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Different properties between patients with combined pulmonary fibrosis and emphysema and patients with idiopathic pulmonary fibrosis

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Abstract

Aim: Combined pulmonary fibrosis and emphysema (CPFE) and idiopathic pulmonary fibrosis (IPF) have been discussed intensively in recent years as two different entities. We aimed to compare the clinical, functional and respiratory parameters, clinical course and mortality rates of patients with CPFE and IPF.

Materials and Methods: 36 patients with a diagnosis of CPFE and 40 IPF who applied between September 2013 and February 2019 were retrospectively included in the study. Demographic data, comorbidities, pulmonary function parameters, mortality, systolic pulmonary artery pressures(sPAP) recorded.

Results: In the CPFE patient group, the ratio of male patients (p=0.02), smoking history (p=0.00), frequency of acute exacerbation (p=0.001) were found to be significantly higher, SF-36 total score (p=0.000) were significantly lower than IPF group. While FVC% (p=0.00), FEV1% (p=0.049) and TLC% (p=0.002) were significantly higher in the CPFE group than IPF group, TLCO% (p=0.002) and FEV1/FVC (p=0.00) was lower. Pulmonary hypertension (PH) was 40% in CPFE and 37% in IPF and no significant difference was found between them (p=0.806). Those who received long-term oxygen therapy (LTOT) were more common in the CPFE group (p=0.04). In CPFE patients; the percentage of those who treated with bronchodilator, antifibrotic, systemic corticosteroid was respectively 52.7%, 36.1%, 5.6%. Mortality from any cause was 9(25%) in CPFE and 8(20%) in IPF, and there was no significant difference between the two groups (p=0.601).

Conclusion: It was observed that lung volumes were preserved and gas exchange of the lung was significantly decreased in patients with CPFE. Compared to IPF, the quality of life was lower and acute exacerbation was more common in CPFE. The frequency of PH and mortality were similar in both groups. Male gender and smoking history were important risk factors for CPFE patients. There is a need for multicenter studies reporting the clinical features, prognosis, and mortality of CPFE.

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive, fibrotic-parenchymal lung disease that has a poor prognosis with gradually increasing symptoms and lung function losses [1]. Emphysema is the trapping of the air, which can result in an obstructive pattern characterized by the enlargement of the air spaces distal to the terminal bronchiole as a result of the destruction of the alveolar walls, and is detected as low attenuation areas on Computed Tomography (CT) [2]. Combined pulmonary fibrosis and emphysema (CPFE) is considered to be a different entity in radiological, pathological, functional and prognostic terms in which emphysema in the upper lobes and fibrosis in the lower lobes co-exist, and awareness is increasing gradually in this respect [3]. The fibrosis component of CPFE consists of both IPF and other forms of pulmonary fibrosis [4]. Lung volumes are preserved or slightly reduced in CPFE, and lung gas exchange is reduced disproportionately at significant levels. CPFE, which has a worse prognosis is more common in men and heavy smokers [5].Two opposing effects (hyperinflation and fibrosis) coexist in CPFE. Thus, while lung volumes are relatively

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preserved, carbon monoxide transfer factor (TLCO) decreases disproportionately with exercise and desaturation increases [6,7].

The 3-year and 5-year mortality were found to be approximately 50% and 80%, respectively in patients who had IPF without lung transplantation; and the prognosis was worse than in other fibrotic lung diseases [1,8]. The average 5-year survival rate was reported to be 35%-80% in CPFE [9]. While some studies found that mortality did not differ between CPFE and IPF groups [4,9,10], another studies also found higher mortality and worse prognosis in CPFE than IPF [11,12]. CPFE and IPF are being discussed intensively in recent years as two different entities or two different manifestations of the same disease. Our study was based on the hypotheses "Is CPFE more mortal than IPF?" and "Is CPFE mortality similar to IPF?". In our study, the purpose was to evaluate CPFE and IPF patients in terms of demographic data, pulmonary function parameters, pulmonary artery pressures, treatment protocols, and mortality.

Materials and Methods

Design of the study

Between September 2013 and February 2019, patients with CPFE and IPF who applied to the Suat Seren Chest Diseases Training and Research Hospital clinic were included in the study retrospectively. The study, which was designed in line with the Declaration of Helsinki and good clinical practices, was approved by the Ethics Committee of Health Sciences University Dr. Suat Seren Chest Diseases And Chest Surgery Training and Research Hospital (No=49109414-806.02.02, date: 09.11.2017).

Patient selection

The diagnosis of IPF was made clinically, radiologically, and/or pathologically according to the Diagnostic Criteria of ATS/ERS/JRS/ALAT [13]. As defined by Cottin et al. and Ryerson et al., patients who had more than 10% centrilobular and/or paraseptal emphysema in the upper lobes radiologically, and pulmonary fibrosis in the lower lobes were included in the CPFE group [5,9].

Inclusion criteria

1. 18 years old
2. Patients diagnosed with IPF
3. Patients diagnosed with CPFE.

Exclusion criteria

1. Being below 18 years old
2. Patients who had the diagnosis of sarcoidosis, connective tissue disease, hypersensitivity pneumonia, pneumoconiosis, lymphangioleiomyomatosis, langerhans-cell histiocytosis-X and eosinophilic pneumonia and those who developed lung fibrosis because of drug toxicity were excluded from the study
3. Patients whose data cannot be accessed.

The initial demographic data, comorbidities, pulmonary function tests at diagnosis, 6-minute walking distance (6 MWD), quality of life assessment scale short form 36 (SF-36) [14], Modified Medical Research Council (mMRC) Dyspnea Scale [15], systolic pulmonary artery pressures (sPAP), medical treatment data, acute exacerbation, and hospitalization rates of all patients in the last year were recorded. At the end of the 2-year follow-up period, it was determined whether the patients were mortal or not. In the study the primary endpoint variable was mortality.

Acute exacerbation in IPF and CPFE is a clinical condition in which clinical worsening, ground glass opacities and/or areas of consolidation in thorax computerized tomography are seen in less than a month and other causes (congestive heart failure, pneumonia, pulmonary embolism, etc.) are excluded [16].

Pulmonary function tests

The pulmonary function tests were made by using the ZAN 300 device (ZAN Messgerate, Oberthulba, Germany) when the patient was in at resting and sitting position. The test was repeated at least three times, and those with a variation between the results of less than 5% were evaluated. The forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC, forced expiratory flow rate between 25%-75% of vital capacity (FEF 25-75), total lung capacity (TLC), residual volume (RV), RV/TLC, TLCO, transfer coefficient (KCO), FVC%/TLCO% were recorded. FEV1, FVC, and TLCO values were evaluated according to the European Respiratory Society (ERS) Guidelines [17]. The corrected value of TLCO was taken for hemoglobin [18].

Computed tomography protocol

High-resolution CT (HRCT) images at initial diagnosis (Hitachi Whole Body X-ray System, Hitachi, Ltd. 2-16-1, Highashi-Ueno, Taito-ku, Tokyo, 110-0015, Japan) in the supine position, with full inspiration were taken with 16 detectors and a section thickness of 1.25 mm. The parenchymal window was evaluated within the range of -700 to 1500 Hounsfield Units (HU). The main pulmonary artery diameter was also measured (in mm), and Thoracic HRCT of all patients were reviewed by two blinded radiologists. CT results were used to identify patient groups.

Echocardiography

The Philips iE33 Echocardiography Device (x4.1 transducer; Philips Medical Systems, Bothell, WA, USA) that had a matrix array ultrasonographic transducer was used for ECHO (conventional 2DE and RT3DE). The ECHO images of the patients were evaluated according to the recommendations of the American and European Society of Echocardiography. The sPAB (mmHg) of the patients were recorded; and if sPAB $\geq$ 35 mmHg, it was evaluated as Pulmonary Hypertension PH [19].

Statistical analysis

The data analysis was made with the Statistical Package for the Social Sciences (SPSS, Inc., Chicago IL), version 22 software for Windows. The patients included in the study were divided into two groups as CPFE and IPF. Using the Kolmogorov-Smirnov and Shapiro-Wilk tests, it was

Table 1. Demographic and clinical characteristics of patients with CPFE and IPF.

	CPFE (n=36)	IPF (n=40)	p value
Age - years (Mean, SD)	66.9 ± 7.5	68.3 ± 7.3	0.422
Male (n,%)	35, 97.2	28, 70	0.002
Smoking history (%)			0.000
Non-smoker	2.8	42.5	
Smoker/ ex-smoker	97.2	57.5	
Smoking (package /year) (n, SD)	51.6 ± 40.6	25.4 ± 15.2	0.004
Symptoms (n,%)			
Shortness of breath	32, 88.9	37, 92.5	0.587
Cough	28, 77.8	33, 82.5	0.606
Sputum	13, 36.1	11, 27.5	0.420
Presence of comorbidity (%)	72.2	67.5	0.655
Comorbidity (n, %)			
DM	4, 11.1	17, 42.5	0.002
HT	12, 33.3	11, 27.5	0.580
KAH	12, 33.3	14, 35.0	0.878
COPD	15, 41.7	3, 7.5	0.000
Hyperlipidemia	1, 2.8	1, 2.6	0.940
Lung cancer	0, 0.0	2, 5.3	0.174
Number of acute exacerbation per year (n, %)	1.1 ± 1.7	0.2 ± 0.5	0.001
Number of hospitalization per year (n, %)	0.7 ± 1.2	0.3 ± 0.5	0.061
Body Mass Index (kg/m^2)	26.1 ± 3.1	27.4 ± 3.8	0.020

DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary Artery Disease, COPD: Chronic Obstructive Pulmonary Disease.

Table 2. Pulmonary function parameters and presence of PH in patients with CPFE and IPF.

	CPFE (n=36)	IPF (n=40)	p value
SF-36 total score	64.5 ± 25.5	81.8 ± 13.1	0.000
mMRC score	2.4 ± 1.3	2.0 ± 0.9	0.113
6 MWD (meter) α	320.2 ± 77.2	343.0 ± 97.0	0.312
TLC %,SD, ß	78.0 ± 13.0	65.8 ± 18.9	0.002
RV %,SD, ß	99.7 ± 32.3	77.7 ± 26.1	0.000
RV/TLC%,SD, ß	96.9 ± 45.9	48.5 ± 18.2	0.000
FEV1 %,SD	80.1 ± 19.1	72.5 ± 15.9	0.049
FVC %,SD	77.2 ± 18.2	64.2 ± 15.7	0.000
FEV1/FVC%,SD	80.6 ± 12.0	90.2 ± 7.0	0.000
MEF25-75 %,SD	67.9 ± 30.4	97.1 ± 30.3	0.000
TLCO%,SD, &	33.8 ± 13.4	46.1 ± 18.2	0.002
KCO %,SD, &	45.4 ± 18.2	76.9 ± 32.6	0.002
FVC/TLCO%,SD,€	2.5±1.1	1.5 ± 0.5	0.000
SPAP(Mean,SD), €	36.5 ± 20.9	33.6 ± 14.0	0.364
PH (%),€	40	37.1	0.806

SF 36: Quality of life Assessment Scale, mMRC: Modified Medical Research Council Dyspnea Scale, 6MWD: 6-Minute Walking Distance, TLC: Total Lung Capacity, RV: Residual Volume, FEV1: Forced Expiratory Volume in One Second, FVC: Forced Vital Capacity, MEF25-75: Maximal Median Expiratory Flow, TLCO: Carbon Monoxide Diffusion Capacity, KCO: Carbon Monoxide Transfer Coefficient (TLCO/Alveolar Volume), SPAB: Systolic Pulmonary Artery Pressure (mmHg), PH: Pulmonary Hypertension.
α: 6 MWD could not be evaluated in 8 patients in CPFE, and in 4 patients in IPF.
ß: Body Plethysmograph could not be performed in 3 patients with CPFE.
&: Carbon Monoxide Diffusion Test could not be performed in 4 patients with CPFE.
€: ECHO could not be performed in 1 patient with CPFE and 5 patients with IPF.

tested whether the quantitative data were normally distributed. The quantitative data that were normally distributed were compared with the Student's T-test. The data were given as mean ± standard deviation. Chi-square test and Fisher's exact test were used to compare qualitative data and results are presented as frequency (%). The Pearson Correlation Test was used to determine if there were any relations between clinical parameters; and $p < 0.05$ was considered to be statistically significant.

Results

Of the 76 patients, 36 were in the CPFE group and 40 in the IPF group. The mean age was 66.9 ±7.5 years in CPFE and 68.3 ±7.3 years in IPF. CPFE group had a significantly higher the rate of male patients (97.2%, p=0.02), smoking (smoker and ex-smoker) (97.2%, p=0.00), cigarette pack/year (51.6±40.6, p=0.004) than the IPF group. No significant difference was found between the groups in terms of the symptoms and incidence of at least one comorbidity. The body mass index (BMI) values of the CPFE group were found to be lower than IPF group (p=0.02). The frequency of acute exacerbations in the last year was significantly higher in the CPFE group than the IPF group (p=0.001) (Table I).

In the CPFE group, the total score of SF-36 was lower than the IPF group in the quality of life assessment scale, which included 36 questions (p =0.001). The mMRC score and 6 MWD were similar in the both groups. When compared with the IPF group; in the CPFE group, FVC% (p=0.00), FEV1% (p=0.049), TLC% (p=0.002), RV% (p=0.00), RV/TLC (p=0.00) and FVC/TLCO% (p=0.00) were higher, TLCO% (p=0.002), KCO% (p=0.002), MEF 25-75% (p=0.001) and FEV1/FVC (p=0.00) were lower than IPF group. It was seen that the echocardiographi-

Table 3. Treatments administered to patients with CPFE and IPF.

	CPFE (n=36)	IPF (n=40)	p value
LTOT (n,%)	15, 41.7	8, 20.0	0.040
Treatment (n, %)			
Antifibrotic	10, 27.8	38, 95.0	
BD	16, 44.4	1, 2.5	
Corticosteroid	1, 2.8	0, 0.0	
Antifibrotic + BD	3, 8.3	0, 0.0	
Corticosteroid + BD	1, 2.8	0, 0.0	

LTOT: Long-Term Oxygen Therapy, BD: Bronchodilator.

cally detected the PH was 40% in CPFE and 37.1% in IPF, and there were no significant differences between them (p=0.806) (Table II).

The two groups were also comparable with regards to the long-term oxygen they (LTOT) ratios at study entry. CPFE patients who LTOT had a significantly graeter than the IPF patients (p=0.04). 95% of patients with IPF were treated with antifibrotic therapy. 52.7% of the patients with CPFE were using bronchodilator, 36.1% antifibrotic, 5.6% systemic corticosteroid (Table III).

From the date of diagnosis, the number of patients who died due to any cause was 9 (25%) in CPFE and 8 (20%) in IPF, and there were no significant differences between the two groups (p=0.601). The mortality rate from any reasons in the last 2 years from the date of diagnosis was 11.1 % (n= 4) in CPFE and 7.5 % (n=3) in IPF. In the IPF group; the number of patients with PH was negatively correlated with TLC, FEV1, FVC, and TLCO (r =-0.353, p=0.037; r =-0.438, p=0.008; r =-0.512, p=0.002; r =-0.424, p=0.011, respectively), and positively correlated with the number of patients who received LTOT (r =0.435; p=0.009). mMRC was negatively correlated with FEV1(r =0.405; p=0.010), and FVC (r =-0.447; p=0.004), in adition it was positively correlated with LTOT (r =0.564; p<0.001) and pulmonary artery diameter (r =0.458; p=0.003).

In the CPFE group; There was a significant negative correlation between the number of patients with PH and TLC (r =-0.381; p=0.031). While pulmonary artery diameter was negatively correlated with TLCO (r =-0.497; p=0.004), it was positively correlated with LTOT (r =0.374; p=0.025). mMRC was negatively correlated with TLCO (r =-0.369; p=0.038), positively correlated with LTOT (r =0.442; p=0.007), sPAP (r =0.335; p=0.049), and pulmonary artery diameter (r=0.390; p=0.019). A positive correlation was found between 6 MWD and FEV1 (r =0.488; p=0.008), FVC (r =0.532; p=0.004).

Discussion

Although the frequency of coexistence of emphysema and fibrosis is not known exactly, high prevalence rates are reported in many studies [20,21]. In CPFE, fibrosis and emphysema have cumulative effects on gas exchange, low DLCO , and pulmonary hypertension [9].

Patients with CPFE are commonly men with a heavy-smoking history. They need more oxygen therapy [22,23]. In our study, it was found that the number of male patients and smoking history were higher in CPFE patients than IPF. Zantah M. et al. found the frequency of acute exacerbations in patients with isolated IPF and patients with CPFE to be similar [24]. We found the frequency of acute exacerbations higher in the CPFE group compared to IPF in our study.

Obstructive airway limitation is observed in spirometry in some patients with CPFE [25]. We found that the incidence of COPD was significantly higher in the CPFE group when compared to the IPF group.

The SF-36 total score was significantly lower in the CPFE group than the IPF group. As the study of Çiftçi F. et al. [23], no significant difference was found between the groups in terms of 6 MWD and mMRC scores in our study. We thought that the inconsistent results in physical function tests were due to the heterogenity of the patients in the CPFE group.

The coexistence of pulmonary fibrosis and emphysema affects pulmonary function tests differently than patients with fibrosis alone [26]. A disproportionate deterioration in gas exchange, that is, a decrease in DLCO while preserving lung volumes, plays a key role in the diagnosis of CPFE [27]. In fibrosis, the thickness of the alveolar membrane increases. In emphysema, the vascular surface area is reduced. Therefore, diffusion capacity is significantly reduced in patients with CPFE compared to patients with fibrosis alone. Alveolar wall damage in emphysema causes air trapping and increases residual volume and total lung capacity [28].

The functions of the alveolo-capillary unit are reduced in the presence of emphysema because there is a destruction of the extracellular matrix. For this reason, there is a significant decrease in carbon monoxide diffusion capacity in CPFE. Lung volumes decrease in pulmonary fibrosis because of the increased elastic recoil power and decreased compliance of the lung [29]. Yoon H-Y et al. found higher TLC% and FVC% levels and lower FEV1/FVC levels in patients with IPF with emphysema when compared to those without emphysema (p<0.05) [22]. Ryerson CJ et al. also detected FVC%, FEV1%, and TLC% at higher levels in CPFE when compared to isolated IPF. In addition, FEV1/FVC and DLCO% were lower in CPFE (p<0.05) [9]. In our patients with CPFE, lung volumes were preserved or a slight decreased, but TLCO was further reduced. TLC, FVC, and FEV1 were higher, FEV1/FVC and TLCO were lower in the CPFE group than IPF.

In CPFE, Cottin V. et all found that risk of developing PH were higher than alone pulmonary fibrosis and alone emphysema [5]. The pulmonary capillary surface area decreases and pulmonary vascular resistance increases in both emphysema and fibrosis [30]. Ryerson CJ. et al. found that the sPAB was significantly higher in ECHO in the CPFE group than the alone IPF group (p=0.008) [9]. In some previous studies, the probability of increased PH was similar in CPFE and IPF patients (p>0.05) [23,31]. We also did not detect any significant differences between the groups in terms of PH (p=0.806).

The treatment options for CPFE are limited because of the scarcity of randomized studies. Smoking cessation, oxygen

therapy in hypoxemic patients [32], bronchodilator [33] use in patients who have airway obstructions and antifibrotic (i.e. pirfenidone, nintedanib) can be used in appropriate patients [34]. In correlation with the decreased TLCO, oxygen desaturation is also observed at rest or exercise in CPFE [10,35]. Emphysema increases exercise desaturation. This also reduces physical activity [36,37].

Costa CM et al. reported that exercise dyspnea and hypoxemia were more common in CPFE compared to patients with IPF due to poor ventilation (dead space ventilation) [37]. In our study, it was found that patients with CPFE needed more oxygen therapy.

For the last decade, nintedanib and pirfenidone, which are FDA-approved antifibrotic agents, were used in the treatment of IPF [38,39]. In this study, approximately half of the patients with CPFE received bronchodilator, 36% antifibrotic, and 5.6% corticosteroid treatment. The majority of patients with IPF used antifibrotic treatment. It is not known whether there is difference in mortality between CPFE and IPF. The reason for this difference depends on the degree of emphysema and fibrosis [40]. In some previous studies, no significant differences were detected between the two groups in terms of survival and mortality rates [4,9]. Another studies have reported that the 5-year survival was lower in the CPFE group ($p< 0.05$), and the mortality rate was higher ($p< 0.05$) in the CPFE group [10,11].

We also found that the mortality rate was similar in the CPFE and IPF groups . It was reported that these different results on mortality may be because of the heterogeneity (i.e. the differences in the degree of fibrosis and emphysema) in patients with CPFE [41].

Conclusion

Patients with CPFE have male dominance, heavy smoking, greater lung volume, reduced diffusion capacity, more severe air trapping, worse life quality, and more severe desaturation. In this study, pulmonary hypertension and mortality have found to be similar in CPFE and IPF. It has concluded that CPFE is an entity with a poor prognosis like IPF. There are also studies reporting that CPFE has a worse prognosis. Large multicenter studies examining the clinical and radiological features of patients with CPFE will yield more satisfactory results about the course of CPFE.

Limitations

The limitations of our study were that the study had a single-centered and retrospective design, the degree of emphysema and fibrosis could not be measured quantitatively in HRCT at the diagnosis stage, and the heterogeneity that was caused by the difference in the emphysema and fibrosis rates of the patients who were included in the CPFE group. Since the number of patients in both groups was small, sample size could not be made.

Conflict of interest statement

We have declared that we do not have any conflict of interest.

Ethical approval

The study, which was designed in line with the Declaration of Helsinki and good clinical practices, was approved by the Ethics Committee of Health Sciences University Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital (No=49109414-806.02.02, date: 09.11.2017).

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