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The predictors of mortality in IPF - Does emphysema change the prognosis?

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Abstract. *Background:* Combined idiopathic pulmonary fibrosis (IPF) and emphysema (CPFE) has been reported to be more common in male smokers. A number of studies comparing CPFE patients with fibrosis-only patients have reported a similar prognosis while others have reported a significantly shorter survival. *Objectives:* In present study, we aimed to compare baseline characteristics of patients with IPF according to emphysema presence. We asssessed the prognostic value of emphysema along with each other parameter. *Methods:* We retrospectively reviewed the clinical, baseline radiological, laboratory and physiological parameters of 92 patients who were diagnosed with IPF. The patients were divided into two groups: those without emphysema (Group 1) and with emphysema (Group 2). All-cause mortality was recorded, and the impact of the variables on survival was evaluated. *Results:* Emphysema was recorded in 23 patients, all of whom were male. While ever-smoker rate was higher in Group 2 laboratory and physiologic parameters were similar. Radiologically, the presence of honeycombing, ground glass opacity, the extension and symmetry of involvement did not differ between the Groups. The median survival time was 29±4 months. Patients in Group 1 and 2 had a median survival of 34 and 9 months, respectively. In univariate analysis; radiological presence of emphysema and honeycombing, male gender, lower baseline levels of albumin and oxygen saturation, forced vital capacity and carbon monoxide diffusing capacity were detected as predictors of mortality. *Conclusion:* In present study, IPF with emphysema was more common in male smokers. When emphysema accompanies IPF, life expectancy is remarkably worse, but not independently so. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 267-274)*

Key words: Emphysema, honeycombing, idiopathic pulmonary fibrosis, prognosis, survival

Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults with a histopathologic and/or radiological pattern of usual interstitial pneumonia (UIP) (1).

Combined fibrosis and emphysema (CPFE) has first been reported as a case series in 1990s, and a CPFE syndrome was described in 2005 as "emphysema in the upper lobes, combined with interstitial lung disease in the lower lobes" (2,3).

The syndrome is more common in male smokers, and the gas exchange is severely impaired whereas lung volumes are relatively preserved (2,3). However, inconsistent results have been published regarding the effect on survival of CPFE. In the first few published series, no significant difference had been

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found, which was followed by reports indicating that the survival time is shorter in CPFE, particularly in relation to pulmonary hypertension (4,5). Recently, conflicting results have been reported on whether emphysema changes life expectancy or not (6,7). Amidst all this debate, there is still no consensus on the definition and the clinical importance of the syndrome in current guidelines.

The first objective of the present study is to compare baseline laboratory, physiological and radiological parameters of IPF patients with and without emphysema. The second objective is to examined the impact of these factors on mortality and seek the most significant predictor for life expectancy.

Methods

Patient selection

Hospital database records had been investigated for all interstitial lung disease codes covering January 2005 - January 2013. Among 382 patients, 182 were excluded who had non-IPF diagnosis and secondary interstitial lung diseases. The medical files of the remaining 205 patients were requested from the archive. High resolution computed tomography (HRCT) images of 37 patients were not available at the time of diagnosis and they were excluded. The medical files of 168 patients were reviewed by 2 pulmonologists. Fifty eight patients whose clinical and radiological criteria were not consistent with IPF were excluded, and HRCT images of remaining 113 patients were examined by an expert thoracic radiologist. Thereafter, 21 patients whose imaging quality or findings of tomography were not sufficient to identify radiological parameters were excluded. Finally, the study included 92 IPF patients. For diagnosis of IPF, 2011 guidelines were used (Figure 1) (8).

Demographic characteristics, baseline laboratory and physiological parameters were recorded from medical files for each patient.

Radiological evaluations

All HRCT images were evaluated by an expert thoracic radiologist for evidence of extension, symmetry and distribution of fibrosis and presence of emphysema in radiological findings.

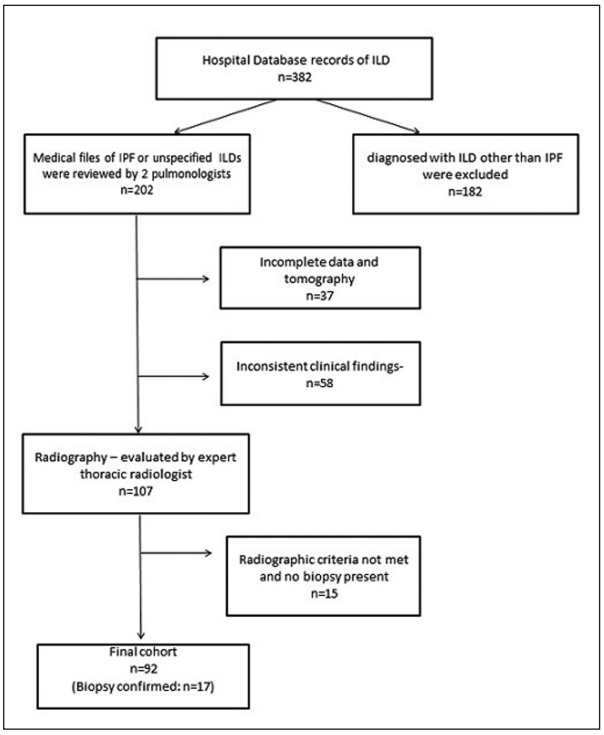

Fig. 1. Flowchart for Patient Selection.
ILD: interstitial lung disease, IPF: idiopatic pulmonary fibrosis

Considering that patients with usual interstitial pneumonia also have fibrosis, CPFE criteria included to presence of low attenuation areas compared to the adjacent parenchyma, having no wall or a wall of <1 mm in thickness and predominance of upper lobe (3).

The pulmonary conus was measured, and a result of 29 mm and above was considered to be pulmonary hypertension (9).

The patients were divided into two groups based on the presence of emphysema:

Group 1: Patients without emphysema (IPF alone)

Group 2: Patients with CPFE

Clinical, laboratory and radiological findings were compared between the Groups.

Survival status

Information on survival status was obtained from the national death records using the identification number of patients. The survival time was recorded based on the all-cause mortality. The impact

of clinical and radiological features on survival was analyzed.

Statistical analysis

All statistical analyses were carried out using a statistical software package (SPSS for Windows, version 16.0; SPSS Inc., Chicago, IL, USA). The values were presented as mean ± SD. Student's t-test and Chi-square analyses were used for intergroup comparisons. The survival time curves were drawn using the Kaplan-Meier method and survival time was measured via log-rank test.

Cox proportional hazards model was used to find out the potential predictors of mortality. The variables associated with mortality in univariate analysis with a p value of <0.05 were then incorporated into a multivariate analysis also based on the Cox proportional model.

The study was approved by the local Ethics Committee of the Institution (Dr. Lutfi Kırdar Training and Research Hospital- No: 89513307/1009/412), and it was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Results

Characteristics of the study population and follow-up

Of all the 92 patients, 68 (74%) were male, and the mean age was 63.5±10 years (38 to 86 years). Seventeen patients (18%) had histopathological diagnosis while others were diagnosed according to IPF guideline (8).

Forty seven patients had at least one concomitant disease. Median symptom duration was 12 months. Sixty four (71%) patients had ever smoked with a mean of 30±26 (range: 3- 120) pack/years. The mean baseline values were as follows; albumin, 3,3±0,6 (g/dL); lactate dehydrogenase, 299±116 (U/L); and oxygen saturation, 91.5±7%, forced vital capacity (FVC) was 61.3±17.5%, and diffusing capacity for carbon monoxide (DLCO) was 45.1±17.4%.

Radiological features

In radiological assessments, emphysema was present in 23 patients. No honeycombing was found in 11 patients, who were histopathologically diagnosed. Ground glass opacity and subpleural cysts were recorded in 31 (34%) and 41 (44%) patients respectively. The mean diameter of pulmonary conus was 29.8±3.4 (22-40) mm.

Comparison of CPFE and IPF-alone patients

Following radiological assessments, there were 69 patients (75%) in Group 1, and 23 patients (25%) in Group 2 (CPFE). All patients in Group 2 were male, and had a higher cigarette smoking rate (P = 0.005). The mean age, duration of complaints, concomitant diseases at diagnosis were similar between the two groups (P > 0.05). There was no statistically significant difference in laboratory and physiological parameters between the groups (Table 1).

Both groups were similar for the presence of ground glass, honeycombing, fibrotic extensions and symmetry of involvement (Table 2). Parenchymal cysts were more frequent in CPFE group.

The diameter of pulmonary conus was 29.4±3.1 mm in Group 1; and 30.8±4 mm in Group 2. No statistically significant difference was observed in pulmonary conus (P = 0.096) and presence of pulmonary hypertension (P = 0.592) between the groups.

Follow-up results

The mean follow-up time was 32±26 months (1 to 95 months). During follow-up, 68 (74%) patients died. Four of the surviving 24 patients were censored.

Table 1. Comparison of demographic characteristics and baseline laboratory values

	Group 1 (n=69)	Group 2 (n=23)	P-value
Male, n (%)	45 (65%)	23 (100%)	0,001
Ever smoker, n (%)	43 (62)	21 (91)	0,005
Age (years)	64±10	61±11	0,23
Albumin (g/dL)	3,4	3,3	0,69
LDH (U/L)	282	348	0,73
Hemoglobin (g/dL)	13,5	13,5	0,74
SpO2 (%)	92,2	89,6	0,15
FEV1%	65	71	0,82
FVC%	60	64	0,94
FEV1/FVC	0,89	0,86	0,40
DLCO(%)	46	41	0,86

DLCO: diffusing capacity of the lung for carbon monoxide, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, FEV1/FVC: the ratio of forced expiratory volume in 1 second to forced vital capacity, LDH: lactate dehydrogenase

Table 2. Comparison of radiological findings at diagnosis between groups

		Group 1 (n=69) n (%)	Group 2 (n=23)n (%)	P- value
Ground glass		22 (32%)	9 (39%)	0,61
Honeycombing		60 (87%)	21 (91%)	0,72
Localization	Only lower zones	56 (81%)	16 (70%)	0,449
	More extensive than lower zones	13 (%19)	7 (30%)	
Subpleural/central	Subpleural	62 (90%)	19 (83%)	0,45
	Subpleural& central	7 (10%)	4 (17%)	
Symmetry	Bilateral symmetric	47 (%68)	17 (74%)	0,68
	Laterality dominance	22 (%32)	6 (26%)	
Symmetry	Right lung dominance	17 (25%)	6 (26%)	0,553
	Left lung dominance	5 (7%)	-	
Cyst		24 (35%)	17 (74%)	0,001

The median survival time was 29.0±4.0 months (Figure 2).

Baseline characteristics and survival

No correlation was found between duration of presenting complaints, concomitant diseases and survival times (P > 0.05). Male gender, ever cigarette smoking, lower levels of baseline albumin, oxygen saturation, FVC and DLCO values were detected to increase mortality (Table 3).

Radiological features and survival

Radiologically, emphysema and honeycombing were found as significant (Figure 3 and 4) in survival. Median survival time of patients with and without emphysema were 9 and 34 months respectively. The extension, symmetry and distribution of fibrosis involvement and the diameter of pulmonary conus did not have a significant effect on mortality (Table 4).

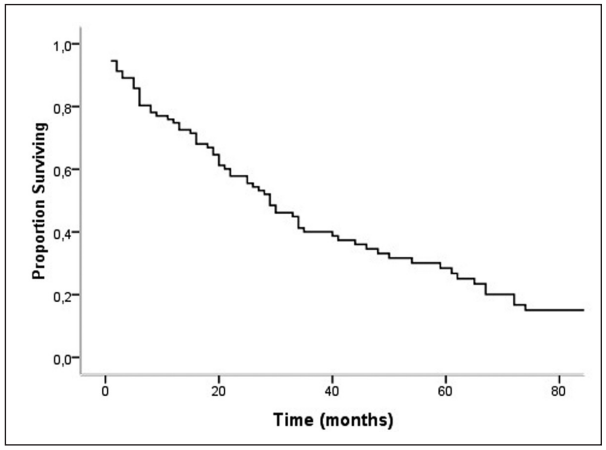

Fig. 2. Survival curve of all patients by Kaplan Meier method

Table 3. Results of univariate analysis of the parameters and mortality

	HR (CI 95%)	CI (95%)	P- value
Gender (male vs. female)	2.539	1.339-4.606	0,001
Age	1.019	0.994-1.044	0,14
Smoking status (ever smoker vs. never smoker)	0.104	0.906-2.873	0,09
Albumin	0.590	0.385-0.906	0,016
LDH(U/L)	1.002	0.999-1.005	0,242
Hemoglobin (g/dl)	1.057	0,931-1.200	0,395
Oxygen saturation (%)	0.970	0.943-0.997	0,030
FEV1 (%)	1.019	0.994-1.044	0,135
FVC (%)	0.982	0.967-0.998	0,024
DLCO (%)	0.970	0.951-0.989	0,002

DLCO: diffusing capacity of the lung for carbon monoxide, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, FEV1/FVC: the ratio of forced expiratory volume in 1 second to forced vital capacity, LDH: lactate dehydrogenase

Multivariate analysis

In multivariate analysis of the parameters except radiological features (with albumin, oxygen saturation, DLCO, FVC levels and gender) lower albumin and oxygen saturation were observed as stronger predictors of mortality (P < 0.05).

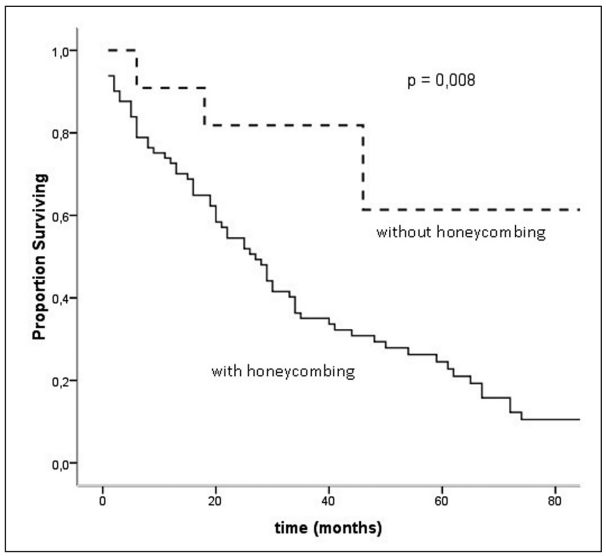

Fig. 3. Kaplan Meier survival curves for patients with and without honeycombing. Patients with honeycombing survived significantly shorter than those without honeycombing (P = 0,008)

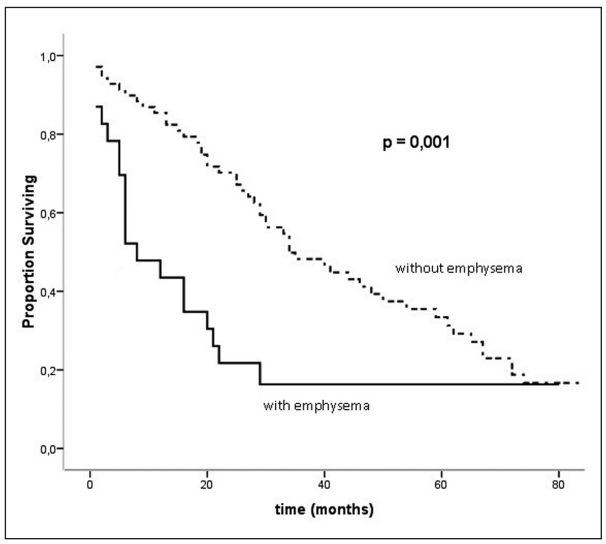

Fig. 4. Kaplan Meier survival curves for patients with and without emphysema. The survival was significantly worse in patients with emphysema than those without emphysema (P = 0,001)

In multivariate analysis with the emphysema, honeycombing albumin and oxygen saturation levels; emphysema and albumin showed significance (P < 0.05).

However, when all the parameters were investigated together, none of them stood ut as an independent predictor of mortality (P > 0.05).

Table 4. Results of univariate analysis of the radiological parameters on mortality

	HR	CI (95%)	P- value
Emphysema	0.399	0.232-0.687	0.001
Honeycombing	0.240	0.075-0.764	0.016
Ground glass opacity	0.861	0.521-1.424	0.560
Cyst	0.697	0.432-1.125	0.697
Lower zones vs. more extensive than lower zones	1.132	0.299-4.284	0.855
Subpleural vs. subleural and central involvement	0.587	0.300-1.150	0.121
Bilateral vs. one lung dominant involvement	1.571	0.926-2.668	0.094
Right vs. left lung dominance	0.526	0.150-1.847	0.316
Pulmonary conus diameter (mm)	1.071	0.990-1.159	0.085

Discussion

In current study, concomitant emphysema was particularly identified with male patients having history of smoking. We found that survival time was shorter when accompanied by the radiologically presence of emphysema. Honeycombing was the other radiological predictor of mortality. Other than radiological features; male gender, lower baseline levels of albumin, oxygen saturation, FVC, DLCO levels predicted mortality as well in univariate analysis. In multivariate analysis, none of these parameters predicted mortality independently. However, when albumin and oxygen levels, as the best laboratory predictors of reduced survival, were evaluated along with radiological predictors; emphysema presence and lower albumin levels were observed as the strongest significant parameters for increased mortality.

The rate of emphysema in fibrosis patients is reported to be between 8% and 28% (5,10). We found this rate as 25%. Consistent with the literature, all CPFE patients were male, and cigarette smoking was rather frequent. The laboratory and physiological parameters at the time of diagnosis, and number of hospitalizations were similar between the two groups (11-13).

Baseline prognostic factors

Male gender, smoking status, FVC and DLCO levels have been reported to predict survival (8, 14). In current study, the survival time was shorter in ever

cigarette smokers. Along with these parameters, albumin, FVC and DLCO levels were associated with mortality. Male gender, smoking status, FVC and DLCO levels have been reported to predict survival (8,14). In present study, albumin and oxygen saturation levels showed stronger significance. Baseline albumin levels are shown to predict overall and cause specific mortality (15). Baseline lower oxygen saturation and exercise desaturation have been reported to be related with shorter survival in IPF (16,17). Low concentration of basal albumin may associate with chronic inflammation and therefore reflect a worse life expectancy. Oxygen levels may also indicate more extensive or severe inflammation in lung parenchyma causing shorter survival.

Radiological prognostic factors

In present study, patients without honeycombing at diagnosis survived longer. Those patients mostly had ground glass opacity in lower zones. Ground glass opacity may reflect fibrosis below HRCT resolution in histopathological examinations (18). The presence of honeycombing and the extent of fibrosis were found to have an impact on survival time (10,19). In this regard, when radiological findings are not suggestive of IPF and histopathological confirmation is required this may associate with a better prognosis when compared to 'definite UIP' pattern.

When we compared the involvement of the lungs, bilaterally-involved patients survived shorter than the patients who had dominantly one lung involved (median 22 and 35 months, respectively). And right lung dominant patients survived shorter than left lung involved ones (median 72 and 34 months respectively). The differences were not statistically significant, most probably due to the insufficient number of left lung-dominance patients. In patients with asymmetric involvement of the lungs, the right lung dominance has been reported to be more common, which might be associated with gastroesophageal reflux (20). There might be a different pathogenesis in left lung dominance but due to inadequate number of patients we could not make a strong comment in this regard.

The mean pulmonary conus diameter was higher in the CPFE group but no significant difference was found between the two groups. Several studies reported a higher association between CPFE and pulmonary hypertension, however we were unable to obtain a similar result measuring the pulmonary conus (5,22).

Emphysema

Except gender, smoking status and parenchymal cysts; the baseline parameters were similar is patients with and without emphysema. The median survival time was significantly shorter in CPFE patients (median 9 vs. 34 months). This distinction should remind the clinician that, when emphysema accompanies IPF, life expectancy is remarkably worse, but not independently so.

Cottin et al. published a series of 61 patients in 2005 by providing a definition of the CPFE syndrome. Patients with IPF and non-specific interstitial pneumonia were included for fibrosis. No criteria were defined for emphysema (10).

In the literature, there are a number of studies comparing survival in patients with and without emphysema. However, the results are not consistent. The reason for such inconsistency may be related to different study designs, study population and different criteria used for the definition of fibrosis and emphysema (Table 5) (22,23).

In terms of emphysema, the extent and subtype of emphysema may be important in prognosis. Todd et al. reported that less extensive and paraseptal type of emphysema causes worse survival (11). Sugino et al. applied a diagnosis of CPFE in the presence of emphysema extending to >25% of upper lobes, and came up with shorter survival in these patients (6). On the other hand, Ryerson et al. applied a diagnosis of CPFE when an emphysema area of >10% was detected. Under this criterion, the percent of the patients decreased from 29% to 8% (7). These results suggest that the subtype and the rate of emphysema are likely to be important. In present study, we did not classify and measure the extent of emphysema. Similar to Ye et al., any rate and type of emphysema were found to reduced survival in present study (23).

In term of fibrosis, a number of studies investigated only IPF patients while few of the series evaluated IPF and non-IPF patients together. Recently, Sugino et al. reported that the prognosis of CPFE/UIP patients is worse than CPFE/non-UIP patients (24). IPF and non-IPF interstitial lung disease ae associated with different rates of life expectancy and we

Table 5. A brief evaluation of the studies on mortality of CPFE

	n Total/ CPFE	Fibrosis	Emphysema	Outcome associated with mortality
Cottin et al. (10)	61	IPF/NSIP	Any emphysema	CPFE mortality incerases in the presence of PHT
Mejia et al. (5)	110/	IPF	10%	Shorter survival outcomes in PHT and CPFE
Akagi et al. (4)	59/25	IPF/NSIP/RB-ILD	Any emphysema	Similar survival in CPFE and IPF alone (P = 0.212)
Jankowich and Rounds (22)	44/20	Any fibrosis	Any emphysema	Similar survival outcomes in patients with CPFE and isolated fibrosis
Todd et al. (11)	102/28	Any fibrosis	3 subgroups: no emphysema/ limited/extensive emphysema	Patients without emphysema have the worst survival; Patients with extensive emphysema have the best survival; Paraseptal emphysema is associated by decreased survival
Sugino et al. (6)	46	IPF	25% of upper lobes	Survival is worse in CPFE patients; the worst prognosis is in combined PHT and CPFE; paraseptal emphysema decreases survival
Ryerson et al. (7)	365/69	IPF	10%	Similar survival outcomes
Ye et al. (23)	70	IPF	Any emphysema	CPFE patients have shorter survival time

CPFE: combined pulmonary fibrosis and emphysema, IPF: idiopathic pulmonary fibrosis, NSIP: non-specific interstitial pneumonia, PHT: pulmonary hypertension, RB-ILD: respiratory bronchilotis- interstitial lung diseas

believe that evaluating these two combined together may constitute a confounding factor. In present study, only IPF patients were evaluated and worse survival has been detected in emphysema with IPF patients.

Limitations of our study: First, it is a retrospective, single centre study. We evaluated the pulmonary hypertension by measuring the main pulmonary conus since it was a retrospective study. Echocardiographic data the mean pulmonary artery pressure values were not available for all patients. The other limitation is that we could not evaluate longitudinal changes of the parameters due to the retrospective design and incompleteness of the data.

In conclusion, emphysema's coexistence with IPF, is often seen in male patients with a history of smoking. Radiological presence of emphysema, honeycombing, male gender lower baseline levels of albumin, oxygen saturation FVC and DLCO levels decrease survival time in an interrelated manner.

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