SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2025; 42 (4): 17187 DOI: 10.36141/svdld.v42i4.17187

Does combined pulmonary fibrosis and emphysema syndrome affect response to antifibrotic therapy and survival? A single-center retrospective cohort study

Nazli Huma Teke[1], Meltem Agca[1], Ayla Turkar[2], Tulin Sevim[3], Eylem Tuncay[4], Sinem Gungor[1], Elif Yıldırım[1], Fatma Ozbaki[1], Baran Gundogus[1], Sibel Arınc[1], Huriye Berk Takır[1], Ipek Ozmen[1]

[1]Department of Pulmonology, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey; [2]Department of Radiology, Umraniye Training and Research Hospital, Istanbul, Turkey; [3]Department of pulmonology, Istanbul Health and Technology University, Istanbul, Turkey; [4]Department of pulmonology, Sancaktepe Prof. Dr. Ilhan Varank State Hospital, Istanbul, Turkey

Abstract. *Objective:* Combined pulmonary fibrosis and emphysema (CPFE) is a clinicoradiological syndrome characterized by upper lobe emphysema and lower lobe fibrosis, most commonly associated with idiopathic pulmonary fibrosis (IPF). This study compared the clinical characteristics, functional parameters, and mortality of patients with CPFE and IPF who received antifibrotic therapy. *Methods:* Between October 2015 and August 2022, patients with IPF treated with antifibrotics for at least 6 months were retrospectively evaluated and divided into two groups: CPFE (emphysema present) and IPF (emphysema absent). Demographic data, antifibrotic therapy, functional parameters before and after treatment (FEV1%, FVC%, DLco %), clinical outcomes (hospital admissions, mortality) were compared. *Results*: Of the 204 patients with IPF, 90 (44%) had CPFE. CPFE patients were more often male, had greater smoking history, higher pack-years, and more lung cancer than IPF patients ($p < 0.001$ for all). Post-treatment FEV1% and FVC% did not significantly differ between the groups, whereas DLco% declined significantly in both ($p < 0.001$ and $p = 0.002$). DLco% decreased more in IPF than CPFE, but the difference was not statistically significant [–3 (–11–3) vs. –0.43 (–1.1–0.2), $p = 0.36$]. The hospital admission rates were similar. Independent risk factors for mortality included CPFE diagnosis (HR: 1.73, 95% CI: 1.06–2.83, $p = 0.029$), low FVC% (HR: 0.970, 95% CI: 0.96–0.98, $p < 0.001$), and device use (long-term oxygen therapy [LTOT] or home non-invasive mechanical ventilation [NIMV]) (HR: 2.48, 95% CI: 1.50–4.09, $p < 0.001$). Mean survival was shorter in patients with emphysema than in those without emphysema (5.08 vs. 5.68 years, $p = 0.08$). *Conclusions:* Despite a decline in DLco%, changes remained below the futility threshold. Clinical outcomes and mortality were comparable. CPFE diagnosis, low FVC%, and LTOT/NIMV use independently predicted higher mortality.

Key words: antifibrotic treatment, combined pulmonary fibrosis and emphysema, idiopathic pulmonary fibrosis

Introduction

Combined pulmonary fibrosis and emphysema (CPFE) is a clinico-radiological syndrome in which emphysema and fibrosis are present in the upper and lower lung zones, respectively(1). Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing interstitial lung disease of unknown etiology that histopathologically and radiologically exhibits the features of "usual interstitial pneumonia"(2). While CPFE is

Received: 20 May 2025
Accepted: 22 August 2025
Correspondence: Nazlı Hüma Teke, MD
Department of Pulmonology, Basakşehir Cam and Sakura City Hospital
Kayabası Mah., Mimar Sinan Cad., No: 1, Basaksehir, 34480 Istanbul, Turkey
E-mail: nazliteke@hotmail.com
ORCID: 0000-0003-2380-5410

most commonly associated with IPF, it has also been reported in other fibrotic lung diseases, such as connective tissue disease-associated interstitial lung disease and fibrotic hypersensitivity pneumonitis (1,3). The estimated prevalence of CPFE in IPF ranges from 8% to 45% (4–8). This variance is attributed to differences in emphysema definitions across studies, as well as the genetic predispositions and smoking histories of the patients included. Numerous studies highlight distinct demographic, clinical, functional, and prognostic features of CPFE compared to IPF(1,5–9). In almost all of these studies, CPFE has been reported predominantly in males and in heavy smokers. These patients exhibit worse quality of life and higher rejection rates post-lung transplantation compared to IPF patients (5,9). Functionally, CPFE patients have higher forced vital capacity (FVC) but lower carbon monoxide diffusion capacity (DLco) than IPF patients (5,10). CPFE is also associated with increased risks of lung cancer and pulmonary hypertension, which adversely affect prognosis (11–13). In the literature, while some studies report higher mortality in CPFE compared to IPF, others show no difference or even better survival (6,8,14,15). Treatment options for CPFE are limited and include smoking cessation, bronchodilators for obstructive lung disease, oxygen therapy for hypoxemia, and lung transplantation in select cases (16). Antifibrotic drugs were first used in Japan in 2008 and subsequently approved in Europe and the United States in 2014. Numerous studies have demonstrated that antifibrotic therapies (pirfenidone or nintedanib) slow the decline in lung function, reduce the risk of acute exacerbations, slow disease progression, and prolong progression-free survival in IPF patients(17,18). However, few studies have compared clinical, functional, and mortality outcomes of antifibrotic therapy between CPFE and IPF patients. The present study aimed to investigate whether clinical outcomes, functional parameters, and mortality differ between CPFE and IPF patients following antifibrotic therapy.

Materials and methods

This single-center, retrospective, observational cohort study was conducted at a tertiary care hospital for respiratory diseases. All data were obtained from the hospital's electronic medical records. Approval was obtained from the Non-Invasive Clinical Research Ethics Committee under protocol code 116. 2017. R-242.

Patient selection

Patients diagnosed with IPF between October 2015 and August 2022 who received antifibrotic treatment (pirfenidone or nintedanib) for at least 6 months were included. Participants were divided into two groups: CPFE (emphysema present) and IPF (emphysema absent). Follow-up continued until March 2023, with a mean follow-up duration of 4.09 years (±1.80).

IPF diagnosis

The diagnosis of IPF was made according to the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society statement (ATS/ERS/JRS/ALAT) guideline criteria: a histopathological or radiological pattern of usual interstitial pneumonia (UIP) and exclusion of other known causes of pulmonary fibrosis (autoimmune diseases and environmental or occupational exposures) (2).

CPFE diagnosis

CPFE was defined as IPF with radiological evidence of emphysema (centrilobular, paraseptal, or mixed patterns) in the upper lung zones (1). Emphysema was assessed using thoracic or high-resolution computed tomography (HRCT) images archived in the hospital's Picture Archiving and Communication System. All scans were performed using a 16-slice Toshiba Alexion 16 CT scanner (Toshiba Corporation, Tokyo, Japan), with slice thicknesses of 4 mm (standard CT) or 1 mm (HRCT). Emphysema was defined as low-attenuation areas in the upper zones with well-defined borders, wall thickness <1 mm or absent walls, and/or multiple blebs >1 cm compared to adjacent normal lung parenchyma(1). Emphysema types were classified into three categories: centrilobular, paraseptal, and mixed (centrilobular + paraseptal). Emphysema scoring was performed using a modified Goddard Score to account for the coexistence of emphysema and fibrosis(19). Scoring was based on the proportion of emphysematous lung parenchyma at axial slices above the highest point where the ascending aorta appeared. Four grades were defined by percentage of affected parenchyma (Figure 1). These were:

- Score 0: no abnormality
- Score 1: 1-25%; mild (minimal apical emphysema)

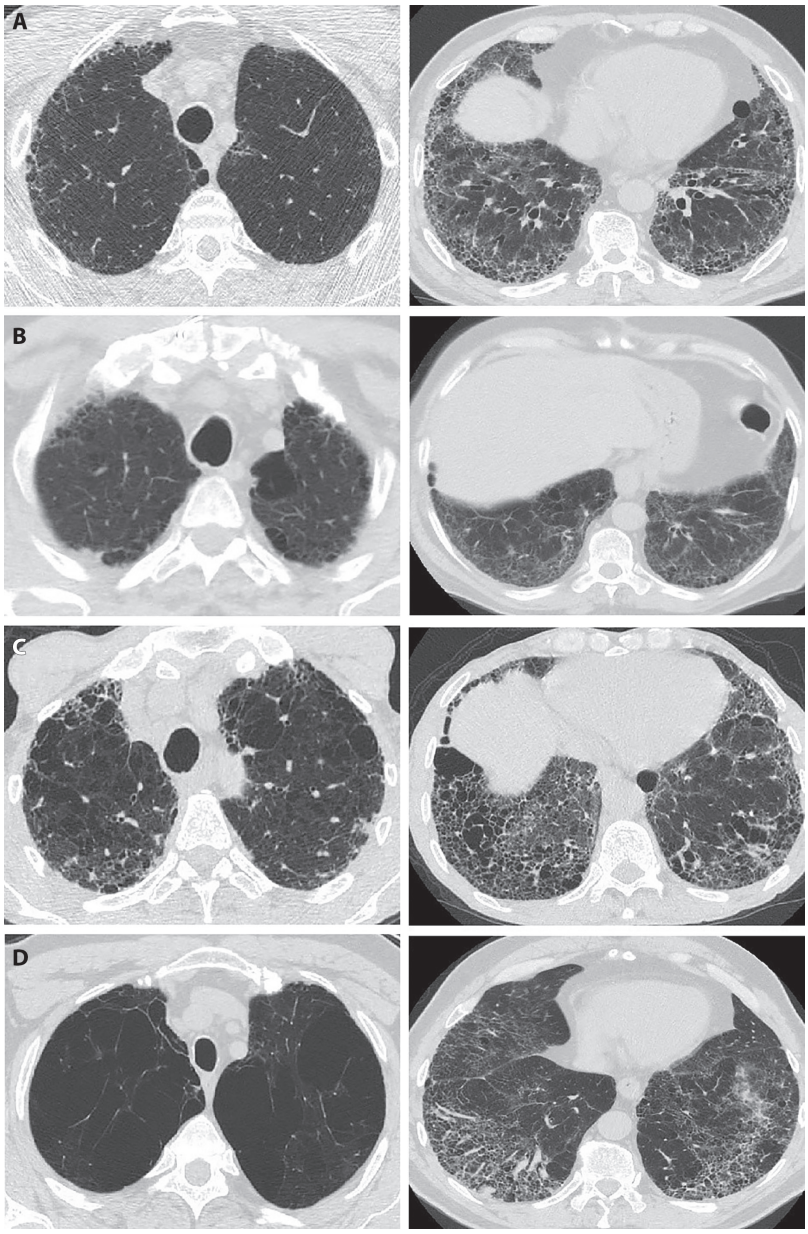

Figure 1. High-resolution computed tomography: Score 1, high-resolution computed tomography in 66-year-old male 22 p/y current(a);Score 2 72-year-old male 40p/y former(b),;score 3, 74-year-old male 20p/y former (c); Score 4, 57-year-old male with lung cancer, 40p/y current (d)

- Score 2: 26%–50%, moderate
- Score 3: 51%–75%, marked
- Score 4: ≥76, severe (parenchyma largely replaced by emphysema)

For patients with emphysema scores between 26% and 75%, to minimize error, each axial slice was divided into four equal quadrants per lung by imaginary straight lines, and the emphysematous/normal parenchyma ratio was classified as 26%–50% or 51%–75%.

All radiological assessments were performed by an experienced thoracic radiologist and a pulmonologist. There were no disagreements between the two doctors regarding emphysema. The final diagnosis of IPF and CPFE was established by a multidisciplinary team (MDT)." Our institution is a tertiary referral center where weekly MDT meetings are

held with a pulmonologist, a rheumatologist, and a thoracic radiologist experienced in interstitial lung diseases. All diagnoses and treatment decisions, including those for IPF and CPFE, are made during these meetings

Inclusion criteria

- Definitive diagnosis of IPF (radiological and/or surgical biopsy confirmation, MDT assessment) (Figure 2).

Exclusion Criteria

- Absence of thoracic CT or HRCT images
- Fibrosis pattern other than UIP
- Incomplete data
- <6 months of antifibrotic therapy (discontinued by patient choice or due to adverse effects)
- Death before completing 6 months of therapy
- Patients receiving another diagnosis during follow-up (Figure 2).

Demographic characteristics (age, sex), smoking status (current/former/never), pack-years, comorbidities (hypertension, diabetes mellitus, chronic lung diseases, lung cancer, etc.), method of IPF diagnosis (surgical biopsy vs. radiological), and device use (long-term oxygen therapy [LTOT], home non-invasive mechanical ventilation [NIMV]) were compared between the two groups. Antifibrotic treatments (pirfenidone, nintedanib), treatment-related side effects, and treatment switches (treatment switches between pirfenidone and nintedanib when no effect was achieved with one of the antifibrotic drugs or when side effects were encountered) were recorded. Pulmonary function parameters (forced expiratory volume in 1 second [FEV1]%, FVC%, and DLco%) measured before and at least 6 months after

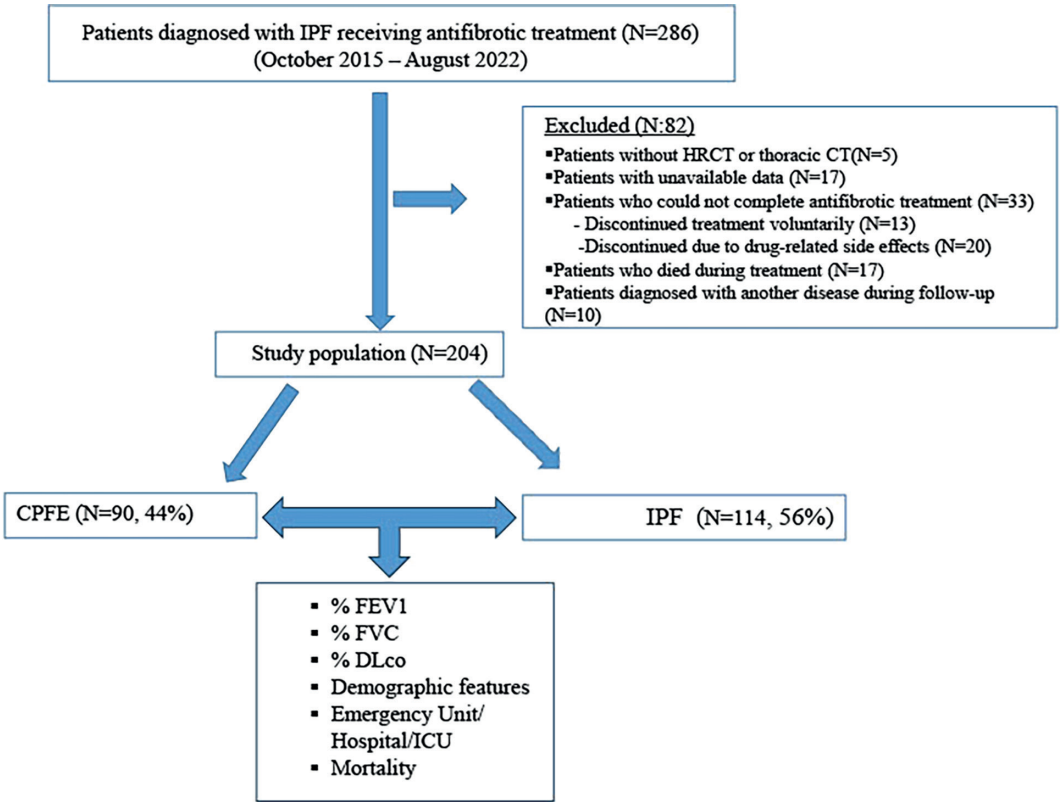

Figure 2. Flow Chart. *Abbrevations:* CT: computed tomography; Dlco, diffusing capacity of the lungs for carbon monoxide; FEV1%, forced expiratory volume in 1 second (percentage); FVC, forced vital capacity; ICU, intensive care unit; IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema; HRCT, high-resolution computed tomography

treatment were compared between the two groups. Clinical outcomes, including emergency department visits, number of hospitalizations, hospitalization setting (ward or intensive care), and mortality, were also compared.

Statistical analysis

All statistical analyses were performed using SPSS 27 (IBM Corp., Armonk, NY, USA). Kolmogorov–Smirnov test was used to assess the distribution of continuous variables. Normally distributed continuous variables were presented as mean ± standard deviation; non-normally distributed variables as median (interquartile range). Categorical variables were expressed as counts and percentages. Relationships between categorical variables were analyzed using Pearson's chi-square or Fisher's exact test. Intergroup comparisons of normally distributed continuous variables were conducted with the Student's t-test, while the Mann–Whitney U test was used for non-normally distributed variables. Within-group pre- and post-treatment comparisons of continuous variables were conducted with the paired-samples t-test for parametric data or the Wilcoxon signed-rank test for non-parametric data. Spearman's correlation coefficient was employed to assess relationships between two non-normally distributed quantitative variables. Survival analyses were performed using the Kaplan–Meier method, and group survival curves were compared using the log-rank, Breslow, and Tarone–Ware tests. Cox regression analysis with backward stepwise selection was used to identify mortality-related factors. In the analysis, variables included CPFE diagnosis, age, baseline FVC%, baseline DLco%, and home device use (LTOT/NIMV). Results were considered significant at $p < 0.05$ (95% confidence interval).

Results

A total of 204 patients who met inclusion criteria and received antifibrotic therapy were divided into two groups: CPFE (n = 90) and IPF (n = 114). Although the mean age was similar in both groups, the proportion of males (92% vs. 63%, $p < 0.001$), smokers (96% vs. 55%, $p < 0.001$), and median pack-years (40 vs. 3 pack-years, $p < 0.001$) were significantly higher in the CPFE group. The prevalence of lung cancer was also significantly greater in the CPFE group (16% vs. 3%, $p < 0.001$). During follow-up, 33% (n = 67) of all patients used LTOT and 4% (n = 9) used home NIMV, with no significant difference in device use between groups (Table 1).

Thoracic CT and HRCT findings

Among the 90 CPFE patients, the most common emphysema phenotype was mixed centrilobular + paraseptal (n = 46, 23%), followed by paraseptal (n = 41, 20%) and centrilobular alone (n = 3, 1%) (Figure 3a). When the emphysema burden was scored, 52 patients (25%) had ≤25% involvement, 20 (10%) had 26%–50%, 10 (5%) had 51%–75%, and 8 (4%) had ≥76% (Figure 3b).

Spearman's correlation analysis showed a moderate positive correlation between emphysema score and pack-years ($r = 0.59$, $p < 0.001$) and a weak negative correlation between emphysema score and DLco% ($r = -0.19$, $p = 0.006$) (Table 2).

Antifibrotic treatments

The majority of patients (79%, n = 159) remained on their initial antifibrotic agent: pirfenidone was used in 56%, and nintedanib in 44%. There were no statistically significant differences between groups in rates of pirfenidone versus nintedanib use or drug switches ($p = 0.07$ and $p = 0.12$, respectively) (Table 1).

Pulmonary function tests before and after treatment

At the end of treatment, there were no significant changes from baseline in mean FEV1% or FVC% in either group. However, median DLco% declined significantly in both CPFE and IPF groups ($p < 0.001$ and $p = 0.002$, respectively). When the delta values of these parameters were compared, no statistically significant differences were observed for any parameter (Table 3).

Clinical Outcomes (Emergency Department Visits, Hospitalizations, Intensive Care Unit [ICU] Admissions)

When emergency department visits, hospitalizations, and ICU admissions during the last year of follow-up were compared, no significant differences were observed between the CPFE and IPF groups (all $p > 0.05$) (Table 4).

Table 1. Baseline characteristics in the over all study population

	Total (N=204)	**CPFE (N=90, 44%)**	**IPF (N=114, 56%)**	**p**
Age, years, mean±SD	70 ±8	69±8	70±8	0.26[a]
Sex, Male, n (%)	155(76)	83(92)	72 (63)	< **0.001**[b]
Smoking history*, *n (%)*				< **0.001**[b]
- Current /Former	124(75)	77(96)	47(55)	
- Never	42(25)	3(4)	39(45)	
Pack-years of cigarette smoking**, median (IQR)	25(0-40)	40 (30-50)	3 (0-30)	< **0.001**[c]
BMI, kg/m^2, median (IQR)	28 (26-31)	28 (25-31)	28 (26-32)	0.14[c]
Comorbidities, n (%)	190 (93)	84(93)	106(93)	0.92[b]
- Hypertension	121(59)	54(60)	67(59)	0.85
- Diabetes	62(30)	27(30)	35(31)	0.91
- Chronic lung diseases	103(51)	48(53)	55(48)	0.47
- Anxiety/mood disorders	47(23)	18(20)	29(25)	0.36
- Malignite	26(13)	19(21)	7(6)	0.003
- Lungcancer	17(8)	14(16)	3(3)	< **0.001**
- Peripheral vascular disease	15(7)	7(8)	8(7)	0.83
- Cerebrovascular diseases	17(8)	7(8)	10(9)	0.78
- Atrial fibrillation/flutter	34(17)	18(20)	16(14)	0.25
- Cardiovascular diseases	82(40)	37(41)	45(40)	0.81
- Reflux/gastritis	22(11)	8(9)	14(12)	0.43
Diagnosis, n (%)				0.41[b]
- Surgical lung biopsy	32(16)	12(13)	20(17)	
- Without surgical lung biopsy	172 (84)	78(87)	94(83)	
Ventilation support, n (%)				
- LTOT	67(33)	33(37)	34(30)	0.30[b]
- Home NIMV	9(4)	5(6)	4(3)	0.51[b]
Pulmonary rehabilitation, n (%)	40 (20)	17 (19)	23(20)	0.81[b]
Antifibrotic therapy, n (%)				0.07[b]
- Pirfenidone	114 (56)	44 (49)	70 (61)	
- Nintedanib	90 (44)	46 (51)	44 (39)	
Antifibrotic therapy switch, n (%)	43 (21)	14(16)	29(26)	0.12[d]
- No switch in antifibrotic therapy	159 (79)	75 (83)	84 (74)	
- Switch from pirfenidone to nintedanib	24 (56)	6 (7)	18 (16)	
- Switch from nintedanib to pirfenidone	19 (44)	8 (9)	11 (10)	
- Follow up year	4.09 (1.80)	3.92 (1.61)	4.23 (1.93)	0.21[a]

Results are presented as n (%), median (IQR: interquartilerange), or mean (SD: Standard deviation). *Smoking status was un available for 38 patients; **pack-year data was unavailable for 55 patients. [a] Student's t-test, [b] Pearson'schi-squared test, [c] Mann–Whitney U test, [d] Fisher'sexact test. *Abbreviations:* BMI, body mass index; NIMV, home non-invasive mechanical ventilation; LTOT, long-term oxygen therapy; IPF, idiopathic pulmonary fibrosis; CPFA, combined pulmonary fibrosis and emphysema.

Mortality and survival

The mean follow-up period was 4.09 (±1.80) years, and 33% (n = 67) of the patients died during the follow-up period. Median overall survival for the entire cohort was 6.76 years. The 1-year survival rate was 92%, the 3-year survival rate was 76%, and the 5-year survival rate was 57% (Figure 4a). When the groups were analyzed separately; median survival was 5.08 years in the CPFE group, with 1-, 3-, and

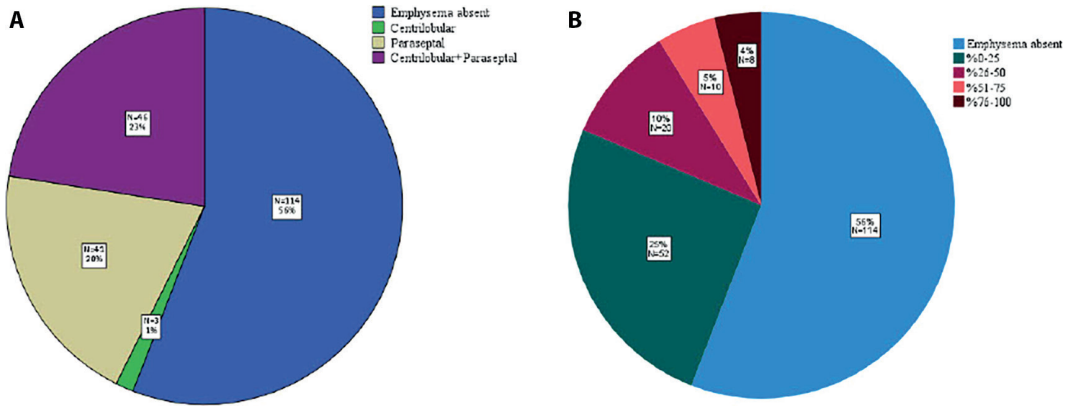

Figure 3. Emphysema Types and Scoring. A) Emphysema Types. B) Emphysema Scoring

Table 2. Correlation analysis between emphysema score and smoking pack-years and pulmonary function tests[a]

	Emphysema score	
	R	*p*
Smoking package years	0.592	< **0.001**
FVC%	0.081	0.25
DLco%	-0.194	**0.006**

Abbrevations: FVC, forced vital capacity; DLCO, diffusing capacity for carbonmonoxide. [a]Spearman correlation

5-year survival rates of 90%, 73%, and 47%, respectively; while median survival was 5.68 years in the IPF group, with 1-, 3-, and 5-year survival rates of 93%, 78%, and 64%, respectively.

Kaplan–Meier survival curves for both groups are shown in Figure 4b. Although median survival was shorter in the CPFE group (5.08 vs. 5.68 years), the difference was not statistically significant according to log-rank, Breslow, or Tarone–Ware tests ($p > 0.05$) (Figure 4). The Cox proportional hazards model was highly significant ($p < 0.001$). In the final backward stepwise model, CPFE diagnosis, lower baseline FVC%, and home device use (LTOT/NIMV) were independently associated with increased mortality. Specifically, CPFE diagnosis was associated with a 1.73-fold increase in mortality risk, each 1% decrease in baseline FVC% was associated with a 3% increase in risk, and device use was associated with a 2.48-fold increased risk (Table 5).

Discussion

In the present study, functional status, clinical features, and mortality after antifibrotic therapy were compared between CPFE and IPF patients. Both groups showed a significant decline in predicted DLco% after treatment compared to baseline. However, this decrease did not exceed the cut-off values established in the national health bulletin for discontinuing antifibrotic therapy. The 6-month changes in pulmonary function, emergency department visits, hospitalizations (ward and ICU), and mortality rates were similar between groups. Across all patients, CPFE diagnosis, lower baseline FVC, and device use for respiratory failure were risk factors associated with increased mortality.

As in almost all previous studies, our CPFE cohort comprised predominantly male patients with heavy smoking histories compared to the IPF group (1,5–8). Smoking is well known to be a major risk factor for both emphysema and fibrosis(20). In a recent large-scale study, smoking doubled the risk of CPFE among interstitial lung disease patients, and, similarly to our findings, a weak but significant correlation was observed between emphysema score and pack-years(21). Schwartz et al. demonstrated a strong relationship between increasing pack-years and impaired gas exchange (reflected by low DLco) (22). Consistently, the present study also showed that higher pack-years were associated with higher emphysema scores and lower DLco. Chae et al. reported that CPFE patients who continued smoking experienced more rapid disease progression compared to those who quit (23). Moreover, longitudinal studies have documented progressive functional decline and structural damage in both diseases over time(10). Therefore, smoking cessation in these patients is crucial to mitigate the expected functional loss. The incidence of lung cancer in IPF is higher than in the general population(24), and emphysema

Table 3. Comparison of delta values indicating response to antifibrotic therapy and pulmonary function tests between patients with CPFE and IPF

	CPFE (N = 90)			IPF (N = 114)		
	Before treatment	6th month of teratment	*p*	Before treatment	6th month of teratment	*p*
FEV1%, median (IQR)	81(69-93)	80 (70-97)	0.78[a]	82 (66-94)	81(66-94)	0.46[a]
FVC % predicted, mean±SD	76.5±17.7	78.1±20.4	0.42[b]	76.6 (19.3)	74.2 (21.7)	0.10[b]
DLco % predicted, median(IQR)	50 (40-61)	44.5 (35-54.8)	**<0.001**[a]	55.5 (43.2-67.8)	50 (41-61)	**0.002**[a]
FEV1 % Δ	-1(-4-5)			-1(-8-6)		0.69[c]
FVC, % Δ	-0.04 (0.35)			-0.05(0.32)		0.79[d]
DLco, % Δ	-0.43(-1.1-0.2)			-3(-11-3)		0.36[c]

[a]Wilcoxon test; [b]Paired samples t-test; [c]Mann–Whitney U test; [d]Student's t-test. *Abbreviations:* IPF, idiopathic pulmonary fibrosis; CPFA, combined pulmonary fibrosis and emphysema; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLco, diffusing capacity for carbonmonoxide

Table 4. Emergency department visits, hospital and intensive care unit admissions in patients with CPFE and IPF

	Total	CPFE	IPF	p
Emergency department visits, median (IQR)	0 (0-2)	0 (0-3)	0 (0-1)	0.14[a]
Hospital admission, median (IQR)	1 (0-3)	1(0-3)	1 (0-3)	0.86[a]
Intensive care uni tadmission, median (IQR)	0 (0-1)	0 (0-1)	0 (0-5)	0.77[a]
Mortality, n (%)	67 (33)	34 (38)	33 (29)	0.74[b]

Results are presented as n (%) or median (IQR: interquartile range). [a] Mann–Whitney U test; [b] Pearson'schi-squared test. *Abbreviations:* CPFA, combined pulmonary fibrosis and emphysema; IPF, idiopathic pulmonary fibrosis

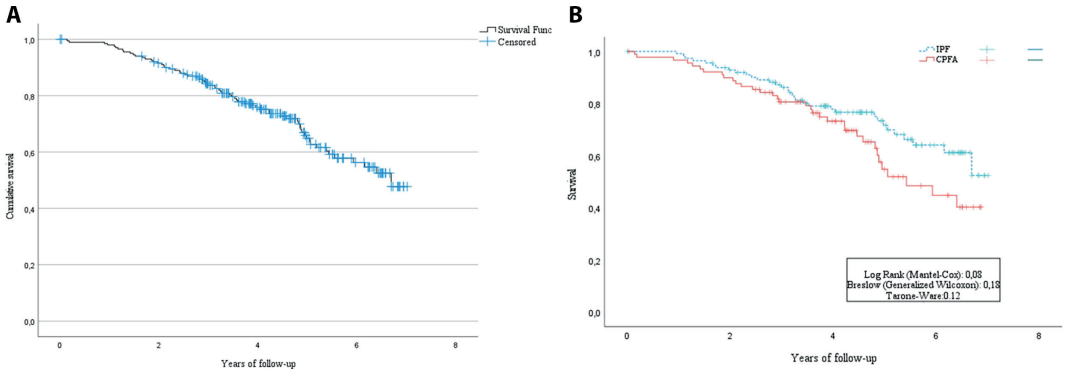

Figure 4. Kaplan-Meier Survival Curves ın The Follow-up Period and Comparison of Both Groups. A) Survival outcomes of the study population based on Kaplan-Meier analysis. B) Comparison of survival outcomes ì between CPFA and IPF groups on Kaplan-Meier analysis. *Abbrevations:* IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema

further increases this risk (25). In line with previous reports, the present study found a higher prevalence of lung cancer in CPFE patients compared to IPF patients. This finding underscores the need for closer surveillance for malignancy in the CPFE population.

Pirfenidone and nintedanib, the antifibrotic agents used in IPF treatment, have been shown to reduce annual FVC decline, decrease exacerbation frequency, and prolong progression-free survival (17,18). In Turkey, pirfenidone has been available since 2014

Table 5. Cox regression analysis of factors associated with mortality in all patients

							95 % CI forExp(B)	
		B	SE	Wald	Sig.	Exp(B)	Lower	Upper
Step 1	CPFE	0.54	.25	4.52	0.03	1.71	1.04	2.81
	Age, years	0.02	0.02	1.06	0.30	1.02	0.98	1.05
	Baseline DLco%	-.00	.01	0.25	0.62	0.99	0.98	1.01
	Baseline FVC %	-.03	.01	15.90	.00	0.97	0.96	0.98
	(LTOT/home NIMV)	0.89	0.26	11.89	0.01	2.4	1.46	4.0
Step 2	CPFE	0.55	.25	4.87	0.03	1.74	1.06	2.85
	Age, years	.01	.02	.90	0.34	1.01	0.98	1.05
	Baseline FVC%	-.03	.01	21.15	0.00	0.97	0.96	0.99
	(LTOT/home NIMV)	.90	.25	12.40	0.00	2.45	1.49	4.04
Step 2	CPFE	0.55	.25	4.78	**0.029**	**1.73**	1.06	2.83
	Baseline FVC%	-.03	.01	20.56	**<0.001**	**0.97**	0.96	0.98
	(LTOT/home NIMV)	0.91	.25	12.67	**<0.001**	**2.48**	1.50	4.09

Abbreviations: CPFA, combined pulmonary fibrosis and emphysema; FVC, forced vital capacity; DLco, diffusing capacity for carbonmonoxide; NIMV, non-invasive mechanical ventilation; LTOT, long-term oxygen therapy.

and nintedanib since 2017. Functional assessments are important for treatment planning, follow-up, and predicting prognosis. While FVC and DLco guide antifibrotic therapy evaluation in IPF, their roles in CPFE remain unclear for several reasons. First, CPFE exhibits distinct functional characteristics from IPF: preserved FVC due to opposing effects of emphysema and fibrosis, and reduced DLco from alveolar–vascular loss (16). Second, the rates of annual functional decline differ between CPFE and IPF. Kurashima et al. reported FVC decline in 71% of IPF patients versus 26% of CPFE patients(7). Akagi et al. found greater functional loss in IPF than CPFE over 1 year (FVC% −8.0 vs. −1.2, $p < 0.001$; DLco −10.7 vs. −3.7, $p = 0.042$), and attributed this to the counterbalancing effects of emphysema and fibrosis in CPFE (10). In our cohort, both groups experienced functional declines by the end of treatment. FVC decline was not significant, whereas DLco decline was significant in both groups. The decline in DLco was greater in the IPF group (−3 vs −0.43, $p = 0.36$), but this difference was not statistically significant ($p = 0.36$). When these post-treatment functional assessments were examined, declines in FVC and DLco did not exceed the national health bulletin's thresholds for defining nonresponse and discontinuation of treatment (≥10% for FVC and ≥15% for DLco). The 6-month treatment evaluation period was selected based on the requirements of national guidelines at the time. Consequently, despite functional decline in both groups, discontinuation of antifibrotic therapy was unnecessary, and treatment was continued (26). Few studies have reported antifibrotic treatment outcomes in CPFE. In a phase 3, double-blind trial conducted across fifteen countries (n = 1,061), subgroup analysis showed that nintedanib significantly reduced annual FVC decline in CPFE patients (27). Another study assessing antifibrotic efficacy at baseline and at 3, 6, and 12 months reported a non-significant 4% decline in DLco over time ($p > 0.05$) (28). Sangani et al. reported no significant functional decline apart from DLco in either CPFE or IPF groups, and noted comparable mortality, suggesting a survival benefit from antifibrotics (7). Studies in which not all patients received antifibrotic therapy reported that the presence of emphysema did not adversely affect mortality (5,12). Consistent with these findings, we observed no difference in mortality between the CPFE and IPF groups. However, CPFE diagnosis, lower baseline FVC, and LTOT emerged as independent risk factors for mortality in the Cox regression model. These discrepancies may stem from heterogeneity in emphysema-fibrosis distribution or patient selection. A recent multicenter investigation recommended that an annual DLco decline of ≥10% should be considered in CPFE patients, whereas an annual FVC decline of ≥5% should guide assessment in IPF patients (29). In our cohort, most CPFE

patients had low emphysema scores and received antifibrotics for less than one year. Future studies should explore longer treatment durations and include patients with more severe emphysema. Oxygen therapy—an indicator of advanced disease—has been previously linked to increased mortality (30). In fact, a multicenter study reported a 2.43-fold higher hospitalization risk among emphysema patients on oxygen therapy compared to those not using oxygen (5). This study has several limitations. First, the study was retrospective and conducted in a single center. Second, pulmonary hypertension—a key prognostic factor in CPFE—was excluded from analysis due to insufficient data. Third of limitations of our study is that the follow-up period for antifibrotic therapy was limited to 6 months due to national health policy regulations at the time. We believe that future studies with longer follow-up periods may provide important additional information. On the other hand, the definitive diagnosis of IPF in all patients, the evaluation of all imaging scans by an experienced radiologist, scoring of emphysema, and the follow-up of the cases by an experienced MDT at a recognized reference center for respiratory diseases are the strengths of the study.

Conclusion

This study evaluated the antifibrotic treatment response, clinical outcomes, and mortality in CPFE and IPF patients. Both CPFE and IPF groups showed significant post-treatment declines in DLco%, though responses were similar overall. These declines remained below the cutoff thresholds for treatment nonresponse, and antifibrotic therapy did not need to be discontinued. Clinical outcomes and survival rates were similar between groups. However, CPFE diagnosis, lower baseline FVC, and home respiratory device use (LTOT/NIMV) were identified as independent risk factors for increased mortality. These findings support the continuation of antifibrotic therapy in CPFE patients and underscore the need for close clinical monitoring and careful management of risk factors in this population.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contribution: NHT: Conceptualization, Methodology, Writing – Original Draft, Supervision; MA: Investigation, Resources, Formal analysis, Writing – Review & Editing; AT: Data curation, Resources; TS: Methodology, Resources, Writing – Review & Editing; ET: Investigation, Resources, Methodology; SG: Data curation, Writing – Review & Editing; EY: Investigation, Resources; FO: Investigation; BG: Data curation; SA: Resources; HBT: Writing – Review & Editing; IO: Writing – Review & Editing, Resources.

References

1. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J. 2005;26(4):586–93. doi:10.1183/09031936.05.00021005.
2. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198(5):e44–68. doi:10.1164/rccm.201807-1255ST.
3. Koo BS, Park KY, Lee HJ, et al. Effect of combined pulmonary fibrosis and emphysema on patients with connective tissue diseases and systemic sclerosis: a systematic review and meta-analysis. Arthritis Res Ther. 2021;23(1):100. doi:10.1186/s13075-021-02494-y.
4. Ryerson CJ, Hartman T, Elicker BM, et al. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. Chest. 2013;144(1):234–40. doi:10.1378/chest.12-2403.
5. Kim HJ, Snyder LD, Neely ML, et al. Clinical outcomes of patients with combined idiopathic pulmonary fibrosis and emphysema in the IPF-PRO registry. Lung. 2022;200(1):21–9. doi:10.1007/s00408-021-00506-x.
6. Kurashima K, Takayanagi N, Tsuchiya N, et al. The effect of emphysema on lung function and survival in patients with idiopathic pulmonary fibrosis. Respirology. 2010;15(5):843–8. doi:10.1111/j.1440-1843.2010.01778.x.
7. Sangani R, Ghio A, Culp S, Patel Z, Sharma S. Combined pulmonary fibrosis emphysema: role of cigarette smoking and pulmonary hypertension in a rural cohort. Int J Chron Obstruct Pulmon Dis. 2021;16:1873–85. doi:10.2147/COPD.S307192.
8. Zhang L, Zhang C, Dong F, et al. Combined pulmonary fibrosis and emphysema: a retrospective analysis of clinical characteristics, treatment and prognosis. BMC Pulm Med. 2016;16(1):137. doi:10.1186/s12890-016-0300-7.
9. Takahashi T, Terada Y, Pasque MK, et al. Clinical features and outcomes of combined pulmonary fibrosis and emphysema after lung transplantation. Chest. 2021;160(5):1743–50. doi:10.1016/j.chest.2021.06.036.
10. Akagi T, Matsumoto T, Harada T, et al. Coexistent emphysema delays the decrease of vital capacity in idiopathic pulmonary fibrosis. Respir Med. 2009;103(8):1209–15. doi:10.1016/j.rmed.2009.02.001.
11. Mejía M, Carrillo G, Rojas-Serrano J, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest. 2009;136(1):10–5. doi:10.1378/chest.08-2306.
12. Çiftci F, Gülpınar B, Atasoy Ç, Kayacan O, Saryal S. Combined pulmonary fibrosis and emphysema: how does cohabitation affect respiratory functions? Adv Med Sci. 2019;64(2):285–91. doi:10.1016/j.advms.2019.03.005.
13. Kitaguchi Y, Fujimoto K, Hanaoka M, Kawakami S, Honda T, Kubo K. Clinical characteristics of combined pulmonary fibrosis and emphysema. Respirology. 2010;15(2):265–71. doi:10.1111/j.1440-1843.2009.01676.x.
14. Jiang CG, Fu Q, Zheng CM. Prognosis of combined pulmonary fibrosis and emphysema: comparison with idiopathic pulmonary

fibrosis alone. Ther Adv Respir Dis. 2019;13:1753466619888119. doi:10.1177/1753466619888119.
15. Tokgoz Akyıl F, Sevim T, Akman C, et al. The predictors of mortality in IPF – does emphysema change the prognosis? Sarcoidosis Vasc Diffuse Lung Dis. 2016;33(3):267–74.
16. Cottin V, Selman M, Inoue Y, et al. Syndrome of combined pulmonary fibrosis and emphysema: an official ATS/ERS/JRS/ALAT research statement. Am J Respir Crit Care Med. 206(4):e7–41. doi:10.1164/rccm.202206-1041ST.
17. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377(9779):1760–9. doi:10.1016/S0140-6736(11)60405-4.
18. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82. doi:10.1056/NEJMoa1402584.
19. Goddard PR, Nicholson EM, Laszlo G, Watt I. Computed tomography in pulmonary emphysema. Clin Radiol. 1982;33(4):379–87. doi:10.1016/S0009-9260(82)80301-2.
20. Kumar A, Cherian SV, Vassallo R, Yi ES, Ryu JH. Current concepts in pathogenesis, diagnosis, and management of smoking-related interstitial lung diseases. Chest. 2018;154(2):394–408. doi:10.1016/j.chest.2017.11.023.
21. Zhai L, Gong H, Yu W. The link between smoking, emphysema, and fibrosis: a retrospective cohort study. Tob Induc Dis. 2024;22:132. doi:10.18332/tid/190689.
22. Schwartz DA, Merchant RK, Helmers RA, Gilbert SR, Dayton CS, Hunninghake GW. The influence of cigarette smoking on lung function in patients with idiopathic pulmonary fibrosis. Am Rev Respir Dis. 1991;144(3 Pt 1):504–6. doi:10.1164/ajrccm.144.3_Pt_1.504.
23. Chae KJ, Jin GY, Han YM, et al. Prevalence and progression of combined pulmonary fibrosis and emphysema in asymptomatic smokers: a case-control study. Eur Radiol. 2015;5(8):2326–34. doi:10.1007/s00330-015-3617-3.
24. Kirkil G, Mogulkoc N, Jovanovic D. Risk factors and management of lung cancer in idiopathic pulmonary fibrosis: a comprehensive review. Sarcoidosis Vasc Diffuse Lung Dis. 2025;42(1):15604. doi:10.36141/svdld.v42i1.15604.
25. Chen Q, Liu P, Zhou H, Kong H, Xie W. An increased risk of lung cancer in combined pulmonary fibrosis and emphysema patients with usual interstitial pneumonia compared with patients with idiopathic pulmonary fibrosis alone: a systematic review and meta-analysis. Ther Adv Respir Dis. 2021;15:17534666211017050. doi:10.1177/17534666211017050.
26. Başbakanlık Mevzuatı Geliştirme ve Yayın Genel Müdürlüğü [Turkish]. Article 32, 2017 Sep 9 [Internet]. Available from: https://www.resmigazete.gov.tr/eskiler/2017/09/20170909-1.htm. Accessed 2024 Feb 7.
27. Cottin V, Azuma A, Raghu G, et al. Therapeutic effects of nintedanib are not influenced by emphysema in the INPULSIS trials. Eur Respir J. 2019;53(4):1801655. doi:10.1183/13993003.01655-2018.
28. Fernandez Romero GA, Marchetti N, Hu A, et al. Efficacy of oral antifibrotic agents in the management of combined pulmonary fibrosis and emphysema. In: A42 ILD scientific abstracts: treatment and acute exacerbation. American Thoracic Society; 2018 [cited 2025 May 20]. p. A1646–A1646. Available from: https://www.atsjournals.org/doi/abs/10.1164/rccm-conference.2018.197.1_MeetingAbstracts.A1646.
29. Zhao A, Gudmundsson E, Mogulkoc N, et al. Mortality surrogates in combined pulmonary fibrosis and emphysema. Eur Respir J. 2024;63(4):2300127. doi:10.1183/13993003.00127-2023.
30. Kim HJ, Weber JM, Neely ML, et al. Predictors of long-term survival in patients with idiopathic pulmonary fibrosis: data from the IPF-PRO registry. Lung. 2025;203(1):40. doi:10.1007/s00408-025-00797-4.