Research Article

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What is the Role of Complications and Comorbidities in Combined Pulmonary Fibrosis and Emphysema Syndrome

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Abstract

Objective: Combined Pulmonary Fibrosis and Emphysema (CPFE) and Idiopathic Pulmonary Fibrosis (IPF) are separate entities characterised by distinct clinical, functional, radiological, and pathological characteristics. Comorbidities and complications are commonly seen in both diseases. Our purpose was to investigate which comorbidities are more common and what is their impact in the outcome of CPFE and IPF. The demographic and clinical data were also studied. Materials and Methods: This is a retrospective cohort study. We have reviewed the medical records of the patients diagnosed with interstitial lung diseases in University Hospital of lung diseases "Shefqet Ndroqi", in Tirana, in the period from January 2012 till April 2016. The subjects (51 in total) were further divided in two groups: the patients diagnosed with CPFE (25) 49% and the others (26) 51% with IPF. For testing the impact of comorbidities in CPFE syndrome, we have used linear regression with multiple factors using EViews 7 program. "The Student test" is used to evaluate the importance of comorbidities and complications in CPFE and IPF. The demographic and clinical data are expressed in average values using standard deviations ± SD. Results: All of the patients had comorbidities and complications. In CPFE syndrome predominate male smokers or ex-smokers. UPY is higher in CPFE. The time from the appearance of symptoms to the diagnosis is longer in CPFE than in IPF patients. Comorbidities have more impact in CPFE syndrome ($p = 0.01$). In IPF we didn"t find any significant relationships in comorbidities, but we have to remind that the number of patients was small. Conclusion: Comorbidities are frequent in CPFE and IPF patients. Some of them, especially lung cancer, influence strongly in the survival rate and some others, like respiratory insuficiency, may play an important role in the outcome of the disease. However, further research is needed to clarify the impact of comorbidities in CPFE syndrome.

Introduction

There is a new syndrome described recently calledCombined Pulmonary Fibrosis and Emphysema (CPFE), by Cottin et al.It is a distinct entity and it is characterised by the coexistence of theupper lobe emphysema and lower lobe fibrosis. CPFE patients are mainly male, heavy smokers or ex smokers. In contrast with their aggravated clinical condition they have almost normal or slightly reduced pulmonary function and significant impairment of diffusion capacity. The prognosis and the mortality are not well known yet. Actually there is no specific treatment for patients with CPFE syndrome [1].

Idiopathic Pulmonary Fibrosis (IPF) is the most usual form of a large group of lung diseased named Interstitial Lung Diseases (ILD). Its most frequent signs and simptoms are dry cough and exertional dyspnea. The lung tissue in IPF is more stiff and hence has lost the compliance and elasticity. There is little known for the etiology and fispathology.

These patients have a high mortality rate. Fortunately for the treatment of IPF there are some new medications approved lately [2, 3, 5]. CPFE and IPF may be associated with a large number of comorbiditiesand complications [4-6].

In our study, we intended to explorethe presence ofcomorbidities and complications in a group of 51 patients; to assesswhich are the most commonand how important they are in CPFE and IPF outcomes. We collected alsoinformation fromthe baseline demographics, including age, gender, smoking habits (pack per year), pulmonary function tests and diagnostic procedures.

All results were discussed in a multidisciplinary board, consisting of clinical, radiological and pathological experts in the field.

Materials and Methods

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

Patient Selection

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

Inclusion Criteria

IPF patients were diagnosed with the HRCTscan imaging patterns according to the new ATS/ERScriteria [2,3]. CPFE pts were identified based to 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 criteria:
- Who haddrug-associated ILD
- Who had occupationally related ILD, such as asbestosis and silicosis

In total26 (51%) diagnosed with IPF and 25 (49%) with CPFE. There were 10 (38. 4%) male and 15 (57.6%) female in IPF and in CPFE group ofpts 16 (64%) males and 14 (36%) females. Mean age for CPFE was 68±7 and for IPF patients 68±8. 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 softwarethat processes econometricvariousstatisticaldifference 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 ofthem in CPFE and IPF is used "The Student test" (t). R-square is used todetermine theimportanceof themodel. As statistically significant, values of $p < 0.05$ were accepted.

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 10 (38. 5%) males and 16 (61.5%) females.As noted in CPFE predominates males, meanwhile in IPFfemalesaremore,considering that all pts weresmokers 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. Tab1 shows some demographic and clinical data as: age, gender,the time of symptoms since diagnosisand smoking history usingUPY. It is clearly visible that the age of the pts for both groups are nearly the same.

Table 1: Demographic and Clinical Data

	CPFE(N=25)	IPF(N=26)
Sex,m/f[20]%	16 (64%)/9 (36%)	10 (38.5%)/16 (61.5%)
Age,years, mean ± SD[21]	68 ± 7	68 ± 8
UPY[22],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 pts with this syndrome are heavier smokers and their clinical characteristics and outcomes are poorer than those with IPF only [14].

[20]Male/female
[21]Standard deviation
[22] Unit pack year

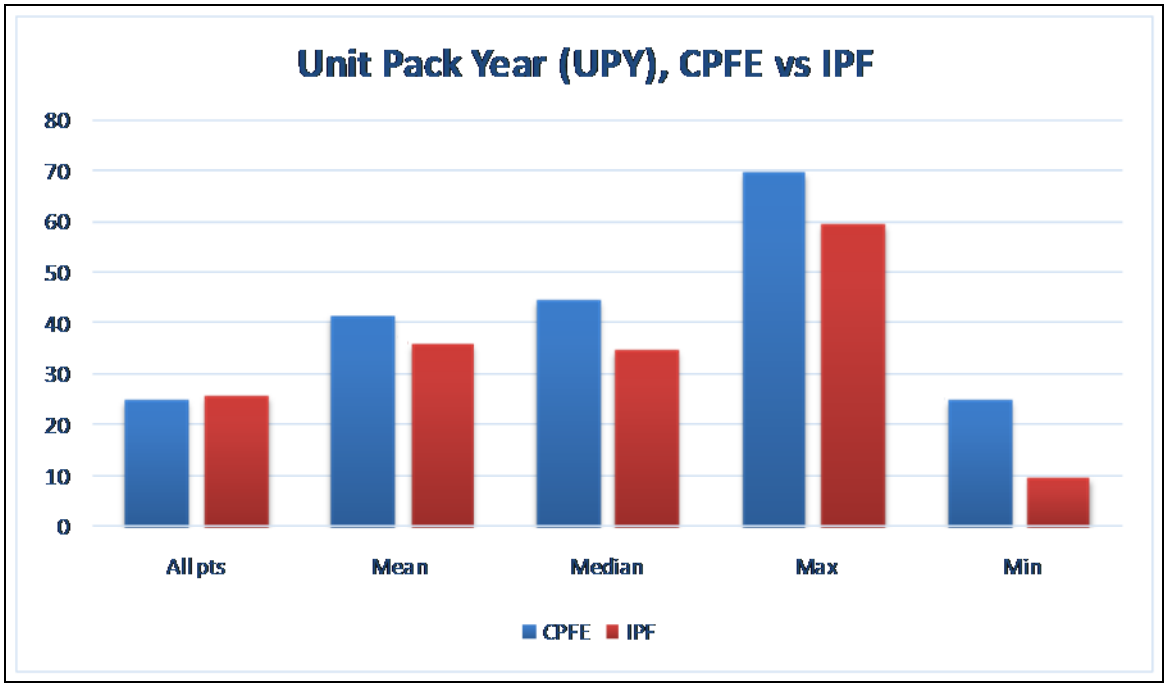

Figure 1: Unit Pack Year (UPY), CPFE vs IPF

In graph 1 we compared UPY values in months for both diseasesand the difference between them is evident. Smoking is the main risk factor inpatients with IPFandin some otherswith CPFEsyndrome [9,14]. The time of symptomshad differences too among both groups.We think that this might be due to underdiagnosing ofCPFEas a resultof itslack of significant changes in pulmonary volumes in spirometry.

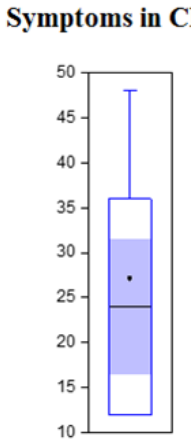

Figure 2: Symptoms in CPFE

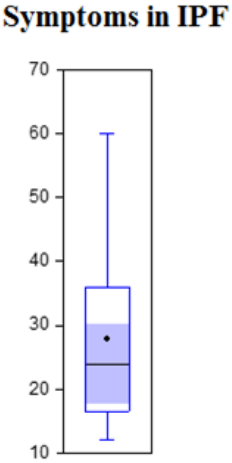

Figure 3: Symptoms in IPF

Patients with CPFE syndrome tend tohave longer time with symptoms compared to those with IPF.

The comorbidities and complicationsthat we found more commonly in the medical recordsin both diseases are as listed: Pulmonary Hypertension, Respiratory Failure, Lung Cancer, Pulmonary Embolism, Arterial Hypertension, Cardiac diseases, Anaemia, Gastritis, Rheumatic diseases, Diabetes Mellitus. Tab 2 analyses and interprets comorbidities and complications in patients with IPF. Ift values > 2, a variable is statistically important. P value express the error margin. If $p<0.05$ with 5% of error margin, this means that statistically these values are correct.

If $p>0.05$, the results may be changed then. As it is noticed in the tab 2, 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: Comorbiditiesand complications inIPF

	Coefficient	Std. Error	t-Statistic	Prob.
Anaemia	0. 235333	0. 336809	0. 698713	0. 4887
L. Ca[23]	-0. 108913	0. 288217	-0. 377884	0. 7075
DM[24]	0. 052993	0. 296853	0. 178516	0. 8592
Gastritis	0. 048979	0. 200653	0. 244100	0. 8084
HTA[25]	0. 566592	0. 143710	3. 942614	0. 0003
HTP[26]	0. 068783	0. 223648	0. 307551	0. 7600
CD[27]	-0. 225784	0. 321192	-0. 702958	0. 4861
RF[28]	-0. 060192	0. 182060	-0. 330618	0. 7426
Rh. Diseases[29]	-0. 413312	0. 306065	-1. 350405	0. 1843
PE[30]	-0. 104099	0. 386508	-0. 269331	0. 7890
R-squared	-0. 019869			

Tab 3 shows comorbidities and complications in CPFE syndrome. Some ofthem havep 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 more important in CPFE syndrome.

In some of the connective tissue diseases, especially rheumatoid arthritis and systemic sclerosis, CPFE syndrome may be present too and it is defined as ‘idiopathic’ (tobacco-related) CPFE [16].

[23] Lung Cancer
[24]Diabetes Mellitus
[25] Arterial Hypertension
[26]Pulmonary Hypertension
[27]Cardiac Diseases
[28]Respiratory Failure
[29]Rheumatic Diseases
[30]Pulmonary Emboli

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 pand t values tend to go respectivelyp=0.1andt=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[31]	0. 419345	0. 268096	1. 564158	0. 1255
DM[32]	-0. 236357	0. 276129	-0. 855966	0. 3970
Gastritis	0. 254718	0. 186645	1. 364720	0. 1798
HTA[33]	0. 095510	0. 133677	0. 714483	0. 4790
HTP[34]	0. 101406	0. 208035	0. 487447	0. 6285
CD[35]	0. 056605	0. 298769	0. 189460	0. 8507
RF[36]	0. 451897	0. 169351	2. 668408	0. 0109
Rh. Diseases[37]	0. 792904	0. 284698	2. 785069	0. 0081
PE[38]	-0. 266165	0. 359525	-0. 740324	0. 4633
R-squared	0. 117557			

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

The variables (comorbidities and complications) studied in regression, according to the r-square values in tab 3, explain 11% ofthe factors affectingthe results in CPFE syndrome.

Table 4: The distribution of comorbidities and complications

	HTP	DM	Rh. D	C. D	R. F	HTA	Gastritis	Anemia	L. Ca	PE
CPFE	0. 38	0. 115	0. 15	0. 115	0. 615	0. 77	0. 27	0. 115	0. 15	0. 115
IPF	0. 28	0. 16	0. 16	0. 12	0. 44	0. 8	0. 28	0. 16	0. 12	0. 08

[31] Lung Cancer
[32]Diabetes Mellitus
[33] Arterial Hypertension
[34]Pulmonary Hypertension
[35]Cardiac Diseases
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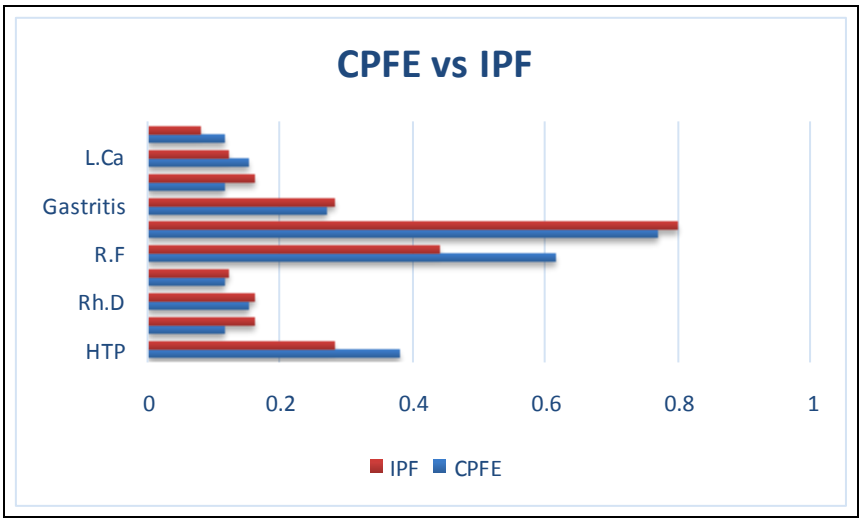

Figure 4: The frequencyof comorbidities and complications

Graph 4 explains the frequency of comorbidities and complications in CPFE vs IPF. It is clearly seen that respiratory failure, pulmonary hypertension and lung cancer are encountered more often in CPFE syndrome. Gastritis and anemia arehighly prevalent in patients with Idiopathic Pulmonary Fibrosis. [13]

Table 5: The correlation of some variables in CPFE

	ANEMIA	L.CA	CPFE/IPF	DM	GASTRITIS	HTA	C D	RF	Rh Disease	PE
Anemia	1. 000000	0. 0065	-0. 064814	0. 33766	0. 265378	0. 070627	0. 561769	0. 376051	-0. 116360	0. 443346
L. Ca[39]	0. 006494	1. 0000	0. 049169	0. 50325	0. 010014	0. 070627	-0. 14564	-0. 08058	-0. 116360	0. 251730
CPFE/IPF	-0. 06481	0. 0492	1. 000000	-0. 06481	-0. 012064	-0. 13276	-0. 00716	0. 175655	0. 286065	0. 059485
DM[40]	0. 337662	0. 5032	-0. 064814	1. 00000	0. 137696	0. 209165	0. 208063	0. 147734	-0. 116360	0. 251730
Gastritis	0. 265378	0. 010	-0. 012064	0. 1377	1. 000000	0. 108921	0. 048131	-0. 12427	-0. 016022	0. 388218
HTA[41]	0. 070627	0. 0706	-0. 132762	0. 20916	0. 108921	1. 000000	0. 191485	-0. 01685	-0. 024338	0. 012574
CD[42]	0. 561769	-0. 1456	-0. 007161	0. 20806	0. 048131	0. 191485	1. 000000	0. 344265	-0. 106525	0. 084270
RF[43]	0. 376051	-0. 0806	0. 175655	0. 14773	-0. 124274	-0. 01685	0. 344265	1. 000000	-0. 163308	0. 178730
Rh. Diseases[44]	-0. 11636	-0.11636	0. 286065	-0. 11636	-0. 016022	-0. 02433	-0. 10652	-0. 16330	1. 000000	0. 149080
PE[45]	0. 443346	0. 2517	0. 059485	0. 25173	0. 388218	0. 012574	0. 084270	0. 178730	0. 149080	1. 000000

Tab 5 shows the correlation of some comorbidities and complications with CPFE syndrome. As it is noticed, rheumatic diseases, lung cancer and respiratory failure have a higher correlation coefficient than the others.

[39] Lung Cancer
[40]Diabetes Mellitus
[41] Arterial Hypertension
[42]Cardiac Diseases
[43]Respiratory Failure
[44]Rheumatic Diseases
[45]Pulmonary Emboli

Discussion

CPFE syndrome is recently recognized. As described in literature, we found that patients with CPFE were current heavy smokers or ex smokers and were predominantly male. Smoking is charged as the main etiologic factor andin all the cohortsreported a history of smoking is a permanent factor [9, 10, 14].

Comorbidities and complications are often meet. They mostly contribute in morbidity and mortality of these two distinct pathologies.[1] Sometimes it is not easyto distinct wich are comorbidities and which are complications in IPF and CPFE syndrome. In our study we did not find any significant correlation between comorbidities andIPF. In CPFE it is rheumatic diseases and respiratory failure that correlate more with it. Our survey had some limitations:the number of record patients was relatively low and it is a retrospective collection of data from one institutiononly.

Conclusion

The number of published papers about CPFE is in rising.The interes for this new phenotype is increasing and this is due to its particular clinical, functional, and radiological profile. Little is known about what role do the comorbidities and complications playin CPFE outcome andsurvival. However, further studies are needed to elucidate certain ambiguities inCPFE syndrome.

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