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The Role of Smoking and Gender in Combined Pulmonary Fibrosis and Emphysema Syndrome Patients

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Abstract

Background: Recently, the co-occurrence of idiopathic pulmonary fibrosis (IPF) and pulmonary emphysema in the same patient has been recognized by the term "combined pulmonary fibrosis syndrome with emphysema" (CPFE), which distinguishes it from pulmonary fibrosis without emphysema. Smoking and male gender has been shown to be the greatest risk factor for IPF and CPFE syndrome also.

Aims: The aim of our study was to evaluate the role of smoking and gender in patients with non-inflammatory pulmonary fibrosis (idiopathic pulmonary fibrosis and pulmonary fibrosis due to connective tissue diseases) with concomitant pulmonary emphysema. We also reviewed the relevant literature to understand the current information and how it correlates with our findings.

Methods: This is a retrospective cohort and case-control study in which the association between different factors (variables) in a group of patients with CPFE syndrome was evaluated. The study was conducted at University Hospital of Lung Disease “Shefqet Ndroqi” and the American Hospital in Tirana, Albania, from the period 2012-2018. We collected medical records of patients with a discharged diagnosis of non-inflammatory pulmonary fibrosis (IPF with emphysema and pulmonary fibrosis due to connective tissue diseases) with emphysema who were over a 50-years of age. A total of 28 patients participated in the study. Of these, 24 had IPF

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with pulmonary emphysema and the remaining 4 had pulmonary fibrosis due to connective tissue disease (CTD) and current pulmonary emphysema (CPFE-CTD). Demographic data are presented as mean ± SD or median (range) depending on distribution. Multivariate analysis expresses the relationship between several variables using simple or complex regression and analysis of variance. A p value < 0.05 was considered statistically significant. The variables "gender" and "cancer" were found to be very important determinants of mortality (HR 41.8, p=0.03, HR 15.2 and p=0.007, respectively).

Conclusion: From the results we can say that smoking is considered a major risk factor for both CPFE and IPF, but CPFE patients tend to have higher UPY values than IPF patients. The male gender was more predisposed and at higher risk for mortality in subjects with CPFE syndrome. Patients should be advised to stop smoking as soon as possible in order to improve their survival and to low mortality.

Keywords: interstitial lung diseases, idiopathic pulmonary fibrosis, pulmonary emphysema

INTRODUCTION

Recently, the co-occurrence of idiopathic pulmonary fibrosis (IPF) and pulmonary emphysema in the same patient has been recognized by the term "combined pulmonary fibrosis syndrome with emphysema" (CPFE), which distinguishes it from pulmonary fibrosis without emphysema. It was named based on the radiological features of upper lobe emphysema and lower lobe pulmonary fibrosis which is mostly idiopathic pulmonary fibrosis (IPF) and often usual interstitial pneumonia (UIP) according to American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus (1).

The importance of distinguishing between these two pathologies is that in CPFE syndrome lung function declines rapidly and more severely than in IPF patients and their survival is less comparing with the patient with IPF alone (2).

Regarding etiologic factors, smoking and male gender have been shown to be the greatest risk factor for IPF and chronic obstructive lung diseases (COPD) as well. Because many studies reported heavy smoking in the majority of patients with CPFE, smoking was also considered a dominant risk factor for CPFE. Several studies have shown that most patients with this syndrome are heavy smokers or ex-smokers and therefore have high unit packs (UPY) smoking exposure time (3,4,5). It is reported that the most frequent and severe complications are pulmonary hypertension and lung cancer. However, the specific pathogenesis of smoking and the process of development of CPFE are still not clear (6,7,8). The aim of our study was to evaluate the role of smoking and gender in patients with non-inflammatory pulmonary fibrosis (idiopathic pulmonary fibrosis and pulmonary fibrosis due to connective tissue diseases) with concomitant pulmonary emphysema. We also reviewed the relevant literature to understand the current information and how it correlates with our findings.

MATERIALS AND METHODS

This is a retrospective cohort and case-control study in which the association between different factors (variables) in a group of patients with CPFE syndrome were evaluated. The study was conducted at University Hospital of Lung Disease “Shefqet Ndroqi” and the American Hospital in Tirana, Albania, from the period 2012-2018. We collected medical records of patients with a discharged diagnosis of non- inflammatory pulmonary fibrosis (IPF with emphysema and pulmonary fibrosis due to connective tissue diseases) with emphysema, who were over a 50-year of age. All medical records included a consent form signed by patients, informing them that they may be subject to research in the future. Clinical and demographic data such as age, gender, smoking history, dyspnea scale, comorbidities, cardiac ultrasound, pulmonary function and comorbidities data were collected. However, in this article, we mainly focus on the

role of gender and smoking as factors affecting the occurrence of emphysema in patients with non-inflammatory pulmonary fibrosis.

Statistical analysis: For statistical analysis, data were processed using EViews version 7 (Econometric Views) and Statistical Package for Social Sciences (SPSS - Statistical Package for Social Sciences Inc., Chicago, IL, USA) version 20.0.

Demographic data are presented as mean ± SD or median (range) depending on distribution. Multivariate analysis expresses the relationship between several variables using simple or complex regression and analysis of variance. A p value < 0.05 was considered statistically significant.

Regarding smoking, subjects were classified as never smokers, former smokers, and current smokers. The unit of measure for smoking was the standardized unit pack-year (UPY), which is calculated using the formula UPY = number of packs smoked per day/20 x number of years of smoking.

The criteria for participation in the study were as follows: patients who were older than 50 years; those diagnosed by high-resolution computed tomography of the chest with or without lung biopsy; who underwent a spirometry test with or without measurement of the test of diffusion capacity of the lung (Dlco); who underwent echocardiography and cases of connective tissue diseases with lung fibrosis. Cases who did not meet the above criteria were excluded from the study.

RESULTS

A total of 28 patients participated in the study. Of these, 24 had IPF with pulmonary emphysema and the remaining 4 had pulmonary fibrosis due to connective tissue disease (CTD) with current pulmonary emphysema (CPFE-CTD). The mean age of the group was 68 ± 6 years, the minimum age was 53 years (1 case) and the maximum age was 78 years (1 case), (figure 1). Patients in the CPFE-CTD group were younger than patients with IPF and emphysema, which lowers the mean age of the entire group. (67,9 ± 6,87).

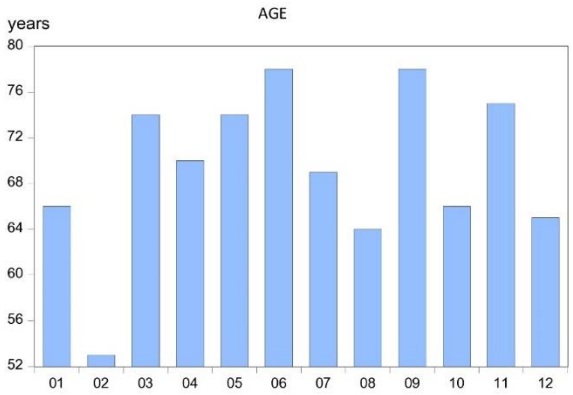

Figure 1. Distribution of patients according to age

It was observed that men dominate significantly (68%) compared to women who were 32% (figure 2).

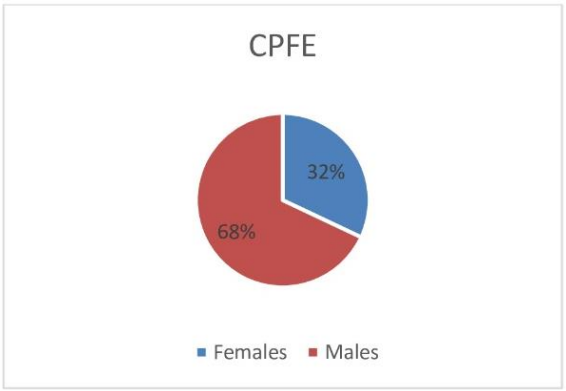

Figure 2. Distribution of patients by gender

Regarding smoking, all current or ex-smoker subjects were male and comprised 94.7%, while none of the females were current or former smokers (figure 3).

High mean UPY values (26 ± 13.2) were observed in patients. These results are also supported by literature data and support the fact that smoking is an important etiological factor in CPFE syndrome. It is reported that CPFE patients have higher mean UPY values than smoking patients with IPF without emphysema 18,21. (figure 4).

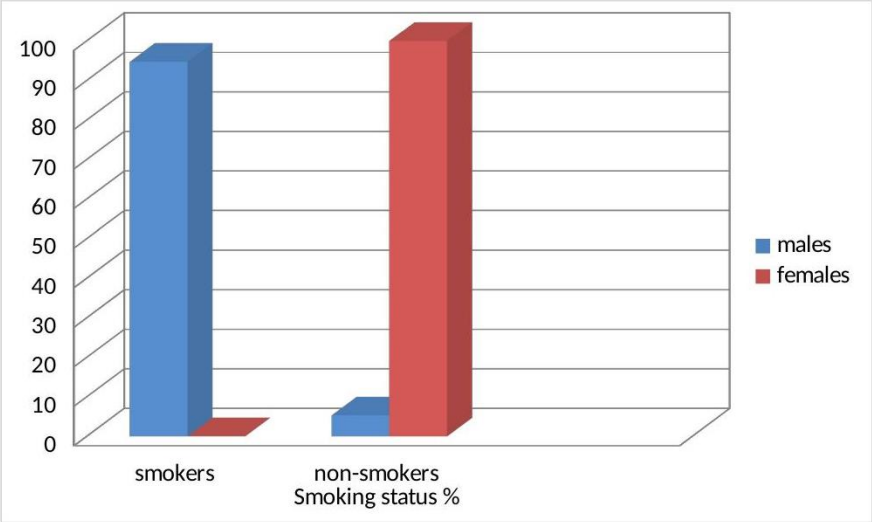

Figure 3. Distribution of smoking by gender

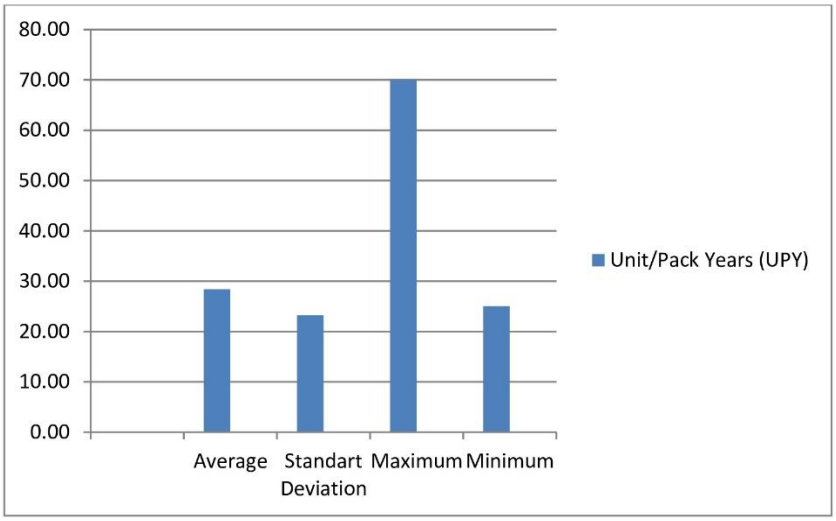

Figure 4. Unit/Pack Years values for smoking

Cox proportional analysis was used to examine prognostic factors influencing mortality in patients with CPFE. Gender was included in the study among demographic factors and common comorbidities such as pulmonary hypertension and lung cancer. The variables "gender" and "cancer" were found to be very important determinants of mortality (HR 41.8, p=0.03, HR 15.2 and p=0.007, respectively), (table 1).

Table 1. Prognostic factors of mortality

Variable	HR (95% CI)	P value
Gender male/female	41.8 (0.232-2.964)	0.03
Pulmonary hypertension	0.94 (0.158 – 5.665)	0.95
Lung cancer	15.297 (0.958-246.8)	0.07

HR-Hazard ratio, CI-Confidence interval

We also used the binary logistic regression test to evaluate the importance in mortality of independent variables age and gender, in comparison with lung function variables such as forced volume expiration in the first second (FVC), partial pressure of oxygen (PO2) and oxygen saturation (SpO2).

As can be seen from table 2, the variable with the highest risk among them was the gender of the subject (regression p = 0.03 and HR = 5.6).

Table 2. Binary logistic regression model

Variables	B	S.E.	Wald	df	P value	HR
Age	-.118	.065	3.260	1	.071	.889
Gender m/f	**1.728**	**.947**	**3.332**	**1**	**.038**	**5.630**
FVC	-.029	.033	.769	1	.380	.971
SPO2	-.082	.041	4.021	1	.045	.922
PO2	.052	.062	.705	1	.401	1.053
Constant	11.901	6.426	3.430	1	.064	147450.882

m-male, f- female, FVC- forced volume expiration in the first second, PO2- partial pressure of oxygen, SpO2- oxygen saturation, HR-hazard ratio

From the results, we can say that the male gender was more predisposed and at higher risk for mortality in subjects with CPFE syndrome. Therefore, our data also agree with the literature data on the important role of gender in mortality in both pathologies (IPF and CPFE syndrome) and mainly in the CPFE syndrome (8,9).

DISCUSSION

Based on data from previous studies emphasizing that patients with CPFE syndrome are older than patients with IPF, our data are contradictory. This is because patients with CPFE in connective tissue diseases, whose average age is lower than that of the idiopathic CPFE group, lowers the average age of the entire group. This fact is emphasized by Todd al (10) in their study, which included 28 patients with CPFE syndrome, where the average age of the subjects was 57 years, contrary to the data of other authors 45. On the other hand, Mejia et al (11) in a study of 31 cases with idiopathic CPFE, reported an average age of the patients 67±7 years, this result is almost the same as our data.

The predominance of the males with a long history of smoking, in the CPFE syndrome, has already been reported in several studies (12,13). Kitaguchi et al (14), in his study also reported that 46 (98%) of 47 patients with CPFE were male. However, data from previous studies show that even in patients with IPF without emphysema, this gender predominates, but in CPFE this is more evident (15). We can also confirm that males constituted 68%, where the p-value of correlation was <0.004, which is statistically very significant, indicating that gender is an independent risk factor in combined pulmonary and emphysema syndrome.

Smoking is considered a major risk factor for both CPFE and IPF, but CPFE patients tend to have higher UPY values than IPF patients (16,17,18). Antoniu et al (19) reported a very strong positive statistical association (CI 1.02-1.06, P < 0.0005) between patients with CPFE syndrome and mean UPY values in their study investigating the prevalence of emphysema in IPF patients and the effect of smoking on them. We also found a strong positive statistical association between smoking and gender (correlation p 0.0001).

The above data are significant regarding this new entity, however the limitation of our study was the small number of cases, which is related to the fact that our country does not yet have a national registry of IPF patients, so the results cannot represent all patients with non-inflammatory pulmonary fibrosis currently existing in Albania.

CONCLUSIONS

Patients with CPFE should be identified by combining clinical data, imaging data, and lung function. Smoking and male gender are significant risk factors for CPFE. Timely diagnosis of this syndrome may be missed due to nonspecific findings of pulmonary function values. HRCT of the chest, respiratory function tests and measurement of Dlco are the main investigations that play a decisive role in its early

diagnosis and progression. For the above reasons patients with non-inflammatory pulmonary fibrosis should be advised to stop smoking as soon as possible in order to improve their survival and to low mortality.

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Conflict of Interest Statement: The author declares that have no conflict of interest.

REFERENCES

1. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J RespirCrit Care Med 2000; 161: 646−64.

2. American Thoracic Society/European Respiratory Society. International multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J RespirCrit Care Med 2002;165: 277−304.

3. Jankowich MD, Rounds SIS. Combined pulmonary fibrosis andemphysema syndrome: a review. Chest 2012;141:222–231.47.

4. Jacob J, Odink A, Brun AL, Macaluso C, de Lauretis A, Kokosi M,et al.Functional associations of pleuroparenchymal fibroelastosis and emphysema with hypersensitivity pneumonitis. Respir Med 2018;138:95–101.48.

5. Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, VasakovaM,et al.Diagnosis of hypersensitivity pneumonitis in adults: an officialATS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med2020;202:e36–e69.

6. Washko GR, Hunninghake GM, Fernandez IE, Mizuki N, Yuka O, Tsuneo Y, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med 2011;364:897-906.

7. Morse D, Rosas IO. Tobacco smoke-induced lung fibrosis and emphysema. Annu Rev Physiol 2014;76:493-513.

8. Cottin V, et al. (eds.), Orphan Lung Diseases: A Clinical Guide to Rare Lung Disease, 327 DOI 10.1007/978-1-4471-2401-6_22, © Springer-Verlag London 2015.

9. Jankowich MD, Rounds SIS. Combined pulmonary fibrosis and emphysema syndrome. A review. Chest 2012;141:222–31.

10. Todd NW , Jeudy J , Lavania S , et al . Centrilobular emphysema combined with pulmonary fibrosis results in improved survival . Fibrogenesis Tissue Repair 2011; 4 (1): 6.

11. Mejıa M, Carrillo G, Rojas-Serrano J, Estrada A, Suarez T, Alonso D, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest 2009;136:10–15.

12. Sangani R, Ghio A, Culp S, Patel Z, Sharma S. Combined pulmonary fibrosis emphysema: role of cigarette smoking and pulmonary hypertension in a rural cohort. Int J Chron Obstruct Pulmon Dis 2021;16:1873–1885

13. Cottin V, Hansell DM, Sverzellati N, Weycker D, Antoniou KM, Atwood M, et al. Effect of emphysema extent on serial lung function in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2017;196:1162–1171.

14. Kitaguchi Y, Fujimoto K, Hanaoka M, Satoshi K, Takayuki H, Keishi K et al. Clinical characteristics of combined pulmonary fibrosis and emphysema.Respirology 2010;15:265–71.

15. Kurashima K, Takayanagi N, Tsuchiya N, Kanauchi T, Ueda M, Hoshi T, et al. The effect of emphysema on lung function and survival in patients with idiopathic pulmonary fibrosis. Respirology 2010;15:843–848.

16. Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I,et al.; Groupe d'Etude et de Recherche sur les Maladies Orphelines Pulmonaires (GERM O P). Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J 2005;26:586–593.

17. Cottin V, Cordier JF. The syndrome of combined pulmonary fibrosis and emphysema. Chest 2009;136:1–2.

18. Wong AW, Liang J, Cottin V, Ryerson CJ. Diagnostic features in combined pulmonary fibrosis and emphysema: a systematic review. Ann Am Thorac Soc 2020;17:1333–1336.

19. Antoniou KM, Walsh SL, Hansell DM, Rubens MR, Marten K, Tennant R,et al. Smoking-related emphysema is associated with idiopathic pulmonary fibrosis and rheumatoid lung. Respirology 2013;18:1191–1196.