Advances in Medical Sciences 64 (2019) 285–291

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original research article

Combined pulmonary fibrosis and emphysema: How does cohabitation affect respiratory functions?

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ARTICLE INFO

Keywords:
Combined pulmonary fibrosis and emphysema
Idiopathic pulmonary fibrosis
Pulmonary function tests
Mortality

ABSTRACT

Purpose: Combined pulmonary fibrosis and emphysema (CPFE) has emerged as a new syndrome with characteristics of both fibrosis and emphysema. We determined the impacts of radiologic emphysema severity on pulmonary function tests (PFTs), exercise capacity and mortality.

Patients and methods: IPF patients (n = 110) diagnosed at the Chest Diseases Clinic between September 2013 and January 2016 were enrolled in the study and followed up until June 2017. Visual and digital emphysema scores, PFTs, pulmonary artery pressure (sPAP), 6-minute walking test, composite physiologic index (CPI), and survival status were recorded. Patients with emphysema and those with pure IPF were compared.

Results: The CPFE-group had a significantly greater ratio of men($p < 0.001$), lower BMI ($p < 0.001$), lower mean PaO_2 ($p = 0.005$), higher mean sPAP ($p = 0.014$), and higher exercise desaturation ($p < 0.001$). The CPFE group had a significantly higher FVC(L)($p = 0.016$), and lower FEV1/FVC ratio ($p = 0.002$), DLCO, and DLCO/VA ratio($p = 0.03$ and $p = 0.005$, respectively). Lung volumes of the CPFE group had significantly higher VC($p = 0.017$), FRC ($p < 0.001$), RV($p < 0.001$), RV/TLC($p < 0.001$), and TLC($p < 0.001$). There were significant correlations between emphysema scores and FVC (L)($p = 0.01$), FEV1/FVC($p = 0.001$), DLCO ($p = 0.003$), VC($p = 0.014$), FRC (L)($p < 0.001$), RV($p < 0.001$), TLC($p < 0.001$), and RV/TLC ($p < 0.001$). Mortality rates were comparable between the two groups. CPI ($p = 0.02$) and sPAP ($p = 0.01$) were independent predictors of mortality in patients with CPFE.

Conclusions: The presence and severity of emphysema affects pulmonary function in IPF. Patients with CPFE have reduced diffusion capacity, more severe air trapping, worse muscle weakness, more severe exercise desaturation, and pulmonary hypertension. CPI and pulmonary hypertension are two independent risk factors for mortality in subjects with CPFE.

1. Introduction

Combined pulmonary fibrosis and emphysema (CPFE) is currently recognized as a syndrome that differs from both pulmonary fibrosis and emphysema by its clinical, physiologic, and radiologic properties [1]. Despite being reported to occur with other fibrotic lung disorders, it is most commonly associated with idiopathic pulmonary fibrosis (IPF). Smoking plays an important role in the development of both IPF and emphysema. Having similar etiologic factors, these two disorders are thought to coincide (occupy the same area) or cohabitate (occur at a site where they interact with each other). Common points have been shown in cellular and molecular pathways of emphysema and fibrosis [2]. Furthermore, a few genetic studies showed that smoking-induced telomere shortening predisposed individuals to emphysema and fibrosis [3,4]. This clinical condition is defined as the presence of emphysema in the upper lung zones and fibrosis in the lower lung zones.

Areas of emphysema and fibrosis may either be clearly distinguished from each other or densely interlaced. A third radiologic form is characterized by areas of paraseptal emphysema within fibrotic lesions in the basal parts of the lungs [5]. Despite being rarely encountered in clinical practice, these two conditions are frequently reported in pathology examinations [1]. Emphysema and pulmonary fibrosis have opposite physiologic effects. Emphysema is characterized by reduced elastic recoil, increased compliance, reduced maximal expiratory flow rates, and increased lung volumes, whereas fibrosis causes a decrease in elastic recoil, compliance, and lung volumes.

The cohabitation of pulmonary fibrosis and emphysema results in different pulmonary function tests (PFT) in patients with either pure

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https://doi.org/10.1016/j.advms.2019.03.005
Received 27 April 2018; Accepted 25 March 2019
Available online 01 April 2019

emphysema or pure IPF. IPF causes restrictive pulmonary physiology, whereas emphysema results in obstructive physiology and air trapping. In CPFE, on the other hand, although air flow rates and lung volumes as determined using spirometry are preserved, there is a marked limitation of gas exchange [1,2]. Patients most commonly present with exertional dyspnea. Additionally, exercise capacity is reduced and marked desaturation occurs with exercise. The impact of co-existence and extent of emphysema on mortality, morbidity, and prognosis of patients with IPF is an area of intense research.

The primary outcome measure of this study was the identification of potential differences of CPFE from pure fibrosis, and to determine the correlation between radiologic signs between pulmonary function tests and exercise capacity. The secondary outcome measure was an assessment of the effects of the presence, severity, and pulmonary function testing characteristics of emphysema on IPF mortality.

2. Patients and methods

2.1. Patients

One hundred and ten patients whose IPF was diagnosed on the basis of clinical, radiologic (chest computed tomography - CT) and pathologic findings at the Chest Diseases Clinic of a Tertiary University Hospital between September 2013 and January 2016 were enrolled in the study and followed up until June 2017. Other conditions causing fibrotic interstitial lung disease (occupational and environmental diseases, drug-related lung disease, connective tissue disease) were excluded and usual interstitial pneumonia pattern on chest CT were observed. Primary or metastatic lung cancer cases were also excluded.

If the patients met the diagnostic criteria for IPF then they were not subjected to surgical lung biopsy (in accordance with the 2011 American Thoracic Society and European Respiratory Society ATS/ERS statement) [6]. However, patients with possible usual interstitial pneumonia (UIP) pattern on CT underwent surgical lung biopsy, and if they received a diagnosis of IPF, they were enrolled to the study.

Emphysema was diagnosed on the basis of the presence of well-demarcated areas of decreased attenuation in comparison with contiguous normal lung and marginated by a very thin (< 1 mm) or no wall, and/or multiple bullae (> 1 cm) with upper zone predominance on chest CT [7].

2.2. Clinical data

Demographic information, respiratory symptoms, clinical characteristics, smoking history, disease duration, number of exacerbations and hospitalizations in the last year, long-term oxygen therapy (LTOT), and medication history were recorded. Dyspnea severity was scored using the modified Medical Research Council (mMRC) scale.

2.2.1. Chest computed tomography

Co-existence of emphysema and fibrosis was assessed using multidimensional computed tomography (MDCT) of the chest. The sections were assessed both visually and digitally. The MDCT images were examined by two experienced radiologists with five and eight years of experience in thoracic imaging. Discrepancies between the readers were resolved by consensus after reevaluation of the images together.

The presence and severity of emphysema were determined. All examinations were performed with a 16-slice MDCT (GE Healthcare Medical Systems, Milwaukee, WI, USA). Patients had a standard non-enhanced chest CT protocol. The parameters of the CT scan included: 120 kV, autotube mAs, 5-mm section thickness, 1-mm reconstruction interval, inter-slice gap 1.3 mm, and resolution 512 × 512.

Emphysema was identified as areas of hypovascular low attenuation. CT scan included images from the lung apex to the lung base with 1-mm-thin section axial MDCT images. The images were evaluated visually and scored according to the modified Goddard scoring system [8], which states that: no signs of emphysema (score 0); emphysema in $\leq$ 5% (score 0.5); $\leq$25% (score 1); 26–50% (score 2); 51–75% (score 3); $\geq$75% (score 4). Then the scoring was repeated after applying a density mask to the image sequence. The density mask is a density threshold (-950 to -1024 HU) that highlights voxels within this density range. This level was chosen because it correlated best to emphysematous changes in the lungs [9].

The local software of the CT workstation (Advantage Windows 4.4 software, GE Healthcare Medical Systems, Milwaukee, WI, USA) was used for the density mask application and CT emphysema index calculation. The CT emphysema index was defined as the proportion of the lung affected by emphysema. Segmentation of the lung was performed as a prior step to exclude soft tissues and fat from the field of analysis. A threshold of -300 to -1024 HU was applied to the entire image sequence and the rest of the tissues were excluded. The trachea, main stem bronchi, bowel gas, and background of the images were manually excluded. The image sequence was then revised for correct segmentation. The images were quantitatively evaluated considering a density level of -950 HU as the threshold level for emphysema [9].

2.2.2. Pulmonary function tests and arterial blood gas analyses

Pulmonary function tests (expiratory air flow rates, static lung volumes, carbon monoxide diffusing testing, maximum inspiratory and expiratory pressures) were performed. Expiratory flow rates, diffusing capacity of the lung for carbon monoxide, maximum inspiratory and expiratory pressures were measured by Vmax 229 Pulmonary Function/Cardiopulmonary Exercise Testing Device (Sensormedics, Bilthoven, Netherlands). A body plethysmograph (Body box SensorMedics 6200 Autobox, Bilthoven, Netherlands) was used to measure lung volumes.

Arterial blood gas samples were obtained through direct vascular puncture of the radial artery at rest, while breathing room air. The samples were instantly studied using an ABL 90 Flex/Blood Gas Analyzer (Radiometer Ltd. Brønshøj, Denmark).

2.2.3. Six-minute walking test

The six-minute walking test was performed walking the longest distance possible on a 20-meter long flat, straight corridor within 6 min [10]. Walking distance was recorded in meters. SpO_2, pulse rate, and dyspnea level (BORG scale) were recorded at the start and the end of the test.

2.2.4. Composite physiologic index (CPI)

The CPI was developed because the presence of emphysema affects the prognostic measures of IPF [11]. The CPI was calculated using the formula below:

CPI: Extent of disease on CT = 91.0 − (0.65 × Carbon Monoxide Diffusing Capacity (DLCO)) − (0.53 × percent predicted Forced Vital Capacity (FVC (%pred)) + (0.34 × percent predicted Forced Expiratory Volume in 1 s (FEV1 (%pred))

2.2.5. Echocardiography

Echocardiographic examinations were performed in the echocardiography laboratory of Ankara University Medical School Cardiology Department (Turkey) using “Vivid S5” devices (GE Vingmed Ultrasound AS, Horten, Norway). The echocardiographic views of each patient were obtained in compliance with the recommendations of the American and European Societies of Echocardiography [12].

2.2.6. Follow up

Each patient had follow-up visits at 3–6 month intervals. At each visit, clinical and physiologic findings were recorded. Mortality and time to mortality were also recorded. Records were updated via telephone calls when needed.

2.3. Statistical analysis

Statistical analyses were performed using SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics are expressed by their distribution including their mean ± standard deviation, median (IQR) or number (percentage). Two-sample comparisons were performed using Student's *t-test*, the Chi-square test, and Mann-Whitney U test, depending on data distribution. Univariate analysis was used to determine individual predictors of mortality; multivariate cox regression analysis was used to determine independent predictors of mortality. Kaplan-Meier survival analysis was used to assess mortality. The significance level was set at $p < 0.05$.

2.4. Ethical issues

This study was approved by Ankara University School of Medicine, Clinical Research Ethics Committee, Turkey (approval number: 12-1205-12) and the studies were conducted in accordance with the 1964 Declaration of Helsinki and Good Clinical Practice guidelines. Written and signed informed consent was obtained from all participants.

3. Results

The study included 110 patients (F, n = 44; M, n = 66) with a mean age of 66.95 ± 10.01 years. Among them, 96 had a definitive UIP pattern on CT and they were directly included in the study. Twenty patients had a possible UIP pattern on CT and underwent surgical lung biopsy after which 14 of them were diagnosed with IPF and enrolled to the study. Seventy-seven (70%) patients had emphysema on CT. These patients were allocated in the CPFE group, and 33 (30%) without emphysema comprised the pure IPF group. The emphysema score was 0.5 in 26 (33.8%) patients; 1 in 35 (45.5%); 2 in 14 (18.2%); and 3 in 2 (2.6%) patients (Table 1).

The comparison of the two groups is shown in Table 2. The CPFE group had a significantly greater male to female ratio (74% vs. 27.3%, respectively) ($p < 0.001$), lower body mass index (BMI) ($p < 0.001$), and greater cumulative smoking (pack-years) ($p < 0.001$) than the pure IPF group. No significant difference was found between the groups with respect to exacerbation and hospitalization rates in the last year ($p = 0.308$). The two groups were also comparable with regards to the LTOT ratios at study entry ($p = 0.887$). CPFE group had a significantly lower mean PaO_2 (50.29 ± 12.36 mmHg) than the pure IPF group (58.10 ± 13.92 mmHg) ($p = 0.005$). The echocardiographically quantified systolic pulmonary artery pressure (sPAP) was significantly greater in the CPFE group (62.31 ± 25.50 mmHg) than in the pure IPF group (41.96 ± 15.56 mmHg) ($p = 0.014$). In the CPFE group 52 (67.5%) patients and in the pure IPF group 10 (30.3%) patients were using short- and long-acting bronchodilator treatment ($p = 0.028$). A total of 67 (60.9%) patients, 49 from the CPFE group and 18 from the IPF group, were treated with antifibrotic drugs. The antifibrotic treatment rates were comparable between the two groups.

The six-minute walking test was completed in 95 (86.4%) patients; 15 patients could not perform the test due to low SpO_2 despite oxygen support, cardiac arrhythmias, and/or orthopedic disability. Although the two groups had comparable six-minute walking distances ($p = 0.797$), the CPFE group had a significantly lower baseline and final SpO_2 values ($p = 0.001$, $p = 0.015$, respectively). The CPFE group showed a significant exercise desaturation than the pure IPF group (-10.55 ± 6.53 vs. -6.02 ± 2.12, respectively) ($p < 0.001$).

On pulmonary function test (Table 3) the mean FVC (% pred) of both, the CPFE (66.18 ± 17.69) and the IPF (64.10 ± 18.25) groups were decreased and mean FEV1/FVC ratios (79.56 ± 10.84, 86.53 ± 7.16 respectively) were within normal limits. However, the CPFE group had a significantly greater FVC (L) ($p = 0.016$) and a significantly lower FEV1/FVC ratio ($p = 0.002$). The mean DLCO (% pred) values of both groups were decreased (39.06 ± 15.40 and 43.19 ± 17.74, respectively). The DLCO (mL/mmHg/min), DLCO (% pred), and DLCO/alveolar volume (VA) (% pred) ratio were significantly lower in the CPFE group ($p = 0.04$, $p = 0.03$, and $p = 0.005$, respectively). The mean vital capacity (VC) (% pred) values of both groups were decreased (72.43 ± 16.55 and 62.08 ± 19.91, respectively). The mean functional residual capacity (FRC) (% pred) and residual volume (RV) (% pred) values were within normal limits in the CPFE group (83.04 ± 19.25 and 89.77 ± 32.83, respectively) but these values were decreased in the pure IPF group (59.04 ± 18.60 and 47.96 ± 35.50, respectively). The CPFE group had significantly greater VC (L) ($p = 0.016$), VC (% pred) ($p = 0.017$), FRC (L) ($p < 0.001$), FRC (% pred) ($p < 0.001$), RV (L) ($p < 0.001$), RV (% pred) ($p < 0.001$), total lung capacity (TLC) (L) ($p < 0.001$) and TLC (% pred) ($p < 0.001$), RV/TLC ($p < 0.001$) values than the pure IPF group. The mean maximal inspiratory pressure (MIP) (% pred) value was decreased in the CPFE group (58.96 ± 20.13) but it was within normal limits in the IPF group (82.12 ± 30.91). The CPFE group had a significantly lower MIP (%) value ($p = 0.006$).

The emphysema score and FVC (L) ($p = 0.01$), FEV1/FVC ($p = 0.001$), DLCO (% pred) ($p = 0.003$), VC (L) ($p = 0.019$), VC (% pred) ($p = 0.014$), FRC (L) ($p < 0.001$), RV (L) ($p < 0.001$), RV (% pred) ($p < 0.001$), TLC (L) ($p < 0.001$), TLC (% pred) ($p < 0.001$), and RV/TLC ($p < 0.001$) were significantly correlated. The two groups were similar in terms of the composite physiologic index (CPI) ($p = 0.425$).

According to the pulmonary hypertension classification, patients were divided into 4 groups: the mild group ($36 \leq$ sPAP < 50 mmHg); the moderate group ($50 \leq$ sPAP < 70 mmHg), the severe group ($70 \leq$ sPAP < 110 mmHg), and the very severe group (sPAP ≥ 110 mmHg) [13]. Out of the CPFE group 20 (26%) patients had mild pulmonary hypertension, 14 (18.2%) moderate pulmonary hypertension, 21 (27.3%) severe pulmonary hypertension, and 2 (2.6%) very severe pulmonary hypertension. Ten (13%) patients in the CPFE group had sPAP < 35 mmHg. In the IPF group, 9 (27.3%) patients had mild pulmonary hypertension, 11 (14.3%) had moderate pulmonary hypertension, and 1 (3.03%) had severe pulmonary hypertension. Twelve (36.4%) patients in the pure IPF group had sPAP < 35 mmHg. Thus, pulmonary hypertension prevalence was significantly higher in the CPFE group when compared with the pure IPF subjects ($p = 0.03$).

During the follow-up visits, 11 (14.3%) patients in the CPFE group needed LTOT. Sixteen (20.8%) patients were admitted to the ICU for various reasons. In 6 (7.8%) patients positive pressure non-invasive ventilation (NIV) was used due to respiratory failure. Ten (12.9%) patients needed invasive mechanical ventilation 8 (7.3%) of whom died. The CPFE group had an all-cause mortality rate of 37.7%. In the pure IPF group, 7 (21.2%) patients were administered LTOT. Six (18.2%) patients required ICU admission during follow-up. Two (6.1%) patients were provided NIV support. Four (12.1%) patients with IPF received invasive mechanical ventilation, 3 (2.7%) of whom died. The all-cause mortality rate of the IPF group was 27.3%. No significant difference was present between the two groups' follow-up characteristics (Table 4).

The mean follow-up period and time to mortality were 39.64 ± 20.25 months and 19.38 ± 18.04 months, respectively. Twenty-nine (37.7%) patients from the CPFE group and 9 (27.3%) from

Table 1
Emphysema rates and scores of the whole study population according to Modified Goddard scoring system on chest computed tomography.

Emphysema score	Emphysema rate	n (%)
0	None	33 (30)
0.5	≤ 5 %	26 (33.8)
1	≤ 25 %	35 (45.5)
2	26-50 %	14 (18.2)
3	51-75 %	2 (2.6)
4	≥75 %	None

Table 2
Comparison of the characteristics of the combined pulmonary fibrosis with emphysema and pure pulmonary fibrosis groups at the first visit.

	Whole population n = 110	CPFE n = 77	IPF n = 33	p
Age	66.95 ± 10.01	66.94 ± 9.99	66.97 ± 10.21	0.909
Sex, Male	66 (60)	57 (74)	9 (27.3)	< **0.001**
BMI, kg/m^2	25.47 ± 4.89	24.22 ± 3.9	28.25 ± 5.74	< **0.001**
Cigarettes (pack-year)	26.19 ± 23.14	33.64 ± 22.89	8.79 ± 11.50	< **0.001**
PaO_2, mmHg	52.7 ± 13.3	50.29 ± 12.36	58.10 ± 13.92	**0.005**
sPAP, mmH_20	48.97 ± 23.20	62.31 ± 25.50	41.96 ± 15.56	**0.014**
sPAP severity	2 (2)	2 (3)	1 (1)	**0.03**
6MWT, m	338.06 ± 138.44	332.51 ± 128.15	340.50 ± 143.62	0.797
Baseline SpO_2	91.06 ± 4.50	90.26 ± 4.67	93.89 ± 3.54	**0.001**
Final SpO_2	81.52 ± 8.0	78.39 ± 8.58	84.07 ± 5.86	**0.015**
Exercise desaturation	−9.86 ± 6.47	−10.55 ± 6.53	−6.02 ± 2.12	< **0.001**
Baseline BORG	0.94 ± 1.00	0.96 ± 1.08	0.87 ± 0.79	0.981
Final BORG	3.37 ± 1.77	3.46 ± 1.93	3.18 ± 1.33	0.447
mMRC	2.05 ± 0.96	2.13 ± 1.02	1.90 ± 0.79	0.305
Bronchodilator treatment	62 (56.4)	52 (67.5)	10 (30.3)	**0.028**
Nintenadib	14 (12.7)	10 (13)	4 (12.1)	0.243
Pirfenidone	53 (48.2)	39 (50.6)	14 (42.4)	0.163

Results given as n (%), median (IQR), or mean ± SD.
BMI - body mass index; LTOT - long-term oxygen treatment; PaO_2 - partial oxygen pressure; $PaCO_2$ - partial carbon dioxide pressure; sPAP - systolic pulmonary artery pressure; 6MWT - 6-minute walking test; SpO_2 - arterial blood oxygen saturation with pulse oximetry; exercise desaturation, Final SpO_2-Baseline SpO_2; mMRC - Modified Medical Research Council dyspnea scale.

Table 3
Comparison of the pulmonary function tests of the combined pulmonary fibrosis with emphysema and pure pulmonary fibrosis groups.

	Whole population n = 110	CPFE n = 77	IPF n = 33	p
FEV1, L	1.70 ± 0.56	1.58 ± 0.51	1.76 ± 0.58	0.142
FEV1, % pred	65.53 ± 18.83	64.38 ± 18.72	68.17 ± 19.12	0.345
FVC, L	2.04 ± 0.72	2.17 ± 0.74	1.78 ± 0.62	**0.016**
FVC, % pred	65.55 ± 17.80	66.18 ± 17.69	64.10 ± 18.25	0.589
FEV1/FVC, %	81.74 ± 10.32	79.56 ± 10.84	86.53 ± 7.16	**0.002**
FEV1/FVC < 70	11 (10)	11 (14.3)	0	**0.012**
DLCO,mL/mmHg/min	9.86 ± 4.5	8.69 ± 4.27	10.25 ± 5.06	**0.04**
DLCO, % pred	41.70 ± 16.09	39.06 ± 15.40	43.19 ± 17.74	**0.03**
DLCO/VA, % pred	63.76 ± 23.03	59.36 ± 22.04	73.62 ± 22.51	**0.005**
VC, L	2.19 ± 0.76	2.34 ± 0.75	1.85 ± 0.70	**0.016**
VC, % pred	69.02 ± 18.27	72.43 ± 16.55	62.08 ± 19.91	**0.017**
FRC, L	2.16 ± 0.73	2.40 ± 0.71	1.66 ± 0.48	< **0.001**
FRC, % pred	75.15 ± 22.06	83.04 ± 19.25	59.04 ± 18.60	< **0.001**
RV, L	1.51 ± 0.64	1.73 ± 0.57	1.07 ± 0.54	< **0.001**
RV, % pred	76.03 ± 38.89	89.77 ± 32.83	47.96 ± 35.50	< **0.001**
RV/TLC, %	39.34 ± 13.53	43.55 ± 13.06	30.75 ± 10.09	< **0.001**
IC, L	1.43 ± 0.51	1.47 ± 0.48	1.34 ± 0.57	0.350
TLC, L	3.48 ± 1.08	3.83 ± 0.99	2.76 ± 0.92	< **0.001**
TLC, % pred	76.92 ± 24.62	85.53 ± 23.52	59.33 ± 16.22	< **0.001**
MIP, % pred	87 ± 27.99	58.96 ± 20.13	82.12 ± 30.91	**0.006**
MEP, % pred	87.21 ± 28.64	81.08 ± 25.04	96.81 ± 31.99	0.086
CPI	51.98 ± 12.43	51.71 ± 11.78	52.63 ± 14.05	0.425

Results given as n (%) or mean ± SD.
FEV1 - forced expiratory volume in the first second; FVC - forced vital capacity; DLCO - diffusing capacity for carbon monoxide; DLCO/VA - diffusion capacity for carbon monoxide/alveolar volume; IC - inspiratory capacity; FRC - functional residual capacity; TLC - total lung capacity; RV - residual volume; MIP - Maximal inspiratory pressure; MEP - Maximal expiratory pressure; CPI - composite physiologic index.

the pure IPF group died during follow-up. The mortality rates of the two groups did not differ significantly (p = 0.282). Time to mortality in the CPFE group and IPF group was 17.68 ± 12.30 months and 24.88 ± 16.97 months, respectively (p = 0.302). There was no significant correlation between emphysema scores and mortality (p = 0.214). The Kaplan-Meier survival curves of the CPFE and IPF groups was shown in Fig. 1.

Twenty-three patients in the antifibrotic treatment group (18 CPFE and 5 IPF) and 15 patients in the non-treatment group (11 CPFE and 4 IPF) died. There was no difference between the mortality rates of the patients who received antifibrotic treatment and those who did not (p = 0.17).

Lung cancer was diagnosed in 6 (7.8%) patients in the CPFE group and 1 (3%) in the pure IPF group. Although the lung cancer incidence was greater, statistical significance was not reached (p = 0.053).

Factors correlating emphysema score in the CPFE group (FEV1 (% pred), FVC (% red), DLCO (% pred), FRC (% pred), RV (% pred), CPI, and PAP) were evaluated for mortality correlation using univariate regression analysis (Table 5). The mortality rate of the CPFE group was significantly correlated to CPI (HR 2.057; 95% CI: (1.003–3.11); p = 0.003), echocardiographically measured sPAP (HR 2.27; 95% CI: (1.072–4.58); p = 0.002), and DLCO (%) (HR 1.98; 95% CI:

Table 4
Follow-up characteristics of the combined pulmonary fibrosis with emphysema and pure pulmonary fibrosis groups.

	Whole population n = 110	CPFE n = 77	IPF n = 33	p
LTOT need	18 (16.4)	11 (14.3)	7 (21.2)	0.127
ICU admission	22 (20)	16 (20.8)	6 (18.2)	0.231
NIV support	8 (7.27)	6 (7.8)	2 (6.1)	0.341
IV need	14 (12.8)	10 (12.9)	4 (12.1)	0.450
Lung cancer	7 (6.36)	6 (7.8)	1 (3%)	0.053
Mortality	38 (34.5)	29 (37.7)	9 (27.3)	0.282
Time to mortality, months	19.38 ± 18.04	17.68 ± 12.30	24.88 ± 16.97	0.302

Results given as n (%) or mean ± SD.
LTOT - long-term oxygen treatment; ICU - intensive care unit; NIV - non-invasive mechanical ventilation; IV - invasive mechanical ventilation.

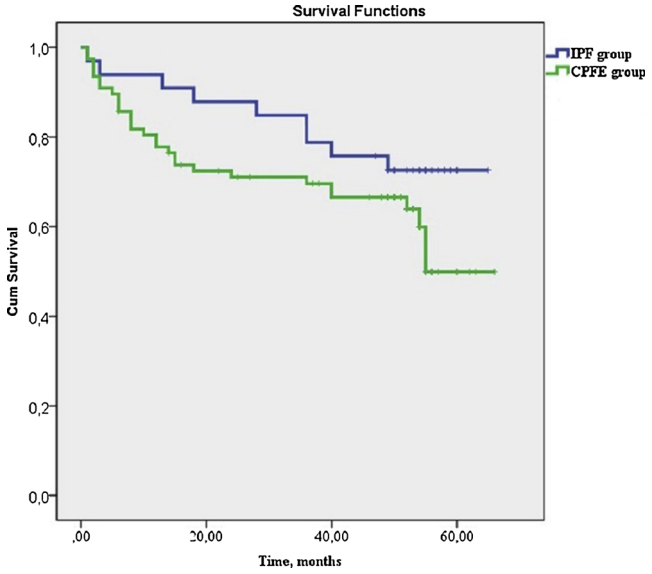

Fig. 1. The Kaplan-Meier survival curves of CPFE and IPF groups show no significant difference between mortality rates.

Table 5
Univariate and multivariate analysis for mortality in the CPFE cohort.

Univariate variable	HR	95% CI	p
FEV1 (%)	0.914	0.829-1.008	0.07
FVC (%)	1.016	0.936-1.103	0.09
DLCO (%)	1.98	1.045-3.37	**0.005**
FRC (%)	0.89	0.80-1.00	0.21
RV (%)	0.94	0.91-1.052	0.17
CPI	2.057	1.003-3.11	**0.003**
PaO_2	1.86	1.23-2.65	**0.01**
sPAP	2.27	1.072-4.58	**0.002**
Multivariate variable	**HR**	**95% CI**	p
CPI	1.98	0.99-2.81	**0.02**
sPAP	2.05	1.03-3.77	**0.01**

FEV1 - forced expiratory volume in the first second; FVC - forced vital capacity; DLCO - diffusion capacity for carbon monoxide; FRC - functional residual capacity; RV - residual volume; CPI - composite physiologic index; PaO_2 - partial oxygen pressure; sPAP - systolic pulmonary artery pressure.

(1.045–3.37); p = 0.005). Multivariate analysis revealed CPI (HR 1.98; 95% CI: (0.99–2.81); p = 0.02) and sPAP (HR 2.05; 95% CI: (1.03–3.77); p = 0.01) as independent predictors of mortality.

4. Discussion

Pulmonary fibrosis and emphysema are two distinct entities with different pathophysiologic and functional properties, with one of them usually predominating in each patient. However, the pathologic changes of these two entities often co-exist among smokers [14]. We compared clinical properties, pulmonary functions, exercise characteristics, and mortality rates of patients with CPFE and those with pure IPF. Although emphysema and fibrosis cohabitance exact prevalence is unknown, studies have indicated that it has a high prevalence rate (> 30%) [15,16]. In another study evaluating emphysema rates in IPF patients, the rate of CPFE was found to be 56% [17]. However, the subjects with CPFE in our study constituted a much higher ratio (70%) among the patients with IPF. The design of the present study, which was aimed to identify the CPFE subjects among the IPF patients, may explain the higher ratio of CPFE in this study. This variation of prevalence in different studies on CPFE may be due to different extent of emphysema evaluated by high resolution computed tomography (HRCT).

The mean ages of the subjects with pure IPF and CPFE in the present study were comparable and all subjects were middle-aged according to the new age classification of the World Health Organization [18]. It is understood that the prevalence of both conditions increases with age. In an autopsy study on smokers and non-smokers [19], it was shown that the prevalence of emphysema and fibrosis increased with chronologic age, and that smoking had a synergistic effect on the increase in every age group. Studies investigating the genetic background of CPFE and IPF indicated that both were associated with telomere shortening, an indication of biologic aging [20,21]. Similar to previous study [22], male predominance was seen in subjects with CPFE in our study. This is most probably due to the higher rate of active and passive smoking among men in Turkey. It has been reported that IPF is more common among men than women, with the gap widening further at later stages of life [23]. It is thought that CPFE co-exists with environmental triggers, smoking being one of the most important, in persons with genetic susceptibility to the disease; therefore, most patients with CPFE are former or current smokers [24].

Chest CT has an important role for diagnosing CPFE, and demonstrates a combination of centrilobular and/or paraseptal emphysema in upper lung zones and fibrosis encompassing subpleural reticular opacities, honeycomb images, and traction bronchiectasis in lower lung zones [25,26]. Our present study rated tomographic emphysema scores in CPFE. Most of our subjects had mild-to-moderate emphysema. A study assessing total emphysema scores in COPD, IPF, and CPFE reported that the emphysema scores of patients with CPFE were similar to those of patients with mild-to-moderate COPD, but lower than those of patients with severe COPD [7]. These results suggest an existing balance between fibrosis and emphysema during the cohabitation process.

The characteristics of the cohabitation of pulmonary fibrosis and emphysema are different than those of pure fibrosis or emphysema alone. Pulmonary function tests are one of the characteristics that are most strikingly affected by these differences. The present study demonstrated that the presence of emphysema in patients with CPFE had a significant impact on pulmonary function tests. The restrictive effect of fibrosis on pulmonary function was counterbalanced by emphysema. In our subjects with CPFE, FEV1 was preserved, but DLCO was further reduced. Airflow collapse caused by emphysematous lesions is prevented by increased traction exerted by pulmonary fibrosis, which leads to the preservation of FEV1 [1]. Our present study also revealed that the FEV1/FVC ratio of the CPFE group was significantly lower. Moreover, unlike IPF, some patients in the CPFE group had an obstructive air flow limitation. Increased emphysema ratios cause some patients with CPFE to exhibit air flow obstruction in spirometry [27].

In CPFE, emphysematous lesions added to fibrosis, which causes shrinkage of the vascular surface area and reduced pulmonary capillary blood volume, in addition to an increased alveolar membrane thickness

by fibrosis, led to a decrease in diffusion capacity [1]. As emphysema severity increases, air trapping and hyperinflation increase in parallel, which augments residual volumes. Pulmonary function test parameters that differentiate more into obstruction and air trapping with increasing severity of emphysema as determined using emphysema scores suggest the importance of the presence and extent of emphysema. In emphysema, airway narrowing and destruction of distal alveoli leads to alterations in static volumes. The alveolar wall's loss of elasticity and ability to empty completely contributes to air trapping, resulting in increased residual volume and functional residual capacity, hence increased total lung capacity [25].

The CPFE group in our study had a significantly lower BMI. Systemic inflammation and increased respiratory workload leads to muscle fatigue and loss [26]. We also detected more severe respiratory muscle weakness as shown by a significant reduction in MIP in patients with CPFE than in those with pure IPF, suggesting that the addition of emphysema to the existing pathology reduces muscle strength. The maximum power generated by respiratory muscles is related to lung volume. Lung volume affects respiratory muscles' length-tension properties such that an increase in lung volumes results in shortening of inspiratory muscles.

To overcome the confounding effect of emphysema on CT in patients with IPF, the CPI was developed and it is considered as a better predictor of mortality than individual pulmonary function parameters [11]. Nevertheless, some conflicting results have been reported [28]. In the present study, subjects with CPFE and IPF did not differ in respect to CPI and mortality, but it was one of the independent risk factors for mortality along with higher sPAP.

The two groups had comparable six-minute walking test distances, although the CPFE group's baseline and final SpO_2 values were lower. Furthermore, the difference between the initial and final saturation levels was also significant, indicating that desaturation in CPFE subjects was more prominent. This suggests that emphysema worsens exercise desaturation [7]. Exercise-induced desaturation is associated with impaired daily physical activity, faster FEV1 decline, and worse prognosis, which supports its clinical importance [21,29].

In our study, the CPFE group had a lower mean PaO_2 in arterial blood and a higher mean sPAP. Reduced diffusion capacity causes a drop of oxygen in arterial blood causing pulmonary hypertension - one of the major complications of advanced parenchymal and airway diseases. Patients with CPFE were reported to have higher rates and greater severity of pulmonary hypertension than patients with pure IPF [30]. Furthermore, in accordance with our findings, Cottin et al. [31] reported a link between pulmonary hypertension and increased mortality for patients with CPFE. In CPFE, it was reported that areas with fibrosis and emphysema and spared areas showed intimal fibrous thickening and medial hypertrophy in arterioles, even in veins and venules [32]. These vascular changes were found to be more closely related to reduced DLCO in CPFE than other groups. Loss of surface area through hyperinflation and thickened membranes as a result of fibrosis may cause a reduced DLCO and increased pulmonary pressures in emphysema.

There is currently no definite consensus on how CPFE patients should be followed up and treated. The patients in the present study received antifibrotic agents when needed. However, there is no recommendation on bronchodilator prescription in consensus papers. CPFE subjects may benefit from such medication, but further studies are needed to answer this question. Nevertheless, we noticed that patients in the CPFE group used bronchodilators at a higher rate.

Studies investigating the effects of emphysema on mortality produced contradictory results. One of the major reasons is the enrollment of patients with different idiopathic interstitial pneumonia with better, albeit variable prognosis, into different cohorts. In a study assessing different phenotypes, the overall survival rate of patients with IPF and emphysema was significantly worse than those with interstitial pneumonia and emphysema clusters [33]. In our study, the two groups were similar in terms of mortality rates and time to mortality; however, when the CPFE group was considered alone, CPI and sPAP were independent factors increasing the risk of mortality. The emphysema score had no discernible effect on the mortality rate. This suggests that it is not the presence of emphysema that affects mortality, but other factors may be influential, such as the extent of fibrosis and the existence of pulmonary hypertension [34].

Lung cancer incidence is increased in smoking-related emphysema and IPF due to lung injury, chronic inflammation, and genetic mutations [35]. For this reason, we also expect a higher incidence of lung cancer in CPFE. A study comparing the incidence of lung cancer between patients with IPF and CPFE failed to show any significant difference, although it demonstrated that lung cancer incidence was higher among patients with CPFE compared with those with emphysema alone [36]. We observed lung cancer in 7 subjects, 6 of whom had CPFE. However, this was not statistically significant.

4.1. Limitations of the study

The present study is a single-center study and as such its results cannot be generalized. No standard therapy protocol was administered to the patients. The lack of radiological evaluation of the degree of fibrosis constitutes another weakness of the study. This assessment may be the subject of another research. Further multicenter studies on larger patient series are needed to confirm the clinical outcome differences of CPFE and IPF and to establish a consensus on how to manage such patients.

5. Conclusion

The presence and severity of emphysema affects pulmonary function in IPF. Patients with CPFE have greater lung volume, reduced diffusion capacity, more severe air trapping, worse muscle weakness, more severe exercise desaturation, and pulmonary hypertension. CPI and pulmonary hypertension are two independent risk factors for mortality in CPFE subjects. These results suggest that CPFE may be a distinct clinical entity.

Acknowledgement

This study was presented at ERS Congress 2017 (Session: Clinical problems, TP-13).

Conflict of interests

The authors declare no conflict of interests.

Financial disclosure

The authors have no funding to disclose.

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Literature search: Fatma Çiftci, Başak Gülpınar

Funds collection: n/a.

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