in the study.

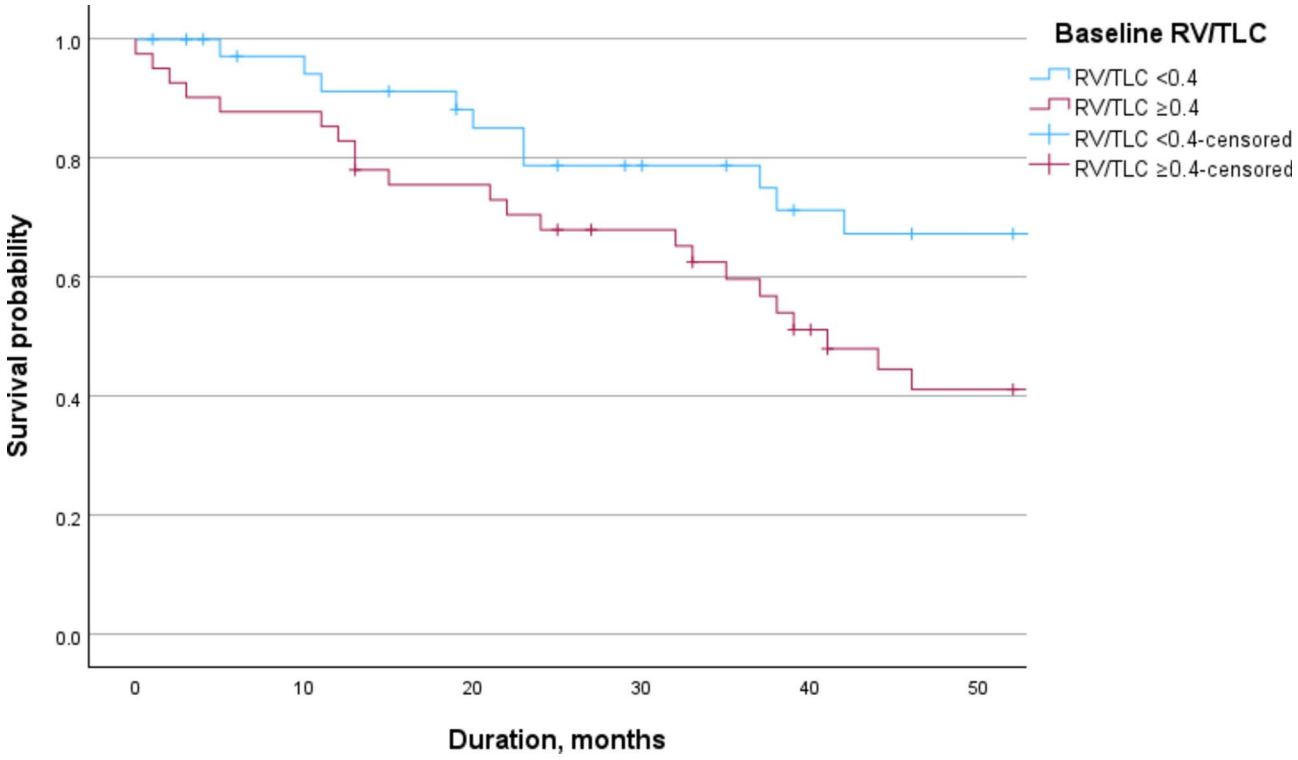

Fig. 2. Kaplan–Meier curve according to RV/TLC ratio.

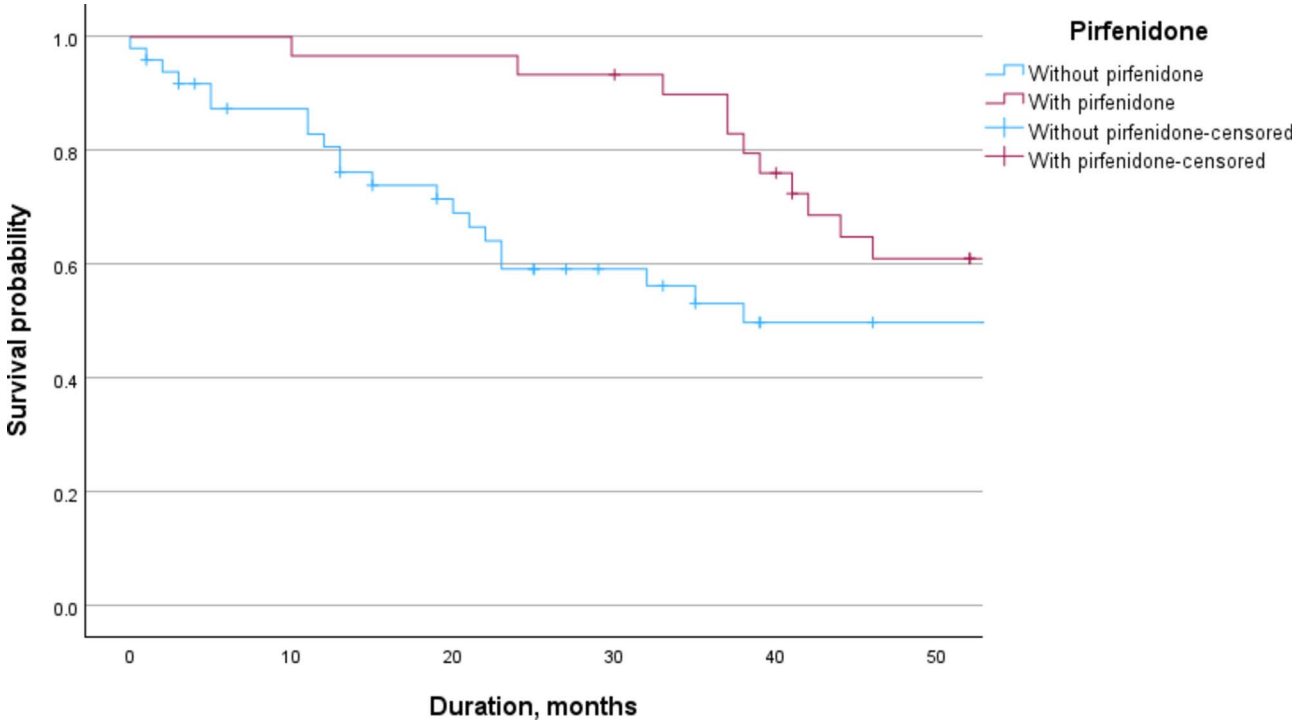

Fig. 3. Kaplan–Meier curve according to pirfenidone.

In the study, we categorised air trapping according to RV/TLC ratio; the cut-off value of air trapping was RV/TLC ≥ 0.40[7]. In this study, we used a case–control design in the context of with and without air trapping. Regarding comparison according to the RV/TLC group, propensity score matching was performed. Data of a total of 79 patients were included in the final analysis (Fig. 4). The two groups were compared in terms of

	Univariable			Multivariable		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.052	1.004–1.102	0.033	1.083	1.017–1.153	0.013
Female sex	0.832	0.413–1.680	0.609	0.803	0.343–1.879	0.612
Pirfenidone treatment	0.443	0.221–0.886	0.021	0.385	0.176–0.840	0.016
FVC (% of predicted)	0.955	0.937–0.973	< 0.001	0.949	0.923–0.977	< 0.001
DL_{CO} (% of predicted)	0.976	0.960–0.991	0.002	0.993	0.975–1.011	0.453
Increased RV/TLC	1.753	1.001–3.411	0.034	1.393	0.628–3.088	0.415

Table 3. Cox regression analysis of all-cause mortality after propensity score matching. *HR* Hazard ratio, *CI* Confidence interval, *FVC* Forced vital capacity, DL_{CO} Diffusion capacity of carbon monoxide, *TLC* Total lung capacity, *RV* Residual volume.

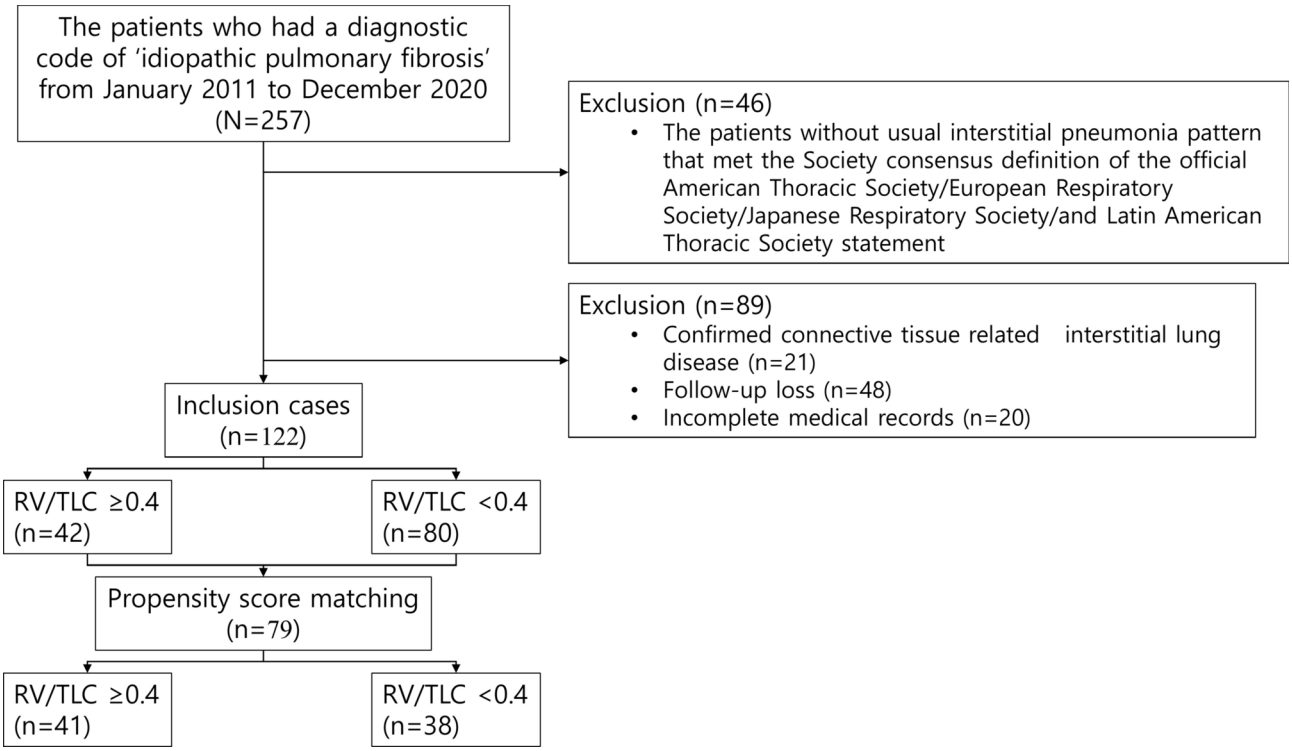

Fig. 4. Flow diagram of the study population.

baseline characteristics, 1-year lung function changes, and survival prognosis. Considering CT emphysema, we categorised emphysema as present or absent. Emphysema grade was defined by a pulmonary radiologist based on the characteristics of low-attenuation areas as follows: grade 0, no low attenuation area; grade 1, > 5 mm of low attenuation area; grade 2, > 10 mm of low attenuation area; grade 3, > 10 mm of low attenuation area and adjacent to or indistinguishable from each other; and grade 4, absence of normal lung parenchyma[24]. Grade 0 was defined as the absence of emphysema and grades 1–4 as the presence of emphysema.

Data collection

Data were collected and analysed retrospectively. The following data were obtained from the patients' electronic medical records, recorded, and analysed: (1) demographic characteristics including sex, age, height and weight, body mass index, comorbidities, and smoking history; (2) results of lung function tests: FVC (L and % of predicted), DL_{CO} (mL/mmHg/min and % of predicted), FEV1/FVC, TLC (% of predicted), RV (% of predicted), and RV/TLC ratio; (3) radiologic characteristics of chest CT including UIP, traction bronchiectasis, and presence or absence of emphysema; (4) treatment with antifibrotic agent pirfenidone, maintenance dose, history of withdrawal, dose reduction, and administration duration; (5) prescription of inhaler at the medical centre (6); and follow-up periods and survival records.

Statistical analysis

Regarding comparison according to the RV/TLC group, propensity score matching was performed including age, sex, pirfenidone treatment, FVC (%), and DL_{CO} (%) as predictors. Data are presented as frequencies (%) for categorical variables and mean (±standard deviation [SD]) for continuous variables. Chi-square test was performed to evaluate the association between two nominal variables. Student's t-test was used for descriptive analysis. Pearson's correlation coefficient was used to analyse the association between two continuous variables. Kaplan–Meier curves were used to visualise survival and log-rank tests were used to compare survival rates according to the aforementioned factors. Cox regression analysis was used to evaluate the prognostic factors. All variables from the univariate analysis were fitted into the multivariate analysis because factors, including lung function and age, are important factors that must be adjusted for to evaluate the impact of air trapping. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA).

Data availability

Data supporting the findings of this study are not openly available because consent to share the data was not obtained from the participants. However, the datasets used and analysed in the current study are available from the corresponding author upon reasonable request.

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Author contributions

THK: Conceptualization (lead), data curation (lead), formal analysis (lead), methodology (equal), visualization (lead), writing the original draft (lead), and writing the review and editing (lead). MK: methodology (equal); writing, review, and editing (equal). SHY: methodology (equal); writing, review, and editing (equal). HJK: formal analysis (supporting); writing, review, and editing (equal). YSK: Conceptualization (supporting); writing—

review and editing (equal). JSP: Conceptualization (lead), writing—review, and editing (equal). SHP: Conceptualization (lead), formal analysis (equal), writing—review and editing (lead).

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval
The study protocol was reviewed and approved by the Institutional Review Board of the Keimyung University College of Medicine (approval no. 2023-07-087-001). The study conformed to the tenets of Declaration of Helsinki (revised edition 2013). The requirement for informed consent was waived by IRB of Keimyung University College of Medicine because of the retrospective nature of the study.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-91060-6.

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