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ORIGINAL RESEARCH

Combined Pulmonary Fibrosis Emphysema: Role of Cigarette Smoking and Pulmonary Hypertension in a Rural Cohort

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Background: Disease heterogeneity in idiopathic pulmonary fibrosis (IPF) often complicates the systematic study of disease, management of patients and clinical investigations.
Objective: To describe combined pulmonary fibrosis emphysema (CPFE) phenotype in a rural Appalachian IPF cohort with the highest smoking rates in the United States.
Methods: CPFE patients (n = 60) in a developed IPF cohort (n = 153) were characterized. Groups (CPFE vs IPF without emphysema) were categorized based on the predominant HRCT patterns of UIP (n = 109). Demographics, clinical variables, and treatment details were recorded. Kaplan–Meier survival and multivariate logistic regression analysis were performed.
Results: The prevalence of CPFE in our IPF cohort was 45% (n = 49). The CPFE group was younger (73.9 vs 78.2), had a more extensive smoking history (93.9% vs 53.3%) with greater mean smoking pack years (49.09 vs 15.39) and had lower percentage predicted DL_{CO} on presentation (38.35 vs 51.09) compared to IPF without emphysema group. Both groups shared equivalent higher burden of comorbidities, including pulmonary hypertension (PH) (46.9% vs 33.3%). One-fifth of patients were prescribed antifibrotics and only a subset (5%) of patients underwent lung transplantation. There was a non-significant trend towards reduced survival in CPFE (p = 0.076). Smoking status and DL_{CO} predicted CPFE in our cohort. Body mass index (BMI), PH, and pirfenidone use were significant predictors of mortality.
Conclusion: CPFE was highly prevalent in our rural IPF cohort. In contrast to previous studies, CPFE group was older and had higher female (approx. 30%) occurrence. A greater exposure to cigarette smoke and reduced DL_{CO} at diagnosis predicted CPFE. Lower BMI and PH predicted higher mortality whereas use of pirfenidone improved survival in our cohort. This study highlights a complex interaction of cigarette smoking, advanced fibrosis of UIP, PH and potential utility of antifibrotic agents in CPFE phenotype. Substantial burden of comorbidities, older age, and the limited utilization of advanced therapeutics in the cohort emphasize the challenges faced by rural Appalachian patients.
Keywords: combined pulmonary fibrosis emphysema; CPFE, cigarette smoking, pulmonary hypertension; PH, pirfenidone, body mass index; BMI, rural population

Introduction

The clinically accepted dichotomy between emphysema and pulmonary fibrosis can reflect the constraints of the current diagnostic approach resulting in an imperfect recognition of the coexistence of these entities in the same individuals.[1] However, there is increasing appreciation that emphysema and pulmonary fibrosis can be documented in the same patient, producing a clinical syndrome known as combined

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pulmonary fibrosis and emphysema (CPFE).[2–4] The diagnosis of the CPFE syndrome is established using high resolution CT (HRCT) imaging with pathology when available. The radiographic appearance includes the presence of upper-lobe emphysema and lower-lobe pulmonary fibrosis.[5–7] Clinical characteristics can include male gender, a heavy smoking history, the presence of significant dyspnea, relatively preserved lung volumes but a disproportionate impairment of gas exchange, and hypoxemia.[8] Pathology frequently reveals both usual interstitial pneumonia and emphysema. The effect of emphysema on pulmonary function tests (PFT) likely contributes to alter or mask the estimation of baseline disease severity and its progression over time.[9] Early identification of this phenotype potentially has important clinical implications as CPFE is often complicated by pulmonary hypertension (PH), lung cancer, acute exacerbation of underlying disease, and postoperative cardiopulmonary complications.[8,10,11]

It has been proposed that a combined syndrome of pulmonary fibrosis and emphysema can be described among individuals with idiopathic pulmonary fibrosis (IPF). Reports suggest that the incidence of such CPFE among IPF cohorts may include up to 35% of patients.[8] The characterization of CPFE as a distinct clinical entity has identified several inherent limitations including a lack of an international consensus definition of CPFE, variable interpretation of honeycombing on radiographs particularly when emphysema is admixed with reticulation, an impact of coincidental findings of smoking related ILDs (e.g., respiratory bronchiolitis-interstitial lung disease [RB-ILD], desquamative interstitial pneumonia [DIP], and unclassifiable smoking-related interstitial fibrosis [SRIF]), and an underestimation of disease severity with employment of FVC for clinical monitoring.[12–14] The recently recognized pattern of airspace enlargement with fibrosis (AEF) can represent an additional complicating feature of CPFE with predominant thick-walled cysts in lower lung zones in association with reticulation.[15] Reflecting this uncertainty, a variable impact of emphysema on survival of IPF patients has been reported.[16]

At our rural central Appalachian academic center, we are uniquely challenged with the highest rates of smoking (26.7%) in the United States.[17] We present a detailed analysis of a locally identified CPFE phenotype and compare it to an IPF cohort without emphysema. Considering the recommended approach of avoiding variable disease severity between the groups, we performed our analysis of outcome measures (CPFE vs IPF without emphysema) in a cohort with radiologic evidence supporting an advanced fibrosis pattern of UIP.[18] While evaluating the complex interactions of smoking with injury patterns of fibrosis, emphysema, and PH, this study also examines the potential role of antifibrotic agents in this challenging population.

Materials and Methods

Subjects

A single-center, retrospective, observational cohort study was conducted at West Virginia University Hospital. The study protocol was reviewed and approved by our institutional review board (ID #1904548975), which waived the requirement for informed consent. During the study period of January 1, 2015 to December 31, 2019, the target patients were identified with International Classification of Diseases (ICD) coding for the idiopathic ILD (ICD 9-CM: 515–516.9; ICD-10-CM J84-84.9) within the electronic medical records (EMR) of West Virginia University Hospital (WVUH) system.

Case Definitions

Charts were reviewed systematically and IPF was diagnosed in accordance to the latest ATS/ERS/JRS/ALAT diagnostic guidelines.[19] These diagnostic criteria require exclusion of other known causes of ILD (domestic and occupational environmental exposures, connective tissue disease and, drug toxicity), and either the presence of the HRCT pattern of UIP or specific combinations of HRCT patterns and histopathology patterns in patients subjected to lung tissue sampling. CPFE was defined as basilar UIP pattern on HRCT with coexisting upper lobe predominant emphysematous changes (centrilobular and/or paraseptal).[8] Patients were further categorized in subgroups of: 1) CPFE; or 2) IPF without emphysema. Figure 1 describes the development of the study groups.

Data Collection

We collected demographic and historical data including age, gender, co-morbid conditions, smoking status, family history, symptom(s) duration prior to diagnosis, years since diagnosis, and whether the patient was evaluated at the tertiary or ILD center. In addition, clinical variables of interest including PFT (maximum of 3 which included that testing at the time of diagnosis, intermediate and the latest), six-minute walk distance (6MWD), use of

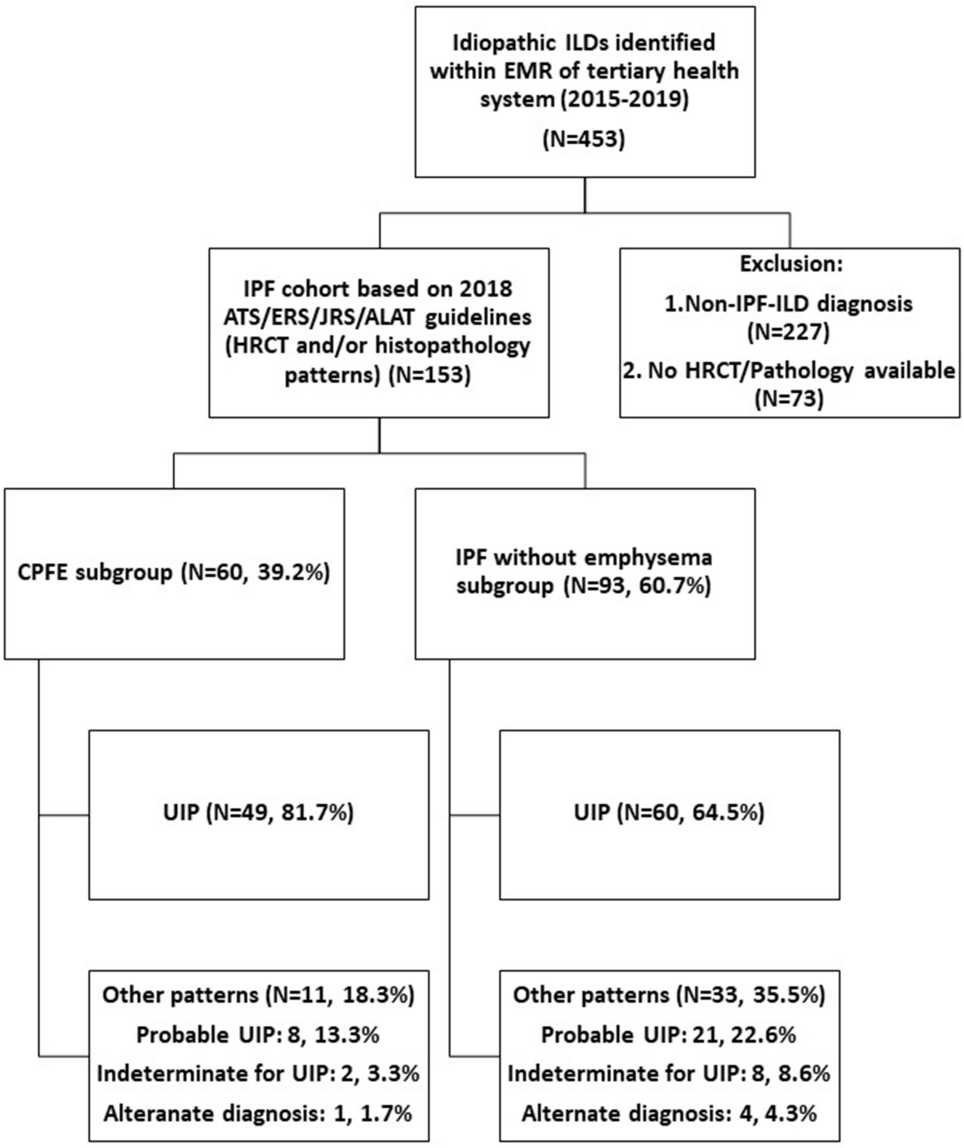

Figure 1 Development of the study groups.

supplemental oxygen, use of antifibrotic agents (pirfenidone and/or nintedanib), and lung transplant status were also recorded. Data was aggregated using REDCap, which is a HIPAA compliant data aggregation tool.[20]

Statistical Analysis

Descriptive statistics were generated, using means, medians, and standard deviations to summarize the continuous variables and frequency distributions to describe the categorical variables. Chi-square tests were used to detect differences in categorical variables by group, while means of continuous variables were compared using two-sided independent-samples t-tests. The Mann–Whitney *U*-test was used when normality could not be assumed. Logistic regression analysis was used to determine significant predictors of group status (CPFE vs IPF without emphysema) and to predict mortality at the end of the study. Kaplan-Meier curves were generated, and the Log rank test was used to compare survival since diagnosis between the two groups. Level of significance $\alpha = 0.05$ was used for all analyses. All analyses were conducted using statistical software SPSS version 26.0.

Results

From 2015–2019, there was a total of 453 patients who had a diagnostic code of idiopathic ILD within the EMR of WVUH system (Figure 1). Applying the most recent ATS/ERS/JRS/ALAT guidelines, 153 of the 453 patients (33.8%) were found to meet the diagnostic criteria for

IPF (Figure 1). Two hundred twenty-seven patients (50.1%) were determined to have non-IPF ILD diagnosis and 73 patients (16.1%) did not have HRCT in the system to allow an independent review (Figure 1). UIP was the most common HRCT pattern (n = 109, 71.2%), followed by probable UIP (n = 29, 19%). A minority of patients had a CT scan which was considered either indeterminate for UIP (n = 10, 6.5%) or supportive of an alternate diagnosis (n = 5, 3.3%). However, with multidisciplinary discussion and availability of pathology reports, we were able to include these patients in the final IPF cohort.

Table 1 describes the baseline demographic, comorbidity, diagnostic and management details of the cohort with UIP pattern in CPFE and IPF without emphysema groups. Of total 109 subjects, there were 49 patients in the CPFE group (45%) and 60 patients in the IPF without emphysema (55%). The CPFE group was significantly younger than the non-CPFE IPF group (73.90±10.42 vs 78.20±9.46 years, p = 0.026) and they had both a higher percentage of ever-smokers (93.9% vs 53.3%m, p < 0.001) and a greater smoking history (49.09±29.58 vs 15.39±14.84 pack years, p < 0.001). Ever smoking history of the CPFE and IPF without emphysema groups consisted of 76.7% (n = 46/60) and 51.6% (n = 48/93) former smokers and 18.3% (n = 11/60) and 1.1% (n = 1/93) current smokers, respectively. Approximately 60% of patients in each group were male and were overweight with a mean body mass index (BMI) of 27.12±4.77 vs 27.17±5.29 kg/m^2, respectively (p = 0.958). A family history of IPF was provided by a minority of patients (10.6% vs 8.8%). An excess of comorbidities was observed among the patients of both groups and these were not significantly different in prevalence. The comorbidities included hypertension (83.7% vs 70%), hyperlipidemia (75.5% vs 73.3%), gastro-esophageal reflux disease (GERD; 73.5% vs 66.7%), coronary artery disease (CAD; 61.2% vs 53.3%), PH (46.9% vs 33.3%), heart failure (HF; 44.9% vs 31.7%), atrial arrhythmia (34.7% vs 33.3%), anemia (32.7% vs 33.3%) sleep disordered breathing (30.6% vs 38.3%), diabetes (30.6% vs 30.6%), anxiety/mood disorders (28.6% vs 28.3%) and lung cancer (10.2% vs 3.3%). Approximately half of patients in each group were seen at the tertiary or specific ILD center. Two thirds of patients in the cohort carried a prevalent diagnosis whereas one third had an incident (within 6 months of presentation) diagnosis and this was not significantly different between the CPFE and non-CPFE groups. The average duration of symptoms prior to diagnosis was 20 months, however it ranged from 1 month to 10 years. A minority of patients (12.2% vs 15%, p=0.678) underwent surgical lung biopsy.

Diagnostic parameters of main pulmonary artery (PA) diameter on HRCT (30.73±3.87 vs 29.72±4.96 in mm, p = 0.254) and transthoracic echocardiography (TTE) measurement of right ventricular systolic pressure (RVSP) (49.47±23.05 vs 42.94±15.13 in mmHg, p = 0.174) were not different between the CPFE vs IPF without emphysema groups, respectively. Interestingly, with inclusion of all HRCT patterns in the analysis, the CPFE group showed higher comorbidity burden of PH (45% vs 29%, p = 0.044), significant dilatation of the main PA on HRCT (30.77±4.08 vs 28.60±4.80 in mm, p = 0.005) and elevated RVSP on TTE (50.52±22.40 vs 42.21±14.11 in mmHg respectively, p=0.044). In our cohort, dilatation of the main PA was noted to be an excellent indicator for PH. Main PA diameter has been shown as an useful non-invasive tool for diagnosing PH.[21] Mean PA diameter was enlarged to 32.41±3.56 mm in patients with PH vs 27.75±4.32 mm in patients without PH (p = 0.0001).

The CPFE group had a significantly reduced percent predicted diffusion capacity for carbon monoxide (DL_{CO}) at diagnosis compared to IPF without emphysema group (38.35±15.45 vs 51.09±15.96 mL/min/mm Hg respectively, p = 0.001). Percent predicted values for forced vital capacity (FVC) and forced expiratory volume at one second (FEV_1) were not statistically different between the groups. In the CPFE and IPF without emphysema groups, mean FEV_1 and FVC values at diagnosis were 2.15±0.57 vs 2.04±0.70 liters and 2.68±0.73 vs 2.49 ±0.95 liters, respectively. During the study, there were decrements in both FEV_1 and FVC with latest values of 2.09±0.5 vs 2.01±0.6 liters and 2.59±0.65 vs.2.42±0.73 liters but these were not significant. Similarly, both groups had reduced six-minute walk distance (6MWD; 242.1 ±114.0 vs 255.2±136.1 meters respectively, p = 0.714). There was progressive decline of pulmonary function over time. Figure 2 demonstrates the trends of FEV_1, FVC and DL_{CO} during the study duration in the two groups.

A majority of the patients included in the study were oxygen dependent at the time of diagnosis. The mean requirement for supplemental O_2 was not dissimilar between the groups (3.05±2.17 vs 2.71±1.63 L/minute respectively, p = 0.374). Approximately 20% of patients were prescribed antifibrotic agents (nintedanib or pirfenidone) and the prescription practice was not different

Table 1 Clinical Characteristics and Outcomes in the CPFE and IPF Without Emphysema Groups

Variables % or Mean±SD	CPFE (UIP) (N=49 45%)	IPF (UIP) without Emphysema (N=60, 55%)	Total IPF (UIP) (N=109, 100%)	p-value
Historic details				
Age (years)	73.90±10.42	78.20±9.46	76.27±10.10	0.026
Gender (male),%	65.3	58.3	61.5	0.457
BMI (kg/m^2)	27.12±4.77	27.17±5.29	27.15±5.05	0.958
Family history of IPF	10.6	8.8	9.6	0.748
Ever-smoker	93.9	53.3	71.6	<0.0001
Smoking pack years	49.09±29.58	15.39±14.84	35.34±29.66	<0.0001
Comorbidities				
Hypertension	83.7	70	76.1	0.096
Hyperlipidemia	75.5	73.3	74.3	0.796
GERD	73.5	66.7	69.7	0.442
CAD	61.2	53.3	56.9	0.408
PH	46.9	33.3	39.4	0.148
CHF	44.9	31.7	37.6	0.156
Atrial arrhythmia	34.7	33.3	33.9	0.881
Anemia	32.7	33.3	33.0	0.940
Sleep apnea	30.6	38.3	34.9	0.400
Diabetes	30.6	30.6	30.3	0.945
Anxiety/mood disorders	28.6	28.3	28.4	0.978
CKD	28.6	21.7	24.8	0.406
Hypothyroidism	28.6	33.3	31.2	0.593
Chronic pain	20.4	21.7	21.1	0.873
PVD	16.3	6.7	11.0	0.109
CVA	14.3	25.0	20.2	0.166
DVT	12.2	13.3	12.8	0.866
Aortic aneurysm	12.2	10.2	11.0	0.710
Lung cancer	10.2	3.3	6.4	0.146
Diagnostics details				
PA diameter on HRCT	30.73±3.87	29.72±4.96	30.20±4.49	0.254
TRV (cm/sec)	3.08±0.58	2.87±0.55	2.96±0.57	0.071
RVSP mmHg	49.47±23.05	42.94±15.13	45.75±19.07	0.174
PFT at the time of diagnosis				
FEV_1% predicted	80.80±14.66	84.30±17.89	82.86±16.57	0.313

(*Continued*)

Table 1 (Continued).

Variables % or Mean±SD	CPFE (UIP) (N=49 45%)	IPF (UIP) without Emphysema (N=60, 55%)	Total IPF (UIP) (N=109, 100%)	p-value
FVC % predicted	73.76±15.65	75.83±18.79	74.98±17.43	0.699
DL_{CO} % predicated	38.35±15.45	51.09±15.96	45.47±16.88	0.001
6MWD (meter)	242.1±114.0	255.2±136.1	249.71±126.23	0.714
Lung biopsy	12.2	15.0	13.8	0.678
Seen at tertiary or ILD center	51.0	52.5	51.9	0.875
Incident diagnosis	38.8	44.8	42.1	0.527
Prevalent diagnosis	61.2	55.2	57.9	0.527
Years since diagnosis	4.45±2.39	4.64±3.26	4.56±2.89	0.421
Symptoms duration prior to diagnosis (months)	20.41±18.96	20.76±22.12	20.60±20.55	0.943
Management details				
Supplemental O_2 prescribed	89.4	87.9	88.62	0.819
O_2 Liter/min	3.05±2.17	2.71±1.63	2.87±1.89	0.374
Antifibrotics				
Nintedanib	20.4	18.3	19.3	0.785
Pirfenidone	14.3	28.3	22.0	0.078
Lung transplant	4.1	5.0	4.6	0.820
Outcomes: Dead	38.8	26.7	32.1	0.178

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; DL_{CO}, diffusion capacity for carbon monoxide; DVT, deep vein thrombosis; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GERD, gastro-esophageal reflux disease; PA, pulmonary artery; PFT, pulmonary function test; PH, pulmonary hypertension; PVD, peripheral vascular disease; RVSP, right ventricular systolic pressure; TRV, tricuspid regurgitant velocity; 6MWD, six-minute walk distance.

between the groups. Only a subset of patients underwent lung transplantation (4.1% vs 5% respectively, p = 0.820).

Table 2 describes the predictors for CPFE in a multivariate logistic model. Ever smoking status and reduced percentage predicted DL_{CO} at the time of diagnosis were found to be significant predictors of CPFE within our cohort (OR = 29.83, 95% CI 3.56–249.82, p = 0.002 and OR = 0.93, 95% CI of 0.89–0.97, respectively; p = 0.001).

Figure 3 shows the Kaplan–Meier survival curve for the two groups. Approximately, one third of patients from our cohort died and there was no significant difference in survival between the subjects in the CPFE vs IPF without emphysema groups (38.8% vs 26.7% respectively, p = 0.178) (Table 1). There was a trend towards a decreased survival for CPFE patients, but this was not statistically significant (Log rank test, p = 0.076). The mean years alive since diagnosis was 3.61±2.62 vs 4.31±3.06 years (p = 0.215), respectively in the groups. The median survival for both groups was 3.00 years. Multivariate logistic regression analysis (Table 3) showed predictors of survival in the total IPF cohort to include BMI (OR = 1.10, 1.005–1.207, 95% CI, p = 0.038), PH (OR = 0.215, 0.085–0.544, 95% CI, p = 0.001), and pirfenidone (OR = 3.698, 1.040–13.153, 95% CI, p = 0.043), indicating that those with a higher BMI, without PH, and taking pirfenidone had an improved survival. With inclusion of percent predicted DL_{CO} into the logistic regression model, significant predictors of survival in the IPF cohort could not be identified due to missing values at the time of diagnosis.

Discussion

Since the introduction of CPFE as a clinical syndrome by Cottin et al in 2005, there has been an ongoing evaluation of the impact of emphysema in the natural history of pulmonary fibrosis.[7,8] The need for future studies to

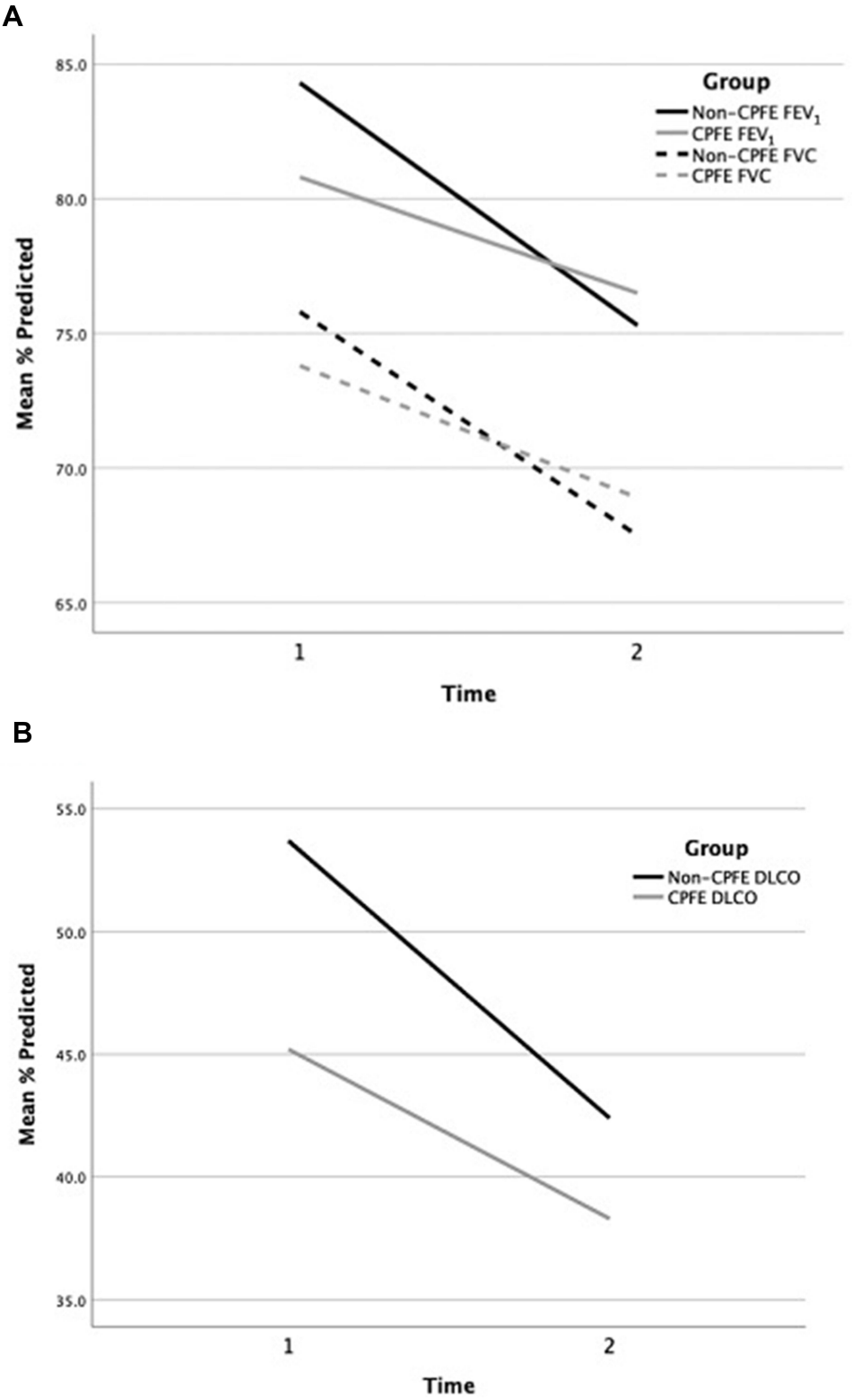

Figure 2 Trend of pulmonary function tests between CPFE vs IPF without emphysema groups. Time 1: at the time of diagnosis; Time 2: latest during the disease course. There was no significant difference in the differences of decline in PFT data when measured at two different time frames of disease course (at time of diagnosis and the latest). (**A**) FEV_1 and FVC % predicted at time 1 and 2 between the groups (non-significant difference). (**B**) DL_{CO} % predicated at time 1 and 2 between the groups. CPFE group had significantly lower DLCO % predicted at the time 1 (38.35±15.45 vs 51.09±15.96, p = 0.001).

Table 2 Multivariate Logistic Regression Analysis: Predictors of CPFE

Factors	Odds Ratio	95% CI	p-value
Age	1.000	0.943–1.061	0.998
Ever-smoker	29.827	3.561–249.817	0.002
Pulmonary hypertension	1.718	0.501–5.888	0.389
Pulmonary artery diameter	0.986	0.868–1.121	0.832
% predicated DL_{CO} at diagnosis	0.928	0.888–0.968	0.001

determine the etiology, morbidity, mortality and novel therapeutics for CPFE either with or without PH, has been emphasized.[22] Accordingly, we identified a cohort with the CPFE phenotype in a rural Appalachian population, demonstrating one of the highest smoking rates in the United States, to delineate associations between cigarette smoking, fibrosis pattern of usual interstitial pneumonia, PH, and potential utility of antifibrotic agent.

In the locally identified IPF cohort included in this investigation, the group demonstrating CPFE manifested several distinctive features. CPFE was highly prevalent (45%) comparable to previous studies.[23] While two thirds of our CPFE patients were male, this is lower compared to a previously noted remarkable (9:1) male predominance.[24] Our cohort demonstrated that females shared a significant smoking habit with males in this rural Appalachian region of WV (25.6% vs 27.8%).[25] Diagnostic delay (approximately 20 months) was common with only half patients were seen at specific ILD center in our rural cohort. Barriers to early diagnosis in IPF were noted to be multifactorial including older age, male gender, referral pattern from general practitioners and impact of comorbid conditions and alternate diagnoses.[26] While our CPFE patients were significantly younger than those in the IPF without emphysema group, they were older than other comparable cohorts included in previous reports.[24] The CPFE group shared an equivalent burden of comorbidities, including obstructive sleep apnea, which were associated with the clinical course of disease.[27,28] Comorbid PH in CPFE has been shown to cause severe dyspnea (functional class III or IV), exercise limitation (reduced 6MWD) and earlier

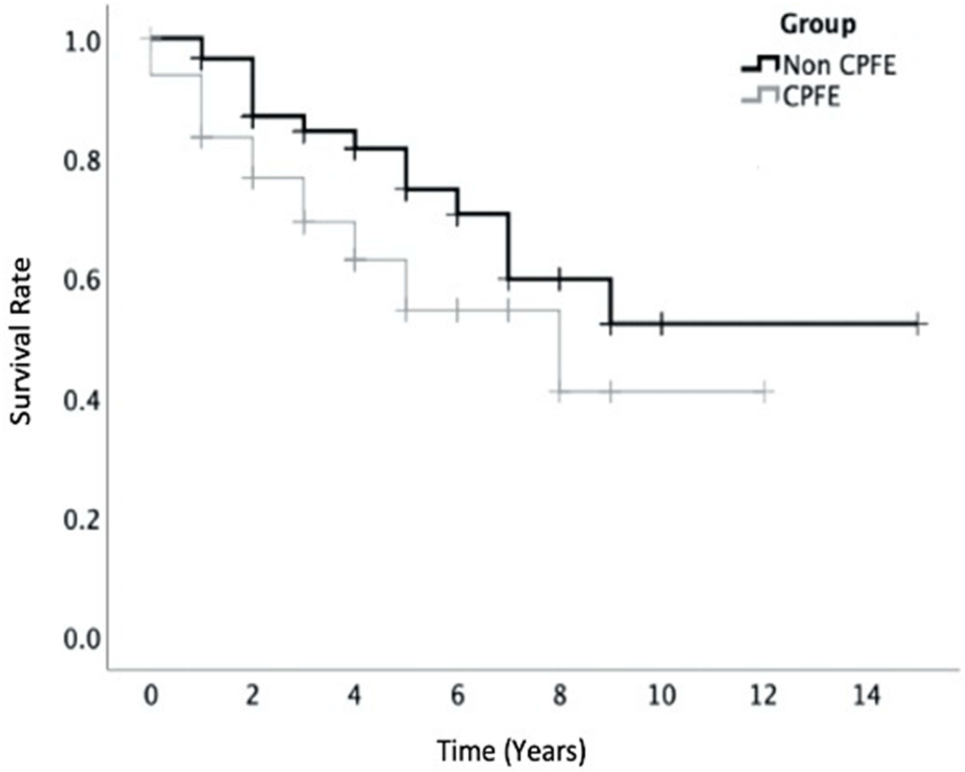

Figure 3 Kaplan–Meier survival analysis of CPFE and IPF without emphysema groups. There was a trend towards reduced survival between the groups over time since their diagnosis, however not statistically different (log-rank p = 0.076). X-axis signifies years alive since diagnosis during the study time frame and Y-axis shows survival rate. The mean years since diagnosis between the groups were 4.45±2.39 vs 4.64±3.26 (p = 0.740), respectively.

Table 3 Multivariate Logistic Regression Analysis: Predictors of Survival for Total IPF Cohort

Factors	Odds Ratio	95% CI	p-value
Body mass index (BMI)	1.134	1.005–1.207	0.038
Ever-smoker	0.839	0.303–2.324	0.735
Pulmonary hypertension	0.215	0.085–0.544	0.001
Nintedanib	2.034	0.577–7.172	0.270
Pirfenidone	3.698	1.040–13.153	0.043

onset hemodynamic changes on right heart catheterization.[29] Similar phenomenon of exercise limitation and relatively severe PH observed in our CPFE group may have contributed to younger age presentation for diagnostic evaluation. Well known physiologic consequences of CPFE were evident with relatively preserved spirometry but severely reduced DL_{CO} compared to IPF without emphysema, both of which decline progressively during the disease course.[23,30] This gas exchange abnormality contributed to the need for supplemental oxygen in the majority of patients.[1] DL_{CO} has been demonstrated to reflect effects of both emphysema and fibrosis and is considered a measure of disease severity for CPFE.[31] For the entire cohort, use of antifibrotics was limited to one fifth of patients whereas only a subset (5%) of patients underwent lung transplantation. Despite the recommendation of prompt initiation of antifibrotics, multiple barriers have been identified for the early adoption of antifibrotics.[32] Rural health disparity in terms of known socio-economic challenges, community hospitals having limited access to an ILD referral or lung transplant center, older age, and a higher burden of comorbidities may have restricted our patients' eligibility for advance therapeutics.

The pathogenesis of CPFE remains poorly understood. Cigarette smoking has been described as a major risk factor for development of both emphysema and IPF.[33,34] A meta-analysis demonstrated that smokers had 1.38 times higher risk for developing IPF.[35] A majority of smokers with IPF do not demonstrate radiographic evidence of emphysema. Likewise, most patients with emphysema/COPD are not reported to manifest interstitial fibrosis. Recent HRCT data indicated that interstitial lung abnormality was inversely associated with the presence of emphysema in smokers,[36] suggesting that these patterns may represent distinct outcomes of smoking that reflect unique individual susceptibilities. Fast metabolizers with greater CYP2A6 activity have been shown to have a higher occurrence of COPD suggesting a production of toxic molecules with smoking.[37] Despite these observations, evidence suggests that these two diseases can assume concomitant courses in smokers. Our CPFE cohort had a higher mean smoking (>40 pack years) exposure and ever smoking status was found to be one of the major determinants of CPFE. Animal experiments have confirmed that tobacco smoke can lead to the occurrence of emphysema and pulmonary fibrosis simultaneously.[38] Histologically, the co-existence of emphysema and fibrosis without craniocaudal segregation has been recognized.[39] In addition, over half of lobectomy specimens from a cohort of smokers with lung cancer have subclinical interstitial fibrosis and have only radiographic evidence of emphysema.[3] Although CPFE has been recently classified in the group of smoking-induced chronic lung diseases,[40] analysis of pathogenic mechanisms of smoke-induced lung diseases can provide insight into the homeostatic pathways critical to preserve lung health.[41]

In addition to airway and parenchymal damage in the lung, there is increasing evidence that cigarette smoke directly impacts the pulmonary vasculature suggesting that PH and cor pulmonale are not products of hypoxia alone.[42] Thickening of the arterial intima and vessel narrowing are noted as early changes in smokers' lungs which correlate with the severity of emphysema and bronchiolitis during disease progression.[43,44] Cigarette smoke exposure produces mediators that control vasoreactivity and vascular cell proliferation ultimately leading to remodeling.[45] In addition, it causes direct oxidative damage, inflammation and hypercoagulability, all potentially contributing to the development of PH.[46] Autopsy series of CPFE, IPF and emphysema patients suggested that pulmonary vasculopathy developed in whole lung tissues including fibrosed, emphysematous and preserved lung areas. Notably, these changes were seen significantly higher in unaffected CPFE lung tissue compared to other groups.[47] Comparing the groups with all HRCT fibrotic patterns, we observed a higher proportion of comorbid PH and its non-invasive markers (main PA diameter on HRCT and TTE defined RVSP) however, such an association was not evident when limiting the groups to the advanced fibrosis of UIP. Comorbid PH has been shown to impact the survival of CPFE patients but the association of PH with survival was no longer significant in these patients after controlling for baseline CT extent of fibrosis and emphysema.[8,10,29,48] This suggests the co-existence of fibrosis, emphysema,

and PH as analogous tissue injuries resulting from exposure to cigarette smoke. Prior systemic study of HRCT has observed excess radiologic severity of emphysema and fibrosis in smokers with IPF relative to smokers with non-IPF UIP pattern, lending credence to the hypothesis of prevailing pathobiologic synergy between IPF, emphysema and smoking.[49] Smoking cessation has been effective in improving several clinical and physiologic parameters in COPD.[50] It may be prudent to design studies which can determine the true order of progression of changes and develop optimal smoking cessation strategy and medications (e.g., antifibrotics) for overlapping therapeutic effects across this spectrum of pathologies.[45,51]

After more than a decade of research in CPFE, the prognostic implication of comorbid emphysema in IPF remains unclear. One third of patients died during our study duration with a non-significant trend toward reduced survival in CPFE compared to IPF without emphysema ($p = 0.076$). A recent meta analysis of 13 studies showed comparable poor survival rates at one, three and five years among CPFE and IPF alone.[52] Most studies evaluating the impact of emphysema on IPF prognosis have failed to adjust for baseline severity and hence yielded mixed results. CPFE patients are likely to have less extensive fibrosis at the time of diagnosis and this is associated with a comparable poor outcome as IPF alone while CPFE portends a worse prognosis when these patients and those with IPF present with similar ILD burden.[18,53] In addition to the visual review of HRCT, the computer-based analytical system of CALIPER has been shown to provide an improved adjustment for baseline severity.[31] Given the inherent limitation of FVC in CPFE, a composite physiologic index (CPI) has similarly been developed to predict mortality in IPF patients with or without emphysema.[54] Longitudinal analysis of an IPF registry has shown an association of disease severity, based on physiological impairment and phenotypic clustering, to the outcomes of patients.[55] While adjusting for a similar UIP pattern between the groups, our multivariate analysis suggested BMI and pirfenidone as predictors of survival in addition to PH. It's not surprising to observe lower BMI reduced survival in CPFE given its known association for poor prognosis in IPF and emphysema individual disease processes.[56,57] Since spirometric endpoints can function as determinants in initiating antifibrotic therapy, the presence of emphysema potentially is problematic since it can affect FVC in a manner dissimilar to fibrosis.[58] A single center retrospective study of 45 CPFE patients detected no significant difference in the efficacy of either pirfenidone or nintedanib on measured variables including mortality.[59] Randomized control trials, meta-analysis, and an observation study of pirfenidone in IPF have observed improved progression-free survival and reduced all-cause mortality.[60–62] However, such an impact has not yet been established in CPFE. Despite a primary end-point focused on FVC, a post-hoc analysis of the INPULSIS trial suggested that the treatment effect of nintedanib was not affected by baseline emphysema.[63] Overall, there's no randomized trial evidence of any impact of antifibrotics on mortality. Notably, given a minority of patients prescribed antifibrotics in our retrospective cohort (22% pirfenidone vs 19.3% nintedanib), such an evaluation for a differential efficacy on mortality is not feasible. Lastly, more than 10% emphysema in IPF provided good discrimination for CPFE where reduced DL_{CO} was the most reliable prognostic marker.[64] Considering lack of quantification of emphysema in our CPFE cohort and missing DL_{CO} values for patients who died during the study, we did not identify DL_{CO} as a significant prognostic marker. In addition, over the course of study duration, DL_{CO} reduction was equivalent between the groups with no significant difference noted in the value at the end of study. Akagi et al have recorded similar slower annual decrease of percentage predicted DL_{CO} in CPFE patients as compared to IPF-alone patients.[12]

Our study notes few limitations. There are several inherent diagnostic challenges described in developing IPF cohorts including evolving diagnostic criteria, data collection practices, identifying an accurate time of diagnosis, and impact of missing values. Certainly, the last was evident in our cohort as 16% patients had missing data precluding their inclusion in the study. HRCT characterization of IPF cohort required exclusion of CTD-associated ILD which can also be associated with CPFE, but such an exclusion may not be totally effective. In addition, we did not quantify the extent of emphysema on HRCT. Survival analysis could have been underestimated as some patients may had shorter follow-up given recent diagnosis, and some patients may have been transferred to other referral centers. Lastly, the unmeasured confounding factors may have contributed to the findings of the study.

Conclusion

Our efforts to define CPFE in a rural Appalachian population with the highest smoking rates in the USA provided

key epidemiological, clinical, radiographic, and pathologic insights. CPFE was highly prevalent (45%) in locally identified IPF cohort. Relative to previously defined cohorts, CPFE patients were older, had a higher prevalence of females, carried a major burden of comorbidities, and had limited implementation of advanced therapeutics. PH was a prevalent (approximately 40%) finding between the groups, however, inclusive of all HRCT patterns, PH was noted to be significantly severe in CPFE group. The results of this investigation support the hypothesis that PH presents as a co-existing smoke-induced pathology rather than a comorbid manifestation of chronic hypoxemia. Smoking status and gas exchange impairment with reduced DL_{CO} were significant predictors of CPFE. Both CPFE and IPF without emphysema were progressively fatal conditions but a non-significant trend towards reduced survival in CPFE was observed. Higher BMI, lack of PH and use of pirfenidone improved survival in our cohort which could propose a potential utility of antifibrotics for CPFE. Our study results suggest that fibrosis, PH, and emphysema likely represent a spectrum of smoke induced injury. Prospective studies are required to confirm these findings, to identify the true order of smoke lung pathology so that preventive measures can be undertaken in timely manner, and to better recognize novel therapeutic targets.

Statement of Ethics

The study protocol was approved by the West Virginia University Institutional Review Board (#1904548975, date 01-10-2020).

Consent to participate not applicable given retrospective nature of the study and was waived by IRB.

All relevant ethical safeguards have been met in relation to patient protection.

The study was conducted in accordance with the Declaration of Helsinki.

Transplant patients: all organs were donated voluntarily with written informed consent, and that this was conducted in accordance with the Declaration of Istanbul.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no relevant conflict of interests in relation to this work.

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