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Global Journal of Health Science and Research

*Review Article*

# Combined pulmonary fibrosis and emphysema: A new horizon of smoker's lung disease with obstructive and restrictive lung functions!

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Received: 20 January 2023
Accepted: 16 March 2023
EPub Ahead of Print: 15 May 2023
Published: 20 September 2023

**DOI**
10.25259/GJHSR_14_2023

**Quick Response Code:**

## ABSTRACT

Combined pulmonary fibrosis and emphysema (CPFE) is underestimated chronic lung disease presenting with a combo of emphysema plus interstitial lung disease. CPFE is a heterogeneous lung disease documented usually in smokers which includes emphysema in the upper lobes and pulmonary fibrosis in the lower lobes. Although CPFE is commonly called as Smoker's lung disease, a proportionate number of cases are having concurrent connective tissue disease. High-Resolution Computed Tomography (HRCT thorax) is a gold standard investigation to evaluate CPFE due less reliability of conventional chest radiography. Pulmonary hypertension and lung cancer are two comorbidities associated with poor outcome in CPFE. Echocardiography, diffusion coefficient, and body plethysmography have documented a role in composite assessment of CPFE. Combination of bronchodilators, oxygen supplementation during rest and ambulation in selected cases and antifibrotics is having a "game changer" role in the management of CPFE.

**Keywords:** Combined pulmonary fibrosis and emphysema, Connective tissue disease, Smoker's lung disease, Interstitial lung disease, Nintedanib, HRCT thorax

## INTRODUCTION

Combined pulmonary fibrosis and emphysema (CPFE) is an underrecognized syndrome characterized by chronic, progressive disease with a dismal prognosis. Frequent comorbidities with a higher incidence than in idiopathic pulmonary fibrosis (IPF) or emphysema alone are pulmonary hypertension (World Health Organization group 3) in 47–90% of the patients and lung cancer in 46.8% of the patients.[1] According to the definition of emphysema, the presence of excess fibrosis has been historically excluded from the diagnosis of emphysema.[2] Therefore, chronic obstructive pulmonary disease (COPD) and idiopathic interstitial pneumonias, with different radiological, pathological, functional, and prognostic characteristics, have been regarded as separate entities for a long time. However, there is an increasing recognition of the coexistence of emphysema and pulmonary fibrosis in individuals. Whether the combination of emphysema and pulmonary fibrosis is a distinct clinical entity or not remains unknown. Some consider it as a coincidence of two smoking-related diseases in one person, comparable to the coexistence of lung cancer and COPD. However, previous data had suggested that interstitial lung abnormalities were inversely associated with emphysema in smokers.[3] Actually, most former smokers with IPF

do not have radiographic evidence of emphysema. Likewise, most patients with emphysema/COPD do not have overt evidence of interstitial fibrosis. Therefore, the combination of pulmonary fibrosis and emphysema may be a distinct consequence of smoking that reflects unique individual susceptibilities.

In 2005, Cottin *et al*. first time put forward a defined syndrome termed "combined pulmonary fibrosis and emphysema (CPFE)," which is characterized by heavy smoking history, exercise hypoxemia, upper lobe emphysema and lower lobe fibrosis, unexpected subnormal lung volumes and severe reduction of carbon monoxide transfer.[4] The CPFE syndrome comprises a heterogeneous population of patients and a consistent definition of CPFE has not been put forward. High-resolution computed tomography (HRCT) is the mandatory tool to diagnose this syndrome. CPFE is frequently complicated by pulmonary hypertension, acute lung injury and lung cancer and the prognosis of it is poor. Treatments for CPFE patients with severe pulmonary hypertension are less effective than lung transplantation.[5] Identification of patients with CPFE is important because this disorder has its unique natural history. However, unfortunately CPFE has not yet attracted wide attention of clinicians and there is no research systematically contrasting the differences among CPFE, emphysema/COPD and pulmonary fibrosis alone at the same time.

## BASIC ASPECTS OF CPFE AND PATHOGENETIC MECHANISMS

CPFE is a clinical entity characterized by the combination of the upper lobe emphysema and lower lobe fibrosis. The advent of computed tomography permitted recognition of the coexistence of pulmonary fibrosis and emphysema (CPFE). Although most cases of CPFE likely represent the common fibrotic pattern of usual interstitial pneumonia (UIP), few cases have been reported as showing desquamative interstitial pneumonia (DIP) or unclassified interstitial pneumonia.[6] Emphysema is defined as an enlargement of the air spaces distal to the terminal bronchioles due to the destruction of the tissues forming their walls. Emphysema secondary to smoking is typically centrilobular, which commonly manifests as small, localized areas of low attenuation within the central portion of the secondary pulmonary lobule on HRCT.[2] IPF is a chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, characterized by progressive worsening of dyspnea and lung function and associated with a poor prognosis. It is the most common ILD with a characteristic histologic pattern of UIP, which is characterized on HRCT by the presence of subpleural and basal predominance, reticular opacities, and honeycombing with or without traction bronchiectasis.[7]

## PATHOGENESIS: FOUR DIFFERENT THEORIES

The pathogenesis of CPFE has not been fully elucidated to date. It is still unclear whether emphysematous and fibrotic lesions progress independently or if one results from the other. Perhaps there are some undiscovered mechanisms, which may involve a variety of cytokines and shared signaling pathways, resulting in both emphysema and pulmonary fibrosis in genetically susceptible individuals after the exposure to environmental triggers such as smoking.

### CPFE starts with fibrosis, subsequently resulting in emphysema

One theory is that the fibrosis, with predominance in the basal lung parts, exerts traction on the upper parts of the lung, resulting in the development of emphysema.[4] However, emphysema most of the time precedes the fibrotic changes, which would question the appropriateness of this theory.[8]

### CPFE is due to gastroesophageal reflux (GER) promoted by smoking behavior

GER has been identified to be associated with interstitial lung diseases (ILDs) and is therefore considered a risk factor for the development of lung fibrosis. Smoking can increase GER and thus be responsible for the development of the emphysema and indirectly (via increased GER) for the fibrotic lung changes that develop over time. This relationship is controversial and can be confounded by other effects of smoking on the lung tissue. The mechanism behind this could also be due to a sequence of events that leads first to emphysema and then additionally to fibrotic changes triggered by late-onset increased gastropharyngeal reflux. In certain individuals who are susceptible to tobacco smoke, a symptomatic smoking-related emphysema might develop. As part of standard care, a smoking cessation intervention is performed, which leads not only to smoking abstinence but also frequently to a relevant weight gain. The weight gain itself promotes increased gastropharyngeal reflux (with micro-aspirations) and thus may trigger development of fibrotic changes in the lungs. This hypothesis is compatible with the frequently observed temporal sequence of development of emphysema prior to the fibrotic changes and also with the frequently observed history (in our cohort) of strong weight gain after smoking cessation. So far, no published case series or cohort studies have systematically documented this sequence of events and the possible role of reflux and micro-aspirations in CPFE patients.[9]

### CPFE as an autoimmune phenomenon

A third hypothesis in a subgroup of CPFE patients could be an autoimmune phenomenon. One multicenter study investigated 40 patients with CPFE and 60 patients with

IPF. A statistically significant number of CPFE patients with elevated serum antinuclear antibody (ANA) with or without positive Perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) titers were observed compared with patients with IPF without emphysema. Patients with CPFE and positive autoimmune markers showed improved survival compared to patients with a negative autoimmune profile. Moreover, a massive infiltration of clusters of CD20+ B cells forming lymphoid follicles within the fibrotic lung in CPFE patients with positive serum immunologic profile compared to patients with negative profile was noted and positively correlated with improved survival.[10] Cottin *et al*. reported a relationship between patients with connective tissue disease (CTD) and CPFE. These CTD patients had rheumatoid arthritis (RA), systemic sclerosis, mixed or overlapped CTD, or other CTDs. In this study patients with combined CTD and CPFE were significantly younger than a historical control group of patients with idiopathic CPFE and were more frequently female. In addition, patients with CTD and CPFE had higher lung volumes, lower diffusing capacity, higher pulmonary pressures, and were more frequently male than those with CTD and lung fibrosis without emphysema.[11]

### CPFE in development pathways based on genetic factors

A genetic component may contribute to the development of CPFE. These studies are complex and so far, cannot explain CPFE development in all patients. Collum *et al*. demonstrated that both adenosine and its receptor ADORA2B are elevated in chronic lung diseases. Activation of ADORA2B leads to elevated levels of hyaluronan synthases and thus a higher concentration of hyaluronan. Hyaluronan is a glycosaminoglycan that contributes to chronic lung injury, suggesting that ADORA2B and hyaluronan contribute to CPFE.[12]

Another study found an association between ABCA3 mutations and CPFE in a 41-year-old non-smoking male presenting with dyspnea on mild exertion. The ABCA3 gene is involved in surfactant metabolism. Recessive loss-of-function mutations in ABCA3 present as lethal surfactant deficiency in the newborn, whereas other recessive mutations in ABCA3 can result in ILD in older children.[13]

## CLINICAL SYMPTOMS

Cough and dyspnea are common symptoms in patients with CPFE or COPD or IPF. However, some differences exist among them. The characteristic symptoms of COPD are chronic cough with daily variable sputum production and progressive dyspnea. Chronic cough and sputum production usually precede airflow limitation by many years.[14] As for patients with IPF, dyspnea is the primary symptom existing in over 90% of patients at the time of diagnosis, followed by frequent dry and non-productive cough experienced by 73–86% of patients in the late stage.[15]

The symptoms of CPFE seem more similar to that of IPF. Progressive shortness of breath is the most common and classical symptom and is usually more severe, especially exertional dyspnea (exists in almost all the patients; functional class III–IV of the New York Heart Association). Other common signs and symptoms of respiratory tract, such as cough, wheezing, perioral cyanosis, asthenia and so on, may also appear in some patients. On physical examination, patients with CPFE usually have inspiratory dry crackles named "Velcro sounds" from the underlying pulmonary fibrosis on chest auscultation, as reported in 87–100% of cases, and a number of them (43–45%) have finger clubbing.[16]

## HIGH-RESOLUTION COMPUTED TOMOGRAPHY (HRCT)

At present, there is no consistent definition of CPFE. HRCT scanning is essential for the diagnosis of CPFE. The diagnostic criteria of CPFE described by Cottin *et al*. included radiological findings of the 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.[4,5] The upper-lobe emphysematous lesions in CPFE mainly include centrilobular emphysema, paraseptal emphysema and bullae, with the prevalence 97%, 93%, and 54%, described, respectively, in a study by Cottin *et al*.[5] There are differences in the distribution of emphysema between CPFE and COPD. Emphysema secondary to smoking was reported typically centrilobular in COPD. However, paraseptal emphysema was much more frequent in the CPFE group than the COPD group and was considered as the most typical presentation of CPFE.[16]

Thick-walled cystic lesions (TWCLs) are considered as unique radiological and pathological features of CPFE as well.[11] Enlargement of TWCLs is probably an indication of interstitial pneumonia deterioration. In recent research, both radiological and pathological TWCLs were observed in 72.7% of the CPFE patients, but not in any patient with IPF or emphysema alone. The authors also found that the extent of emphysema was greater in the CPFE patients with TWCLs than that in the patients without TWCLs.[16]

As for the lower-lobe fibrosis lesions, honeycombing, reticulation and traction bronchiectasis are the top-three common imaging features, with the prevalence of 75.6–95%, 84.4–87% and 40–69% reported in cases with CPFE.[16,17] Except the abnormalities mentioned above, areas of ground glass attenuation are also common in CPFE, as reported by 62.2–66%, being the unique feature suggesting possible smoking-related ILD, such as DIP.[18]

In the aspect of HRCT scores, the total emphysema scores were reported highest in COPD and higher in CPFE than in IPF. Besides, the total emphysema scores of CPFE were similar to that of mild to moderate COPD and lower than that of severe COPD.[19] Fibrosis scores are generally higher in CPFE and IPF than that in COPD. However, the difference of fibrosis scores between CPFE and IPF was still controversial. Some reports found no difference while others showed the lower total fibrosis scores in CPFE than IPF and found the difference was consistent in the upper, mid, and lower lung zones.[19,20]

Recently, there is a new report about the comparison of CPFE patients with and without airflow obstruction (CPFE OB+ group and CPFE OB− group). The degree of emphysema represented by LAA scores on HRCT was significantly lower in the CPFE OB− group than the CPFE OB+ and COPD groups, while the severity of pulmonary fibrosis was greater in the CPFE OB− group than the CPFE OB + group. Different mechanisms may be involved in the development of clinical phenotypes of CPFE, which might be classified into "emphysema-dominant" phenotype or "fibrosis-dominant" phenotype.[17]

The distribution of emphysema and fibrosis in patients with CPFE are not completely independent from each other. Brillet *et al*. had described three patterns of distribution in CPFE: A progressive transition from apical emphysema to a zone of transition between bullae and honeycombing; paraseptal emphysema with areas of fibrosis; separate processes with independent areas of fibrosis and emphysema.[21] Sometimes differentiating emphysema from pulmonary fibrosis may be complex and difficult. For example, wall-thickened emphysematous changes may be mistaken for honeycomb cysts. Moreover, as reported by Cottin *et al*. only 50% of patients with CPFE had simultaneous emphysema and pulmonary fibrosis at diagnosis; others might develop another lesion after a long history of emphysema or pulmonary fibrosis.[5] Hence, patients with suspected CPFE should be followed up on a regular basis.

## PULMONARY FUNCTION TESTS (PFTS)

CPFE has a characteristic pulmonary function feature different from pure emphysema and IPF, which is characterized by the unexpected relatively normal lung volumes contrasted by a severely reduced diffusing capacity. In many research, mean values of forced vital capacity (FVC) and total lung capacity (TLC) in CPFE are usually within a relatively normal range, whereas Diffusing capacity of lung for carbon monoxide (DLCO) is severely diminished.[17,20,22] The preserved lung volumes may be attributed to the counterbalanced effects of the hyperinflation defect of emphysema and the restrictive defect of pulmonary fibrosis. And the reduced diffusing capacity may be due to the overlapping negative effects of both emphysema and pulmonary fibrosis on the gas exchange.[3,22,23]

For emphysema/COPD, it tends to increase lung compliance, enlarge lung volumes and residual volume (RV) with reduced maximal expiratory flows and decreased DLco. In most research, higher forced expiratory volume in the first second (FEV1) and FEV1/FVC, lower RV and TLC, and lower DLco are usually observed in patients with CPFE than in patients with COPD.[20,24] In one study showing annual changes of lung function between CPFE and COPD, Kitaguchi *et al*. reported that annual decreases in lung volumes (VC and FVC) and gas-exchange (DLco) were significantly higher in the CPFE group than the COPD group. However, the annual decrease in airflow limitation represented as FEV1/FVC was significantly lower in the CPFE group than the COPD group. This may be explained by the traction caused by pulmonary fibrosis in CPFE, which prevents the typical expiratory airway collapse seen in emphysema and strengthens the support of the small airways.[23]

For pulmonary fibrosis, it tends to decrease lung compliance and reduce TLC, RV and RV/TLC ratio with preserved or increased maximal expiratory flow rates and reduced DLCO. In general, patients with CPFE usually have higher lung volumes, lower FEV1/FVC ratio and lower DLco than patients with IPF.[3,25] In spite of a lower baseline DLco in the CPFE group than that in the IPF group, Akagi *et al*. reported that the annual rates of decline in DLco and FVC were also significantly lower in the CPFE group.[26] The existence and range level of emphysema are important factors promoting decline in the pulmonary function of IPF, such as FEV1/FVC. In several studies showing annual changes of lung function between CPFE and IPF, the FEV1/FVC ratio in CPFE significantly decreased during the follow-up period while that in IPF remained nearly consistent over time.[24,26,27] These results suggest that CPFE is more associated with a progressively obstructive pattern over time and highlight the importance of bronchodilator therapy in CPFE.

The different pulmonary function impairment between CPFE patients with and without airflow obstruction has been recently reported.[24] Impairment of diffusion capacity was severe in both CPFE OB− and CPFE OB+ groups. Although there were no significant differences in the dynamic hyperinflation between CPFE OB− and CPFE OB + groups, lung hyperinflation and respiratory resistance were significantly lowest in CPFE OB− group and lower in CPFE OB+ group than the COPD group. In addition, CPFE OB+ patients with more emphysema were also found to have a worse survival than CPFE OB− patients.

In the end, it is worth noting that the pattern of normal lung volume with severely decreased DLco in PFTs does not necessarily mean CPFE syndrome. It may be explained by other abnormalities, such as pulmonary vascular disease, emphysema and ILD. In a report, only 16% of patients with severely diminished capacity of gas exchange had CPFE,

with the remainder having emphysema (46%), ILD (28%) or pulmonary arterial hypertension (PAH) (8%).[28]

## BLOOD GAS ANALYSIS

Resting and exercise hypoxemia are most frequent in patients with CPFE because of the severely damaged capacity of gas exchange, whereas hypercapnia hardly appears, usually with normal average levels of $PaCO_2$.[3] Hypoxemia in the CPFE syndrome is generally moderate or above at rest and gets worse during exercise.[29] The blood gas analysis of CPFE is different from that of COPD and seems more similar to IPF. For patients with advanced COPD, gas exchange abnormalities usually result in hypoxemia and hypercapnia. The carbon dioxide retention in COPD can be explained by reduced ventilation due to severe obstruction and hyperinflation with ventilator muscle impairment.[14]

## COMPLICATION

### PAH

PAH, defined as mean pulmonary arterial pressure >25 mmHg, is the most important complication in COPD and IPF, which usually correlates with worse survival.[30] The prevalence of PAH was reported 50% in COPD and 31–46% in advanced IPF.[30,31] As for patients with CPFE, the prevalence of PAH was observed 47–90% in previous studies, which was much higher than COPD and IPF.[4,30,31] In a study by Cottin *et al*.,[4] the prevalence of PAH was present in 47% of CPFE patients at diagnosis, and in 55% during follow-up. In another recent research, there was no difference in estimated systolic pulmonary arterial pressure (esPAP) between CPFE and IPF at diagnosis, but after 12 months the esPAP significantly increased in CPFE.[32] Most CPFE patients have moderate to severe PAH whereas that in COPD or IPF alone is usually mild to moderate.[31] The phenomenon may be explained by an additional/synergistic effect of hypoxic pulmonary vasoconstriction and reduced capillary beds due to the combination of pulmonary fibrosis and emphysema in CPFE.[5] PAH contributes to the functional profile of CPFE (severe dyspnea, markedly impairment of gas transfer, and exercise hypoxemia) and is associated with a poor prognosis in CPFE. Higher pulmonary vascular resistance, higher HR, lower cardiac index, and lower DLco are associated with a worse prognosis in CPFE-associated PAH.[29]

### Lung cancer

Emphysema and IPF have also been regarded as independent risk factors for lung cancer. The incidence of lung cancer is reported 22.4–31.3% in IPF patients and 6.8–10.8% in COPD patients.[17] Therefore, CPFE, which is associated with smoking and has the features of both IPF and emphysema, may also be an independent risk factor for lung cancer. A much higher prevalence of lung cancer (35.8–46.8%) has been reported in patients with CPFE than either entity alone, with squamous cell carcinoma being the most common histologic type. The highest proportion of squamous cell carcinoma may be related to a heavy smoking history in almost all the CPFE patients, because it has been reported to be more significantly associated with tobacco smoking than adenocarcinoma.[33,34] Kitaguchi *et al*. had found a significantly increased prevalence of lung cancer in CPFE than in COPD (46.8% vs. 7.3%).[18] Another recent study also reported a higher prevalence of lung cancer in CPFE than in IPF (50% vs. 14.5%).[32] Inversely, the prevalence of CPFE in the lung cancer population was found higher (8.9%) than isolated pulmonary fibrosis (1.3%).[34]

## TREATMENT OPTIONS IN CPFE

There are no specific effective treatments for the CPFE syndrome at present. It seems logical to make treatment decisions based on recommendations separately for emphysema and pulmonary fibrosis.

1. Smoking cessation, which is the first recommended treatment for COPD and IPF, should be encouraged for CPFE as well because it may stop the progression of disease. For those who are associated with other environmental exposures, keeping away from the exposures is the most important.[14,35]
2. To lessen acute exacerbations and infections, patients are suggested to accept a long-term oxygen therapy and take vaccination against influenza viruses and streptococcus pneumonia. Oxygen therapy is known as the most appropriate treatment for hypoxemia and pulmonary hypertension in CPFE. Supplemental oxygen therapy is used in the context of resting hypoxemia and may also have benefits when prescribed only for hypoxemia that occurs during exercise and nocturnally, even in those patients who are normoxemic at rest[36]
3. Regular exercise and pulmonary rehabilitation are provided to most patients with CPFE. Although no studies have evaluated pulmonary rehabilitation in CPFE, pulmonary rehabilitation and regular exercise are a cornerstone of management of patients with emphysema and are increasingly used in patients with fibrosing ILD (fILD)[37]
4. As most exacerbations of both COPD and fILD are thought to be triggered by a respiratory tract infection (either from a virus or bacteria), influenza, pneumococcal, and coronavirus disease vaccination are also provided at standard intervals, unless contraindicated.

### Treatment of pulmonary fibrosis

Decisions about pharmacologic treatment are guided by the underlying diagnosis of fILD.[38] Management of pulmonary

fibrosis in the setting of CPFE is informed by the landmark clinical trials of nintedanib and pirfenidone.[39,40] Both antifibrotic medications slow the progression of mild-to-moderate IPF and other subtypes of progressive pulmonary fibrosis by approximately 50% at 12 months. 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 a slow decline in FVC in the placebo arm in CAPACITY 1.[39] 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.[41] 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 benefits 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.[38]

### Treatment of pulmonary emphysema

Recognition of the individual phenotype of each patient is recommended, given the lack of controlled data specific to the treatment of CPFE.[44] Inhaled bronchodilators may have benefits in select patients with CPFE who have significant airflow limitation (i.e., COPD),[45] and one uncontrolled cohort study has suggested a possible improvement in $FEV_1$ after the use of a combination of inhaled corticosteroid and long-acting bronchodilator.[36,45] Further studies of inhaled bronchodilators with or without corticosteroids are needed in patients with CPFE because of the relatively well-preserved spirometric values.[21]

### Treatment of pulmonary hypertension

Management of PH in the presence of CPFE is based on managing the underlying respiratory disorder, treating hypoxemia with supplemental oxygen, and ensuring optimal timing for lung transplant referral.[5] Controlled data do not support the use of oral PH-specific therapies, including endothelin receptor antagonists (bosentan and ambrisentan), phosphodiesterase-5 inhibitors (sildenafil and tadalafil), or stimulator of soluble guanylate cyclase (riociguat), although uncontrolled observational studies show possible benefit from PH therapies, and there are encouraging secondary endpoint trends in trials using sildenafil in IPF. Particular caution should be exercised, as treatment with ambrisentan and riociguat may be detrimental in patients with fILD and especially those with CPFE.[46,47]

## PREDICTORS OF SURVIVAL OR OUTCOME

Different longitudinal measurements such as lung function (FEV1, FVC, DLCO), symptoms and radiological studies (HRCT scans), are used to classify disease severity. However, none of these parameters are fully satisfactory in predicting prognosis in CPFE patients. Wells *et al*. tried to develop a more reliable predictor of prognosis in IPF patients, by using the composite physiologic index (CPI).[48] This index was derived to represent the extent of fibrosis in IPF patients, with adjustment for the emphysema component. In IPF patients, the extent of IPF on CT was calculated by a formula incorporating multiple components of pulmonary function: the extent of disease on CT = 91.0 – (0.65 × percent predicted DLCO) – (0.53 × percent predicted FVC) + (0.34 × percent predicted FEV1). In IPF patients, CPI and longitudinal changes in DLCO were more predictive than FVC and FEV1.[49] However, CPI is not helpful in predicting prognosis in CPFE patients: Schmidt *et al*. demonstrated that longitudinal change in FEV1 was most predictive of mortality in CPFE patients, whereas a significant increase (i.e., by at least five points over 6 or 12 months) in CPI was the best predictor in patients with IPF without emphysema.[49]

The clinicoradiological patterns of the fibrotic disease of CPFE are also relevant in the estimation of the prognosis. The study of Alsumrain *et al*. showed that the overall mortality for the study period (11 years) was greatest in those with CPFE with UIP/IPF pattern, compared to other classifiable and unclassifiable ILD patterns (69% vs. 45% vs. 38%, respectively, $P = 0.016$).[50]

## CONCLUSIVE REMARKS AND CLINICAL LESSONS

Progressive shortness of breath with partial response to inhaled bronchodilator and antimuscarinic needs prompt evaluation in COPD to rule out other causes of failure of treatment. Chest X-ray gives definite clues for alternate diagnosis in cases with partial response to inhaled medicines in COPD. Chest radiology showing blurred cardiac and diaphragmatic margins needs interstitial disease to rule out. In fact, loss of demarcation of cardiac and diaphragmatic margins in chest X-ray is "earliest marker" of ILD. Velcro crepitations on auscultation in COPD cases are "clinical clues" to suspect IPF in cases with chronic tobacco exposure.

HRCT is the gold standard test to evaluate ILD. Honeycombing, tractional bronchiectasis, and reticular opacities in bilateral lower lobes with peripheral, subpleural distribution suggestive of UIP pattern. Combination of UIP pattern in lower lobes with emphysema in upper lobe is CPFE in cases with chronic smokers. With the typical radiological pattern of CPFE, lung biopsy is not necessary for further confirmation.

Large number of CPFE cases with poor exercise tolerance (i.e., 6-min walk distance) necessitates echocardiography to rule out pulmonary hypertension which is common but underestimated cause of persistent dyspnea in these cases. Although DLCO is decreased in both emphysema and ILD independently, it can be assessed with lung volumes. Normal lung volumes with reduced DLCO are rare in CPFE.

Proportionately large number of CPFE cases are having rheumatological symptoms with positive RA factor. ANA blot needs strict evaluation in all cases of CPFE to rule out concurrent CTD. Myositis and undifferentiated CTDs are common in CPFE. Bronchodilators, antifibrotics with or without pulmonary vasodilators and oxygen supplementing as per oxygen saturation and echocardiography findings is mainstay therapy for CPFE.

### Declaration of patients consent

Patient's consent not required as there are no patients in this study.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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**How to cite this article:** Patil S, Toshniwal S. Combined pulmonary fibrosis and emphysema: A new horizon of smoker's lung disease with obstructive and restrictive lung functions! Glob J Health Sci Res 2023;1:76-83.