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THE EXTENT OF EMPHYSEMA IN PATIENTS WITH CPFE AND IPF: PROGNOSTIC SIGNIFICANCE AND CLINICAL IMPLICATIONS FOR THERAPEUTIC APPROACH

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Thesis summary

Background

Combined Pulmonary Fibrosis and Emphysema Syndrome (CPFE) is a smoking-related interstitial lung disease characterized by the coexistence of emphysema and pulmonary fibrosis. This combination results in relatively preserved lung volumes due to the counterbalancing effects of restriction and obstruction, but it is accompanied by severely impaired lung diffusion. While it is well established that emphysema significantly worsens survival outcomes in patients with pulmonary fibrosis, limited evidence exists regarding the predisposing factors influencing the interaction between these two conditions. Additionally, the extent of emphysema and its implications for prognosis and other clinical outcomes remain poorly understood. Although long-acting β2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) have demonstrated effectiveness in improving quality of life (QoL) in patients with obstructive lung diseases, their role in managing CPFE has not been adequately investigated, leaving a critical gap in current knowledge. The clinical implications of emphysema in pulmonary fibrosis warrant focused investigation, as its extent may define a distinct phenotype that represents more than the mere coexistence of two diseases. However, robust data addressing these issues from both epidemiological and clinical perspectives are lacking, emphasizing the urgent need for comprehensive studies to improve understanding and management of this complex condition.

Aim and structure of the research project

This research project is structured as follows. Initially, a comprehensive review of the literature was conducted to provide an in-depth introduction to the disease, encompassing the available pathophysiological, epidemiological, and clinical evidence. Building on this foundation, an experimental design was developed to investigate the clinical significance of emphysema in patients with pulmonary fibrosis, with a focus on the predisposing factors influencing its association with lung fibrosis, its impact on prognosis, and the determinants predicting both prognosis and response to bronchodilator therapy. To achieve these objectives, the project evaluates the therapeutic benefits of bronchodilator therapy and its implications for management strategies, examines the relevance of emphysema with particular attention to its relationship with lung fibrosis and its prognostic impact, and explores the factors predicting clinical outcomes and survival in patients with concurrent

pulmonary fibrosis and emphysema. These aims were addressed through three focused studies, as outlined below:

- The first project was conducted with an exploratory monocentric prospective study that enrolled patients with CPFE referred to the Rare Lung Diseases Center of Modena, aimed at evaluating changes in self-reported symptoms, QoL, respiratory function, and functional performance following bronchodilator therapy. Patients with obstructive deficit were excluded. The patients received inhaled bronchodilator therapy for three consecutive months. Symptoms, QoL (measured by SGRQ, mMRC, CAT), pulmonary volumes through pulmonary function tests (PFT), and functional performance via the 6-minute walk test (6MWT) were assessed at baseline and three months later. A total of 30 patients were enrolled (mean age 75, range 70-80, M=29). At baseline, the average QoL scores were 33 (23-46) for SGRQ, 2 (2-3) for mMRC, and 15 (11-21) for CAT. At three months, a significant decrease in all three scores was recorded (SGRQ -10.9, mMRC -0.82, and CAT -4.9 points, $p<0.0001$). Additionally, a significant reduction in RV was measured ($p=0.048$) and there was a trend towards increased distance in the 6MWT ($p=0.07$). This exploratory study showed the effectiveness of bronchodilator therapy on self-reported QoL and residual lung volume in patients with CPFE.

- The second project was conducted with a retrospective, observational and longitudinal study that collected data (epidemiology, comorbidities, pulmonary function, and mortality) from 155 patients of Bellvitge University Hospital (Barcelona) at diagnosis, 1, 3, and 5 years: 43 CPFE (>10% emphysema identified via high resolution computed tomography by experienced radiologist), 31 IPF with emphysema (5% and 10% emphysema), 31 IPF without emphysema, and 50 COPD with emphysema. The study showed that patients with CPFE and IPF with emphysema had greater exposure to smoking and a higher prevalence of pulmonary hypertension (PH), lung cancer, paraseptal emphysema and pneumothorax. Patients with CPFE exhibited greater dyspnea and oxygen (O2) requirements at diagnosis, with more rapid progression during the first year after diagnosis (assessed based on distance and O2 therapy in the 6MWT). The survival rate was worse and proportional to the extent of emphysema (E), with even poorer outcomes in CPFE-IPF (CPFE-IPF

> IPF with E > IPF without E; p<0.001). At diagnosis, patients with CPFE compared to those with IPF had higher values of FVC, RV, and FRC, which gradually increased with the extent of emphysema; and lower values of MEF50% and 25% (maximum expiratory flow), FEV1 and KCO (carbon monoxide transfer coefficient) that decreased gradually with the extent of emphysema. The study found that mortality in patients with CPFE-IPF and IPF was proportional to the extent of emphysema. Patients with CPFE had a higher prevalence of comorbidities and a greater rate of progression during the first year after diagnosis. Comorbidities were also directly proportional to the extent of emphysema.

- The third project was a retrospective, observational, and longitudinal multicenter study designed to explore the factors predicting clinical outcomes and survival in patients with concurrent pulmonary fibrosis and emphysema. The study included patients with CPFE and IPF with emphysema (IPF with E) who were referred to the Interstitial Lung Disease Unit of Bellvitge University Hospital (Barcelona) and the Rare Lung Disease Center of Modena. A total of 88 patients with CPFE and 35 patients with IPF with E were evaluated. Prognostic factors were assessed, with a particular focus on respiratory function parameters, such as the decline in FEV_1+FVC over the previous 12 months. The study found that patients with CPFE who exhibited a decline in FEV_1+FVC greater than 5% within a 12-month period had significantly higher 5-year mortality from the time of diagnosis (p=0.04), underscoring the prognostic value of tracking pulmonary function decline in this population.

Conclusion

In conclusion, this research project provided significant insights into the clinical significance of emphysema in patients with pulmonary fibrosis by addressing its key objectives. First, it evaluated the therapeutic benefits of bronchodilator therapy, demonstrating that such treatment, regardless of the presence of an obstructive pattern, improved symptoms, enhanced QoL, and reduced hyperinflation in patients with CPFE. Second, it examined the relevance of emphysema in this population, showing that mortality and comorbidities are directly proportional to the extent of emphysema, with CPFE exhibiting more rapid disease progression compared to IPF during the first year after diagnosis. Finally, it explored factors predicting clinical outcomes and survival, identifying a decline in FEV_1 + FVC > 5% over 12

months as a significant prognostic indicator of higher 5-year mortality rates. Together, these findings emphasize the need for tailored management strategies in this complex condition.

Chapter 1. Combined Pulmonary Fibrosis and Emphysema: state of the art

Definition

Combined Pulmonary Fibrosis and Emphysema Syndrome (CPFE) is a smoking-related interstitial lung disease characterized by the coexistence of emphysema with pulmonary fibrosis. Pulmonary fibrosis is primarily localized in the lower lobes, while emphysema is more commonly found in the upper lobes [1].

History

In 1948 was published the first case report of CPFE, associated to right heart failure, by Mallory et al. [2] and the first description of areas of fibrosis interspersed with areas of emphysema on chest radiograph by Robbins et al. [3]. The histopathological coexistence of pulmonary fibrosis and emphysema was first recorded in 1974 by Auerbach and colleagues, who described the presence of both entities in autopsies of smokers' lungs. Its association with cigarette smoking has been demonstrated in numerous studies. Auerbach, in a pathological study of autopsies from the lungs of 1824 subjects, clarified that smoking is responsible for the onset of both emphysema and fibrosis in the pulmonary parenchyma [4]. Additionally, experimental studies on animals showed that cigarette smoke exposure also leads to pulmonary fibrosis and emphysema in dogs [5]. Later, in 1990, Wiggins et al. identified the combination of these two distinct entities on HRCT scans in eight patients: cryptogenic fibrosing alveolitis (as idiopathic pulmonary fibrosis (IPF) was then called) confirmed by histological examination in four patients, and emphysema, predominantly in the upper lobes. All the patients were smokers or former heavy smokers. The study also showed that all patients had severe dyspnea, a reduced diffusion capacity for carbon monoxide (DLCO median 32.4%), preserved lung volumes (mean VC 98.7%, mean TLC 92.5%), and no evidence of airflow obstruction (FEV1/FVC 84.6%). These results already indicated that pulmonary function tests alone can be misleading when evaluating patients with interstitial lung disease, highlighting the importance of computerized tomography [6].
A few years later, in 1993, a Japanese study by Hiwatari described a syndrome composed of two diseases that were distinct in both clinical and pathological aspects: pulmonary fibrosis and emphysema. However, it was not clear whether the onset of emphysema was

due to fibrosis, and it was hypothesized that both entities might arise from the same harmful processes/elements followed by different repair mechanisms [7].

After numerous studies, it was only in 2005 that Cottin used the term CPFE, thus giving a name to the condition. He defined it as a syndrome consisting of both pulmonary fibrosis and emphysema, as seen on computerized tomography. The characteristic pulmonary functional profile manifests as subnormal spirometry characterized by preserved lung volumes. The syndrome is also marked by severe gas exchange impairment, hypoxemia during exercise, a high prevalence of pulmonary hypertension, and poor survival [1].

Epidemiology

The exact incidence of CPFE in the general population remains unknown. Many patients initially diagnosed with IPF may actually have CPFE. Emphysema is common in current of former smokers with fILD.

Prevalence estimates of CPFE vary depending on the population studied and the definition used, ranging from 8-67% of patients with IPF.

CPFE is reported in 26-54% of patients with IPF, with higher prevalence in those requiring hospital admission.

The average age of onset of CPFE is 65 years, and most patients are male smokers or former heavy smokers (> 40 pack-years) [8, 9, 10].

Etiology and pathogenesis

Exposure

Cigarette smoking and male sex are consistently associated with CPFE. CPFE occurs nine times more often in males, and this discrepancy is not wholly attributable to a greater history of smoking in males.

Almost all patients with CPFE report a history of smoking with an average exposure of 40 pack-years, with notable exceptions of some patients with connective tissue disease (CTD) or fibrotic hypersensitivity pneumonitis (fHP) who on average have less smoking exposure.

Multiple occupational and inhalation exposures are associated with CPFE. CPFE is reported in patients with asbestosis and silicosis. Interestingly, emphysema occurs in 7-23% of patients with fHP. Occupational exposure to vapors, dusts, gases and fumes is associated with more extensive radiologic emphysema after adjusting for smoking pack-years [11,12].

Genetic predisposition

Genetic predisposition in combination with risk factors, including smoking or exposure to other aerocontaminants, may predispose individuals to develop both fibrosis and emphysema, both of which involve aging and cell senescence. Genetic predilections for CPFE are not well understood, with only a few cases reported of mutations carrying a Mendelian risk of CPFE or IPF. CPFE has been reported in patients carrying mutations in genes associated with surfactant (SFTPC, ABCA3) or telomeres (TERT, TERT1) or other genes (Naf1, PEPD, MMP-9, TGF-B1, AGER, rs2076295 GG). Shorter telomeres are associated with both chronic obstructive pulmonary disease (COPD) and IPF and are thus likely associated with CPFE. If confirmed, CPFE would represent a model of smoking-induced, telomere-related lung disease. Epigenetic alterations may also be important [13,14,15].

Pathogenesis

The pathogenic mechanisms leading to the coexistence of emphysema with IPF and other fILDs remain unclear. Clustering of pulmonary fibrosis and emphysema supports the notion of a shared pathophysiology. There is a bidirectional interaction between emphysema and fibrosis through mechanical forces. Many pathways and pathogenetic mechanisms are shared between fibrosis and emphysema, including gene expression and pathways, gene variants, telomere dysfunction and shortening, alveolar alterations, epigenomic reprogramming and enzymatic activity, especially matrix metalloproteinases with the increased elastolytic and neutrophil elastase activity and the involvement of fibrocytes [16,17].

Clinical Presentation

Clinically, patients present with chronic cough and dyspnea, more pronounced during exertion. The cough can be either productive or non-productive. On pulmonary auscultation, a reduction in vesicular murmur breath sounds due to emphysema and bibasilar inspiratory crackles, may be detected. These characteristic lung sounds are referred to as "Velcro crackles" and are similarly heard in patients with IPF. Occasionally, digital clubbing may be present. Other less common symptoms include wheezing, perioral cyanosis, and fatigue. In most cases, the patient experiences fatigue and dyspnea with activities below their normal capacity. In more severe cases, the patient may experience symptoms even at rest, and any

physical activity will increase the discomfort experienced [18]. A recent study confirmed that, contrary to common belief, hypoxemia is not in itself the main factor responsible for respiratory difficulty in CPFE patients. Instead, dyspnea seems more related to excessive ventilation due to exertion, which leads to a downward shift in PaCO2 values. Hypoxemia and respiratory failure are common in these patients due to severely compromised gas exchange capacity, while hypercapnia occurs less frequently compared to COPD patients [19]. Patients with CPFE have a mean age of 65-70 years (comparable to IPF and COPD), with 73-100% male predominance [1].

Diagnosis

For the diagnosis, high-resolution CT (HRCT) is used in combination with respiratory function tests. Radiologically, the coexistence of a pattern of fibrosis, mostly at the bases, and emphysema, mostly in the upper fields, is required. Spirometry shows that flows and volumes remain relatively preserved, while there is a severe reduction in DLCO. A chest X-ray usually reveals an interstitial pattern and reticular-nodular infiltrates in both lung bases and in the subpleural region. Additionally, hypodyaphania is present at the apices with thinning of the pulmonary vessels and a reduction in their number.

However, the radiological findings of this entity may go unnoticed on a simple chest X-ray, and for this reason, HRCT scanning is the most appropriate technique to confirm the diagnosis [20].

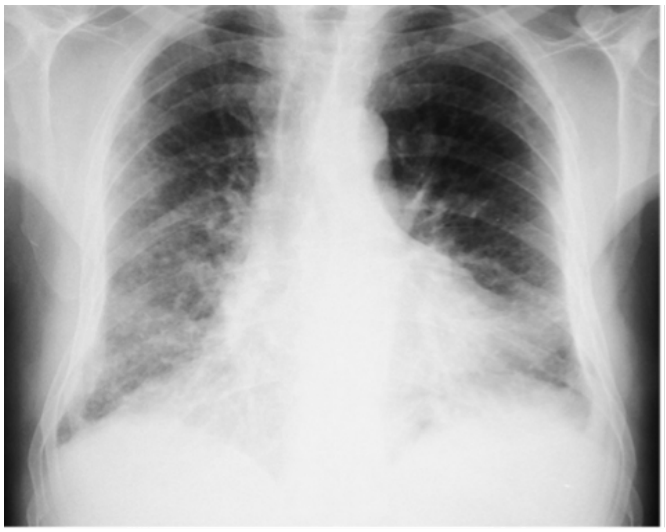

Figure 1. Chest X-ray of a patient diagnosed with CPFE.

Radiological features

In order to diagnose CPFE, radiological evidence of interstitial fibrosis and emphysema on chest HRCT is needed. Emphysema is identified as a region of low attenuation or density, not bounded by visible walls on CT and it can be categorized as centrilobular, paraseptal or panacinar.

Interstitial fibrosis is identified as regions of increased parenchymal attenuation, appearing as reticulation and/or ground glass opacities, variably associated with honeycombing and/or traction bronchiectasis. No studies have formally compared patterns of emphysema in CPFE versus COPD. Classical HRCT patterns may be altered when emphysema and fibrosis are spatially superimposed. For example, expansion of the interobular septa with collagen fibrosis can make paraseptal emphysema appear as a honeycomb cysts. Therefore, distinguishing admixed emphysema from honeycomb cysts is challenging. The coexistence of emphysema and fibrosis can also create an imaging pattern of thick-walled cystic lesions, thought to reflect the expansion of emphysema as it is pulled apart by adjacent contracting fibrotic lung. This process could be termed traction emphysema given its putative mechanistic similarity to tractionally dilated bronchioles commonly seen within areas of fibrosis [20,21].

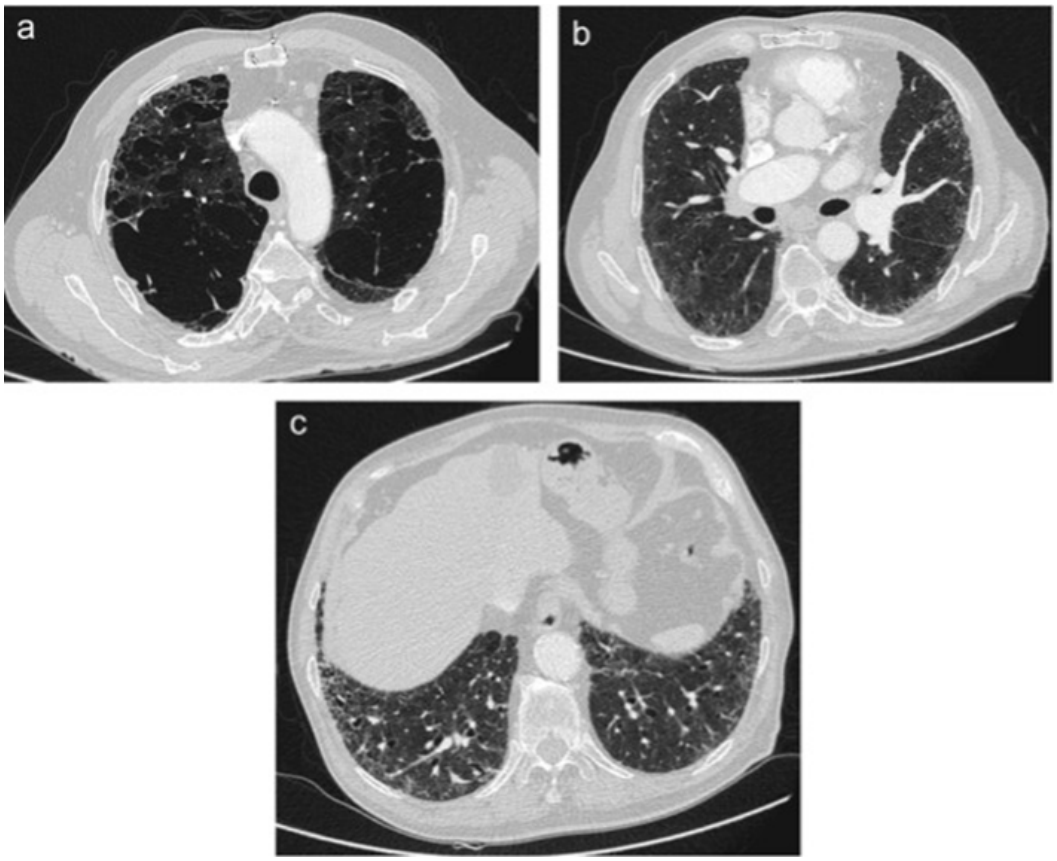

Figure 2. HRCT images of CPFE with emphysema in the upper lobes and fibrosis in the lower lobes.

Emphysema quantification

Emphysema is a lung disease characterized by the dilation of the airspaces distal to the terminal bronchioles (i.e., the cavities formed by the alveoli) due to the destruction of their walls. The result is a loss of elasticity in the organ. The various structural changes caused by emphysema lead to an obstructive deficit, a typical pattern of chronic obstructive pulmonary disease (COPD). Based on the location of the affected acini, different types of emphysema can be distinguished:

- **Centrolobular (or centroacinar) emphysema**, which appears on radiological images as small focal areas with reduced attenuation located in the central portion of the lung lobe. It is mainly associated with cigarette smoking;
- **Panacinar emphysema** (more commonly observed in patients with α-1-antitrypsin deficiency), which affects terminal bronchioles, central acini, and peripheral acini;

- **Paraseptal emphysema**, which may occur alone or in combination with the above types, and involves changes in the peripheral acini of one or more lobes.

The emphysema component of CPFE has been evaluated by imaging rather than lung function tests, given the confounding impact of fibrosis on lung physiology. Reliable estimation of emphysema extent in patients with established pulmonary fibrosis poses significant challenges. Most studies use visual assessment of emphysema by an experienced radiologist, a method that is readily available and has moderate interrater agreement.

Emphysema thresholds used to characterize a CPFE phenotype on imaging, include: <5%, >5%, >10%, and >15% of total lung volume [10]. Quantitative methods for scoring emphysema using computer-based measurement of lung density (e.g., density masking) are typically used in studies of COPD and remove the problem of observer variability. However, this methodology of emphysema quantification is poorly suited to CPFE despite being attempted in some series, because it fails to discriminate between low-density areas due to emphysema and low density due to honeycomb cysts, traction bronchiectasis, or nonemphysematous mosaic attenuation due to small airway disease. Until this limitation can be overcome (possibly by artificial intelligence), visual quantification of emphysema extent remains the method of choice in CPFE. Differences in morphological patterns of emphysema (subtype: paraseptal vs. centrilobular vs. mixed vs. indeterminate; predominant distribution in the axial plane) have also been used to describe CPFE subtypes [10,22]. Large multicentered studies are required to determine whether these morphological CPFE subtypes correlate with distinct functional or prognostic disease groups. The subtypes identified on HRCT imaging could also be confirmed using histopathological correlative studies.

Fibrotic pattern

The most common radiological pattern of fibrosis seems to be UIP (Usual Interstitial Pneumonia), but the literature reports various cases of other patterns consistent with interstitial lung diseases. This suggests a wide heterogeneity in presentation. Studies on CPFE have described cases of nonspecific interstitial pneumonia (NSIP), chronic hypersensitivity pneumonia (HP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), or cases of unclassified interstitial lung disease. CPFE has also been described in the context of smokers with

interstitial lung disease associated with connective tissue diseases (CTDs), especially in association with rheumatological diseases such as rheumatoid arthritis and systemic sclerosis.

The interstitial lung diseases (ILD) that characterize CPFE can therefore be idiopathic pulmonary fibrosis with a UIP pattern, various diseases from the more diverse group of ILD that are classifiable, or other unclassified ILDs [20,23].

Pathology features

CPFE was originally defined based on clinical, physiologic, and HRCT features [2]. Histopathologic studies of patients with severe CPFE defined in this way are limited to small series of autopsy cases or explants, given the risk of surgical lung biopsy in this population. Overlapping patterns of smoking-related abnormalities are common in lung biopsies from patients undergoing elective lung biopsy for fILD, including some for whom a diagnosis of CPFE is uncertain or unanticipated. Here we review patterns of smoking-related abnormalities and pulmonary fibrosis, with a focus on features characteristic of CPFE. Emphysema is required for a diagnosis of CPFE and is defined as abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by the destruction of their walls, without obvious fibrosis. Centrilobular emphysema is an upper-lobe–predominant form of emphysema caused by cigarette smoking that is often accompanied by paraseptal emphysema in patients with CPFE. Emphysema is common in surgical lung specimens and frequently coexists with other smoking-related abnormalities, including respiratory bronchiolitis (RB) and SRIF. RB occurs almost exclusively in cigarette smokers and is defined by the presence of pigmented alveolar macrophages clustered within the lumens of respiratory bronchioles and peribronchiolar air spaces without significant inflammation or fibrosis.

RB-ILD is a diagnosis of exclusion reserved for patients in whom RB is thought to explain diffuse ILD after elimination of diagnostic alternatives, a circumstance histologically indistinguishable from incidental RB. RB by itself is not a fibrotic lesion and is therefore an insufficient explanation for fibrosis in patients suspected of having CPFE.

Patterns of fibrosis observed in patients with CPFE are histologically heterogeneous. These patterns include a distinctive form of fibrosis linked to cigarette smoking, for which Katzenstein proposed the term SRIF. SRIF overlaps with previous descriptions of AEF, RB-associated ILD with fibrosis, RB with fibrosis, and DIP. Some cases with a pattern of fibrotic

NSIP may also be related to smoking [10].

SRIF is characterized by densely eosinophilic collagen deposited in expanded alveolar septa with preservation of lung architecture and little or no inflammation.

SRIF has a distinct predilection for peripheral subpleural and peribronchiolar parenchyma without the variegated “patchwork” distribution more characteristic of UIP. When combined with paraseptal emphysema, SRIF may account for the “thick-walled cystic lesions” that are unique to CPFE and distinct from the honeycomb cysts of UIP. SRIF without other patterns of concomitant fibrosis has not been established as a cause of CPFE; therefore, attributing pulmonary fibrosis to SRIF in patients with CPFE requires exclusion of other fibrotic patterns, including most importantly UIP.

LCH is a potentially fibrotic form of smoking-related ILD that may occur in combination with other smoking-related abnormalities, including emphysema, RB, SRIF, and DIP. Advanced disease is characterized by cystic change on HRCT that may be difficult to distinguish from emphysema and a pattern of fibrosis in surgical specimens that may mimic other forms of fILD. Histopathological examination of surgical specimens from patients with advanced LCH, whether explants or diagnostic biopsies, is often complicated by the absence of diagnostic Langerhans cells. Microscopic features helpful in separating LCH from other patterns of fibrosis include stellate bronchiolocentric nodules and a characteristic pattern of affiliated paracicatricial airspace enlargement (“scar emphysema”) without subpleural honeycomb change. There are no criteria for establishing a diagnosis of CPFE on the basis of histopathological findings alone. Supportive features include a combination of emphysema and a pattern of fibrosis other than SRIF or LCH. UIP is the most commonly reported pattern of pulmonary fibrosis in patients with CPFE. Identifying UIP typical of IPF in the setting of emphysema requires recognition of patchy fibrosis, fibroblast foci, and honeycombing without histologic features to suggest an alternative such as LCH, f-HP, or CTD-associated UIP. Unique to UIP in CPFE is the presence of thick- walled cysts resulting from the combination of emphysema and SRIF. Other less commonly described patterns of fibrosis include fibrotic nonspecific interstitial pneumonia (NSIP) and DIP.

Classifying subtypes of pulmonary fibrosis may be challenging, and therefore the histopathological features may remain indeterminate for UIP in the setting of concomitant emphysema [10,23,24].

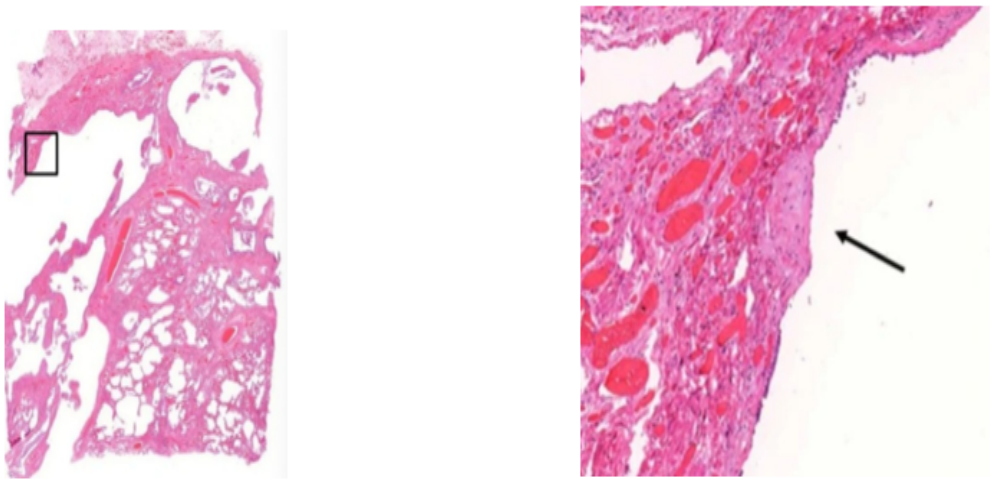

Figure 3. Histological findings of emphysema and fibrobastic foci (arrow).

Lung function

Patients with CPFE have relatively preserved airflow rates and lung volumes, contrasting with limited exercise capacity and severely impaired DLCO and transfer coefficient (KCO). Fibrosis is a condition that leads to a restrictive defect, while emphysema, on the other hand, causes an obstructive defect. These results have a counteracting effect, meaning that the values obtained in spirometry fall within normal limits. Therefore, the preservation of pulmonary function may not only be misleading, potentially underestimating the severity of CPFE, but it could also delay the diagnosis. Compared with isolated IPF, patients with CPFE have higher volumes (FVC, TLC), generally comparable FEV1, higher Residual Volume (RV), lower DLCO and KCO. The mean FEV1/FVC ratio is usually normal or slightly reduced, may increase with progression of fibrosis, but is usually lower than isolated IPF [25,26].

Compared with COPD, patients with CPFE have relatively preserved FEV1 and FEV1/FVC, less hyperinflation and lower DLCO. The isolated emphysematous component typically shows a low FEV1/FVC ratio. This is caused by a reduction in lung elastance and an increase in compliance and lung volume, leading to airway collapse and hyperinflation (air trapping). Specifically, a reduction in FEV1 is observed due to bronchoconstriction, which in turn leads to a reduction in pulmonary flows. Hyperinflation also explains the elevated RV and/or the increased RV/TLC ratio commonly seen in these patients. Conversely, fibrosis leads to increased elastance and a reduction in compliance and lung volumes (reduced TLC

and FVC), producing a restrictive pattern on pulmonary function tests. These different physiological effects caused by the underlying diseases of CPFE result in a generally normal FEV1/FVC ratio and an unaltered RV and/or RV/TLC ratio [27]. Thus, the relative preservation of spirometric values leads to underdiagnosis of chronic lung disease if only spirometry is obtained. The relative preservation of flow rates and lung volumes is attributed to the counterbalancing effects of the restrictive physiology from pulmonary fibrosis and the effect of emphysema on the airways. Conversely, both disease components reduce alveolar capillary gas exchange through either decreased capillary blood volume or alveolar membrane thickening, resulting in greater reductions in DLCO.
Severe decrease in arterial oxygen saturation and hypoxemia at exercise is very common in CPFE, as assessed by 6-minute walking test (6MWT), especially when complicated by severe PH. Hypercapnia occurs only very late in the disease course [28,29]. Patients with CPFE experience a slower decline in FVC than patients with isolated IPF, whereas decline in DLCO and increase in the Composite Physiologic Index (CPI) are less affected. Consequently, no optimal parameter has been validated to monitor disease progression in CPFE. Changes in FVC, commonly used to monitor IPF progression, are not reliable indicators of disease progression in patients with CPFE. Serial change in DLCO may be a helpful marker of disease progression but is additionally affected by other factors, including vasculopathy, hemoglobin concentration and measurement variation [30,31,32].

Natural history and prognosis

The natural history of the disease differs from that of its individual components. Although there are varying opinions in the literature regarding prognosis, CPFE seems to be associated with higher mortality than emphysema alone, while it is unclear whether the prognosis is better or worse compared to pulmonary fibrosis alone. The median survival ranges from 2.1 to 8.5 years and is related to complications such as pulmonary hypertension, acute exacerbation, and lung cancer, which further worsen the prognosis. Various studies in the literature report worse survival in CPFE patients compared to those with isolated IPF, but some researchers suggest better survival in these patients compared to those with IPF alone. Other studies report comparable mortality. These conflicting results could be attributed to sample selection, diagnostic contamination with a higher proportion of non-IPF cases in CPFE population with better survive, attrition bias, difference in the relative extent of emphysema and the lack of formally established diagnostic criteria [8, 10, 26, 29].

There are several important outcomes/complications that have specific relevance affecting the prognosis in patients with CPFE, with lung cancer, PH and acute exacerbation being the most clinically relevant. Possible predictors of mortality in patients with CPFE include DLCO, age, CPI (Composite Physiologic Index) and the presence of specific comorbidities such as PH and lung cancer. Although DLCO is not a specific index of pulmonary disease, because it also depends on cardiovascular factors. FVC has not been shown to be a predictor of death among patients with CPFE, unless the FVC is less than 50% predicted. The lower rate of FVC decline in CPFE is related to the preservation of volumes by emphysema, especially when admixed with fibrosis rather than to slower progression of fibrosis [29,30,31].

However, predictors of mortality in CPFE, including the impact of PH, are not identified consistently in all studies, and further work is needed to determine risk factors for mortality among patients with CPFE. Overall, the data suggest that outcomes are worse for a given extent of fibrosis, when there is emphysema in addition to fibrosis. However, the risk of mortality and of developing PH does not differ in patients with both IPF and emphysema compared with those with fibrosis alone when adjusting for severity using baseline DLCO or total disease extent on HRCT [10, 32].

Pulmonary hypertension

Pulmonary hypertension (PH) has been reported in 15-55% of patients with CPFE, some studies have suggested that the severity of PH is worse among those with CPFE compared with both IPF and COPD or emphysema alone. Estimated systolic pulmonary artery pressure are higher in patients with CPFE than in those with isolated IPF. The additional burden of emphysema, over and above a given extent of fibrosis, increase the risk of PH.

The severe prognosis associated with CPFE seems, at least in part, to be related to the development of severe pulmonary arterial hypertension (PAH). PAH is defined as a mean pulmonary arterial pressure (mPAP) ≥ 20 mmHg at rest. A study has shown that the extent of emphysema observed on HRCT scans is strongly associated with a high estimated pulmonary artery systolic pressure (PAPs), suggesting that a worse prognosis in these patients is related to severe PAH. In cases of pulmonary hypertension observed on CT with contrast, one can see dilation of the central pulmonary arteries [34].

Lung cancer

Lung cancer has been reported in 2-52% of CPFE patients, who have a higher risk of lung cancer than patients with IPF alone. The most common histotype is squamous cell carcinoma, followed by adenocarcinoma, with a predominance of radiological presentation in the lower lobes. In most cases, the patients were male and heavy smokers.
Moreover, the presence of CPFE is associated with worse survival in patients with non-small-cell lung cancer: the presence of honeycombing and emphysema reduces feasibility of surgical resection. The poor outcome is in part related to increased morbidity and mortality of cancer treatments, which often limits standard therapy [35,36].

Acute exacerbations

Acute Exacerbations of IPF have been reported in CPFE patients with different prevalence, diffuse ground-glass and/or consolidation of chest HRCT or XR helps to differentiate exacerbations of fibrosis from exacerbations of emphysema in CPFE. Acute exacerbation (AE-CPFE) is the second main complication. Although the frequency is not known, AE in CPFE is rarer than AE in IPF. Disease exacerbation can be attributed either to the emphysematous component (AE-CPFE of the COPD type) or to the fibrotic component (AE-CPFE of the ILD type). Treatment differs depending on the underlying exacerbation that predominates. In the first case, AE-CPFE of the COPD type, a situation that generally requires hospitalization. The exacerbation presents with an acute worsening of respiratory symptoms and is clinically characterized by airflow obstruction and acute bronchospasm. Radiologically, it can be observed airway wall thickening, atelectasis, consolidations, and mediastinal lymphadenopathy. Standard therapy includes inhaled bronchodilators and systemic corticosteroids. In the case of concomitant bacterial infection, antibiotic therapy is recommended. In the second case, exacerbation is characterized by clinical and radiological criteria like those of acute exacerbations of ILD. These include an acute and clinically significant respiratory decline, characterized by new “ground-glass opacities” on HRCT along with fibrotic foci in the lower lobes. The result is acute hypoxemic respiratory failure. Standard treatment includes high-dose systemic corticosteroids and/or antibiotic therapy. A relatively recent study showed that patients with AE-CPFE of the IPF type have significantly higher mortality compared to patients with AE-CPFE of the COPD type. Moreover, they more frequently require invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO) [37].

Follow-up

Close monitoring is strongly recommended for these patients. Currently, there are no guidelines on the frequency of follow-up visits. Typically, visits are scheduled every 4-6 months and include a complete examination, respiratory function tests, and exercise capacity tests. These include spirometry, carbon monoxide diffusion (DLCO), blood gas analysis, and the 6-minute walk test (6MWT). Every 1-2 years, or in the case of exacerbations, an HRCT is generally requested, while an echocardiogram is typically required annually or when clinically indicated [38].

Terminology and definitions

The contemporary terminology and definition of CPFE was provided in a 2005 publication that described a total of 61 patients who were retrospectively selected from a French multicentric study [1]. In this publication, CPFE was described as the presence of upper-zone–predominant emphysema on HRCT plus a peripheral and basal predominant diffuse parenchymal lung disease with significant fibrosis. Emphysema was not quantified. A recent systematic review identified the heterogeneous definitions and diagnostic criteria previously used in 72 previous studies on CPFE [38]. CPFE was diagnosed based on criteria proposed by Cottin and colleagues [1] in 53% (51/96) of all eligible studies. A diagnosis of IPF was required in 47 studies (49%), whereas 49 (51%) included a variety of non-IPF fILD. The extent of fibrosis was determined visually in 89 studies (93%). A minimal extent of 10% fibrosis on chest HRCT was required in three studies. The majority of studies (75%) diagnosed CPFE if there was any emphysema present on chest HRCT, whereas 25% used a specific threshold: >5%, >10%, >15%, >20%, and >25% of total lung volume. The emphysema was assessed visually in most of the studies [10]. A major limitation of previous CPFE research is the heterogeneity of study populations and criteria used to define CPFE, prohibiting direct comparison of different cohorts and validation of key findings. Both imaging and histopathologic studies indicate that CPFE can include a variety of ILDs. Given its association with smoking IPF is more frequently associated with emphysema than are CTL-ILD of fHP [23]. Studies evaluating prognosis should require separation of patients with and without IPF. Furthermore, few studies have quantified the extent of fibrosis and emphysema on chest HRCT. Automated quantification is challenging when both components are present. It is also debated whether disease extent should be quantified by visual or quantitative methods. Using such thresholds increases the specificity for CPFE, but at the

expense of excluding patients with less extent of either component.

Given the lack of diagnostic criteria the committee of CPFE ATS/ERS/JRS/ALAT Research Statement proposed a common terminology; a provisional, broad *research definition* for CPFE that will enable future research; and provisional classification criteria of CPFE *clinical syndrome* intended to serve clinicians managing patients with CPFE (Table 1). Therefore, the CPFE *clinical syndrome* was identified based on clinical utility, whereas the *research definition* of CPFE delineates a larger group of patients that should continue to be studied, with the goal of reviewing the syndrome threshold as further clinical and pathogenetic data emerge. Similarly, the committee proposes retention of the literal definition of CPFE as the coexistence of both pulmonary fibrosis and emphysema. All subtypes of fILD and emphysema are thus included in the overall CPFE population, but with an important requirement that the fILD subtype be clearly described, given the potential biases that can be introduced by including multiple ILDs in this definition. However, it was proposed that studies on CPFE include a comprehensive description of the radiologic and, when available, of the pathological patterns (e.g., “CPFE–IPF,” or “CPFE–radiologic UIP,” or “CPFE–histologic NSIP,” or “CPFE–radiologic SRIF”) or the underlying disease when known (e.g., “CPFE–fHP” or “CPFE–RA”). This would facilitate comparison between studies through a common terminology and emphasize the heterogeneity of what can be grouped under the umbrella term of CPFE. The committee proposed that in CPFE, emphysema may be present in other areas of the lung, may be admixed with fibrosis, or may be replaced by thick-walled large cysts >2.5 cm in diameter (“CPFE, thick-walled large cysts variant”). Some studies have required a specific extent of emphysema, with 15% predicting a distinct outcome for patients with more than this threshold and 10% being a more commonly used threshold. For research purposes, the committee proposed to define CPFE based on emphysema extent >5% of total lung volume (Table 1). For clinicians managing patients with CPFE, the committee proposed classification of CPFE *clinical syndrome* based on emphysema extent >15% of total lung volume and/or in cases of disproportionately decreased DLCO or precapillary PH not related to the sole presence of emphysema, fibrosis, or etiological context. The committee acknowledged that further research is needed to refine criteria of CPFE *clinical syndrome* [10]. Despite physiological differences compared with isolated ILD and COPD, lung function and especially FEV_1/FVC is not sufficiently sensitive or specific to be useful in defining CPFE; more studies are needed to assess the potential value of Kco or FVC/DLCO. The committee did not recommend a minimal extent of fibrosis on HRCT;

however, they acknowledged that fILD (not ILA) is required to defined CPFE. The committee, however, recommended that fibrosis extent and emphysema extent should both be assessed in future studies, using visual assessment. Finally, the committee indicate that CPFE should be considered a syndrome based on distinct clinical features and pathogenic considerations. The strongest argument is that monitoring of disease progression cannot be reliably based on FVC in patients with CPFE, as it is in IPF. The higher prevalence of cancer and HP further supports the designation of CPFE as a syndrome. In general, additional emphysema alerts the clinician of a greater likehood of PH and greater mortality than might be expected for a given extent of fILD.

Considering the pathogenic aspects thick-walled cystic lesions (with emphysematous destruction and surrounding dense wall fibrosis) may represent a unique imaging pattern of CPFE and the pattern of AEF (airspace enlargement with fibrosis) and SRIF may represent a unique histopathologic pattern of CPFE [10].

Table 1: Proposed ***Research Definition*** of Combined Pulmonary Fibrosis and Emphysema (to Serve Research Purposes) and Classification Criteria of Combined Pulmonary Fibrosis and Emphysema ***Clinical Syndrome*** (Intended to Have Clinical Relevance)

Research definition of CPFE	Coexistence of both pulmonary fibrosis and emphysema Patients must have both criteria on HRCT: • Emphysema of any subtype at HRCT defined as well-demarcated areas of low attenuation delimitated by a very thin wall (<1 mm) or no wall and involving at least 5% of total lung volume • Lung fibrosis of any subtype
Classification criteria of CPFE ***clinical syndrome***: These additional criteria serve research purposes and may be considered depending on the objective of the study	Patients must have CPFE (***see above***) and one or more of the following: • Emphysema extent >15% of total lung volume • Relatively preserved lung volumes and airflow with very or disproportionately decreased D_{LCO}, especially in patients with limited extent of HRCT abnormalities, and in the absence of pulmonary hypertension • Precapillary pulmonary hypertension is considered not related to the sole presence of emphysema (FEV_1 >60%), fibrosis (FVC>70%), or the etiological context (e.g., absence of connective tissue disease)

Therapy

Currently, there are no specific therapeutic treatments for these patients, there is a paucity of data and no clinical practice guidelines. The pathology causing pulmonary fibrosis is typically treated, while for emphysema, bronchodilators may be administered in cases of bronchoconstriction. The choice of therapy follows the guidelines for IPF and, to some extent, for emphysema. The treatment options chosen will therefore be specific to each individual patient and tailored based on the symptom presentation and the severity of the disease.

- **Smoking cessation** is certainly the first and most important reasonable therapeutic

choice for these patients, as well as avoidance of any other potential inhalational exposures. While smoking cessation does not allow for a complete regression of the disease, it may reduce the risk of further deterioration.

- **Supplement oxygen therapy** is used in the contest of resting hypoxemia and showed benefits when used only for hypoxemia that occurs during exercise and nocturnally
- **Pulmonary rehabilitation** remains, as in IPF and COPD patients, an excellent practice for improving the quality of life and exercise capacity in these patients, but there are currently no guidelines for the use of these interventions.

Considering that most exacerbations of both COPD and fILD could be triggered by a respiratory tract infection (either from a virus or bacteria) influenza, pneumococcal and coronavirus (Covid-19) **vaccination** are also provided. In the most severe cases of advanced disease, and for patients who meet the selection criteria, the only definitive treatment is **lung transplantation**. A recent study described the clinical characteristics and outcomes of CPFE after the procedure. This study showed that recipients were more likely to develop primary graft dysfunction (PGD), acute cellular rejection (ACR), and chronic lung allograft dysfunction (CLAD) compared to transplanted IPF patients [38,39]

Treatment of pulmonary fibrosis

Recognition of the individual phenotype of each patient is recommended. Decisions about pharmacologic treatment are guided by the underlying diagnosis of fILD. Management of pulmonary fibrosis in the setting of CPFE is informed by the landmark clinical trials of nintedanib and pirfenidone [40]. Although patients with significant emphysema (greater than the volume of fibrosis on HRCT) and those with significant airflow obstruction have generally been excluded from these studies, the presence of emphysema in a proportion of patients might have contributed to slow decline in FVC in the placebo arm in CAPACITY [41] . A subgroup analysis of the IPF INPULSIS trials with nintedanib found no difference in the magnitude of the treatment effect with regard to the presence of mild-to-moderate emphysema. Importantly, in the INBUILD trial of nintedanib in fibrotic lung disease other than IPF, progressing despite management, the treatment effects were uniform across individual ILDs [42,43]. Therefore, antifibrotic medications may have benefit in patients with IPF with CPFE, and in other forms of pulmonary fibrosis with CPFE, progressing despite management. In patients with fILD other than IPF, combined with emphysema, including fHP and CTD-ILD, glucocorticoids and/or immunosuppressive therapy may be beneficial.

However, there is a need to specifically study CPFE in future trials, given its unique physiology. Specifically, the preserved FVC and slower rates of FVC progression indicate that FVC, the traditional endpoint for IPF trials, may be seriously flawed as a primary endpoint in CPFE, as discussed earlier [30,44].

Treatment of pulmonary hypertension

The use of specific therapies for pulmonary hypertension, including prostanoids, endothelin-1 receptor antagonists, or phosphodiesterase type 5 inhibitors, has shown a poor risk/benefit ratio in treating PAH in patients with CPFE. These drugs have also been shown to worsen hypoxemia due to the vasodilation effect that further aggravates the ventilation/perfusion ratio. Vasodilators would inhibit the hypoxic vasoconstriction mechanism present in these patients, which aims to counteract the worsening of arterial oxygenation. Therefore, no pharmacological therapy is recommended for treating pulmonary hypertension, except for long-term oxygen therapy [34].

Treatment of lung cancer

The overall approach to management of lung cancer in CPFE is similar to other populations, with prioritization of surgical resection where possible (e.g., stage I and II non–small-cell lung cancer), multiple additional options considered in other situations (e.g., chemotherapy, targeted medications, radiotherapy), and palliation appropriate for many patients. Unfortunately, relatively more patients with CPFE are not candidates for various forms of treatment, and complication rates are generally higher for those who are treated, with harm likely driven by the combined severity of emphysema and underlying fILD. For example, standard-of-care cancer treatment could not be instituted in 17% of patients with CPFE and lung cancer because of limitations in treatment directly attributable to CPFE. CPFE is a risk factor for postsurgical morbidity and mortality compared with lung cancer without CPFE, with high rates of acute lung injury, acute disease exacerbations, and tumor recurrence. The risk of treatment-associated acute exacerbation of ILD is of particular concern in patients with CPFE, with increased rates of exacerbation after surgical resection, radiation, and many forms of chemotherapy. Lung-preserving resection options, improved anesthetic considerations, targeted medications, and stereotactic ablative radiotherapy may conceivably all reduce this risk to some extent, although there are currently limited direct data to guide risk estimation. Additional studies will continue to test the safety and efficacy

of these treatment options in patients with fILD, with these results likely to be generalizable to patients with CPFE [35,36].

Palliative care

In the most severe cases, such as with a pulmonary neoplasm and/or serious complications, therapeutic strategies are limited to palliative care only.

- **Use of bronchodilators in COPD:** Inhaled bronchodilators cause the relaxation of the muscles surrounding the bronchi, resulting in improved breathing. The medications used may include:
- **Short-acting bronchodilators**: These produce a rapid effect, but bronchodilation is not prolonged. They are recommended primarily as an initial empirical treatment, as needed, to relieve dyspnea and limit exertion. This class includes short-acting β2-agonists (Short Acting β2-Agonists - SABA) and short-acting muscarinic antagonists (Short Acting Muscarinic Antagonists - SAMA).
- **Long-acting bronchodilators**: In this case, the bronchodilator effect lasts longer (approximately 12-24 hours), so depending on the active ingredient, these medications are used as regular therapy for the disease. This improves symptoms progressively and reduces the risk of exacerbations. The pharmacological class of long-acting bronchodilators includes long-acting β2-agonists (Long Acting β2-agonists - LABA) and long-acting muscarinic antagonists (Long-Acting Muscarinic Antagonists - LAMA).

For mild COPD, bronchodilators should be used exclusively as needed (SABA or SAMA). If, on the other hand, the disease is moderate to severe and the patient, despite therapy, presents significant symptoms and exacerbations, the use of long-acting bronchodilators regularly is recommended. In this case, LAMAs are the first choice, as they have shown a greater effect in reducing exacerbations compared to LABAs and also reduce hospital admissions. In patients with poor control of respiratory activity and frequent exacerbations the combination of LAMA + LABA may be considered. In addition to bronchodilation, inhaled corticosteroid (ICS) therapy may be indicated. This therapy is particularly recommended in severe cases with recurrent exacerbations or when COPD is associated with asthma [45].

Use of bronchodilators in CPFE

Recognition of the individual phenotype of each patient is recommended, given the lack of controlled data specific to the treatment of CPFE. Patients with a CPFE diagnosis who

present with an obstructive or mixed deficit could benefit from the use of inhaled bronchodilators [46]. This therapeutic strategy is commonly used in COPD patients, but there is still limited data in the literature on its use in CPFE patients. Inhaled bronchodilators may have benefit in select patients with CPFE who have significant airflow limitation (i.e., COPD) [47], and few studies have suggested a possible improvement in FEV_1 or symptoms after the use of a combination of inhaled corticosteroid and long-acting bronchodilator, however, even patients with obstructive pattern at spirometry were included [48,49]. Further studies of inhaled bronchodilators with or without corticosteroids are needed in patients with CPFE because of the relatively well-preserved spirometric values. Surgical or bronchoscopic lung volume reduction therapy removes emphysematous tissue, enabling relatively normal tissue to expand; however, most patients with CPFE would be precluded from such procedure, given the frequently severe reduction in DLCO. Bronchoscopic approach with endobronchial valves is generally safer, although no direct comparison with surgery was performed. It is uncertain, however, whether removal of emphysematous tissue will lead to improvements or worsening of lung mechanics in those with CPFE [46].

Unmet needs and clinical perspective

Clinical trials on CPFE are limited, in part because of its complicated pathophysiology and the lack of a standardized definition. The potential impact of emphysema (CPFE) on commonly used outcomes in COPD and ILD, and the change of these variables over time is uncertain and presents difficulty when considering how to include and study these patients in clinical trials. In particular, the use of FVC is not a reliable endpoint in CPFE because of its relative stability [30, 50], despite disease progression and a high risk of mortality. The use of DLCO is limited by the general functional severity of disease (i.e., floor effect), variability of measurement, and its multiple determinants (cardiovascular determinants, haemoglobin) [51]. CPI is not validated as an endpoint. Consideration could be given to a composite endpoint (e.g., death, respiratory hospitalization, or categorical FVC decline). However, composite endpoints are usually driven by, and are only as meaningful as, their least-severe component. HRCT analysis of fibrosis either using visual methods or future quantitative computer tools that can discriminate emphysema accurately and/or blood biomarkers may be particularly useful if validated as endpoints.

One retrospective series suggesting that change in FEV_1 (decline in FEV_1 >10% over 12 months) was the best physiologic predictor of increased risk of mortality in patients with at

least moderate CPFE [52]. Although further study is needed, these limited data may have important implications during the design and execution of future clinical trials [10]. The observation that serial change in FVC, now the favoured primary endpoint in IPF treatment trials, is confounded by concurrent emphysema, has major implications for future IPF trial design [30]. In future IPF trials, patients with a significant functional impact from concurrent emphysema are likely to be excluded. The approach taken in the CAPACITY and ASCEND trials of pirfenidone was to exclude patients with obstructive lung disease based on FEV1/FVC ratio ,0.7 or ,0.8, respectively [41]. Thus, the effect of pirfenidone on patients with IPF and airflow obstruction is unknown. However, physiology variables are insensitive in excluding patients with emphysema in the setting of IPF [53], and imaging criteria such as extent of emphysema on HRCT may be more appropriate. In the INPULSIS trials of nintedanib, patients with an FEV1/FVC ratio of <0.7 were also excluded. A post hoc analysis found that 39.6% of patients had emphysema (scored yes or no at baseline), and 38.8% had an FEV1/FVC ratio >0.7 and <0.8 . The treatment effect of nintedanib versus placebo was similar between patients with and without emphysema and when comparing different thresholds of FEV_1/FVC (0.7 <FEV_1/FVC> 0.8 or FEV_1/FVC >0.8) [42]. Further study is needed to better understand the impact of presence and severity of CPFE and effect of treatment with pirfenidone or nintedanib [10]. After identifying CPFE, additional history and diagnostic testing may be warranted, similar to what is appropriate in patients with isolated ILD. In general, the presence of emphysema is associated with a worse outcome and a greater likelihood of PH than might be expected for a given extent of ILD. Future research is also needed for the evaluation of lung cancer risk in this population. Although both IPF and COPD increase the risk for lung cancer compared with the general population, lung cancer risk for patients with CPFE (or ILAs and emphysema) may be elevated beyond emphysema or IPF alone [35]. Such patients also have generally poor prognosis.

Research priorities

The CPFE task force committee identified several gaps in our knowledge that need to be addressed, including:

- to understand the pathogenetic mechanisms in CPFE, the phenotyping, considering both fibrosis and emphysema: the differences in ILD patterns, the amount of emphysema and the difference between paraseptal and centrilobular emphysema.
- to understand disease behaviour, prognosis and natural history, in order to monitor

disease progression and the best physiologic measure to follow the patients

- to improve methods that allow an early diagnosis, and detect comorbidities
- to evaluate potential therapeutic opportunities, the possible use of bronchodilators that can be effective on symptoms, the effect of antifibrotic drugs, the management of complications and how to differentiate exacerbation of COPD from exacerbation of fibrosis.

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Chapter 2. Bronchodilator Therapy in Patients with Combined Pulmonary Fibrosis and Emphysema

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Background

Combined Pulmonary Fibrosis and Emphysema (CPFE) is a challenging condition characterized by a combination of emphysema and pulmonary fibrosis, where bronchial obstruction is often undetectable on spirometry due to the compensatory effect of restrictive deficits. This unique pathophysiology contributes to a poor prognosis and severely compromised quality of life (QoL), driven by disabling symptoms such as cough and dyspnea, limited physical activity, and the lack of effective therapeutic options [1]. The psychological burden, including anxiety and depression, further exacerbates the patient's distress, particularly due to the insidious onset of the disease and the fear of respiratory fatigue. While inhaled bronchodilator therapy with long-acting β-agonists (LABAs) or muscarinic antagonists (LAMAs) has proven effective in improving QoL and reducing symptoms in patients with emphysema and chronic obstructive pulmonary disease (COPD) with obstructive deficits [2], its efficacy in CPFE remains unclear. The obstructive component of CPFE, often masked by fibrosis, complicates the evaluation of bronchodilator therapy's role in this population. This study aims to address this gap by assessing the impact of bronchodilator therapy on the QoL of CPFE patients, alongside its effects on symptoms, respiratory function, and exercise capacity. The primary objective is to evaluate changes in the Saint George Respiratory Questionnaire (SGRQ) score over time, while secondary objectives include assessing variations in the Modified British Medical Research Council (mMRC) and COPD Assessment Test (CAT) scores, as well as changes in pulmonary function and exercise performance.

Materials and methods

Study design and setting

This study was a prospective monocentric study conducted on a cohort of CPFE patients followed at the Center for Rare Lung Diseases (MaRP) at the University Hospital of Modena.

Study Population

Patients for the study were selected based on specific inclusion and exclusion criteria. Inclusion criteria required participants to be over 18 years of age, have a radiological diagnosis of CPFE characterized by the presence of emphysema and concurrent interstitial lung disease, and present with respiratory symptoms. Exclusion criteria ruled out patients with an obstructive pattern on spirometry, defined as an FEV_1/FVC ratio below 70%, and those without significant symptoms warranting the use of bronchodilators.

Procedures and measurements

After enrollment, patients received inhaled bronchodilator therapy for a consecutive 3-month period. Data related to symptoms and quality of life were collected before and 3 months after the start of bronchodilator therapy using three questionnaires: the Saint George Respiratory Questionnaire (SGRQ), the Modified British Medical Research Council Questionnaire (mMRC), and the COPD Assessment Test (CAT). Pulmonary function was assessed through global spirometry and DLCO, while exercise capacity was evaluated using the 6-minute walking test (6MWT). Based on the inclusion criteria, a group of 28 patients was created, who were followed at the MaRP Center between February 2020 and August 2021.

St. George's Respiratory Questionnaire

The St. George Respiratory Questionnaire (SGRQ) is a standardized questionnaire designed to assess respiratory symptoms and their impact on the patient's health and quality of life. It was created and validated by P.W. Jones of St. George's Hospital Medical School and has an Italian version developed by Carone and Bertolotti. The questionnaire consists of 50 questions, which are weighted to form 76 elements. It is divided into three domains: respiratory symptoms, activities, and impact. The first part investigates respiratory symptoms, while the second focuses on the psychosocial impact of the disease and quality of life. Each item is associated with a score that correlates with appropriate comparative

measures related to the pulmonary disease itself. The total score ranges from 0, indicating good quality of life, to 100, indicating very poor quality of life. The questionnaire is ideally self-administered, under supervision, and takes about 15-20 minutes to complete. It is administered during the initial interview and follow-up visits. The SGRQ is widely used to assess the effectiveness of bronchodilators, oxygen therapy, and specific treatments, and can significantly predict the short-term progression of the disease, independent of physiological measurements [3].

Modified British Medical Research Council Questionnaire

The Modified British Medical Research Council Questionnaire (mMRC) is used to evaluate dyspnea in patients with respiratory diseases and COPD. It is designed to identify the level of disability, caused by dyspnea, in performing daily activities. Patients are asked to indicate the degree to which perceived respiratory difficulty affects their mobility. The grades range from 0 (mild disability) to 4 (very severe/disabling disability). Higher grades reflect greater difficulty in performing exercise tasks [4].

COPD Assessment Test

The CAT is a short questionnaire (Appendix A.6) used for assessing and monitoring the health status of patients with COPD (Chronic Obstructive Pulmonary Disease). The questionnaire was initially developed and validated in English [117]. The test analyzes eight items: cough, sputum, chest tightness, shortness of breath, activity limitation, insecurity when leaving the house, insomnia, and lack of energy. The item scores range from 0 to 5, providing a total CAT score between 0 and 40 points. The higher the score, the greater the impact of the disease (low, medium, high, very high). Significantly relevant improvements are assessed by a difference of at least 2 points [5,6,7].

Data collection

Starting from 2020, the SGRQ, mMRC, and CAT questionnaires were administered for the first time during the visit when the decision was made to initiate bronchodilator therapy. This allowed for the evaluation of reported symptoms and the collection of information regarding the patients' quality of life (QoL). After starting bronchodilator therapy, each patient entered a follow-up program. During follow-up visits, which occurred 3–6 months after the initiation of therapy, patients were given the questionnaire again to assess any potential worsening

or improvement in QoL and disease-related symptoms. Along with these data, information regarding respiratory function tests and exercise capacity before and after using the bronchodilator were also collected.

The data collected were provided by the Rare Lung Disease Center of the University of Modena and Reggio Emilia and were entered into a database after reviewing electronic health records, radiological images, and spirometry results from hospital software systems. The results obtained from the completion of the questionnaires were entered into a database created using Microsoft Excel version 16.53 (Microsoft, Redmond, WA, USA). The database also contains information for each patient such as: Sex, Age, Family history, Date of first and subsequent follow-up visits, Pulmonary volumes from global spirometry using plethysmography, distance in metres from the 6-Minute Walk Test (6MWT), Oxygen therapy status, Use of antifibrotic therapy, Type of interstitial lung disease, Smoking history, Relevant comorbidities, Bronchodilator used.

Statistical analysis

Given that this was an exploratory study, no power analysis was conducted. The variables under study were compared using the Wilcoxon test and the Mann-Whitney test for continuous variables, and the Chi-square test and Fisher's test for dichotomous variables, as appropriate.

Based on the median change in the SGRQ score (primary outcome), the study population was divided into two cohorts: "high responders" (change > median value) and "low responders" (change < median value). The association of each baseline variable with the degree of response to bronchodilator therapy was assessed using a univariate logistic model. The strength of the association was expressed using the odds ratio (OR). Variables that were statistically significant were then included in a multivariate logistic regression model. The significance level was set at $p < 0.05$. The statistical analysis was performed using SPSS version 25.0 (IBM Corp., NY, USA) and GraphPad Prism version 8.2 (GraphPad Software, Inc., La Jolla, CA, USA).

Results

A total of 28 patients were consecutively enrolled. **Table 1** presents the demographic and clinical characteristics of the study population. Most patients were male (96%) and predominantly had a normal weight (median = 24 kg/m², IQR [21-28]). All patients had a history of smoking. Four subjects were current smokers (median = 30 pack/years, IQR 25-30), while 24 were ex-smokers (median = 40 pack/years, IQR 30-56). 18% of patients had respiratory failure requiring long-term home oxygen therapy. The most common comorbidities were cardiovascular diseases and gastroesophageal reflux. The most frequent interstitial lung disease was idiopathic pulmonary fibrosis (79%), followed by undetermined interstitial lung disease (14%). Most patients were on active antifibrotic therapy (53%), with a predominant use of nintedanib (73%). The most used bronchodilator was umeclidinium (61%), followed by tiotropium (14%) and glycopyrronium (11%).

Table 1.

Parameter	Value
Number of patients	28
Age, years (IQR)	76 (71-80)
Male, n (%)	27 (96)
BMI, kg/m^2 (IQR)	24 (21-28)
Current smoker, n (%)	4 (14)
Pack-years (IQR)	30 (25-30)
Ex-smoker, n (%)	24 (86)
Pack-years (IQR)	40 (30-56)
Comorbidity	2 (2-3)
Ischemic heart disease, n (%)	6 (21)
Chronic heart failure, n (%)	5 (18)
Arrhythmia, n (%)	5 (18)
Gastroesophageal reflux disease, n (%)	4 (14)
Chronic kidney disease, n (%)	3 (11)
Chronic liver disease, n (%)	1 (4)
Lung cancer, n (%)	1 (4)
Home long-term oxygen therapy, n (%)	5 (18)
Interstitial lung disease	95 (81-109)
Idiopathic pulmonary fibrosis, n (%)	22 (79)
CTD-ILD, n (%)	1 (4)
Undetermined ILD, n (%)	4 (14)
Exposure ILD, n (%)	1 (4)
Active antifibrotic therapy	
Pirfenidone, n (%)	4 (14)
Nintedanib, n (%)	11 (39)
Bronchodilator therapy	
Umeclidinium, n (%)	17 (61)
Glycopirronium, n (%)	3 (11)
Aclidinium, n (%)	2 (7)
Tiotropium, n (%)	4 (14)
Formoterol, n (%)	2 (7)

Legenda

BMI = body mass index; CTD-ILD = connective tissue related interstitial lung disease; ILD = interstitial lung disease; IQR = interquartile range.

Table 1. General and clinical characteristics of the study population at the time of enrollment. Data are presented as numbers (n) and percentages (%) for dichotomous variables or as median and interquartile range (IQR) for continuous variables.

Table 2 shows the spirometric characteristics, symptom perception, and quality of life, as well as functional performance on the 6-minute walk test. The enrolled patients had relatively preserved lung volumes and flows. However, DLCO (diffusing capacity for carbon monoxide) was markedly reduced (36% of predicted), even after correction for alveolar ventilation (52%). The median distance walked in the 6MWT was 395 meters (IQR 333–442). The median scores from the questionnaires were as follows: 2 (IQR 2–3) on the modified mMRC scale, 15 (IQR 11–21) on the CAT, and 33.3 (IQR 23.3–46.4) on the SGRQ.

Table 2.

Parameter	Value
mMRC, score (IQR)	2 (2-3)
CAT, score (IQR)	15 (11-21)
SGRQ, mmHg (IQR)	33.3 (23.3-46.4)
FVC%pred, % (IQR)	87 (77-96)
FEV1%pred, % (IQR)	86 (84-98)
FEV1/FVC, % (IQR)	77 (73-84)
TLC%pred, % (IQR)	89 (79-100)
RV%pred, % (IQR)	95 (81-109)
RV/TLC, % (IQR)	46 (40-51)
DLCO%pred, % (IQR)	36 (27-49)
DLCO VA corr%pred, % (IQR)	52 (43-61)
6MWDT, m (IQR)	395 (333-442)

Legenda

mMRC = modified medical resource council scale; CAT = COPD assessment test; SGRQ = Saint George respiratory questionnaire; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; TLC = total lung capacity; RV = residual volume; DLCO = diffusion lung test for carbon dioxide; DLCO VA = DLCO alveolar ventilation corrected; 6MWDT = 6 minutes walking distance test; IQR = interquartile range

Table 2. Spirometric, symptomatic, and quality of life characteristics of the study population at the time of enrollment. Data are presented as numbers (n) and percentages (%) for dichotomous variables or as median and interquartile range (IQR) for continuous variables.

Figure 1 shows the results of the primary outcome, illustrating the change in the SGRQ score after 3 months of bronchodilator therapy. Patients demonstrated a significant average decrease in the score (-10.9, SD = 6.9, $p < 0.0001$).

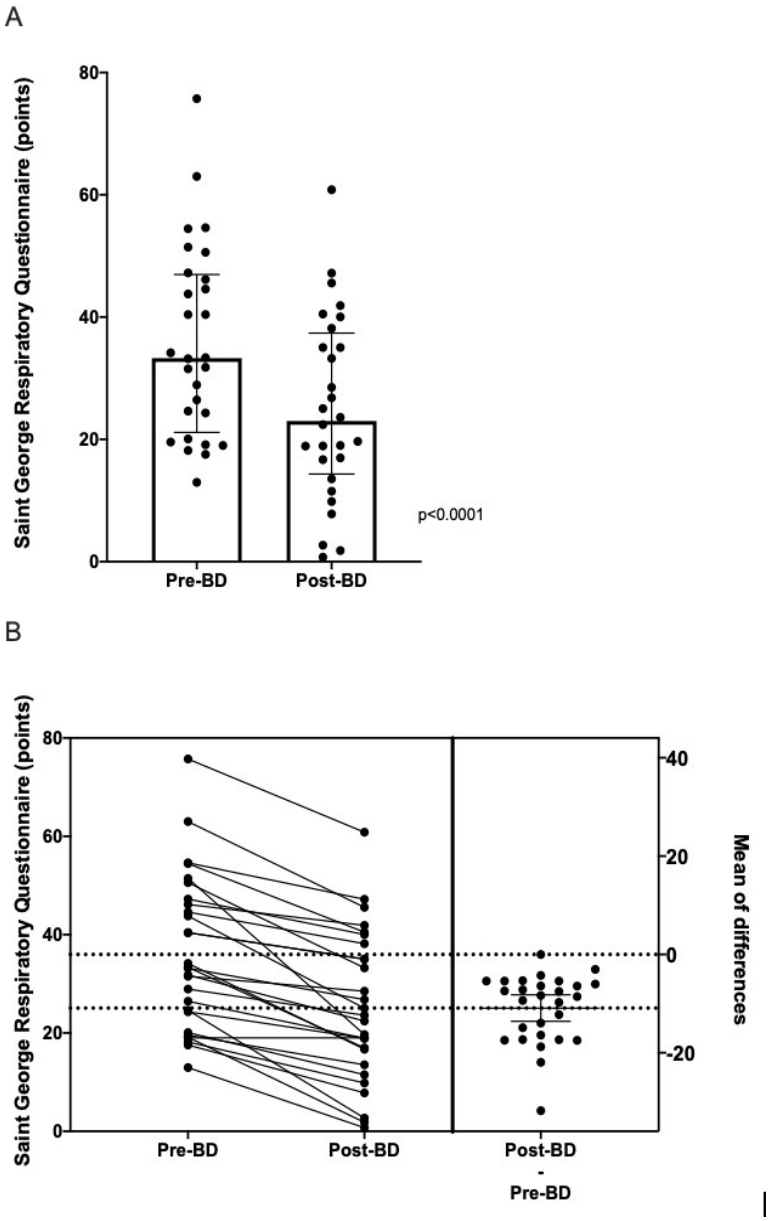


Figure 1. Panel A. Median values with interquartile ranges for the SGRQ score at baseline and after 3 months of bronchodilator therapy. Panel B. Change in the SGRQ score after 3 months of bronchodilator therapy.

Figure 2 shows the change in the mMRC score after 3 months of bronchodilator therapy. Patients showed a significant average decrease in the score (-0.82, SD = 0.47, $p < 0.0001$).

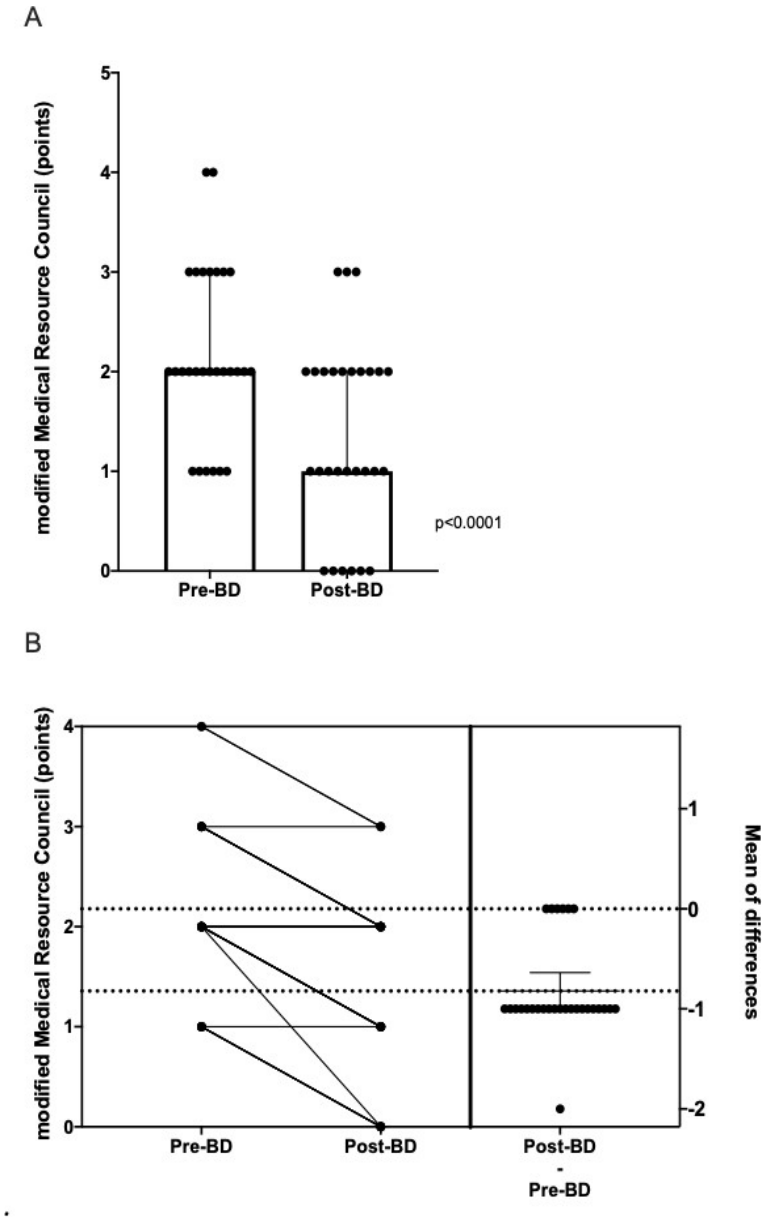


Figure 2. Panel A. Median values with interquartile ranges for the mMRC score at baseline and after 3 months of bronchodilator therapy. Panel B. Change in the mMRC score after 3 months of bronchodilator therapy.

Figure 3 shows the change in the CAT score after 3 months of bronchodilator therapy. Patients showed a significant average decrease in the score (-4.9, SD = 2.7, $p < 0.0001$).

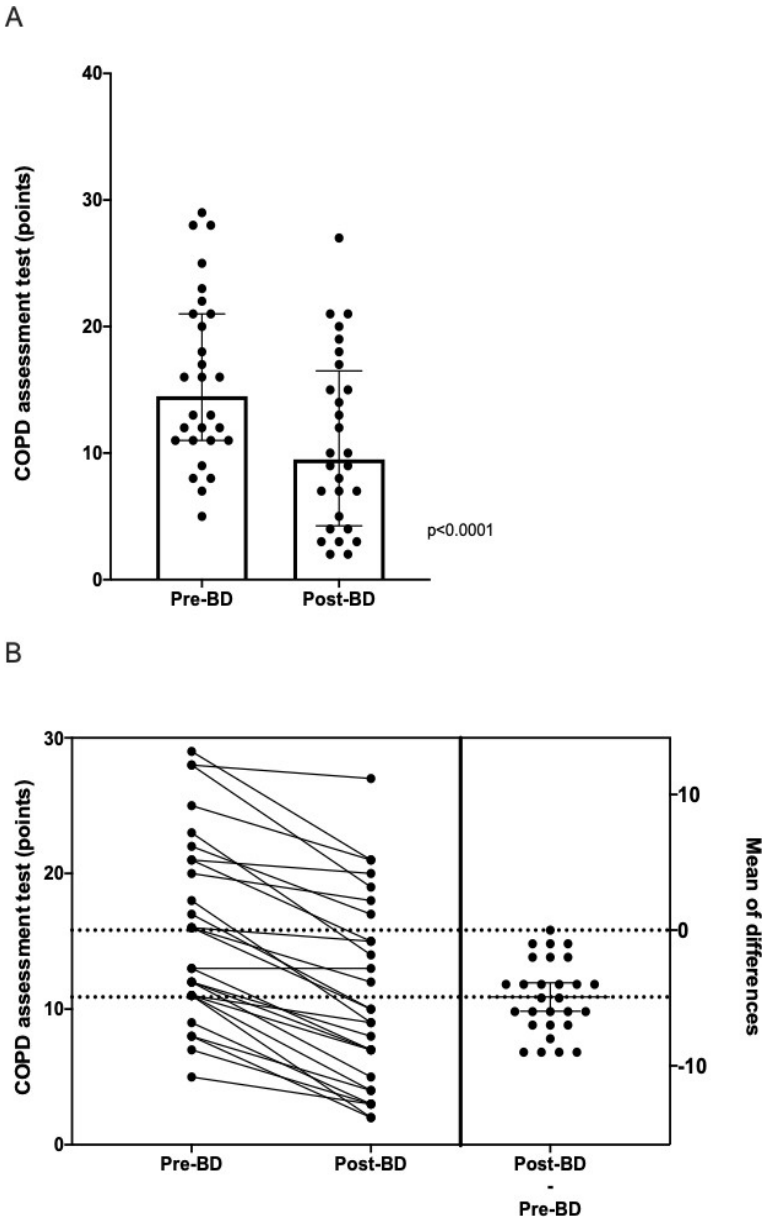
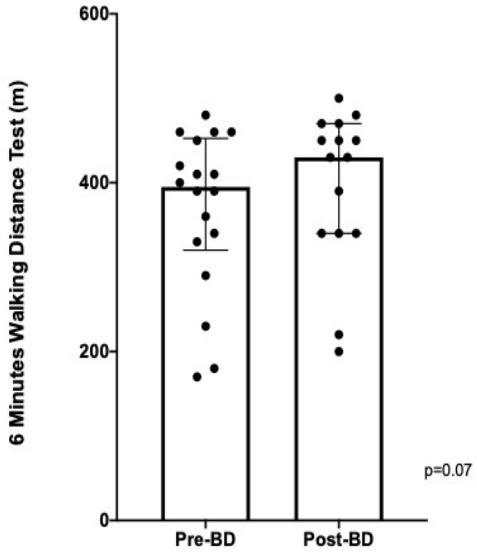


Figure 3. Panel A. Median values with interquartile ranges for the CAT score at baseline and after 3 months of bronchodilator therapy. Panel B. Change in the CAT score after 3 months of bronchodilator therapy.

Figure 4 shows the change in the distance walked on the 6MWT after 3 months of bronchodilator therapy. Patients showed an average increase in distance, although not statistically significant (+55 m, SD = 94, p = 0.07).

A



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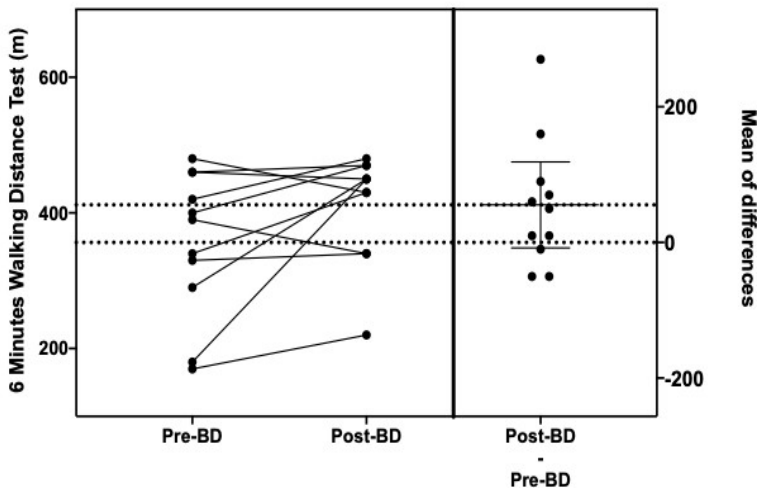

Figure 4. Panel A. Median values with interquartile ranges for the distance walked on the 6MWT at baseline and after 3 months of bronchodilator therapy. **Panel B**. Change in distance walked on the 6MWT after 3 months of bronchodilator therapy.

Figure 5 shows the change in forced expiratory volume in 1 second (FEV1) after 3 months of bronchodilator therapy. Patients showed no statistically significant changes (-0.3%, SD = 4, p = 0.8).

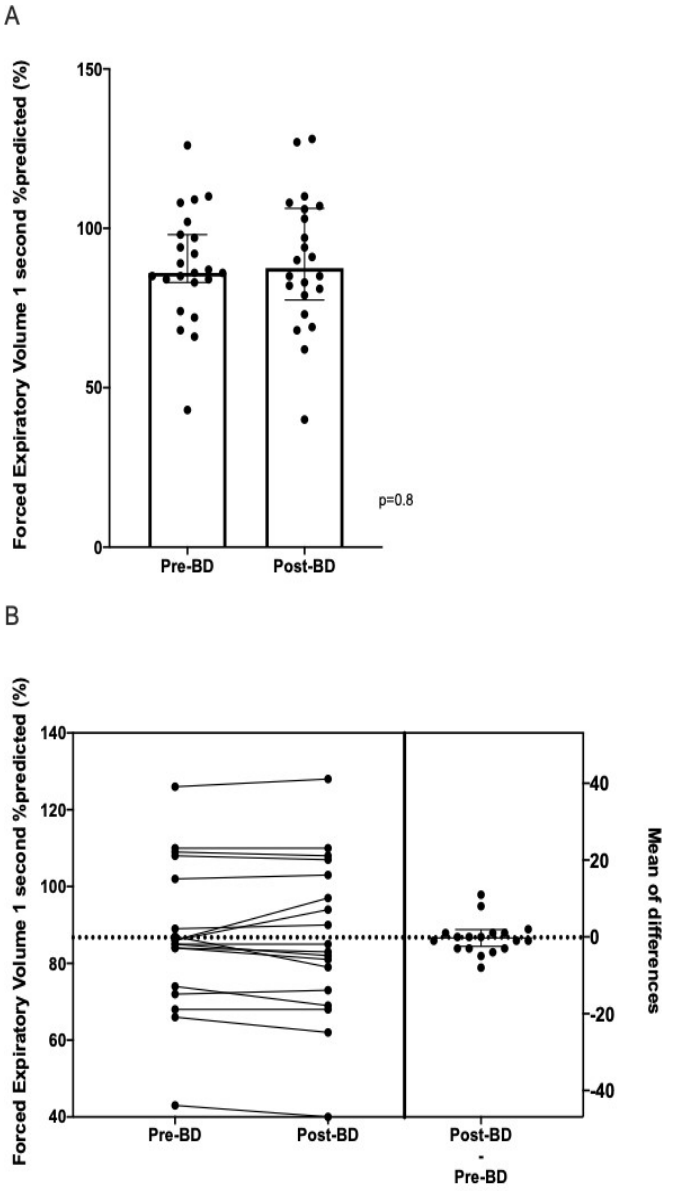

Figure 5. Panel A. Median values with interquartile ranges for FEV1 expressed as a percentage of predicted at baseline and after 3 months of bronchodilator therapy. Panel B. Change in FEV1 after 3 months of bronchodilator therapy.

Figure 6 shows the change in forced vital capacity (FVC) after 3 months of bronchodilator therapy. Patients showed no statistically significant changes (-0.7%, SD = 7, p = 0.7).

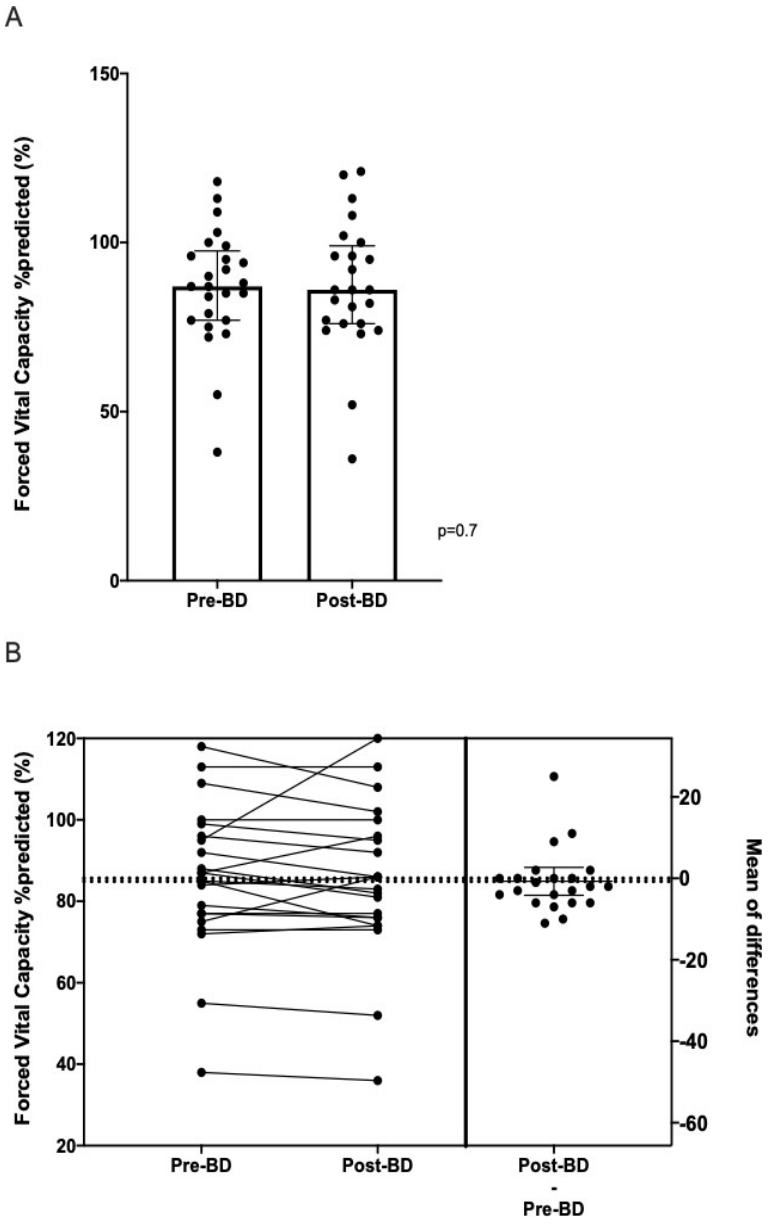

Figure 6. Panel A. Median values with interquartile ranges for FVC expressed as a percentage of predicted at baseline and after 3 months of bronchodilator therapy. Panel B. Change in FVC after 3 months of bronchodilator therapy.

Figure 7 shows the change in residual volume (RV) as a percentage of predicted after 3 months of bronchodilator therapy. Patients showed a statistically significant decrease in this parameter (-0.13.4%, SD = 24, p = 0.048).

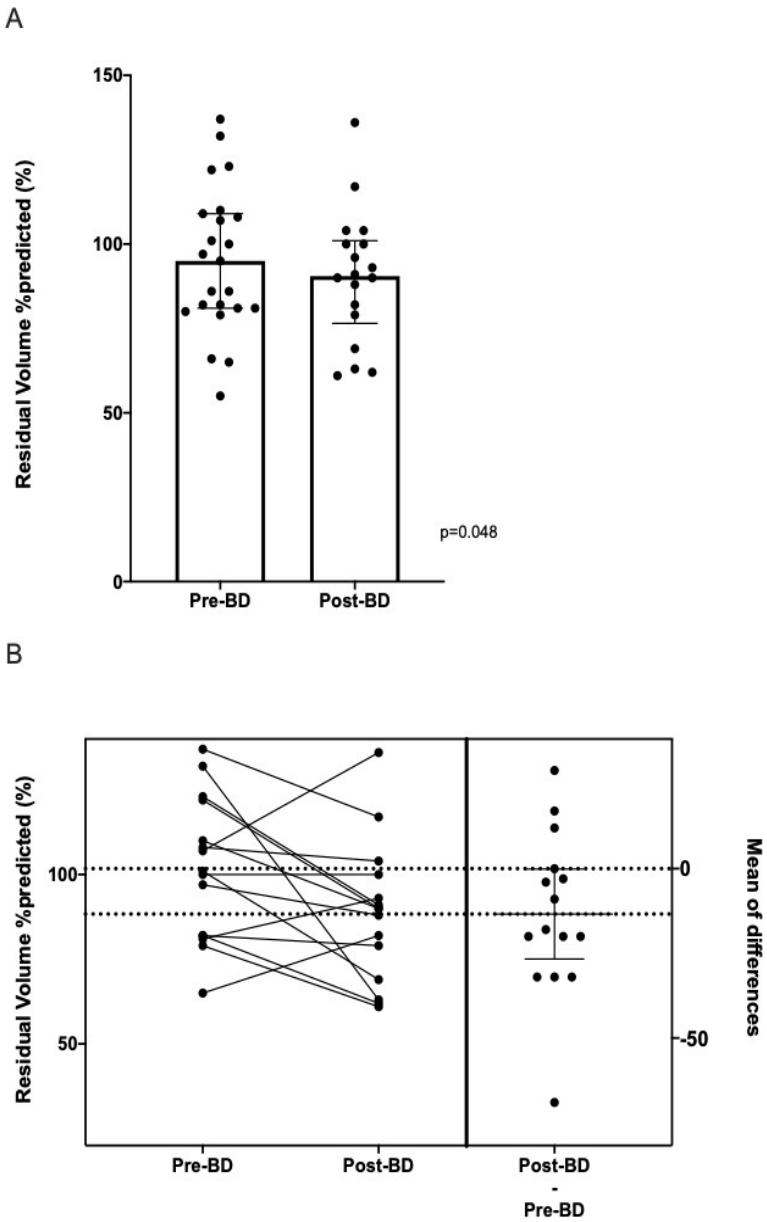

Figure 7. Panel A. Median values with interquartile ranges for RV expressed as a percentage of predicted at baseline and after 3 months of bronchodilator therapy. Panel B. Change in RV after 3 months of bronchodilator therapy.

Table 3 shows the association of each baseline variable with the response to bronchodilator treatment, categorized into "high responders" and "low responders" based on the median change in SGRQ score (-8.45). The univariate logistic analysis revealed that higher baseline values or CAT (OR = 2 [1.2-3.5], p = 0.04), SGRQ (OR = 2.3 [1.5-4.2], p = 0.02), and residual volume (OR = 2.5 [1.3-5], p = 0.01) were associated with a better response to bronchodilator therapy.

Table 3.

Parameter	High responders	Low responders	Odds ratio	p value
Number of patients	13	15		
Age, years (IQR)	75 (67-80)	76 (71-80)	1.2 (0.3-8)	0.9
Male, n (%)	13 (100)	14 (96)	1.1 (0.6-8)	0.9
BMI, kg/m² (IQR)	25 (22-28)	24 (21-27)	1.2 (0.2-14)	0.9
Comorbidity				
Ischemic heart disease, n (%)	3 (23)	3 (20)	1.2 (0.2-6)	0.9
Chronic heart failure, n (%)	2 (15)	2 (13)	1.2 (0.2-8)	0.9
Arrhythmia, n (%)	3 (23)	2 (13)	2 (0.3-12)	0.6
Gastroesophageal reflux disease, n (%)	2 (15)	2 (13)	1.2 (0.2-8)	0.9
Chronic kidney disease, n (%)	2 (15)	1 (7)	2.5 (0.3-39)	0.6
Chronic liver disease, n (%)	1 (8)	0 (0)	1.4 (0.3-12)	0.8
Lung cancer, n (%)	0 (0)	1 (7)	0.7 (0.1-8)	0.8
Home long-term oxygen therapy, n (%)	2 (15)	3 (20)	0.5 (0.1-3)	0.6
Interstitial lung disease				
Idiopathic pulmonary fibrosis, n (%)	10 (79)	12 (80)	0.8 (0.2-4.2)	0.9
CTD-ILD, n (%)	1 (8)	0 (0)	1.1 (0.3-12)	0.8
Undetermined ILD, n (%)	2 (15)	2 (13)	1.2 (0.2-8)	0.9
Exposure ILD, n (%)	0 (0)	1 (7)	0.7 (0.1-8)	0.8
Active antifibrotic therapy				
Pirfenidone, n (%)	2 (15)	2 (13)	1.2 (0.1-10)	0.9
Nintedanib, n (%)	5 (38)	6 (40)	0.8 (0.1-7)	0.9
Bronchodilator therapy				
Umeclidinium, n (%)	10 (79)	7 (47)	3.8 (0.8-16)	0.1
Glycopirronium, n (%)	0 (0)	3 (20)	0.8 (0.1-31)	0.9
Aclidinium, n (%)	1 (8)	1 (7)	1.2 (0.1-23)	0.9
Tiotropium, n (%)	2 (15)	2 (13)	1.2 (0.1-8)	0.9
Formoterol, n (%)	0 (0)	2 (13)	0.7 (0.02-45)	0.8
mMRC, score (IQR)	2 (2-3)	2 (1.5-3)	1.2 (0.7-2.7)	0.5
CAT, score (IQR)	17 (13-26)	12 (8-20)	2 (1.2-3.5)	0.04
SGRQ, mmHg (IQR)	40 (31-53)	26 (19-43)	2.3 (1.5-4.2)	0.02
FVC%pred, % (IQR)	96 (85-102)	85 (76-91)	2 (0.7-4.3)	0.1
FEV1%pred, % (IQR)	96 (87-108)	84 (73-89)	3.2 (0.8-3.7)	0.1
FEV1/FVC, % (IQR)	78 (73-86)	77 (73-84)	1.1 (0.7-2.4)	0.5
TLC%pred, % (IQR)	92 (72-100)	84 (77-100)	1.3 (0.8-3.4)	0.9
RV%pred, % (IQR)	110 (85-123)	82 (78-98)	2.5 (1.3-5)	0.01
RV/TLC, % (IQR)	44 (36-49)	46 (42-53)	0.8 (0.2-5.6)	0.2
DLCO%pred, % (IQR)	36 (22-48)	36 (26-50)	1.1 (0.7-2.1)	0.8
DLCO VA corr%pred, % (IQR)	50 (31-57)	54 (42-66)	0.7 (0.3-3.2)	0.2
6MWDT, m (IQR)	395 (255-443)	400 (328-460)	0.8 (0.7-4)	0.7

Legenda

mMRC = modified medical resource council scale; CAT = COPD assessment test; SGRQ = Saint George respiratory questionnaire; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; TLC = total lung capacity; RV = residual volume; DLCO = diffusion lung test for carbon dioxide; DLCO VA = DLCO alveolar ventilation corrected; 6MWDT = 6 minutes walking distance test; IQR = interquartile range

Table 4 shows the multivariate logistic regression analysis including only the variables that were significant in the univariate analysis. Elevated residual volume at baseline was found to be the only factor independently associated with a greater response to bronchodilator therapy in terms of improvement in the SGRQ score. Patients with elevated residual volume as a percentage of predicted were 2.4 times more likely to show a better response to bronchodilator therapy compared

Table 4.

Parameter	High responders	Low responders	Odds ratio	p value
CAT, score (IQR)	17 (13-26)	12 (8-20)	1.8 (1.1-3)	0.2
SGRQ, mmHg (IQR)	40 (32-53)	26 (19-43)	2 (1.3-3.5)	0.1
RV%pred, % (IQR)	110 (85-123)	82 (78-98)	2.4 (1.3-5)	0.02

Legenda

CAT = COPD assessment test; SGRQ = Saint George; RV = residual volume; IQR = interquartile range

Discussion

This prospective pilot study demonstrated that in a population of patients with CPFE (combined pulmonary fibrosis and emphysema), the addition of bronchodilator therapy resulted in significant improvements in respiratory symptoms and quality of life over a 3-month period. The observed reduction in residual volume might be responsible for these clinical improvements, while a high residual volume at the initiation of therapy appears to be the independently associated factor with a better response to bronchodilator treatment.

Epidemiological characteristics

The characteristics of the enrolled population align with those seen in other studies on CPFE. Most of the subjects were male and all were smokers or former heavy smokers (> 40 pack-years), reaffirming the association between male sex and smoking habits with CPFE. The average age of the patients (75 ± 7) is higher than the average age of onset (> 65 years) reported in several studies. The interstitial lung disease (ILD) patterns observed on HRCT were predominantly indicative of idiopathic pulmonary fibrosis (IPF, 79%), followed by unclassifiable ILD (14%) and classifiable ILD (8%). Therefore, the majority of CPFE diagnoses are made based on the presence of IPF combined with emphysema. On the other hand, the presence of one subject with ILD associated with rheumatoid arthritis (RA) confirms that among connective tissue diseases (CTDs) commonly associated with pulmonary interstitial disease in CPFE patients, rheumatoid arthritis is a notable factor. Additionally, 5 patients (18%) required oxygen therapy, either at rest or under exertion, highlighting that CPFE causes significant desaturation, leading to the need for home oxygen therapy in these patients.

Impact of bronchodilator therapy on quality of life

CPFE is a syndrome characterized by the coexistence of two diseases: pulmonary fibrosis and emphysema. The prognosis for this condition is often poor, and patients' quality of life is significantly compromised. Currently, there are no therapies with proven efficacy for CPFE, and smoking cessation remains the most important intervention. Health-Related Quality of Life (HRQoL) has become a key focus of research, and many studies have explored this aspect globally. Patients with CPFE experience symptoms from both underlying diseases, which result in significant impairment, especially in terms of dyspnea and chronic cough. The lack of an effective treatment for CPFE leaves patients with a

severely compromised quality of life, limiting daily activities and affecting their psychological well-being [1]. A 2015 study from China investigated the effectiveness of bronchodilator therapy (LABA and inhaled corticosteroids) in a CPFE cohort, regardless of the presence of bronchoconstriction, and demonstrated that this treatment not only slows disease progression but also improves clinical characteristics [8]. A later study at Korea University Hospital tested LAMA bronchodilators in CPFE patients, regardless of obstruction, and observed improvements in CPI scores among patients treated with LAMA compared to those treated with immunosuppressants. Although these studies were conducted before the introduction of antifibrotic therapy with pirfenidone and nintedanib, they highlight the potential benefits of bronchodilator therapy [9]. A study by Zhang L. et al. showed that bronchodilators combined with corticosteroids and oxygen therapy led to improvements in prognosis, assessed via the CPI score [10]. However, these studies suffer from important biases as they did not distinguish between patients with and without bronchial obstruction, making it necessary to exclude patients with COPD from studies investigating the effects of bronchodilators in CPFE patients. In this study, a statistically significant improvement in respiratory symptoms was observed in CPFE patients without obstructive deficit. This was indicated by a decrease in SGRQ scores, supported by reductions in mMRC and CAT scores, showing a reduction in the perception of dyspnea and improvement in overall health status. The use of bronchodilators in this group could be considered an important therapeutic tool aimed at improving health status in a condition still lacking curative strategies. Given their respiratory condition, CPFE patients are subject to significant deconditioning, leading to a marked limitation of daily activities. Therefore, improvement in respiratory symptoms could enhance physical activity and social interactions, ultimately leading to a considerable improvement in their global quality of life. However, it is important to note that no therapy is currently approved to reverse pulmonary fibrosis, with only antifibrotic medications like pirfenidone and nintedanib available to halt its progression. Thus, the effect of bronchodilator therapy on symptoms may be limited by the advancement of the fibrotic disease. Moreover, the three-month endpoint was chosen because it was sufficient to assess the effectiveness of bronchodilator therapy and because conducting the assessment at a later time might limit the evaluation of bronchodilator therapy, given the progressive nature of pulmonary fibrosis.

Impact of bronchodilator therapy on respiratory function

The study demonstrated a significant change in residual volume after 3 months of bronchodilator therapy. However, no significant changes were observed in spirometric parameters such as FEV1 and FVC. CPFE patients typically show preserved flow and volume values due to the balance between the obstructive deficit caused by emphysema and the restrictive deficit caused by fibrosis, with significantly reduced DLCO. A 2015 prospective study by Dong F. et al. showed that LABA+ICS therapy in CPFE patients slows disease progression, reduces exacerbations, and improves clinical and spirometric characteristics (FEV1, FVC, and DLCO) [8]. Another study in 2013 found that the annual decline in the FEV1/FVC ratio was significantly lower in CPFE patients compared to COPD patients, suggesting that fibrosis in CPFE might support small airway function [11]. In contrast, the data in this study confirm a positive impact on symptoms and quality of life due to bronchodilator therapy. The effect of bronchodilators on residual volume may be explained by the reduction in air trapping and dynamic hyperinflation, both common in CPFE. The observed reduction in residual volume may lead to better mechanical alignment of the respiratory system, with less diaphragm displacement and greater resistance to physical fatigue. Although the increase in distance in the six-minute walk test did not show significant improvement, further studies with adequate sample sizes are needed to better investigate this outcome.

Predictive factors for response to bronchodilator therapy

This study demonstrated that higher baseline scores on symptom questionnaires were associated with a more pronounced response to bronchodilator therapy. Patients with more severe symptoms at baseline experienced significant improvements after three months of treatment, whereas those with milder symptoms showed less notable changes. The primary aim of bronchodilator therapy was to alleviate symptoms and enhance quality of life. Because severe symptoms are perceived more acutely, the resulting improvements were more substantial and could be attributed to the therapy. Conversely, patients with mild symptoms experienced only modest benefits, as their symptoms had a minimal impact on daily life. High baseline questionnaire scores emerged as a predictive factor for meaningful improvement in both symptoms and quality of life.

The study also identified higher baseline residual volume as an independent predictor of a positive response to bronchodilator therapy. Patients with elevated residual volumes prior to treatment demonstrated greater improvements in respiratory parameters and clinical

outcomes. This finding suggests that the air trapping characteristic of obstructive diseases contributes to elevated residual volumes in CPFE patients. By reducing air trapping, bronchodilator therapy likely alleviates clinical symptoms and enhances overall health.

Study Limitations

The study has several limitations. Firstly, its exploratory nature and lack of sample size calculation prevent generalization of the results. Secondly, the absence of a control group limits the strength of the observations. The low prevalence of CPFE led to the choice of an experimental design without a control group, while the rapid decline in patients' health precluded the use of a crossover design. Moreover, the lack of homogeneity in bronchodilator therapy use could introduce bias. Not all patients were receiving active antifibrotic therapy, which may have influenced the clinical outcomes. Finally, the study did not include objective measurements of diaphragm function to assess the effect of bronchodilator therapy on hyperinflation.

Conclusions

CPFE is a progressive respiratory disease with a significant clinical impact, combining the clinical-functional impairments of pulmonary fibrosis and emphysema. There are currently no approved therapies that can alter the disease natural history, and no guidelines for managing respiratory symptoms [12]. The rationale for using bronchodilators in CPFE patients is based on the presence of emphysema and bronchoconstriction. This pilot study has shown that bronchodilator therapy can effectively improve respiratory symptoms and quality of life in CPFE patients without evidence of bronchoconstriction. A reduction in residual volume was the only independent predictor of clinical improvement following therapy. Despite the study's limitations, it lays the groundwork for multicenter studies with larger populations and enhanced power to investigate the effects of bronchodilators on clinical-functional outcomes like diaphragmatic ultrasound.

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Chapter 3. The extent of emphysema plays a role in morbidity-mortality in patients with Combined Pulmonary Fibrosis and Emphysema and Idiopathic Pulmonary Fibrosis

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Background

Combined Pulmonary Fibrosis and Emphysema (CPFE) is an interstitial lung entity related to smoking and recently considered as a Syndrome by the official ATS/ERS/JRS/ALAT Research Statement. CPFE is characterized by the coexistence of pulmonary fibrosis with emphysema and accounts for the 35% of total patients with Idiopathic Pulmonary Fibrosis (IPF). Some studies have required a specific extent of emphysema, and most commonly CPFE was considered in patients with emphysema involving at least 10-15% of the whole lung, otherwise the entity was called fibrosis and emphysema (if emphysema involves less than 10% of the whole lung). The last 2022 Statement considered CPFE with a research purpose with at least 5% of emphysema and the CPFE clinical syndrome with emphysema that involves at least 15% of the whole lung [1]. The diagnostic criteria of CPFE described by Cottin et al. included radiological findings of upper-lobe centrilobular and/or paraseptal emphysema with multiple bullae and lower-lobe honeycombing with subpleural reticular opacities and traction bronchiectasis, and sometimes ground-glass opacities [2]. Although, High Resolution Computed Tomography (HRCT) is essential for the diagnosis of CPFE, pulmonary function tests (PFT) are also important in its diagnosis; however, lacking a good prognostic marker as IPF has (forced vital capacity, FVC) [3]. The behaviour of lung function in CPFE is marked by a balanced effect of the restrictive defect of fibrosis and the hyperinflation of emphysema. This causes an unexpected subnormal lung volume and flows at pulmonary function tests (PFTs) with normal FVC, responsible of the under-recognition of this syndrome. On the other hand, the diffusing lung capacity for carbon monoxide

(DLCO) is severely decreased in CPFE [4]. To the best of our knowledge, there is not a clear functional respiratory prognostic factor that could predict the prognosis of this syndrome. The FVC was shown to not be a good prognostic factor in CPFE, as it is in IPF, because emphysema delays the decrease of FVC and only one study has shown that the decline of FEV1 might be a prognostic factor [3, 5]. The natural course of CPFE seems to be different from patients with classic emphysema or fibrosis. Most studies reveal a worse prognosis of CPFE compared to emphysema alone [6], and a controversial prognosis in comparison to IPF alone [7]; while in some studies mortality rate is similar to IPF[8], in others is worse [1,9]. CPFE patients suffer from symptoms associated with both conditions (fibrosis and emphysema) and, due to the lack of any approved effective therapy, present an extremely impaired quality of life and poor prognosis. Median survival in reported series ranges from 2.1 to 8.5 years. Survival is also linked to the development of complications such as pulmonary hypertension, acute lung injury and lung cancer which are associated with a worse clinical course and lower survival rates [1]. Understanding the pathophysiology of this combined process and the abnormalities that manifest on PFTs will be likely helpful to clinicians involved with the care of patients with CPFE. In this retrospective study we try to examine plethysmography values of PFTs to determine if there is any parameter or the combination of some of them that could help clinicians to early detect fibrosis progression and poor prognosis.

The aim of this study was to analyse clinical and functional features and to evaluate the incidence of comorbidities, death and transplant of patients with CPFE compared to patients with IPF with different extent of emphysema, in order to assess if morbidity, mortality and prognosis could be associated with the entity of emphysema in patients with pulmonary fibrosis.

Materials and methods

Study design

This study is an observational, monocentric, restrospective and non aleatorized study with the evaluation of 155 patients from the ILD Unit of University Hospital of Bellvitge (L'Hospitalet de Llobregat, Barcelona, Spain).

The project complies with the law 14/2007 of the Biomedical Research and the postulates of the Declaration of Helsinki (Fortaleza Brasil, 2013) of the Word Medical Association with ethical principles for medical research involving human subjects. The centre and the

investigators guarantee that the personal data of the patients were processed according to the LOPD law, 3/2018 of the protection of personal data and digital rights, and the Regulation EU 2016/679 of the European Parliament on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. The anonymity of the subjects included in the project was maintained, pseudonymizing each patient by a coding process performed by a person independent of the research team. Data used for the publication did not contain personal data. This retrospective study obtained the information from the already recorded data in the clinical history. We did not modify clinical practice or to contact patients to ask for more information. As it is a retrospective study it was not necessary to sign an informed consent.

The project was approved by the Ethic Comittee of the University Hospital of Bellvitge/IDIBELL (CEIC, Acta 03/23, Ref PR364/22).

Study population

The inclusion criteria encompassed adult patients aged over 18 years who were diagnosed with CPFE, IPF, fibrosis with mild emphysema (involving less than 5% of the whole lung), moderate emphysema (6–14% involvement), or COPD with emphysema (mild, moderate, or severe) between January 2011 and December 2019. CPFE was defined according to the 2022 guidelines, requiring emphysema to involve at least 15% of the whole lung. Eligible patients had functional parameters and radiological findings available over time, specifically at diagnosis and at 1, 3, and 5 years post-diagnosis. Exclusion criteria included patients younger than 18 years, those recently diagnosed, individuals with predominant ground-glass patterns on CT scans, and patients without at least two sets of functional parameters recorded over the study period

Study procedure

Demographic data, comorbidities, clinical-radiological and functional parameters were obtained from the electronic clinical history of each patient in each center. Data were collected over time: at diagnosis, at 1, 3 and 5 years of diagnosis since 2015 to 2022.

We have performed a database including parameters of PFT (FVC, FEV1, FEV1/FVC, MEF50, MEF25, TLC, RV, RV/TLC, IC, FRC, ERV, DLCO, VA, KCO), 6 Minute Walking Test, Borg of dyspnoea Index, respiratory rate, Oxygen saturation, comorbidities, such as pulmonary hypertension, pneumothorax, gastroesophageal reflux disease and lung cancer,

therapies, CT pattern and lesions extent (evaluated visually by pulmonologists and radiologists), smoking status, age and sex. Each patient had a pseudonymized Identification number to preserve their anonymity; as required in Additional Provision 17 of the Organic Protection Law of Data (LOPD, in Spanish acronym) 3/2018 on the Protection of Personal Data and Guarantee of Digital Rights.

Statistical analysis

We enrolled 31 patients with IPF-ILD, 43 patients with CPFE and 31 patients with Fibrosis and Emphysema and 50 patients with COPD-emphysema from University Hospital of Bellvitge. A descriptive analysis of the demographic and clinical profile of the included subjects was carried out. Categorical variables were described using absolute and relative frequencies. Continuous variables will be described by mean and standard deviation (SD), and by median and interquartile range in case of a non-normal distribution. Lung function was analysed with a paired design by baseline. The results were analysed with statistical program with the necessary tests (Student t test, Wilcoxon test or multivariable regression models, among others). Whenever possible, 95% confidence intervals were estimated on the evaluated estimators.

Results

The analysis of comorbidities (**Table 1**) revealed that Pulmonary Hypertension (PH), lung cancer, pneumothorax, paraseptal emphysema, and acute exacerbations of COPD (AE-COPD) were significantly more frequent in CPFE and IPF with emphysema (IPF+E) patients compared to IPF without emphysema. These comorbidities are critical as they directly contribute to the clinical deterioration and poor outcomes observed in CPFE patients.

	COPD	CPFE	IPF+E	IPF
	N=50	N=43	N=31	N=31
PH	14 (28%)	34 (81%)	20 (64.5%)	15 (48.4%)
Lung Cancer	3 (7.5%)	4 (10.3%)	3 (10%)	2 (6.6%)
Pneumothorax	10 (23%)	6 (14%)	0	0
AE	15 (35%)	18 (42%)	10 (32.3%)	10 (32.3%)
AE-IPF	0	14 (32.6%)	9 (29%)	9 (32.3%)
AE-COPD	15 (35%)	4 (9.3%)	1 (3.3%)	0
Non-smokers	0	0	1 (3.2%)	7 (22.6%)
Former-smokers	22 (4%)	4 (9.3%)	5 (16%)	1 (3.23%)
Smokers	28 (56%)	39 (90.7%)	25 (80%)	23 (74.2%)
Pack-years (average)	55.4	68.5	54.8	31.7
Predominance of Paraseptal emphysema	15 (30%)	31 (72.1%)	22 (69.9%)	0

Table 1. Comorbidities. Pulmonary Hypertension (HP), Lung cancer, Pneumothorax, Paraseptal emphysema and Acute Exacerbation-COPD (AE-COPD) are more frequent in CPFE and IPF+E (Emphysema) patients than in IPF without emphysema patients.

According to the modified Medical Research Council (mMRC) scale (Table 2), CPFE patients exhibited higher dyspnea scores at diagnosis than IPF patients. Furthermore, CPFE and IPF+E patients experienced a more significant increase in dyspnea severity one year after diagnosis, indicating a faster progression of symptoms in these groups.

	COPD	CPFE	IPF + Enfisema	IPF
Mmrc at diagnosis				
0	4 (8%)	1 (2.3%)	6 (19.5%)	4 (13%)
1	39 (78%)	29 (67.4%)	20 (64.5%)	27 (87%)
2	7 (14%)	12 (27.9%)	5 (16%)	0
3	0	1 (2.33%)	0	0
mMRC after 1 year				
0	3 (6.4%)	1 (2.4%)	2 (6.45%)	4 (13%)
1	30 (63.8%)	22 (53.7%)	20 (64.5%)	23 (74.2%)
2	12 (25.5%)	14 (34%)	4 (13%)	4 (13%)
3	2 (4.2%)	4 (9.8%)	5 (16.1%)	0

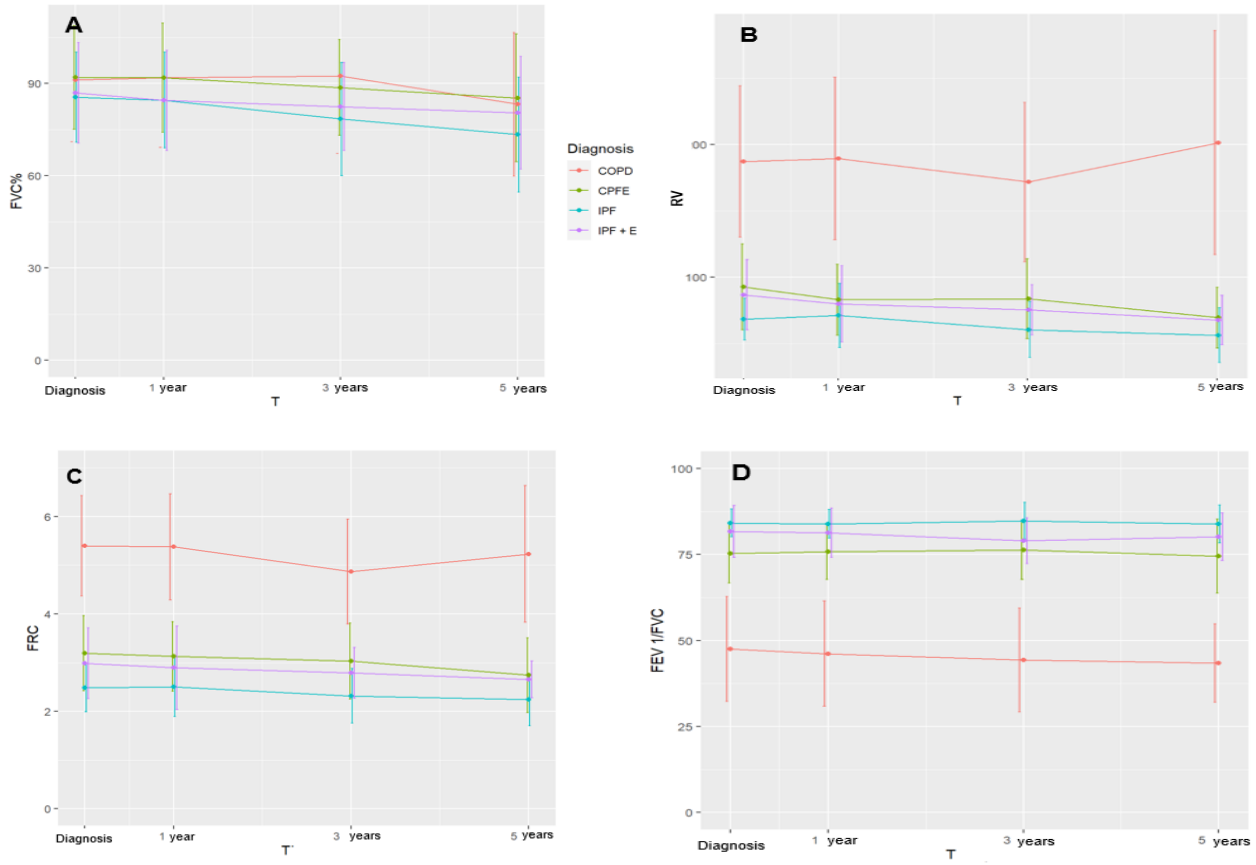
Table 2. Dyspnea (mMRC scale). CPFE patients showed a higher dyspnoea score at diagnosis than IPF patients. Moreover, CPFE and IPF+E patients revealed a greater increase in dyspnoea after 1 year.

As shown in **Table 3**, patients with CPFE and IPF+E required more oxygen therapy both at diagnosis and after one year compared to IPF without emphysema. These patients demonstrated a higher progression rate of respiratory failure over time, with statistical significance ($p<0.05$).

	COPD	CPFE	IPF+E	IPF
O2 therapy at diagnosis	2 (4%)	9 (21%)	2 (6.45%)	1 (3.45%)
O2 therapy after 1 year	3 (6%)	15 (35%)	8 (26.7%)	3 (10%)

Table 3. O_2 therapy: patients with CPFE and IPF+E (IPF+ Emphysema) showed a higher need for Oxygen therapy at diagnosis and after 1 year than IPF without emphysema (IPF), with a higher progression rate of the respiratory failure ($p<0.05$).

Figure 1 illustrates the evolution of pulmonary function tests. At diagnosis, CPFE patients had higher Forced Vital Capacity (FVC, **Figure 1A**), Residual Volume (RV, **Figure 1B**), and Functional Residual Capacity (FRC, **Figure 1C**) compared to IPF patients, with these values increasing progressively with emphysema extent. Conversely, CPFE patients had lower maximal expiratory flow rates (MEF50% and MEF25%), Forced Expiratory Volume in one second (FEV_1, **Figure 1E**), and Carbon Monoxide Transfer Coefficient (KCO), with these values decreasing further as emphysema severity increased. CPFE and IPF+E patients also displayed higher FVC and a slower decline over time compared to IPF patients, consistent with findings in the literature.



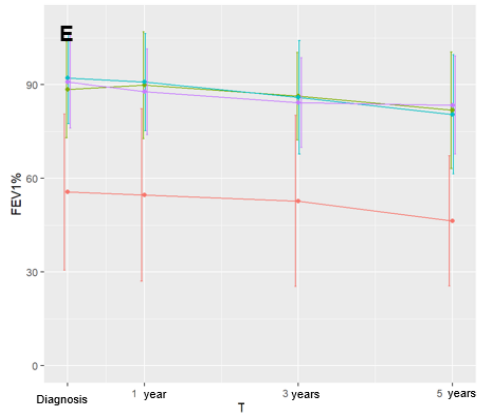
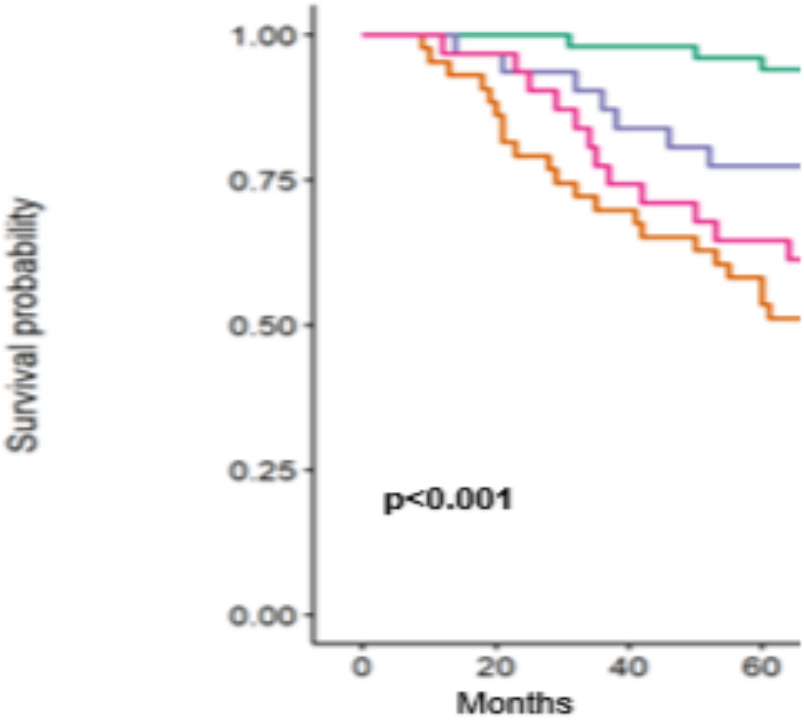


Figure 1. Pulmonary function test evolution. At diagnosis, CPFE compared to IPF patients had higher values of FVC (Figure 1 A), RV (Graph 1 B), FRC (Graph 1 C), which increased gradually with the extent of emphysema; and lower values of MEF50% and 25% (maximal expiratory flow), FEV1 (Figure 1 E) and KCO (carbon monoxide transfer coefficient) that decreased gradually with the extent of emphysema. Moreover, patients with CPFE and IPF+Emphysema showed a higher FVC and a less reduction over time than IPF patients (Figure 1 A).

Figure 2 and 3 illustrates survival analysis. Mortality rates were directly associated with emphysema extent. CPFE patients demonstrated higher mortality compared to IPF patients, with worse outcomes observed as the emphysema burden increased. While statistical significance for subgroup differences was limited by sample size, trends indicated that greater emphysema involvement correlates with poorer survival outcomes.

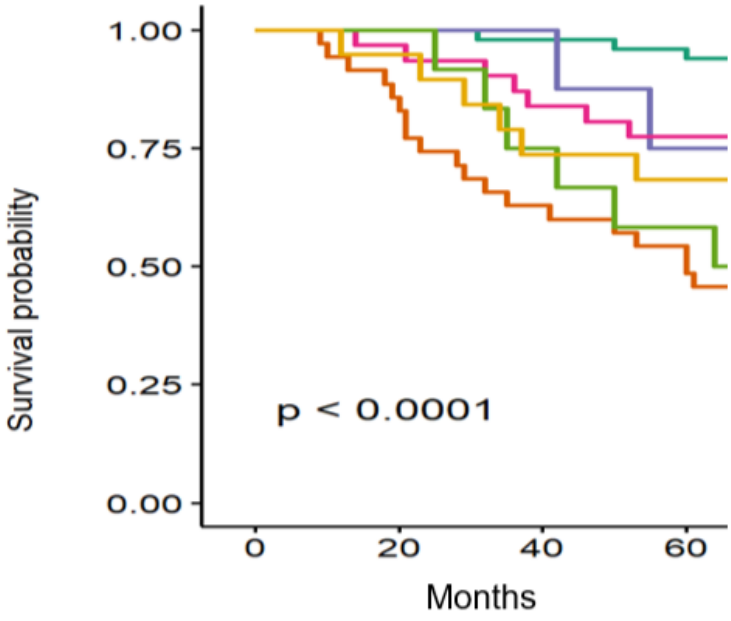
Figure 2.



Graph 2. Survival Kaplan-Maier Curve at 5 years (60 months). ILD patients had worse survival rate proportional to the extent of emphysema (E) and even worse in CPFE (CPFE > IPF+ E > IPF without E; p<0.001).

CPFE (Combined Pulmonary Fibrosis Emphysema)
IPF+E (Idiopathic Pulmonary Fibrosis + Emphysema)
IPF (Idiopathic Pulmonary Fibrosis)
COPD (Chronic Obstructive Pulmonary Disease)

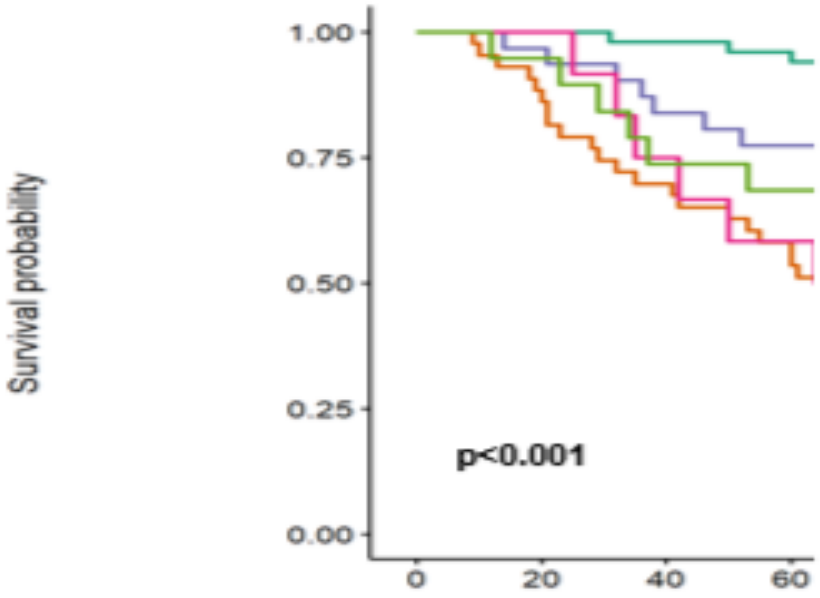
Figure 3.



Graph 3. Survival Kaplan-Maier Curve at 5 years (60 months) in CPFE+IPF, IPF+E 10%, IPF+E 5%, IPF, Other CPFE and COPD patients.
CPFE-IPF (Combined Pulmonary Fibrosis Emphysema in IPF patients)
IPF+E 10% (Idiopathic Pulmonary Fibrosis + Emphysema 10%)
IPF+E 5% (Idiopathic Pulmonary Fibrosis + Emphysema 5%)
IPF (Idiopathic Pulmonary Fibrosis)
Other CPFE (Combined Pulmonary Fibrosis Emphysema without IPF)
COPD (Chronic Obstructive Pulmonary Disease)

CPFE patients had higher lung transplant rates compared to IPF patients (**Figure 4**). This finding highlights the severe progression of CPFE and underscores the importance of advanced treatment strategies, such as transplantation, in improving survival for these patients.

Figure 4.



Graph 3. Survival Kaplan-Maier Curve at 5 years (60 months).
CPFE (Combined Pulmonary Fibrosis Emphysema)
IPF+E 10% (Idiopathic Pulmonary Fibrosis + Emphysema 10%)
IPF+E 5% (Idiopathic Pulmonary Fibrosis + Emphysema 5%)
IPF (Idiopathic Pulmonary Fibrosis)
COPD (Chronic Obstructive Pulmonary Disease)

Discussion

The progression of Combined Pulmonary Fibrosis and Emphysema (CPFE) differs significantly from that of classic emphysema or pulmonary fibrosis. Most studies report a worse prognosis for CPFE compared to emphysema alone [6], while its prognosis relative to idiopathic pulmonary fibrosis (IPF) remains controversial [7]. In some studies, the mortality rate of CPFE is similar to IPF[8], whereas others show worse outcomes [9]. CPFE patients experience symptoms from both emphysema and fibrosis, and their quality of life is severely impaired due to the absence of approved effective therapies. Reported median survival varies between 2.1 and 8.5 years, and survival is closely linked to complications such as pulmonary hypertension (PH), acute lung injury, and lung cancer, all of which contribute to a worse clinical course and reduced survival rates. These discrepancies in outcomes may arise from differences in sample selection, diagnostic contamination by a higher proportion of non-IPF cases in CPFE cohorts (which may have better survival), attrition bias, variations in the extent of emphysema, and the absence of formally established diagnostic criteria [1]. Lung cancer, PH, and acute exacerbations are particularly relevant to CPFE prognosis [10-13]. Understanding the pathophysiology of this combined syndrome, as well as its pulmonary function test (PFT) abnormalities, could significantly aid clinicians in managing CPFE patients.

CPFE phenotypes and comorbidities

In this study, we phenotyped CPFE syndrome by assessing comorbidities, symptoms, respiratory function, and mortality, stratified by the extent and type of emphysema and interstitial lung disease (ILD). Our findings revealed that CPFE and IPF with emphysema (IPF+E) were associated with a higher prevalence of comorbidities, including pulmonary hypertension, lung cancer, pneumothorax, paraseptal emphysema, and acute exacerbation of COPD (AE-COPD), compared to IPF without emphysema. Pneumothorax emerged as a newly recognized comorbidity with a higher prevalence in CPFE patients. The number of pack-years smoked correlated with the extent of emphysema, suggesting smoking as a key contributor to emphysema severity. Acute exacerbations of CPFE were not more frequent overall; however, when subtypes of exacerbations were analyzed, IPF exacerbations were similar across groups, whereas bronchitis exacerbations were more frequent in CPFE and IPF+E patients. Radiological findings, such as diffuse bilateral ground-glass opacities or consolidations, guided the differentiation between exacerbations of ILD and COPD.

Symptoms, quality of life, and oxygen therapy

CPFE patients exhibited higher dyspnea scores (mMRC) at diagnosis compared to IPF patients and experienced a greater increase in dyspnea severity after one year. CPFE and IPF+E patients also required more oxygen therapy at diagnosis and displayed a higher progression rate of respiratory failure over time compared to IPF without emphysema.

Pulmonary function and emphysema extent

At diagnosis, CPFE patients had higher FVC, RV, and FRC values, which increased progressively with the extent of emphysema. In contrast, MEF50%, MEF25%, FEV_1, and KCO values were lower in CPFE patients and declined further as emphysema severity increased. Compared to IPF patients, CPFE and IPF+E patients exhibited higher FVC values and a slower decline over time, aligning with existing literature [3].

Prognosis and mortality

Our findings confirmed that CPFE patients had significantly higher 5-year mortality rates compared to IPF patients. Mortality increased with emphysema extent, with CPFE patients exhibiting the worst outcomes, followed by IPF patients with 10% and 5% emphysema, and then IPF without emphysema. While the differences in mortality between subgroups were not statistically significant due to small sample sizes, the trend was evident. Statistical significance in 5-year mortality rates increased when distinguishing CPFE patients with IPF from those with other ILDs, such as rheumatological diseases, which generally have better prognosis. Additionally, CPFE patients exhibited higher lung transplant rates than IPF patients, reflecting the severe progression of the disease.

Limitations and implications for future research

This study had several limitations. The small size of subgroups and the challenges in visually assessing emphysema extent between 5%, 10%, and 15% complicated the analysis. Phenotyping CPFE subgroups remains difficult, underscoring the need for larger multicenter studies to confirm these findings. Our results suggest that greater emphysema extent correlates with worse prognosis in CPFE. However, in IPF populations, the extent of emphysema may also reflect fibrosis traction rather than emphysema severity alone. Before the distinction between SRIF and IPF was made, studies suggested emphysema might be

protective in pulmonary fibrosis. Later research clarified that fibrosis cases with better outcomes were associated with SRIF, not IPF, emphasizing that the fibrosis type plays a critical role [9,14,15]. In CPFE, fibrosis typically develops over pre-existing emphysema, with fibrosis contributing significantly to poor outcomes. Minimal emphysema (≤5%) has limited impact on prognosis, but greater emphysema involvement worsens outcomes. Additionally, UIP patterns can increase emphysema severity over time, even in former smokers, due to fibrosis-induced traction. This progression increases the risk of pulmonary arterial hypertension, further complicating the prognosis. Future studies should focus on sub-analyzing IPF-emphysema cases without CPFE, stratified by fibrosis extent at diagnosis. Dichotomizing cases into indeterminate/probable UIP versus consistent UIP could help determine whether differences in outcomes are due to emphysema severity or delayed UIP diagnosis and fibrosis progression. This approach would provide a deeper understanding of the complex interplay between emphysema and fibrosis in CPFE.

Conclusions

This study highlights the significant impact of emphysema on the clinical outcomes, progression, and comorbidities associated with CPFE, particularly in the context of IPF. Mortality in CPFE-IPF and IPF patients was found to be strongly correlated with the extent of emphysema, with greater emphysema involvement associated with worse survival outcomes. These findings underscore the role of emphysema as a critical prognostic factor. The combined effects of emphysema and fibrosis significantly exacerbate respiratory dysfunction, accelerate disease progression, and contribute to reduced survival, highlighting the need for thorough evaluation of emphysema extent during diagnosis and follow-up. The study also revealed a higher prevalence of comorbidities in CPFE compared to IPF alone, with conditions such as pulmonary hypertension (PH) and pneumothorax being directly proportional to the extent of emphysema. These complications not only worsen clinical outcomes but also impair quality of life, emphasizing the importance of early detection and management. Pulmonary hypertension exacerbates dyspnea and increases the risk of right heart failure, while pneumothorax poses a significant risk of acute respiratory decompensation. Addressing these complications early could play a crucial role in improving patient outcomes. Furthermore, CPFE patients exhibited a higher rate of disease progression during the first year after diagnosis, characterized by worsening respiratory symptoms, increased oxygen dependency, and functional decline. This rapid deterioration underscores the aggressive nature of CPFE compared to IPF alone and highlights the critical need for closer monitoring and early therapeutic interventions in the initial stages of the disease. The findings of this study underscore the importance of a comprehensive approach to managing CPFE, focusing on the assessment of emphysema extent, early identification of comorbidities, and proactive management strategies to slow disease progression. Further research is warranted to explore targeted therapies and interventions that address the unique challenges posed by this complex condition.

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Chapter 4. Respiratory functional prognostic factors in Combined Pulmonary Fibrosis and Emphysema

Background

CPFE is characterized by the coexistence of pulmonary fibrosis with emphysema and accounts for the 35% of total patients with Idiopathic Pulmonary Fibrosis (IPF). Some studies have required a specific extent of emphysema, and most commonly CPFE was considered in patients with emphysema involving at least 10-15% of the whole lung, otherwise the entity was called fibrosis and emphysema (if emphysema involves less than 10% of the whole lung). The last 2022 Statement considered CPFE with a research purpose with at least 5% of emphysema and the CPFE clinical syndrome with emphysema that involves at least 15% of the whole lung [1]. Although, High Resolution Computed Tomography (HRCT) is essential for the diagnosis of CPFE, pulmonary function tests (PFT) are also important in its diagnosis [2]; however, lacking a good prognostic marker as IPF has (forced vital capacity, FVC) [3]. The behaviour of lung function in CPFE is marked by a balanced effect of the restrictive defect of fibrosis and the hyperinflation of emphysema. This causes an unexpected subnormal lung volume and flows at pulmonary function tests (PFTs) with normal FVC, responsible of the under-recognition of this syndrome. On the other hand, the diffusing lung capacity for carbon monoxide (DLCO) is severely decreased in CPFE [4]. To the best of our knowledge, there is not a clear functional respiratory prognostic factor that could predict the prognosis of this syndrome [1]. The FVC was shown to not be a good prognostic factor in CPFE, as it is in IPF, because emphysema delays the decrease of FVC and only one study has shown that the decline of FEV1 might be a prognostic factor [5].

The natural course of CPFE seems to be different from patients with classic emphysema or fibrosis. Most studies reveal a worse prognosis of CPFE compared to emphysema alone [6], and a controversial prognosis in comparison to IPF alone [7]; while in some studies mortality rate is similar to IPF [8], in others is worse [9]. CPFE patients suffer from symptoms associated with both conditions (fibrosis and emphysema) and, due to the lack of any approved effective therapy, present an extremely impaired quality of life and poor prognosis. Median survival in reported series ranges from 2.1 to 8.5 years. Survival is also linked to the development of complications such as pulmonary hypertension, acute lung injury and lung cancer which are associated with a worse clinical course and lower survival rates [10,11,12]. Understanding the pathophysiology of this combined process and the abnormalities that

manifest on PFTs will be likely helpful to clinicians involved with the care of patients with CPFE. In this retrospective study we tried to evaluate plethysmography values of PFTs to determine if there is any parameter or the combination of some of them that could help clinicians to early detect fibrosis progression and poor prognosis.

The aim of this study was to detect a functional respiratory parameter or the combination of several of them which could predict prognosis in patients with CPFE, evaluating, retrospectively, changes on PFTs over time.

Materials and methods

Study Design

This study was an observational, multicentric, restrospective study with the evaluation of patients with CPFE from two different ILD Units from Europe (Azienda Ospedaliero Universitaria Policlinico Modena (Modena, Italia) and University Hospital of Bellvitge (L'Hospitalet de Llobregat, Barcelona, Spain). The study was carried out in accordance with the protocol. The project complies with the law 14/2007 of the Biomedical Research and the postulates of the Declaration of Helsinki (Fortaleza Brasil, 2013) of the Word Medical Association with ethical principles for medical research involving human subjects. The centre and the investigators guaranteed that the personal data of the patients were processed according to the LOPD law, 3/2018 of the protection of personal data and digital rights, and the Regulation EU 2016/679 of the European Parliament on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. The anonymity of the subjects included in the project was maintained, pseudonymizing each patient by a coding process performed by a person independent of the research team. Data used for the publication did not contain personal data. This retrospective study obtained the information from the already recorded data in the clinical history. We did not modify clinical practice or contact patients to ask for more information. As it was a retrospective study it was not necessary to sign an informed consent. The project will be approved by the Ethic Comittee of the University Hospital of Bellvitge/IDIBELL (CEIC, Acta 03/23, Ref PR364/22) and then to the other collaborative centres (Módena).

Study population

The study included adult patients aged 18 years or older diagnosed with CPFE syndrome, defined according to the 2022 guidelines as emphysema involving at least 15% of the total

lung volume. Eligible patients were diagnosed between 2011 and 2022 and had longitudinal data available, including functional parameters and radiological findings, recorded at baseline (diagnosis) and annually for up to five years. Patients younger than 18 years, those recently diagnosed, individuals with a predominant ground-glass pattern on CT scans, or those without at least two functional parameter measurements over time were excluded from the study.

Study procedures and data collection

Demographic data, comorbidities, clinical-radiological and functional parameters were obtained from the electronic clinical history of each patient in each center. Data were collected over time: at diagnosis, at 1, 2, 3, 4 and 5 years of diagnosis since 2015 to 2024. We have performed a database including parameters of PFT (FVC, FEV1, FEV1/FVC, MEF50, MEF25, TLC, RV, RV/TLC, IC, FRC, ERV, DLCO, VA, KCO), 6 Minute Walking Test, Borg of dyspnoea Index, respiratory rate, Oxygen saturation, comorbidities (pulmonary hypertension, gastroesophageal reflux disease, lung cancer, obstructive sleep apnoea, therapies, CT pattern and lesions extent, smoking status, age and sex. Each patient had a pseudonymized Identification number to preserve their anonymity; as required in Additional Provision 17 of the Organic Protection Law of Data (LOPD, in Spanish acronym) 3/2018 on the Protection of Personal Data and Guarantee of Digital Rights. Functional progression in CPFE was defined by identifying specific functional parameters or combinations of parameters that indicated disease advancement or susceptibility to death. Parameters from clinical assessments, PFTs, walking tests, and radiologic findings were utilized to evaluate disease progression.

Statistical analysis

The statistical analysis employed Cox proportional hazard models and Kaplan-Meier survival analysis to assess the relationship between functional declines and mortality in CPFE patients. Unadjusted Cox models were used initially to examine the direct association between functional parameter declines, including both individual and combined measures and survival outcomes, without accounting for confounding variables. To ensure robustness, adjusted Cox models were developed by incorporating potential confounders such as age, sex, smoking history. Kaplan-Meier survival analysis was utilized to visually depict differences in survival stratified by the extent of functional decline. The log-rank test was

applied to determine statistical significance between survival curves, providing a graphical representation of survival trends based on the degree of functional impairment.

Results

Demographic characteristics

A total of 88 patients with CPFE were enrolled. The median age at diagnosis was 70.4 years (IQR: 11.9 years), with 88% of the patients being male. The median smoking exposure was 60 pack-years (IQR: 40 pack-years), reflecting substantial tobacco-related risk. Comorbidities were frequent in this group, with pulmonary hypertension (PH) present in 32% of patients, lung cancer in 18%, and pneumothorax in 14%. These conditions contributed significantly to disease burden and progression. Pulmonary function tests showed a median predicted Forced Vital Capacity (FVC) of 89% (IQR: 22.7%), and a median Forced Expiratory Volume in 1 second (FEV_1) of 89% (IQR: 20.0%). The Total Lung Capacity (TLC) had a median of 85.2% (IQR: 21.8%), while the Diffusion Capacity for Carbon Monoxide (DLCO) was markedly reduced, with a median of 41.0% (IQR: 18.9%). The median survival from diagnosis was 3.8 years, with 22% of patients experiencing acute exacerbations during the follow-up period. CT progression was observed in 54% of the cases, characterized by worsening fibrotic and emphysematous changes.

Predictors of mortality

Table 1 presents the findings from a Cox regression analysis evaluating the association between several covariates and mortality in patients with CPFE. Both unadjusted and adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CI) and p-values are reported. Adjustments were made for age at diagnosis, sex, and smoking status. Acute exacerbation was significantly associated with increased mortality risk. In the unadjusted analysis, the HR was 2.18 (95% CI: 1.12–4.27, $p<0.05$), and the association remained significant after adjustment, with an HR of 1.89 (95% CI: 0.94–3.82, $p<0.05$). Home oxygen therapy at the time of diagnosis was also a strong predictor of mortality, with an unadjusted HR of 3.03 (95% CI: 1.35–8.01, $p<0.05$), which remained significant after adjustment (HR: 2.63, 95% CI: 1.15–7.11, $p<0.05$). Evidence of progression on CT scans showed a significant relationship with mortality. The unadjusted HR was 2.97 (95% CI: 1.17–9.98, $p<0.05$), and the adjusted HR remained significant at 2.77 (95% CI: 1.08–9.38, $p<0.05$). In contrast, a decline in FEV_1 of more than 10% within one year was not significantly

associated with mortality, with an unadjusted HR of 0.72 (95% CI: 0.41–2.42, p>0.05) and an adjusted HR of 0.67 (95% CI: 0.34–3.08, p>0.05). Similarly, a decline in FVC of more than 10% over the same period did not show a significant association, with an unadjusted HR of 1.02 (95% CI: 0.39–1.52, p>0.05) and an adjusted HR of 1.10 (95% CI: 0.64–1.08, p>0.05). Combined declines in FVC and FEV_1 exceeding 10% in one year also did not significantly predict mortality, with an unadjusted HR of 1.90 (95% CI: 0.82–5.56, p>0.05) and an adjusted HR of 1.84 (95% CI: 0.77–5.41, p>0.05). However, a combined decline in FVC and FEV_1 exceeding 5% over one year was strongly associated with increased mortality risk. The unadjusted HR was 6.02 (95% CI: 1.30–106, p<0.05), and the adjusted HR remained significant at 6.01 (95% CI: 1.31–108, p<0.05).

Table 1

Covariate	Unadjusted			Adjusted*		
	Estimate	*CI*	*p*	*Estimate*	*CI*	*p*
Acute exacerbation	**2.18**	**1.12 – 4.27**	**0.02**	1.89	0.94 – 3.82	0.07
Home oxygen therapy at diagnosis	**3.03**	**1.35 – 8.01**	**0.01**	**2.63**	**1.15 – 7.11**	**0.03**
Evidence of progression on CT	**2.97**	**1.17 – 9.98**	**0.04**	**2.77**	**1.08 – 9.38**	**0.05**
FEV1 decline > 10% in 1 year	0.72	0.41 – 2.42	0.59	0.67	0.34 – 3.08	0.82
FVC decline > 10% in 1 year	1.02	0.39 – 1.52	0.47	1.1	0.64 – 1.08	0.86
FVC + FEV 1 decline > 10% in 1 year	1.9	0.82 – 5.56	0.19	1.84	0.77 – 5.41	0.21
FVC + FEV1 decline > 5% in 1 year	**6.02**	**1.3 – 106**	**0.04**	**6.01**	**1.31 – 108**	**0.04**

Table 1. Cox regression analysis on mortality for CPFE patients with raw and adjusted hazard ratios and related 95%CI. Significance was set for p value <0.05.
**adjusted for age at diagnosis, sex and smoking status*

Impact of pulmonary function decline on survival

Figure 1, panels A-D display Kaplan-Meier survival curves at 5 years (60 months) assessing the impact of functional declines on the survival of CPFE patients. Each panel illustrates the probability of survival stratified by specific thresholds of decline in pulmonary function over a 12-month period. The Kaplan-Meier survival analysis highlights the impact

of pulmonary function decline on survival outcomes in CPFE patients over a 5-year period. Patients experiencing a combined decline in FVC and FEV_1 exceeding 5% within 12 months (**Figure 1, panel A**) demonstrated a significantly lower survival probability compared to those with declines less than 5%. This difference was statistically significant, with a log-rank p-value of 0.004, underscoring the importance of even modest functional declines in predicting survival outcomes. Conversely, when the threshold for combined decline in FVC and FEV_1 was set at greater than 10% (**Figure 1, panel B**), no significant difference in survival probabilities was observed between the groups (log-rank p=0.61). This suggests that more substantial combined functional declines did not further worsen survival outcomes beyond those associated with smaller declines. Similarly, for patients with an FVC decline greater than 10% over 12 months (**Figure 1, panel C**), there was no significant survival difference compared to those with less than a 10% decline. The Kaplan-Meier curves for these groups overlapped throughout the 60-month follow-up period (log-rank p=0.89). A similar trend was observed for FEV_1 decline exceeding 10% (**Figure 1, panel D**), where the survival probabilities between the groups were not significantly different (log-rank p=0.07), with minimal divergence in the curves over time. These findings suggest that smaller declines in pulmonary function (FVC and FEV_1 >5%) are more predictive of survival outcomes in CPFE patients than larger declines (>10%), emphasizing the need to monitor even moderate changes in lung function for clinical prognosis.

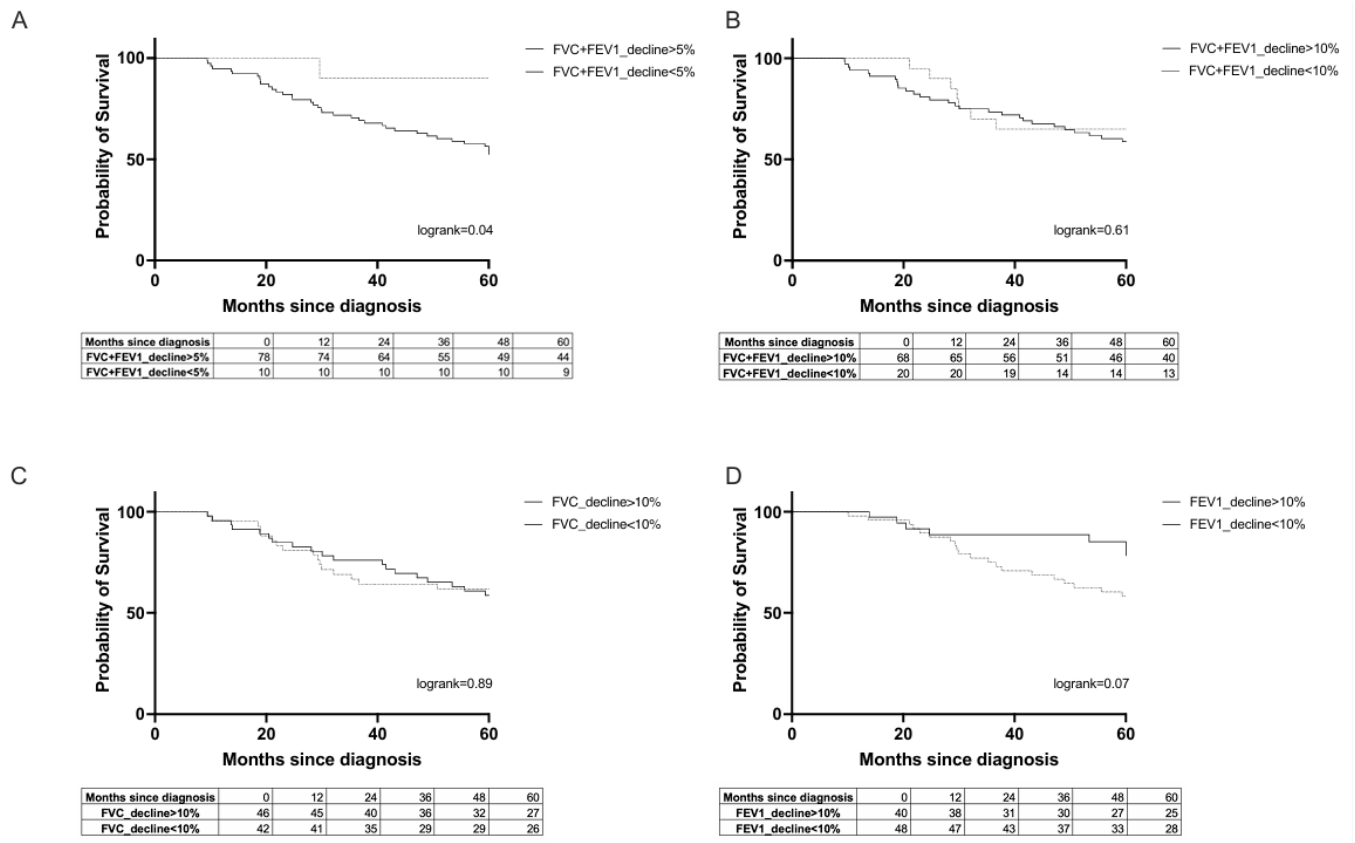

Figure 1. Impact of pulmonary function decline on survival. Panel A. Survival Kaplan-Maier Curve at 5 years (60 months). CPFE patients with a decline over 12 months of FVC+FEV1 > 5% had worse survival rate ($p<0.004$). Panel B. Survival Kaplan-Maier Curve at 5 years (60 months). CPFE patients with a decline over 12 months of FVC+FEV1 > 10% had not worse survival rate. Panel C: Survival Kaplan-Maier Curve at 5 years (60 months). CPFE patients with a decline over 12 months of FVC> 10% had not worse survival rate. Panel D: Survival Kaplan-Maier Curve at 5 years (60 months). CPFE patients with a decline over 12 months of FEV1 > 10% had not worse survival rate.

Discussion

PFTs are integral to understanding the physiological impact of CPFE, but they fall short as reliable prognostic tools. CPFE represents a unique interplay between the restrictive effects of fibrosis and the obstructive or hyperinflation effects of emphysema, leading to what is often a deceptive normalization of lung volumes such as FVC. Unlike IPF, where FVC decline robustly correlates with disease progression and mortality, the dual contributions of fibrosis and emphysema in CPFE dampen the sensitivity of FVC as a prognostic marker. This "masking" effect, where emphysema's hyperinflation counterbalances fibrosis-induced restriction, results in misleadingly stable FVC values over time, contributing to the under-recognition and underestimation of disease severity [3]. The DLCO, though consistently and significantly reduced in CPFE, is similarly limited in its prognostic utility. While DLCO reflects the extent of gas exchange impairment, it is also influenced by extrinsic factors such as haemoglobin levels, pulmonary vascular involvement, and comorbid cardiovascular disease, particularly pulmonary hypertension [4]. These factors make it an unreliable stand-alone marker for disease-specific progression in CPFE. Furthermore, the mixed pathology of fibrosis and emphysema creates heterogeneity in lung function test results, complicating efforts to identify universal thresholds for predicting clinical outcomes.

Combined functional decline as a potential prognostic marker

Given the limitations of isolated parameters like FVC or DLCO, our study explored the prognostic potential of combining declines in FVC and FEV_1 over 12 months. This combined metric aimed to capture the effects of both restrictive (fibrosis-driven) and obstructive (emphysema-driven) components of CPFE. Physiologically, FVC reflects the lung's restrictive capacity, which diminishes with worsening fibrosis, while FEV_1 is sensitive to airway collapse and obstruction associated with emphysema. By integrating these two parameters, we sought to create a more comprehensive marker of overall disease progression. Our findings suggest that a combined FVC and FEV_1 decline greater than 5% within 12 months is significantly associated with 5-year mortality, even after adjusting for confounding factors such as age, sex, and smoking history. This threshold likely reflects a critical tipping point in the balance between fibrosis and emphysema, where both components are contributing to accelerated physiological decline and clinical deterioration. Interestingly, a higher threshold (FVC + FEV_1 decline >10%) did not correlate with 5-year mortality but may indicate more rapid progression within the first two years post-diagnosis.

This suggests that larger declines may reflect an acute or aggressive phase of disease progression, warranting closer monitoring and potentially earlier interventions.

Physiological considerations

The physiological implications of these findings highlight the complex interaction between CPFE's dual pathologies. The observed prognostic value of combined FVC and FEV_1 decline underscores the need to move beyond single-parameter evaluations in CPFE. The restrictive defect from fibrosis contributes to reduced lung compliance and gas exchange abnormalities, while emphysema leads to increased lung compliance, airway instability, and ventilation-perfusion mismatch. These opposing physiological effects create challenges in accurately assessing disease severity and trajectory using traditional PFT metrics.

Moreover, the relationship between emphysema extent and mortality may reflect the impact of associated comorbidities, such as pulmonary hypertension and right heart dysfunction, which are exacerbated by the loss of alveolar-capillary units in emphysema. The fact that larger functional declines (>10%) may predict early mortality points to the need for a deeper understanding of the mechanisms driving rapid decompensation in CPFE.

Clinical implications

The identification of combined FVC and FEV_1 decline as a potential prognostic marker has significant clinical implications. First, it emphasizes the importance of serial PFT monitoring in CPFE patients to detect subtle but clinically meaningful declines in lung function. By focusing on a combined metric, clinicians may be able to identify patients at higher risk for mortality earlier, enabling closer follow-up and timely interventions.

Second, this approach aligns with the mixed pathophysiology of CPFE, providing a more tailored assessment that accounts for both fibrotic and emphysematous contributions to disease progression. This could help stratify patients for clinical trials or therapeutic interventions, where those with early functional declines might benefit from more aggressive antifibrotic or anti-inflammatory therapies.

Finally, the potential association between larger functional declines (>10%) and early mortality highlights the need for proactive management in patients demonstrating rapid progression. This could include early consideration for lung transplantation, initiation of oxygen therapy, or enrollment in pulmonary rehabilitation programs to optimize functional capacity and quality of life.

Limitations and future directions

Despite its promise, the combined FVC and FEV_1 decline metric requires further validation in larger, multicenter cohorts to confirm its prognostic utility and refine its thresholds. The relatively small sample size in our study, reflective of the rarity of CPFE, limits the generalizability of our findings. Additionally, the heterogeneity of CPFE, including variations in the relative contributions of fibrosis and emphysema, may influence the applicability of a single prognostic marker across all patients.

Future research should focus on integrating additional functional, radiological, and molecular markers to develop a more comprehensive risk stratification model for CPFE. The inclusion of advanced imaging techniques, such as quantitative CT analysis of emphysema and fibrosis extent, or biomarkers reflecting inflammation and extracellular matrix remodeling, may enhance the predictive accuracy of functional metrics. These efforts will be crucial in addressing the unmet need for reliable prognostic tools in CPFE and improving outcomes for this challenging patient population.

Conclusion

This study aimed to identify potential prognostic factors in pulmonary function tests (PFTs) for CPFE, considering the mixed restrictive and obstructive patterns inherent to the disease. Among the parameters analysed, the combined decline in FEV_1 and FVC greater than 5% over 12 months emerged as a significant predictor of 5-year mortality. This finding underscores the prognostic value of monitoring both restrictive and obstructive components of lung function in CPFE. While this combined metric offers promise as a prognostic factor, further studies with larger cohorts are needed to validate these results and refine the thresholds for clinical use. These efforts will help establish more robust prognostic tools, ultimately enhancing the management and outcomes of patients with CPFE.

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Chapter 5. General conclusions

Combined Pulmonary Fibrosis and Emphysema (CPFE) is a complex and challenging syndrome characterized by the coexistence of pulmonary fibrosis and emphysema, predominantly observed in male smokers or former heavy smokers [1]. The interaction between these two pathological entities results in unique pathophysiological characteristics, clinical manifestations, and prognostic implications. This research project explored the prognostic significance and clinical impact of emphysema in patients with CPFE and idiopathic pulmonary fibrosis (IPF), yielding critical insights into therapeutic approaches and disease management.

Prognostic impact of emphysema extent

The extent of emphysema has a profound influence on survival outcomes and the progression of disease in patients with CPFE and IPF [2]. This study found that patients with more extensive emphysema experienced significantly worse survival rates, particularly within the first year of diagnosis. The rapid disease progression observed during this period emphasizes the critical need for early detection and stratification of patients. Such proactive approaches could facilitate timely therapeutic interventions aimed at mitigating poor outcomes, slowing disease progression, and improving survival. Comorbid conditions were more prevalent in patients with greater emphysema severity, adding complexity to disease management. Pulmonary hypertension (PH), lung cancer, and pneumothorax were among the most observed complications. These conditions not only exacerbate the clinical severity of CPFE and IPF but also serve as independent predictors of mortality. For instance, PH increases pulmonary vascular resistance, worsening dyspnea and cardiovascular strain, while lung cancer introduces diagnostic and therapeutic challenges [3,4]. Pneumothorax, often linked to alveolar rupture, can lead to acute respiratory distress, necessitating urgent intervention. Managing these comorbidities effectively is crucial to improving patient outcomes and extending survival. Lung function progressively deteriorates with increasing emphysema, as evidenced by significant impairments in forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and diffusing capacity for carbon monoxide (DLCO). Of these measures, DLCO is particularly affected, reflecting the severe damage to the alveolar-capillary interface inherent in CPFE. This decline in gas exchange capacity not only limits oxygenation but also diminishes exercise tolerance and contributes to overall

functional impairment [5]. These physiological changes compound the already substantial disease burden, further impacting quality of life and independence.

Therapeutic interventions

Bronchodilator therapy in patients with CPFE has shown significant improvements in quality of life (QoL) and clinical symptoms. These improvements are reflected in reductions in validated symptom scores, such as the Saint George Respiratory Questionnaire (SGRQ), Modified British Medical Research Council Questionnaire (mMRC), and the COPD Assessment Test (CAT). The physiological basis for these improvements lies in bronchodilators' ability to relax smooth muscles in the airways, which reduces airway resistance, enhances airflow, and facilitates better ventilation, thereby reducing symptoms like dyspnea and improving overall function. In addition to improvements in symptom control, bronchodilators have been associated with a statistically significant reduction in residual volume (RV). This reduction is particularly noteworthy, as hyperinflation is a hallmark of CPFE, resulting from the combination of emphysema and fibrotic changes in the lung tissue. Emphysema leads to the destruction of alveolar walls and a loss of elastic recoil, which results in air trapping during expiration. This trapping exacerbates hyperinflation, impairing gas exchange and increasing the work of breathing. Fibrosis, on the other hand, reduces lung compliance and further limits the ability to expel air fully. By reducing RV, bronchodilators alleviate the hyperinflation that typically occurs in these patients, thus improving pulmonary mechanics. This reduction in hyperinflation also directly correlates with better symptom control, as patients experience improved lung function and reduced respiratory discomfort [6]. From a physiological standpoint, the improvement in symptom control with bronchodilator therapy is significant, particularly in CPFE patients who do not exhibit obstructive spirometry patterns. In CPFE, the presence of both fibrosis and emphysema leads to a complex pulmonary function profile. While spirometry may not show classic obstructive patterns due to the opposing effects of these two pathologies—emphysema causing airflow limitation and fibrosis reducing lung compliance—bronchodilators still provide symptomatic relief. This highlights their role in mitigating respiratory symptoms even in the absence of overt airflow obstruction. Moreover, bronchodilators may work by enhancing the distribution of ventilation, promoting more efficient gas exchange. In CPFE, areas of the lung with emphysematous changes tend to be poorly ventilated, while fibrotic areas, though restrictive, may still benefit from better

ventilation due to improved airflow dynamics. This dual benefit of bronchodilator therapy underscores its value in managing CPFE, where conventional spirometry-based treatment approaches may not always apply.

Disease monitoring

Serial monitoring of pulmonary function is crucial for predicting outcomes in CPFE, but traditional and single PFT values, such as FEV_1, FVC, and DLCO, may not provide a reliable reflection of disease progression. This is particularly true in CPFE, where the counterbalancing effects of fibrosis and emphysema complicate the interpretation of these parameters. While FVC is commonly used as a marker in many pulmonary diseases, it may not accurately capture the complex interplay of restrictive and obstructive patterns seen in CPFE. The presence of both emphysema and fibrosis often masks the true functional status, making single values of FVC and FEV_1 inadequate for reflecting the disease's progression or prognosis [7]. As the interaction between restrictive and obstructive components in CPFE complicates spirometric assessments, there is a growing need for additional markers that can more accurately assess disease activity and progression [8]. Emerging composite indices and imaging-based measures offer promising alternatives to traditional PFTs, providing a more nuanced and comprehensive understanding of disease dynamics. For example, a combined decline in FEV_1 and FVC greater than 5% has been identified as a significant prognostic factor for predicting 5-year mortality in CPFE, demonstrating the value of monitoring both restrictive and obstructive components of lung function in tandem. This combined metric highlights the limitations of relying on single PFT values, as it incorporates a broader spectrum of pulmonary function alterations. While this combined metric offers useful prognostic information, further research is necessary to refine its thresholds and validate its clinical utility across diverse CPFE patient populations. Ultimately, the development and incorporation of more robust, multi-dimensional tools for assessing disease activity will be essential for optimizing patient management and improving outcomes in CPFE.

Research gaps

There are several critical areas that require further exploration to enhance our understanding and management of CPFE. First and foremost, the pathogenetic mechanisms of the disease remain insufficiently understood. To truly refine our understanding of the disease's

heterogeneity, it is essential to delve deeper into the molecular and genetic factors that contribute to CPFE. By identifying new therapeutic targets, we could open the door to more personalized and effective treatment strategies. Another significant gap lies in the realm of early diagnosis. Currently, the diagnosis of CPFE can be challenging, especially in its early stages when symptoms may be subtle. Developing reliable biomarkers and advanced imaging techniques is crucial for enabling earlier detection of CPFE, which could drastically improve the chances of successful intervention. With earlier identification, we may be able to slow the progression of the disease and reduce its long-term impact on patients' lives. In terms of treatment, there is a pressing need for more research into therapeutic strategies that are specifically tailored to CPFE. While bronchodilators and antifibrotic therapies have shown promise, we still lack definitive evidence regarding their long-term efficacy in CPFE populations [8]. Randomized controlled trials are necessary to evaluate how these treatments perform over time, and to determine their true impact on disease progression and symptom management. Equally important is the need for reliable composite endpoints to measure the multifaceted nature of CPFE. Traditional endpoints that focus on single aspects of the disease, such as lung function or symptoms alone, fail to capture the full complexity of the condition. Future research should focus on developing composite endpoints that include measures of disease progression, symptom burden, and patient-centered outcomes, allowing for a more comprehensive assessment of treatment effectiveness.

To move forward with evidence-based treatments for CPFE, it is vital that CPFE patients are included in clinical trials. However, conducting trials in this population comes with unique challenges, primarily due to the complexity of CPFE itself. This complexity means that traditional endpoints may not be sufficient to assess the effectiveness of treatments. Therefore, trials must consider incorporating composite endpoints that take into account both the restrictive and obstructive aspects of the disease. Additionally, advanced imaging techniques should be used to capture the interaction between emphysema and fibrosis, providing a clearer picture of disease progression. Furthermore, clinical trials should explore the potential role of emerging therapies, particularly those based on precision medicine approaches. These therapies, which target specific molecular pathways, may offer more effective treatments tailored to individual patients. By incorporating precision medicine into clinical trials for CPFE, we could improve the chances of finding therapies that truly address the unique needs of this heterogeneous population.

Conclusion

This research underscores the importance of emphysema in defining CPFE as a distinct clinical entity with significant prognostic and therapeutic implications. The findings highlight the necessity for tailored management strategies and robust clinical trials to improve outcomes for this vulnerable population. A multidimensional approach—encompassing early detection, targeted therapies, and comprehensive follow-up—is essential for advancing care in CPFE. Continued exploration of the interplay between emphysema and fibrosis will be pivotal in refining our understanding and treatment of CPFE, ultimately improving the lives of those affected by this challenging syndrome.

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