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INTERSTITIAL LUNG DISEASE (G TINO, SECTION EDITOR)

Combined pulmonary fibrosis and emphysema

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Abstract
The purpose of this review is to provide an update on combined pulmonary fibrosis and emphysema (CPFE), with specific focus on the definition of CPFE and potential management options. There is no consensus regarding criteria for a diagnosis of CPFE, and multiple definitions of CPFE have been used in previous studies. Patients with CPFE have relatively preserved airflow and lung volume, with disproportionately impaired oxygenation. The risk of lung cancer and pulmonary hypertension is higher for CPFE than for idiopathic pulmonary fibrosis alone, but the effect of CPFE on overall mortality is unclear. There are no evidence-based recommendations for management of CPFE, and patients are currently managed according to individual guidelines for chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. Further research is required to determine the biological mechanisms of CPFE, and to establish whether it is a distinct biological condition or a coincidental occurrence of two separate conditions.

Key points
- Previous studies have used multiple definitions of CPFE. A broad definition of CPFE that includes any type of interstitial lung disease and any amount of emphysema is not appropriate for all research questions.
- Combined pulmonary fibrosis and emphysema (CPFE) is a distinct clinical phenotype that predominantly includes male smokers with pulmonary function tests characterized by relatively preserved flow rates and lung volumes, with markedly reduced carbon monoxide diffusion capacity.
- Lung cancer and pulmonary hypertension seem to be more common in CPFE than in IPF, and these complications are associated with a particularly poor prognosis.
- There are no evidence-based recommendations for the management of CPFE. In the absence of direct evidence, patients with CPFE are usually managed according to the principles that guide therapy for isolated chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.
- Future studies are required to determine the underlying biological mechanisms of CPFE and to establish whether CPFE is a biologically distinct condition or an overlap of two separate conditions that share similar risk factors.

Keywords Interstitial lung disease · Pulmonary emphysema · Pulmonary fibrosis · Combined pulmonary fibrosis and emphysema

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Background

Recent studies have described combined pulmonary fibrosis and emphysema (CPFE) as a distinct phenotype of interstitial lung disease (ILD), with coexisting pulmonary parenchymal fibrosis and emphysema detectable via either radiological imaging or pathology. These studies have provided multiple definitions of CPFE, which vary in the extent of emphysema and subtypes of ILD required for diagnosis; these differences probably account for some of the discrepancies reported in the literature. However, several findings are consistent among these studies, and have provided valuable insight into this syndrome. In this review we discuss different definitions of CPFE and how these should be used, summarize what is known about the clinical features and outcomes of this disease, and provide some initial guidance on patient management.

Definition of CPFE

Diagnosis of CPFE is primarily established on the basis of high-resolution computed tomography (HRCT) findings, with supplementary clinical data and pathological findings helpful in some cases. A consensus definition of CPFE does not exist, and previous studies have used a variety of criteria. Each of these definitions has strengths and limitations, and the most appropriate definition of CPFE depends on the research question being asked.

The broadest and most commonly used definition of CPFE includes all patients with both any type of pulmonary fibrosis and any amount of radiological emphysema. Most cohorts defined by these criteria have included patients with either idiopathic pulmonary fibrosis (IPF) or other idiopathic interstitial pneumonias [1–7]. This definition has the advantage of identifying a large number of patients by use of a simple and broad definition that can be used in diverse clinical settings. There is substantial inter-observer variability in ILD diagnosis even among experts [8], and this broad definition of CPFE minimizes the effect of this variability by combining all ILD subtypes, thus avoiding potential bias that arises from inaccurate classification of the underlying ILD. Misclassification of ILD may be even more common in CPFE because the coexistence of emphysema and fibrosis of any etiology can mimic honeycombing, falsely suggesting an usual interstitial pneumonia pattern that would support clinical diagnosis of IPF [9]. This especially applies to the distinction between IPF and idiopathic nonspecific interstitial pneumonia (NSIP), in which the presence of radiographic honeycombing can be a crucial component of the diagnostic algorithm.

Despite some potential benefits, a broad definition of CPFE has two important limitations that restrict its use for many research questions. First, inclusion of multiple ILD subtypes results in a heterogeneous cohort with mixed pathophysiology and clinical features, which can produce bias when comparing this CPFE population with other ILD subtypes. For example, unlike some ILD subtypes, IPF has common risk factors with chronic obstructive pulmonary disease (COPD), including a strong association with increased age and with smoking. Emphysema is, therefore, a more likely complication in IPF than in most other fibrotic ILDs, meaning the CPFE cohort will include a disproportionate number of patients with IPF and the non-CPFE cohort will, conversely, include a disproportionate number of patients with other fibrotic ILDs. Inclusion of other fibrotic ILDs, for example idiopathic NSIP, therefore produces bias resulting from the different symptoms and prognosis of IPF compared with other ILDs. Several studies have addressed this potential for bias by restricting the definition of CPFE to IPF patients only [10–12, 13•, 14]. This enables less biased comparison of IPF patients with and without emphysema, and direct evaluation of how comorbid emphysema affects clinical features and outcomes for a more uniform population.

A second limitation of a broad definition of CPFE is that the absence of a threshold for emphysema means that some patients diagnosed with CPFE will have little radiological emphysema, which is unlikely to be clinically relevant. Inclusion of these patients in the CPFE population will attenuate any difference between patients with and without clinically meaningful emphysema. Some studies have therefore required CPFE patients to have more than a specific amount of emphysema, with two studies using a threshold of 10 % emphysema visible on HRCT [13•, 14]. Although this definition is not formally validated, it does have high inter-rater reliability [13•, 14] and potential clinical relevance, with some evidence suggesting that ≥10 % emphysema corresponds to global initiative for chronic obstructive lung disease (GOLD) grade II or worse rating for patients with isolated COPD [15]. Further research is required to determine the optimum definition of CPFE.

Future studies should acknowledge that a single definition of CPFE is not appropriate for all research questions, and researchers should choose a definition in the context of their study objectives, taking into account the above factors (Table 1). For example, a broad definition including all ILD would be appropriate for a study examining the physiological implications of overlapping restrictive and obstructive lung disease. Alternatively, a study evaluating the effect of emphysema on outcomes may require a more homogenous ILD subset (e.g. inclusion of only patients with IPF). Finally, a specific emphysema threshold may not be required if investigating the pathobiology of CPFE, because the presence of any emphysema on HRCT indicates a predisposition to both fibrosis and emphysema and to at least focal activation of the relevant biological pathways.

Features of CPFE

Emphysema has been reported in up to half of patients with IPF [10], but a recent cohort study with a narrower definition of CPFE suggests the prevalence of clinically significant emphysema in IPF may be as low as 8 % for a North American population [13•]. The wide variability in the incidence of CPFE among patients with ILD is probably caused by differences in how studies defined CPFE and how study patients were recruited, by smoking heterogeneity in the population, and by other baseline clinical features. Most reported subjects with CPFE have a history of cigarette smoking, and this seems to be the main environmental risk factor. Other organic and mineral dust exposure, to asbestos and coal, for example, have also been implicated in a small number of cases [16–18].

Despite the variability in their definitions of CPFE, studies have consistently observed that these patients are usually older

Table 1 Definitions of CPFE

Definition of CPFE	Advantages	Disadvantages	Example of use
Pulmonary fibrosis of any etiology + emphysema of any severity	• Identifies a large number of patients • Reduces potential bias resulting from misclassification of ILD • Simple criteria that can be used in broad clinical settings (e.g. centers without a multidisciplinary ILD clinic)	• Includes multiple ILD subtypes, which introduces bias when comparing CPFE with other ILDs • Heterogeneous pathobiology confounds mechanistic studies • Some patients have minimal emphysema that is of unclear clinical significance	• Comparison of physiological implications of overlapping restrictive and obstructive lung disease
IPF + emphysema of any severity	• Enables direct comparison of CPFE with IPF to determine the incremental effect of emphysema when there is a previous diagnosis of pulmonary fibrosis	• Requires accurate ILD diagnosis • Excludes patients with non-IPF ILDs • Some patients have minimal emphysema that is of unclear clinical significance	• Identification of disease mechanisms
IPF + total emphysema score ≥10 %	• Enables direct comparison of CPFE with IPF to determine the incremental effect of emphysema when there is a previous diagnosis of pulmonary fibrosis • Only includes patients with a clinically meaningful amount of emphysema • Good inter-rater reliability for emphysema score	• Requires accurate ILD diagnosis • Excludes patients with non-IPF ILDs • Excludes patients with mild or trivial emphysema, which may have some subtle effect on clinical features and outcomes	• Evaluation of the effect of emphysema on patients with pulmonary fibrosis

Abbreviations: CPFE, combined pulmonary fibrosis and emphysema; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

men with a substantial smoking history [6, 10–12, 13•, 14, 19, 20]; that the most common symptoms are exertional dyspnea and cough [2]; and that clinical examination often reveals finger clubbing and crackles on chest auscultation [2, 3]. The striking male predominance seems to exceed the number of cases that would be expected if this were solely a result of more smoking by men. Other authors have proposed alternative explanations for the male predominance (e.g. increased age-related susceptibility of men to the effects of cigarette smoke) that require further study [21].

The coexistence of emphysema and fibrosis in CPFE leads to relatively preserved airflow and lung volume despite radiographic evidence of extensive parenchymal lung disease [6, 7, 11, 12, 13•, 19, 20, 22]. The finding that patients with CPFE have less severe fibrosis at the time of presentation probably accounts for some of the preserved spirometry and lung volume measurements [13•]. In addition, there is probably a balance of obstructive and restrictive physiology that largely accounts for the relatively preserved airflow and lung volume, often resulting in measurements that are within the normal range.

Outcomes of CPFE

Patients with CPFE seem to be at increased risk of lung cancer and pulmonary hypertension [1, 2, 4, 5, 7, 14], although the magnitude of this risk varies between studies and remains unclear. The increased risk of lung cancer is probably caused by additive or synergistic effects of smoking, emphysema, and pulmonary fibrosis, which are all associated with lung cancer development. The increased risk and severity of pulmonary hypertension in CPFE is probably related to the combined fibrotic and emphysematous destruction of the pulmonary parenchyma and the resulting reduction in the cross-sectional area of the pulmonary vasculature [14].

It remains unknown whether fibrosis in CPFE progresses at a similar rate to IPF without emphysema. Change in forced vital capacity (FVC) over time is the most commonly used surrogate of disease progression in recent IPF clinical trials, despite the recognized limitations of this measure. Progression of fibrosis is even more challenging to assess in CPFE patients, because the presence of emphysema alters the normal association between progressive pulmonary fibrosis and FVC decline. A previous study revealed that patients with CPFE have less FVC decline than patients with IPF alone [11], and a more recent study confirmed that change in FVC was only a weak predictor of mortality in CPFE [10]. This latter study suggested that a 10 % or greater decline in forced expiratory volume in 1 s (FEV_1) over 6–12 months may be a more useful measure of progression for this population [10]. A decline in carbon monoxide diffusing capacity (DLCO) may be an additional surrogate for ILD progression, but could instead indicate development or progression of pulmonary hypertension.

The limitations of single variables for use in prognostication of IPF have led to evaluation of composite measures of progression that include a combination of clinical and physiological variables [23–26]. The composite physiologic index (CPI) was originally derived to estimate the extent of fibrosis on HRCT on the basis of commonly obtained measures of pulmonary function [26], but has also been tested in multiple settings for its ability to predict mortality in IPF. This index

focuses on FVC and DLCO as predictors of radiological fibrosis severity but also includes FEV_1, primarily as a means of adjusting for the effect of emphysema on these other lung function tests. By indirectly adjusting for the extent of emphysema, the CPI may be more useful than individual measures of pulmonary function as a predictor of outcome for CPFE [10]. However, an important limitation of the CPI for prediction of CPFE mortality is that it was originally derived to estimate the extent of radiological fibrosis and is therefore probably an imperfect tool for predicting mortality. Newly developed clinical prediction tools for use with IPF have not been studied specifically for patients with CPFE.

There is substantial heterogeneity in the reported median survival for CPFE, ranging from 2.1 to 8.5 years [5, 7, 11, 12, 13•, 14, 22]. This variability is partially explained by the different definitions of CPFE used for these cohorts, in particular whether the study population was restricted to patients with IPF. Survival was more consistently between 2.1 and 4.5 years in studies that only included patients with a multidisciplinary diagnosis of IPF [10, 11, 13•, 14]. In addition, the proportion of patients with poor prognostic factors, for example pulmonary hypertension (PH) or lung cancer, affects overall mortality estimates, which have also varied across studies. CPFE patients with PH confirmed by use of right heart catheterization have a one-year survival of only 60 % [27], and CPFE patients with lung cancer have a median survival of 11 months [28].

Studies have disagreed on whether the presence of emphysema affects mortality for patients with ILD (Table 2). These inconsistent findings are largely the result of different analysis techniques, specifically the lack of a standardized approach to adjustment for ILD severity and subtype. For example, the finding for some cohorts that CPFE has improved survival compared with IPF alone could be explained by lead-time bias and less-advanced fibrosis at baseline in the CPFE group. The presence of long-term symptoms related to slowly progressive emphysema could prompt serial clinical and radiological evaluation, enabling diagnosis of IPF at an earlier stage of fibrosis that may have been asymptomatic without the coexistent emphysema. This earlier diagnosis of IPF would suggest a longer survival time for these patients, but only because their IPF was detected at an earlier stage. Another potential source of bias, as described above, arises from inclusion of multiple ILD subtypes that have different associations with smoking. Compared with most other ILDs, the stronger association between IPF and cigarette smoking places a disproportionate number of IPF patients in the CPFE group. This could result in the opposite bias, with CPFE patients having relatively poor outcomes that are comparable with IPF outcomes and that are worse than those for a more heterogeneous population of ILD patients. This effect could explain at least some of the increased mortality for CPFE patients observed by one recent study that included a variety of idiopathic interstitial pneumonias [5].

It seems logical that the presence of significant emphysema should increase mortality when diagnosed in addition to IPF. This hypothesis is supported by one of the larger and more rigorously studied CPFE cohorts in which mortality was higher for CPFE patients than for patients with IPF alone [14]. This study was restricted to patients with IPF and included an adjustment for fibrosis severity (HRCT fibrosis score) that attempts to eliminate the potential biases discussed above. A second study with similar methods reported comparable findings, although the increased mortality for CPFE patients in this study was less consistent and statistical significance depended on the method of analysis [13•]. None of the studies that reported increased survival in CPFE included an adjustment for severity of fibrosis [7, 11, 12], and some of these studies had other flaws that could have similarly produced bias in this comparison.

Treatment of CPFE

There is no evidence to support any specific treatment for CPFE, because these patients are usually excluded from major

Table 2 Survival in ILD with and without emphysema

Outcome	Ref.	Definition
CPFE worse	Mejia et al., 2009 [14]	IPF + total emphysema score ≥10 %
	Lee et al., 2011 [5]	IIP + any emphysema
No difference	Ryerson et al., 2013[a] [13•]	IPF + total emphysema score ≥10 %
	Jankowich et al., 2010 [22]	Pulmonary fibrosis and either radiological or pathological emphysema/bullous disease
CPFE better	Akagi et al., 2009 [11]	IPF + any emphysema
	Todd et al., 2011 [7]	IPF or idiopathic fibrotic NSIP + emphysema score > 2 (more than trivial emphysema)
	Kurashima et al., 2010 [12]	Radiological UIP of unknown etiology + any emphysema in two or more lung zones

[a] Adjusted transplant-free survival for CPFE was worse than for IPF alone. There was no statistically significant difference for time to death (excluding lung transplant patients) or when using a competing risk analysis (the primary outcome of this study)

Abbreviations: CPFE, combined pulmonary fibrosis and emphysema; CT, computed tomography; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia

IPF and COPD clinical trials and it is challenging to conduct trials on CPFE itself because of its low prevalence. Current recommendations are therefore made on the basis of extrapolating evidence related to the underlying conditions of COPD and IPF and of guideline recommendations developed for these individual diseases [29, 30].

There is general consensus that several nonspecific treatments used for isolated COPD and IPF are also appropriate for CPFE, including smoking cessation, vaccination against common pulmonary infections, pulmonary rehabilitation, and lung transplant. Additional disease-specific treatments should be considered on a case-by-case basis. For example, IPF patients with significant emphysema (e.g. ≥10 % emphysema volume on HRCT) may benefit from bronchodilator therapy, and CPFE patients with frequent exacerbation of airway disease may benefit from inhaled corticosteroids. These treatments were each used for a minority of CPFE patients in one cohort, and may be underused for this population [13•]. Novel antifibrotic treatments effective for IPF may also be considered for CPFE, however there is no direct evidence to support this approach because patients with significant emphysema are usually excluded from IPF clinical trials. In addition, pulmonary vasodilator therapy (e.g. sildenafil) should also be considered for patients who have pulmonary hypertension disproportionate to the extent of parenchymal destruction. This is a complex decision because the extent of parenchymal involvement is not accurately estimated by use of pulmonary function testing, and pulmonary vasodilators could increase ventilation-perfusion mismatch and worsen hypoxemia for some patients. Initiation of pulmonary vasodilator therapy should usually be done only in collaboration with a pulmonary hypertension specialist. Screening for lung cancer may also be appropriate for selected patients, particularly if it is believed that they could tolerate potentially curative treatment of a malignancy if lung cancer was detected.

Future directions

CPFE is a distinct clinical phenotype, but it remains unknown whether CPFE is a biologically distinct condition or an overlap of two separate conditions that share similar risk factors. Several molecular pathways have been implicated in animal models of both emphysema and pulmonary fibrosis [31–34], however other studies have identified activation of distinct pathways in these conditions [35•]. These observations require further study in larger and more carefully phenotyped cohorts. Additional prospective population-based studies are also needed to confirm previous observations and to provide additional guidance on how these patients should be managed.

Compliance with ethics guidelines

Conflict of Interest Rachel Jen declares that she has no conflicts of interest. Christopher J. Ryerson is a paid consultant for Intermune and receives honoraria, payment for educational presentations, and travel and accommodation expenses from them.

Human and Animal Rights and Informed Consent All studies by Christopher J. Ryerson involving human subjects were performed after approval by the appropriate Institutional Review Boards. Written informed consent was obtained from all participants.

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