PULMONARY HYPERTENSION AND LUNG CANCER IN COMBINED PULMONARY FIBROSIS AND EMPHYSEMA SYNDROME

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Abstract

Introduction: Combined pulmonary fibrosis with emphysema syndrome and idiopathic pulmonary fibrosis represent different conditions defined by unique clinical, functional, radiological and pathological characteristics. Both diseases frequently exhibit comorbidities and complications.

Objectives: Our aim was to examine which comorbidities are more prevalent and what is their impact on the outcome of this syndrome and idiopathic pulmonary fibrosis. Their demographic and clinical information was also analyzed.

Materials and Methods: This is a retrospective study. We examined the medical record data of individuals diagnosed with interstitial lung disease at the University Hospital of Lung Diseases "Shefqet Ndroqi", Tirana, during the timeframe from January 2012 to April 2019. The patients (51 in total) were categorized into two groups: those diagnosed with pulmonary fibrosis syndrome in combination with emphysema (25) 49% and the second group (26) 51% comprising those with a diagnosis of idiopathic pulmonary fibrosis. To assess the influence of comorbidities on this syndrome, we employed linear regression with multiple factors utilizing the EViews 7 software. Student's t test was applied to determine the significance of comorbidities and complications across both groups. Demographic and clinical information was reported in mean values using standard deviations .

Results: All patients presented with comorbidities and complications. In cases of pulmonary syndrome combined with emphysema, there was a predominance of male current or former smokers. The annual smoking measurement unit was greater in the group of patients with syndromes. The duration from symptom onset to diagnosis was also extended in this group compared to patients with idiopathic pulmonary fibrosis. Comorbidities exerted a more significant influence on the syndrome ($p = 0.01$) than in the group with idiopathic pulmonary fibrosis, where no statistically significant correlation with comorbidities was identified, possibly due to the small sample size of patients in the study.

Conclusions: Comorbidities are prevalent in both groups of individuals with pulmonary fibrosis combined with emphysema and in those with idiopathic pulmonary fibrosis.Certain conditions, particularly lung cancer, significantly affect the survival rate, while others, like respiratory failure, may have a crucial impact on the disease's mortality. Nonetheless, additional studies are required to better understand the effects of comorbidities on this syndrome in larger groups of patients and for a longer time.

Keywords: Combined Pulmonary Fibrosis and Emphysema, Idiopathic Pulmonary Fibrosis

HIPERTENSIONI PULMONAR DHE KANCERI I MUSHKËRIVE NË SINDROMËN E KOMBINUAR TË FIBROZËS PULMONARE DHE EMFIZEMËS

Abstrakt

Hyrje: Sindroma e fibrozes pulmonare te kombinuar me emfizeme dhe fibroza pulmonare idiopatike janë entitete të veçanta të karakterizuara nga karakteristika të dallueshme klinike, funksionale, radiologjike dhe patologjike. Komorbiditetet dhe komplikimet zakonisht shihen në të dyja sëmundjet.

Objektivi: Qëllimi ynë ishte të hetonim se cilat sëmundje shoqëruese janë më të zakonshme dhe cili është ndikimi i tyre në rezultatin e kesaj sindrome dhe fibrozes pulmonare idiopatike. U studiuan gjithashtu të dhënat demografike dhe klinike te tyre

Materiali dhe metoda: Ky është një studim retrospektiv. Ne kemi shqyrtuar të dhënat e karteles mjekësore të pacientëve të diagnostikuar me sëmundje intersticiale të mushkërive në Spitalin Universitar të Sëmundjeve të Mushkërive "Shefqet Ndroqi", Tiranë, në periudhën janar 2012 deri në prill 2019. Subjektet (51 në total) u ndanë më tej në dy grupet: pacientët e diagnostikuar me sindromen e fibrozes pulmonare te kombinuar me emfizeme (25) 49% dhe grupi tjeter (26) 51% ata me diagnoze fibroze pulmonare idiopatike. Për testimin e ndikimit të komorbiditeteve në kete sindromë, ne kemi përdorur regresionin linear me faktorë të shumtë duke përdorur programin EViews 7.Testi i Studentit u përdor për të vlerësuar rëndësinë e sëmundjeve shoqëruese dhe komplikacioneve në te dy grupet.Të dhënat demografike dhe klinike u shprehen në vlera mesatare duke përdorur devijimet standarde ± deviacioni standart.

Rezultatet: Të gjithë pacientët kishin komorbiditete dhe komplikacione. Në sindromën pulmonare te kombinuar me emfizemë mbizotëronin meshkujt duhanpirës aktual ose ish-duhanpirës. Njesia matese e duhanpirjes per vit ishtë më e lartë në grupin e pacienteve me sindrome. Koha nga shfaqja e simptomave deri në vendosjen e diagnozës gjithashtu ishtë më e gjatë në kete grup sesa në pacientët me fibroze pulmonare idiopatike. Komorbiditetet kishin më shumë ndikim në sindromë ($p = 0.01$) krahasuar me grupin me fibroze pulmonare idiopatike, ne te cilin nuk u gjet lidhje statistikisht e rendesishme me semundjet shoqeruese, ndoshta sepse numri i pacientëve te mostres studiuese ishte i vogël.

Konkluzionet: Semundjet shoqeruese janë të shpeshta në si ne pacientët me fibroze pulmonare te kombinuar me emfizemë ashtu edhe ne ata me fibrozë pulmonare idiopatike. Disa prej tyre, veçanërisht kanceri i mushkërive, ndikojnë fuqishëm në shkallën e mbijetesës dhe disa të tjera, si insuficienca respiratore, mund të luajnë një rol të rëndësishëm në mortalitetin e sëmundjes. Megjithatë, nevojiten kërkime të mëtejshme për të sqaruar ndikimin e sëmundjeve shoqëruese në kete sindrome ne grupe me te medha pacientesh dhe per nje kohe me te gjate.

Fjalë kyçe: fibroza pulmonare e kombinuar me emfizemë, fibrozë pulmonare idiopatike

Introduction

A recently described syndrome called Combined Pulmonary Fibrosis and Emphysema (CPFE) was introduced by Cottin et al in 2005 (1). It is a unique condition characterized by the simultaneous presence of upper lobe emphysema and lower lobe fibrosis. Most CPFE patients are male, heavy smokers, or former smokers. Despite their worsening clinical state, they tend to have nearly normal or slightly reduced pulmonary function along with significant diffusion capacity impairment. The prognosis and mortality associated with this condition are not yet clearly understood. Currently, there is no targeted treatment for individuals with CPFE syndrome (1).

Idiopathic Pulmonary Fibrosis (IPF) represents the most common type of interstitial lung disease (ILD). The typical signs and symptoms of IPF include a dry cough and dyspnea during exertion. The lung tissue affected by IPF is stiffer, leading to a loss of elasticity. The etiology and physiopathology related to IPF are not well understood. Patients with IPF experience a high mortality rate (2,3,5).

Both CPFE and IPF can be linked to various comorbidities and complications (4-6). In our investigation, we aimed to examine the presence of comorbidities and complications in a cohort of 51 patients; to identify the most prevalent and their significance in the outcomes of CPFE and IPF. We also gathered data regarding the baseline demographics, such as age, gender, smoking habits (pack years), pulmonary function tests, and diagnostic methods. All findings were reviewed during discussions in a multidisciplinary board comprised of clinical, radiological, and pathological specialists within our hospital.

Materials and Methods

The research protocol was approved by Ethics Committees of the University of Medicine and the University Hospital "Shefqet Ndroqi", Tirana, Albania; the institutions in which the work was undertaken.

Patient selection: 51 patients in total with Interstitial Lung Diseases (ILD) were included in the study.

Inclusion criteria: IPF patients were diagnosed with the HRCT scan imaging patterns according to the new ATS/ERS criteria (2,3). CPFE patients were identified based on the following features prescribed by Cotin et al on CT findings (1).

- The presence of bilateral emphysema and/or multiple bullae (>1 cm) with upper zone predominance
- The presence of bilateral significant pulmonary fibrosis, with peripheral and basal predominance

Exclusion criteria: Patients were not included in this study if they exhibited any of the following:

- Who had drug-associated ILD
- Who had occupationally related ILD, such as asbestosis and silicosis

In total 26 (51%) were diagnosed with IPF, and 25 (49%) with CPFE. There were 10 (38. 4%) male and 15 (57.6%) female in IPF, and in the CPFE group 16 (64%) males and 14 (36%) females. Mean age for CPFE group was 68 ± 7 years, and for IPF patients 68 ± 8 years. All patients were current smokers or ex-smokers. Smoking status for every patients was estimated using the Unit Pack Year (UPY).

Statistical analysis

All data recorded in the study were analyzed using EViews 7 program, a software that processes econometric various statistical differences for testing any hypothesis. Average values and standard deviations ± SD for the demographic data were collected. For determining the relationship between comorbidities in CPFE and IPF we have used the analysis of the logistic regression. To test the impact of variables in CPFE syndrome we have used linear regression with multiple factors. As influential variables are taken comorbidities and complications.For testing the importance of them in CPFE and IPF is used "The Student test" (t). R-square is used to determine the importance of the model. As statistically significant we have accepted $p < 0.05$ values.

Results

In our group we had in total 51 subjects with ILD. 26 (51%) with IPF and 25 (49%) with CPFE.The subdivision of male/female ratio in CPFE was 16 (64%) males and 9 (36 %) females, in IPF group 10 (38. 5%) males and 16 (61.5%) females.As noted in CPFE predominates males, meanwhile in IPF are females,considering that all patients were smokers or heavy ex smokers. Almost always different studies have shown that more men have been diagnosed with IPF than women, but IPF in women appears to be on the rise (15). Mean age for CPFE was 68 ± 7 and for IPF patients 68 ± 8. Table 1 shows some demographic and clinical data as: age, gender, the time of symptoms since diagnosis and smoking history using UPY. It is clearly visible that the age of the patients for both groups are nearly the same.

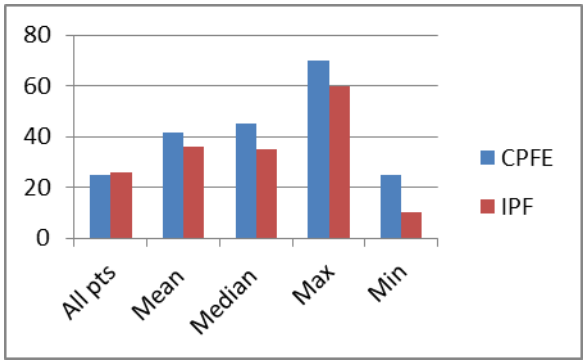
Table 1. Demographic and clinical data

	CPFE (N=25)	**IPF** (N=26)
Gender, male/female %	16 (64%)/9 (36%)	10 (38.5%)/16 (61.5%)
Age, years, mean ± SD	68 ± 7	68 ± 8
UPY, mean ± SD	45 ± 7	36.15 ± 10
Symptoms, months,mean ± SD	27.07 ± 5	27.8±8

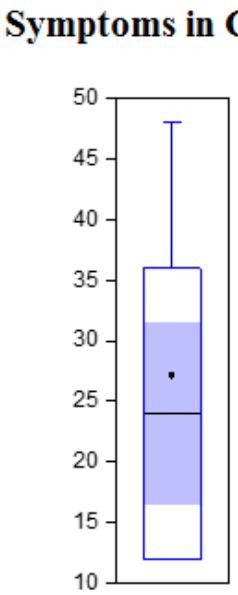
Patients with CPFE had higher values of UPY compared to the other group. This supports the fact that patients with this syndrome are heavier smokers and their clinical characteristics and outcomes are poorer than those with IPF only (14).

We compared UPY values in months for both diseases and the difference between them is evident (Graph 1). Smoking is the main risk factor in patients with IPF and in some others with CPFE syndrome (9,14). The time of symptoms had differences too among both groups. We think that this might be due to underdiagnosing of CPFE as a result of its lack of significant changes in pulmonary volumes in spirometry.

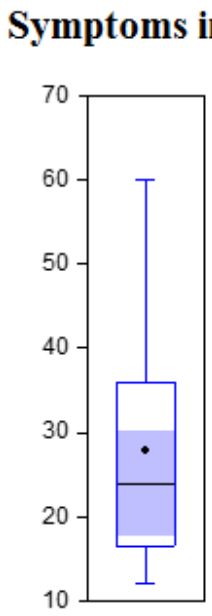
Graph 1. Unit Pack Year (UPY), CPFE vs IPF



Patients with CPFE syndrome tend to have longer time with symptoms compared to those with IPF. Probably this is due to the fact that these patients until recent years, have been misdiagnosed as IPF .(graph 2 and 3).



Graph 2



Graph 3

The comorbidities and complications that we found more commonly in the medical records in both diseases are as listed: Pulmonary Hypertension (PH), Respiratory Failure (RF), Lung Cancer (L.Ca), Pulmonary Embolism (PE), Arterial Hypertension (HTN), Cardiac diseases (CD), Anemia,Gastritis,Rheumatic Diseases (Rh. D), Diabetes Mellitus (DM).

Table 2 analyses and interprets comorbidities and complications in patients with IPF. If t values > 2, a variable is statistically important. P value expresses the error margin. If $p < 0.05$ with 5% of error margin, this means that t value is correct (17). If $p>0.05$,the results may be changed. As it is noticed in the following table, nearly all comorbidities and complications have $p>0.05$, $t < 2$in all of them and $r = - 0.01$.

These statistical findings of our study explain that none of the comorbidities is so important to affect the outcome of the diseases in our group,but the small number of subjects participating in the survey should be noted.

Table 2. Comorbidities and complications in IPF

	Coefficient	Std. Error	t-Statistic	Prob.
Anemia	0. 235333	0. 336809	0. 698713	0. 4887
L. Ca	-0. 108913	0. 288217	-0. 377884	0. 7075
DM	0. 052993	0. 296853	0. 178516	0. 8592
Gastritis	0. 048979	0. 200653	0. 244100	0. 8084
HTN	0. 566592	0. 143710	3. 942614	0. 0003
PH	0. 068783	0. 223648	0. 307551	0. 7600
CD	-0. 225784	0. 321192	-0. 702958	0. 4861
RF	-0. 060192	0. 182060	-0. 330618	0. 7426
Rh. Diseases	-0. 413312	0. 306065	-1. 350405	0. 1843
PE	-0. 104099	0. 386508	-0. 269331	0. 7890
R-squared	-0. 019869			

Table 3 shows comorbidities and complications in CPFE syndrome. Some of them have p value > 0.05 such as RF ($p=0.01$, $t=2.6$), Rh. d ($p=0.008$, $t=2.7$). These two factors, rheumatic diseases and respiratory failure are statistically important in CPFE syndrome.The variables (comorbidities) studied in regression, according to the r-square values in table 3, explain that 11% of the factors affect the results in CPFE syndrome.

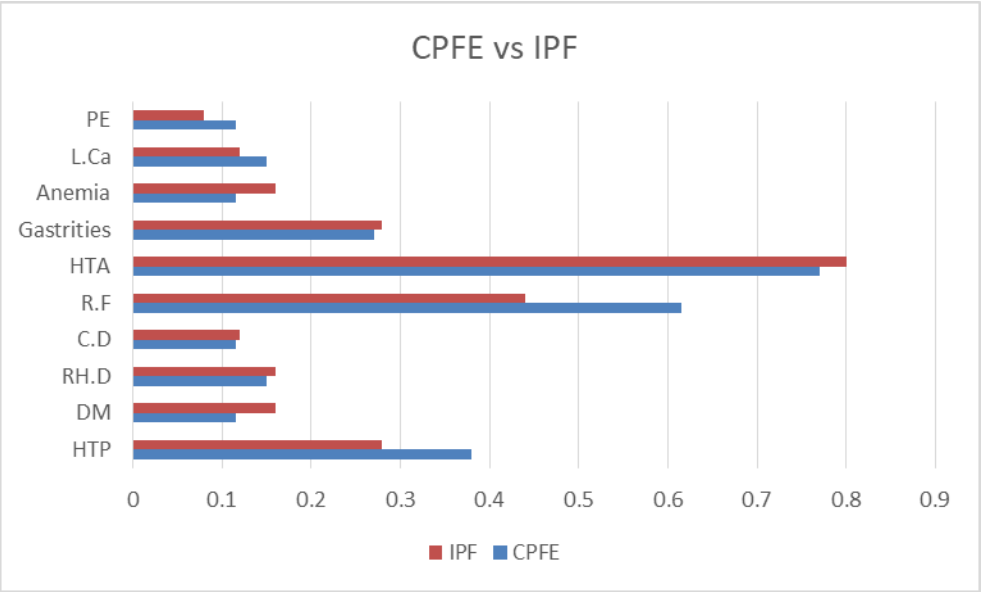
There are several papers that have investigated the prevalence of CPFE in patients with lung cancer more than fibrosis and they have concluded that CPFE patients had a poor prognosis (8,11,12).

CPFE syndrome may be present too in some of the connective tissue diseases, especially rheumatoid arthritis and systemic sclerosis and here it is defined as 'idiopathic' (tobacco-related) CPFE (16). Another factor that plays an important role in the exacerbation of CPFE is respiratory failure (7). If we analyze the results for lung cancer, interestingly p and t values tend to go respectively p = 0.1 and t = 1.5.

Table 3. Comorbidities and complications in CPFE syndrome

	Coefficient	Std. Error	t-Statistic	Prob.
Anemia	-0. 200062	0. 313296	-0. 638572	0. 5267
L. Ca	0. 419345	0. 268096	1. 564158	0. 1255
DM	-0. 236357	0. 276129	-0. 855966	0. 3970
Gastritis	0. 254718	0. 186645	1. 364720	0. 1798
HTN	0. 095510	0. 133677	0. 714483	0. 4790
PH	0. 101406	0. 208035	0. 487447	0. 6285
C. D	0. 056605	0. 298769	0. 189460	0. 8507
RF	0. 451897	0. 169351	2. 668408	0. 0109
Rh. D	0. 792904	0. 284698	2. 785069	0. 0081
PE	-0. 266165	0. 359525	-0. 740324	0. 4633
R-squared	0. 117557			

Graph 4. The frequency of comorbidities and complications



Graph 4 explains the frequency of comorbidities and complications in CPFE vs IPF. Gastritis and anemia are highly prevalent in patients with Idiopathic Pulmonary Fibrosis (13). It is clearly seen that respiratory failure, pulmonary hypertension and lung cancer are encountered more often in CPFE syndrome. CPFE patients appears to have a higher incidence of lung cancer (6.1–46.8%) compared to IPF (7–20%) . Lung cancer in CPFE was typically diagnosed in elderly, heavy smokers who are predominately male with a median survival

time of 19.5 months . The most common histopathologic subtypes of lung cancer in CPFE are squamous cell carcinoma and adenocarcinoma ((16,17).

Table 4. The correlation of some variables in CPFE

	Anemia	L.Ca	CPFE/IPF	DM	Gastrities	HTA	C. D	RESP	RHEUMO	TEP
Anemia	1. 000000	0. 006494	-0. 064814	0. 337662	0. 265378	0. 070627	0. 561769	0. 376051	-0. 116360	0. 443346
L. Ca	0. 006494	1. 000000	0. 049169	0. 503247	0. 010014	0. 070627	-0. 145644	-0. 080582	-0. 116360	0. 251730
CPFE/IPF	-0. 064814	0. 049169	1. 000000	-0. 064814	-0. 012064	-0. 132762	-0. 007161	0. 175655	0. 286065	0. 059485
DM	0. 337662	0. 503247	-0. 064814	1. 000000	0. 137696	0. 209165	0. 208063	0. 147734	-0. 116360	0. 251730
Gastrities	0. 265378	0. 010014	-0. 012064	0. 137696	1. 000000	0. 108921	0. 048131	-0. 124274	-0. 016022	0. 388218
HTN	0. 070627	0. 070627	-0. 132762	0. 209165	0. 108921	1. 000000	0. 191485	-0. 016855	-0. 024338	0. 012574
C. D	0. 561769	-0. 145644	-0. 007161	0. 208063	0. 048131	0. 191485	1. 000000	0. 344265	-0. 106525	0. 084270
R. F	0. 376051	-0. 080582	0. 175655	0. 147734	-0. 124274	-0. 016855	0. 344265	1. 000000	-0. 163308	0. 178730
Rh. D	-0. 116360	-0. 116360	0. 286065	-0. 116360	-0. 016022	-0. 024338	-0. 106525	-0. 163308	1. 000000	0. 149080
PE	0. 443346	0. 251730	0. 059485	0. 251730	0. 388218	0. 012574	0. 084270	0. 178730	0. 149080	1. 000000

The correlation of some comorbidities and complications with CPFE syndrome are evaluated in table 4.As it is noticed, rheumatic diseases, lung cancer and respiratory failure have a higher correlation coefficient than the others.

Discussion

CPFE is a clinical condition impacting heavy smokers and is defined by a mix of upper lobe emphysema and lower lobe fibrosis. CPFE symptoms involve hypoxemia during exercise and later while at rest, normal lung volumes, and a considerable decline in diffusing capacity, often linked with pulmonary hypertension. It is a diverse condition affecting a wide range of individuals (1). As noted in the literature, we observed that patients with CPFE were either current heavy smokers or ex-smokers and were mainly male. Smoking is identified as the primary causative factor and in all reported cohorts, there is a consistent history of smoking as a persistent factor (9,10,14).

This condition exhibits a broad range of imaging and histopathological features. From a clinical viewpoint, CPFE merges the impacts of emphysema and fibrosis, leading to patients experiencing heightened symptoms that are often associated with serious comorbidities like lung cancer and pulmonary hypertension, which contribute to a poor prognosis and higher mortality. Comorbidities and complications are frequently encountered. They primarily add to the morbidity and mortality associated with these two distinct conditions. At times, it can be challenging to discern which conditions are comorbidities and which are complications in IPF and CPFE syndrome. In our research, we did not identify any significant link between comorbidities and IPF. In CPFE, it is rheumatic diseases and respiratory failure that show a stronger correlation. Our study had certain limitations: the number of recorded patients was somewhat low and this is a retrospective data collection from just one institution (17).

Conclusion

The number of published papers about CPFE is in rising.The interest for this new phenotype is increasing and this is due to its particular clinical, functional, and radiological profile. Little is known about what role the comorbidities and complications play in CPFE outcome and survival. However, further studies are needed to elucidate certain ambiguities in CPFE syndrome because despite numerous case series and studies, many important questions remain unanswered.

Conflicts of Interest: No conflict of interest

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