Spontaneous Pneumomediastinum as a Potential Predictor of Mortality in Patients with Idiopathic Pulmonary Fibrosis

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Key Words

Computed tomography · Idiopathic pulmonary fibrosis · Outcome · Pneumomediastinum · Prognosis

Abstract

Background: Spontaneous pneumomediastinum (PM) is a rare event in patients with idiopathic pulmonary fibrosis (IPF) with unknown prognostic implications. **Objectives:** To analyze the incidence and prognostic impact of PM in a cohort of patients with IPF. **Methods:** PM diagnosed by computed tomography was identified retrospectively in the clinical and radiological records of 182 patients with IPF who were admitted to our center between August 2006 and July 2013. PM patients were compared to matched IPF patients not affected by PM and analyzed for survival. **Results:** PM occurred in 9/182 IPF patients [5%; 6 males; median age: 63 years; median percent predicted of vital capacity (VC%) at baseline: 53%]. The median time between IPF diagnosis and PM occurrence was 3 months (interquartile range: 0–33). The

control group included 36 IPF patients (28 males; median age: 69 years; VC% at baseline: 57%). In a multivariate Cox regression analysis, PM was a significant predictor of mortality [hazard ratio (HR): 3.0; $p = 0.032$]. Considering only patients experiencing PM at the time of IPF diagnosis ($n = 4$), PM was a strongly significant predictor of mortality in multivariate analysis (HR: 6.4; $p = 0.007$). **Conclusions:** Spontaneous PM is a rare but serious complication in patients with IPF and may be considered as a potential predictor of mortality.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonias, and is associated with a poor prognosis with a median survival

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of 2.5–3.5 years [1–4]. Several studies have focused on identifying predictors of mortality in patients with IPF, including both baseline and longitudinal predictors [3, 5–9]. Currently, the most widely accepted prognostic factors are age, comorbidities and their treatments, a history of hospitalization for respiratory causes, and functional parameters such as forced vital capacity or the 6-min walk test, evaluated at baseline and longitudinally [3, 5–12]. Also composite parameters such as the gender-age-physiology (GAP) index and the longitudinal GAP index may help to predict mortality in patients suffering from IPF [13–15]. Furthermore, computed tomography (CT) assessment of fibrosis extent, honeycombing pattern, and traction bronchiectasis are regarded as potential predictors of survival [16–18]. Moreover, several biomarkers (e.g. KL-6, SP-A, MMP-7, and CCL-18) and self-reported daily activity have recently been related to the outcome of the disease [19, 20].

Patients suffering from IPF are at a significant risk of several complications – including acute exacerbation, infection, pulmonary hypertension, lung cancer, and spontaneous pneumothorax – that affect both prognosis and treatment [21–25]. In addition, spontaneous pneumomediastinum (PM) has been reported as a rare event in IPF [26]. However, to our knowledge, there are no reports in the literature regarding the association between PM and mortality in IPF patients. We therefore aimed to analyze the incidence and prognostic impact of PM in patients with IPF.

Subjects and Methods

Patients

We retrospectively reviewed the clinical records of 182 patients suffering from IPF consecutively admitted to our center for interstitial and rare lung diseases between August 2006 and July 2013 who underwent at least one multidetector CT (MDCT). All procedures were in accordance with the Declaration of Helsinki. The study was approved by the local ethics committee (Institutional Review Board approval No. S-318/2013). All patient records were anonymized and deidentified prior to analysis.

IPF was diagnosed in all patients according to the international consensus statement at the time of first diagnosis, excluding other causes of fibrotic interstitial lung disease, especially connective tissue-associated interstitial lung diseases. For this, clinical and laboratory markers were employed; no patient exhibited signs of dermatomyositis-polymyositis [1, 27]. The diagnosis of IPF was established for each patient in a multidisciplinary team discussion meeting consisting of pulmonologists, radiologists, and pathologists experienced in the diagnosis and treatment of IPF.

Patients with PM were identified from our radiological and clinical database. Patients with potential risk factors for the devel-

opment of PM, such as intubation, lung biopsy, esophageal rupture, or major trauma, were excluded from the analysis. In order to analyze the prognostic significance of PM, a control group of IPF patients not affected by PM was randomly matched for age, gender, smoking history, pulmonary function status, GAP stage, and treatment. In addition, a second subgroup of patients who had experienced PM at the time of IPF diagnosis were compared with the control group defined above.

Clinical Assessment and Pulmonary Function Testing

Age, gender, and smoking history were noted for each patient. In addition, pulmonary function testing was assessed (total and percent predicted), including vital capacity (VC), total lung capacity (TLC), diffusion capacity of the lung for carbon monoxide (DLCO), and arterial oxygen tension at rest (PaO_2) [28]. The GAP index was calculated as suggested by Ley et al. [13]. The development or the worsening of dyspnea, cough, and thoracic pain within 6 weeks prior to the MDCT examination was recorded for patients experiencing PM. At the time of PM occurrence, the cases were reevaluated for acute exacerbation of IPF, which was defined according to Collard et al. [29] as unexplained worsening or development of dyspnea within 30 days, new parenchymal opacity on MDCT, and exclusion of alternative causes including infection, left heart failure, or identifiable causes of acute lung injury.

Moreover, medical treatment for the underlying IPF, chosen on the basis of the interdisciplinary statement and according to current guidelines at the time of diagnosis, was recorded [30]. The following therapeutic schemes were applied: (1) immunosuppressants (concomitant or sequential treatment with corticosteroids, azathioprine, and cyclophosphamide) or (2) pirfenidone. In addition, the use of long-term oxygen therapy (LTOT) was noted for all patients.

Radiological Analysis

All patients underwent MDCT of the entire chest at inspiratory breath hold in the supine position on a 4-slice, 6-slice, or 64-slice scanner (Volume Zoom, Emotion, or Somatom Definition AS; Siemens AG, Forchheim, Germany). The technical parameters were as follows: tube voltage, 100–120 kV; reference or effective tube current-time product, 70 mAs; collimation, 0.6–1.25 mm; increment, 1 mm; rotation time, 0.33–0.75 s; pitch, 1.5–2 (typical $\text{DLPw} = 37\text{--}127 \text{ mGy cm}$, $E = 0.6\text{--}1.6 \text{ mSv}$, and scan time = 3–18 s). On the basis of clinical indication, some few patients underwent contrast-enhanced MDCT of the chest (i.e. suspicion of pulmonary embolism). Image data sets were reconstructed using both sharp kernels (B70f or I70f) with a standard lung window (1,500 width; –500 center) and medium-soft kernels (B40f or I40f) with a soft-tissue window (400 width; 30 center) [31].

All the available MDCT scans of the 182 patients were analyzed in retrospect by two independent readers, and the final diagnosis of PM was assessed in consensus. In patients with PM, air location within the mediastinum was evaluated by anterior, middle, and posterior compartments as defined by Felson [32]. Furthermore, specific air dissection of the visceral sheaths was assessed (esophagotracheal, peribronchovascular, and perivascular sheaths of the cephalic vessels).

Statistical Analysis

Continuous variables are expressed as medians and interquartile ranges. Differences in age, gender, smoking history,

Table 1. Patient characteristics at the time of IPF diagnosis

	Overall cohort (n = 45)	PM cohort (n = 9)	Control group (n = 36)	p value
Demographics				
Age, years	69 (62–73)	63 (54–73)	69 (63–73)	0.706
Males, n	34/45	6/9	28/36	0.666
Smoking history (current or former), n	16/45	2/9	14/36	0.456
Functional status				
VC, % predicted ^a	57 (46–62)	53 (32–70)	57 (46–62)	0.958
TLC, % predicted ^b	51 (43–59)	53 (43–59)	51 (43–58)	0.735
DLCO, % predicted ^c	36 (27–43)	41 (34–51)	34 (27–42)	0.213
PaO ₂ , mm Hg ^d	63 (55–75)	64 (54–78)	62 (55–73)	0.382
GAP stage, n ^e				
I	5/45	1/9	4/36	–
II	20/45	4/9	16/36	–
III	20/45	4/9	16/36	1.000
Therapy, n				
Immunosuppressants ^f	34/45	7/9	27/36	–
Pirfenidone	11/45	2/9	9/36	1.000
LTOT	23/45	4/9	19/36	0.722

Data are presented as absolute numbers of patients or medians (interquartile ranges). Differences between the PM cohort and the control group were tested using the Mann-Whitney U test for continuous variables, while the χ^2 test and Fisher's exact test were used for categorical variables.

^a In 3 patients of the PM cohort, symptoms and/or lung function prohibited performance of VC%.

^b In 2 patients of the PM cohort, symptoms and/or lung function prohibited performance of TLC%.

^c In 10 patients, 5 in the PM cohort and 5 in the control group, symptoms and/or lung function prohibited performance of the DLCO maneuver.

^d In 5 patients, 2 in the PM cohort and 3 in the control group, symptoms and/or lung function prohibited performance of PaO₂.

^e GAP categories were identified on the basis of the index calculated as suggested by Ley et al. [13], based on gender, age, and both VC% and DLCO%.

^f Concomitant or sequential treatment with corticosteroids, azathioprine, and cyclophosphamide.

functional impairment, GAP stage, and therapy between the two groups were tested with the Mann-Whitney U test for continuous data and both the χ^2 test and Fisher's exact test for categorical data. Overall survival (OS) was calculated from the time of the IPF diagnosis to the time of death from any cause. Patients not experiencing the event of death by the time of analysis were censored at the last known date of follow-up. Potential predictors of mortality were characterized using categorical variables. Thresholds separating categories for a given predictor were defined based on the quartiles of their distributions. Survival probabilities as a function of time in the independent groups of IPF patients categorized by PM occurrence were computed by the Kaplan-Meier method (product limit). The survival functions were compared between the independent groups of patients by log-rank test. Univariate Cox proportional-hazards regression analysis was used to examine the association between prognostic variables of mortality and OS and to estimate both hazard ratios (HRs) and 95% confidence intervals (CIs). Variables with a p value <0.25 in univariate analysis were then evaluated by multivariate analysis using Cox proportional-hazards regression anal-

ysis with backward stepwise Wald elimination. A p value <0.05 was considered significant. Statistical analysis was performed with SPSS software version 20 (SPSS, Inc., Chicago, Ill., USA).

Results

Patient Characteristics

Spontaneous PM was detected in 9 of the 182 IPF patients (5%). The characteristics of the PM patients at IPF diagnosis were as follows: 6 males and 3 females with a median age of 63 years (interquartile range: 54–73). The majority of the patients in the PM group were non-smokers (7/9). At IPF diagnosis, the PM patients had a median VC% of 53% (interquartile range: 32–70) and a median DLCO% of 41% (interquartile range: 34–51), and they showed a median PaO₂ of 64 mm Hg (interquartile range:

Table 2. Characteristic of the patients with concomitant IPF diagnosis and PM occurrence

	PM cohort (n = 4)	Control group (n = 36)	p value
Demographics			
Age, years	68 (48–80)	69 (63–73)	0.913
Males, n	3/4	28/36	1.000
Smoking history (current or former), n	1/4	14/36	1.000
Functional status			
VC, % predicted ^a	35 (29–52)	57 (46–62)	0.433
TLC, % predicted ^a	55 (49–59)	51 (43–58)	0.735
DLCO, % predicted ^b	n.c.	34 (27–42)	0.213
PaO ₂ , mm Hg ^c	59 (52–74)	62 (55–73)	0.795
GAP stage, n ^d			
I	0/4	4/36	–
II	2/4	16/36	–
III	2/4	16/36	1.000
Therapy, n			
Immunosuppressants ^e	4/4	27/36	–
Pirfenidone	0/4	9/36	0.557
LTOT	1/4	19/36	0.605

Data are presented as absolute numbers of patients or medians and (interquartile ranges). Differences between the PM cohort and the control group were tested using the Mann-Whitney U test for continuous variables, while the χ^2 test and Fisher's exact test were used for categorical variables. n.c. = Not calculable.

^a In 1 patient of the PM cohort, symptoms and/or lung function prohibited performance of both VC% and the TLC%.

^b In 8 patients, 3 in the PM cohort and 5 in the control group, symptoms and/or lung function prohibited performance of the DLCO maneuver; thus, the median values for the PM group were not calculable.

^c In 3 patients of the control group, symptoms and/or lung function prohibited performance of PaO₂.

^d GAP categories were identified on the basis of the index calculated as suggested by Ley et al. [13], based on gender, age, and both VC% and DLCO%.

^e Concomitant or sequential treatment with corticosteroids, azathioprine, and cyclophosphamide.

54–78). One out of the 9 PM patients was in GAP stage I, 4 were in GAP stage II, and 4 were in GAP stage III. Two of the 9 PM patients received pirfenidone treatment, and the remaining 7 were treated with immunosuppressant therapy. Four of 9 PM patients received LTOT. The median time between IPF diagnosis and PM was 3 months (interquartile range: 0–33). The most common symptom among the patients experiencing PM was worsening of dyspnea in the preceding 6 weeks, occurring in 7 of the 9 patients. Deterioration of cough was noted in 4 of the 9 patients, whereas only 2 patients complained of new-onset thoracic pain. At PM presentation, the patients had a median age of 68 years (interquartile range: 58–78). At the time of PM, the patients had a median VC% of 48% (interquartile range: 23–57), a median DLCO% of 36% (interquartile range: 21–49), and a median PaO₂ of 66 mm Hg (interquartile range: 54–73). Acute IPF exacerbation was diagnosed in 2 of the 9 patients at PM occurrence,

while 7 patients did not show signs of acute exacerbation at the time of PM diagnosis. No single case of mediastinitis was identified. PM was managed with broad-spectrum antibiotics and with high-dose steroids for acute progression of the disease in 22% of the cases. No chest tube/mediastinal drainage was inserted. Three of the 9 patients died (5, 10, and 23 days after PM occurrence, respectively); the first 2 of these 3 patients exhibited concomitant IPF exacerbation. In the remaining patients, no progression of PM was observed. Patients receiving immunosuppressants who manifested PM continued the same therapeutic scheme.

The control group included 36 IPF patients (28 males and 8 females) with a median age of 69 years (interquartile range: 63–73). As in the PM group, the majority of the IPF patients in this group were non-smokers (22/36). At the time of diagnosis, the median VC% was 57% (interquartile range: 46–62), while the median DLCO% was 34%

Fig. 1. Patient suffering from IPF with new-onset dyspnea and cough. Axial MDCT image at the level of the pulmonary trunk showing diffuse parenchymal abnormalities, such as ground-glass opacity, peripheral reticulations mixed with interlobular septal thickening, and honeycombing areas. PM was documented in the anterior and middle mediastinal compartments (arrowheads) as defined by Felson [32]; air outlined the peribronchovascular bundle (interstitial emphysema) along the posterior subsegmental bronchi of the right upper lobe (arrows).

(interquartile range: 27–42). The controls showed a median PaO_2 of 62 mm Hg (interquartile range: 55–73). Four of 36 controls were in GAP stage I, 16 were in GAP stage II, and 16 were in GAP stage III. Immunosuppressant therapy was used in 27 of the 36 controls, whereas the remaining 9 patients were treated with pirfenidone. Nineteen of the 36 controls received LTOT. Detailed data about demographics, smoking history, functional status, and therapy in the PM group and in the controls are summarized in table 1. No significant differences were found between the PM and the control group at IPF diagnosis with regard to age ($p = 0.706$), gender ($p = 0.666$), smoking history ($p = 0.456$), functional impairment ($\text{VC}\%$, $p = 0.958$; $\text{DLCO}\%$, $p = 0.213$; PaO_2 , $p = 0.382$), GAP stage ($p = 1.000$), therapy ($p = 1.000$), and LTOT ($p = 0.722$).

In a subgroup analysis, PM was detected at the time of IPF diagnosis in 4 of the 9 PM patients. Table 2 shows a summary of the demographics, smoking history, functional status, and therapy for the patients with concomitant PM and IPF diagnosis. Also this group was similar to the control group with regard to age ($p = 0.913$), gender

Fig. 2. Kaplan-Meier estimates of OS for controls and PM patients with IPF. Although not significantly different ($p = 0.282$), the Kaplan-Meier curves show a trend for worse survival in the PM group (median OS: 20 months; 95% CI: 0–40) compared to the control group (median OS: 39 months; 95% CI: 27–51).

($p = 1.000$), smoking history ($p = 1.000$), functional impairment ($\text{VC}\%$, $p = 0.433$; $\text{DLCO}\%$, $p = 0.213$; PaO_2 , $p = 0.795$), GAP stage ($p = 1.000$), therapy ($p = 0.557$), and LTOT ($p = 0.605$).

Radiological Analysis

Mediastinal air was in the anterior compartment in 8 of the 9 PM patients, in the middle compartment in 5 cases, and in the posterior compartment in 4 cases. In 6 of the 9 patients, PM was found in two compartments, while 2 patients showed air located in all three zones simultaneously. Air dissection of the visceral sheaths was detected along the esophagotracheal space in 6 of the 9 patients, along the peribronchovascular sheaths in 5 patients, and along the cephalic vessels in 4 patients (fig. 1). Six of the 9 patients with PM underwent chest X-ray in two planes in the upright position within a median time of 2 days (interquartile range: 1–3) prior to MDCT. Mediastinal air was detectable during the retrospective review of the images only in 2 of the 9 patients.

Fig. 3. Kaplan-Meier estimates showing a median OS of 11 months (95% CI: 0–29) for patients experiencing PM at the time of IPF diagnosis, which is significantly worse ($p = 0.035$) than in the control group (median OS: 39 months; 95% CI: 27–51).

Survival Analysis

The median OS of the entire patient cohort analyzed ($n = 45$ patients) was 36 months (95% CI: 28–44). Although not significantly different ($p = 0.282$), the Kaplan-Meier curves (fig. 2) showed a trend for worse survival in the PM group (median OS: 20 months; 95% CI: 0–40) than in the control group (median OS: 39 months; 95% CI: 27–51). However, PM occurrence was significantly associated with poorer survival and proved to be an independent predictor of survival in Cox regression (table 3) both by univariate (HR: 3.1; 95% CI: 1.1–8.7; $p = 0.033$) and multivariate analysis (HR: 3.0; 95% CI: 1.1–8.3; $p = 0.032$).

Patients experiencing PM at the time of diagnosis ($n = 4$) had a median OS of 11 months (95% CI: 0–29), which was significantly worse ($p = 0.035$) than in the control group (median OS: 39 months; 95% CI: 27–51) (fig. 3). This finding was confirmed by Cox regression analysis (table 4), which demonstrated that PM occurrence was an independent predictor of survival by univariate (HR: 6.9; 95% CI: 1.6–29.1; $p = 0.009$) and multivariate analysis (HR: 6.4; 95% CI: 1.7–24.5; $p = 0.007$).

Table 3. Univariate and multivariate Cox proportional-hazards regression analysis results considering the overall cohort of patients ($n = 45$)

	HR	95% CI	p value
<i>Cox univariate results</i>			
Occurrence of PM	3.1	1.1–8.7	0.033
Age (>62 years) ^a	1.2	0.5–2.7	0.672
Gender (female)	1.6	0.7–3.8	0.309
Smoking history (current or former)	1.4	0.7–3.1	0.354
VC% (>57%) ^{a,b}	1.3	0.6–3.0	0.528
Therapy (immunosuppressants) ^c	3.2	0.8–11.7	0.085
<i>Cox multivariate results</i>			
Occurrence of PM	3.0	1.1–8.3	0.032
Therapy (immunosuppressants) ^c	2.9	0.9–9.7	0.081

Statistically significant predictors according to Cox proportional-hazards analysis are set in italics.

^a Thresholds separating categories for a given predictor were defined based on the quartiles of their distributions.

^b In 3 patients of the PM group, symptoms and/or lung function prohibited performance of VC%.

^c Concomitant or sequential treatment with corticosteroids, azathioprine, and cyclophosphamide.

Discussion

Our study demonstrates that PM is a rare but serious event during the course of disease in IPF patients. The incidence of PM in IPF patients as reported here is in line with prior series. A similar incidence was detected by Franquet et al. [33], who identified PM in 4 of 78 patients with IPF (5%). In two studies, the incidence of PM in IPF patients was reported to be slightly higher. Fujiwara [26] reported an incidence of 15% in a heterogeneous study population including patients with the usual interstitial pneumonia pattern other than IPF and connective tissue disease associated with fibrotic lung disease. In another series, the marginally higher incidence of PM (12%) in IPF patients was potentially related to the design of the study, based on the longitudinal observation of each patient using MDCT; in addition, no data about the functional impairment of PM patients were detailed in the study by Iwasawa et al. [34]. Yet, none of these studies reported on the impact of PM on survival in IPF patients.

Our results indicate that PM is a potential predictor of mortality in IPF patients. To the best of our knowledge, this is the first study demonstrating an independent association between PM and mortality in IPF. Furthermore,

Table 4. Univariate and multivariate Cox proportional-hazards regression analysis results considering the control group and the patients experiencing PM at IPF diagnosis (n = 40)

	HR	95% CI	p value
<i>Cox univariate results</i>			
Occurrence of PM	6.9	1.6–29.1	0.009
Age (>62 years) ^a	1.2	0.4–3.4	0.828
Gender (female)	1.5	0.6–3.8	0.453
Smoking history (current or former)	1.7	0.8–3.8	0.199
VC% (≤45%) ^{a, b}	1.2	0.5–2.9	0.789
Therapy (immunosuppressants) ^c	2.2	0.6–7.8	0.213
<i>Cox multivariate results</i>			
Occurrence of PM	6.4	1.7–24.5	0.007
Smoking history (current or former)	1.7	0.8–3.6	0.163
Therapy (immunosuppressants) ^c	2.9	0.9–9.7	0.081

Statistically significant predictors according to Cox proportional-hazard analysis are set in italics.

^a Thresholds separating categories for a given predictor were defined based on the quartiles of their distributions.

^b In 1 patient of the PM group, symptoms and/or lung function prohibited performance of the pulmonary function tests.

^c Concomitant or sequential treatment with corticosteroids, azathioprine, and cyclophosphamide.

we could demonstrate that most patients die shortly after the occurrence of PM. A comparable observation was described in the study by Fujiwara [26], in which 4 of 5 patients died within 6 months after the occurrence of PM. Similarly, the poor outcome of air leak syndromes, mainly pneumothorax or PM in different interstitial lung diseases, has already been described before. IPF patients presenting with pneumothorax had a detrimental prognosis in two prior studies [34, 35]. In a study by Oda et al. [36], all patients suffering from pleuroparenchymal fibroelastosis died from chronic respiratory failure with recurrent pneumothorax or PM.

PM can be either spontaneous or secondary [37]. Besides fibrotic interstitial lung diseases such as IPF, also asthma, emphysema, and bronchiectasis are common conditions predisposing to spontaneous PM development [33, 38]. The first theory of spontaneous PM pathogenesis was proposed by Macklin, who described the ‘Macklin effect’ [39]. According to his hypothesis, a sudden change in intrathoracic pressure may lead to an increase in intra-alveolar pressure, which results in rupture of the terminal alveoli. The pleura remains intact and air

dissects the pulmonary interstitium and peribronchovascular sheaths, migrating toward the mediastinum down a pressure gradient. In the present study, air along the peribronchovascular sheaths was detected in 5 of 9 patients, which could represent an anatomical equivalent of the pathogenetic PM mechanism described by Macklin [39]. Furthermore, the predominant location of air in the anterior mediastinum described in the present study was reported in a prior series as well [36]. Indeed, Ho et al. [37] demonstrated that the presence of air in the anterior mediastinal space favors a diagnosis of spontaneous PM in a population mainly composed of patients affected by interstitial lung disease. Other conditions are related to the development of PM [37]. For example, Boerhaave’s syndrome is a rare condition characterized by spontaneous esophageal rupture, caused by forceful emesis against the closed cricopharyngeus muscle [40]. Mortality rates with this condition exceed 90% if left untreated, and have been reported to be around 20% even after appropriate surgical/endoscopic management [40]. In these cases, the cause of death is primarily overwhelming sepsis associated with mediastinal and pleural contamination [40].

Our study has several limitations. First, it was a retrospective single-center study, and the number of IPF patients with PM was small. However, PM is a rare complication of IPF; thus, a prospective study design is difficult. In addition, the PM patients received different treatments, and this could affect patients’ prognosis. Second, while the groups were similar with regard to patient characteristics, other variables may have influenced our results, such as comorbidities or the concurrent use of drugs such as anticoagulants or antiacid drugs. Third, although not statistically significant, VC% differed to some extent between groups. Yet, percent predicted of TLC, an often accepted measure of the extent of a restrictive lung disease, was very similar across groups.

In conclusion, spontaneous PM is a rare but serious complication in patients with IPF, associated with an unfavorable outcome. As an independent risk factor, PM may be considered as a potential predictor of mortality in IPF. Additional investigations into the pathophysiology of PM occurrence in IPF are required to identify predisposing conditions and the possibility of prevention and treatment of PM in patients with IPF.

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