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# Interstitial lung disease: Retrospective study of the prognostic impact of acute exacerbations

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**Abstract.** *Background:* Interstitial lung diseases have high mortality associated with hospitalization for decompensation. There are doubts about the factors involved in the progression of fibrosis, for example the role played by acute exacerbations. With this work, the authors intend to analyze whether there are predictive parameters of mortality related to exacerbations. *Methods:* A retrospective study was carried out of patients admitted to the Pulmonology department of Coimbra University Hospital Center for exacerbation of fibrosing lung disease between January 2019 and December 2020. These were classified as: idiopathic pulmonary fibrosis (IPF), fibrosing hypersensivity pneumonitis (FHP) and other fibrosing lung diseases. Statistical analysis was performed using SPSS 26.0 considering statistically significant p<0.05 values. *Results:* The results show that IPF is associated with longer hospital stay in relation to fibrosing HP and other fibrosing lung diseases mean of 20.93 days (95% CI: 14.69-27.18) vs 11.8 days (95% CI: 1.05-17.22, p=0.023) vs 12.23 days (95% CI: 2.06-15.34, p=0.007), respectively. Regarding mortality, there was no difference between IPF, PH and other fibrosing diseases (p=0.631). *Conclusion:* This study demonstrated that IPF, compared to PH and other fibrosing diseases, is associated with longer hospital stays, probably due to its progressive course despite the institution of corticosteroid therapy. As shown in previous studies, it was concluded that there is no difference in terms of mortality between IPF exacerbations and other forms of fibrosing lung disease.

**Key words:** interstitial lung disease, pulmonary fibrosis, acute exacerbation

## Introduction

Interstitial lung diseases (ILD) are a group of diseases that diffusely affect the lung parenchyma and present high morbidity and mortality associated with hospitalization. Biomarkers have been proposed with the aim of predicting prognosis among patients with the same condition. Comorbidities are also recognized as crucial factors in the clinical course of these patients, so their early identification and treatment allow the prevention of frequent decompensations (1). Even so, there are doubts about factors involved in the progression of pulmonary fibrosis (PF), for example the role played by acute exacerbations (AE). Among the most studied possible causes of AE are infectious ones, as these patients are more predisposed to opportunistic infections given the immunosuppressive therapies to which they are subject (2). On the other hand, in *post mortem* analyses, clinically unidentified infections are described in about one third. According to Natalya Azadeh et. al., there is no difference in terms of mortality associated with AE between patients with Idiopathic pulmonary fibrosis (IPF) and other forms of fibrosing lung disease (2). With this work, the authors intend to analyze whether there are predictive parameters of mortality related to acute exacerbation and stratify patients according to the severity of their condition upon admission.

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## Material and methods

A retrospective study was carried out of patients admitted to the Pulmonology department of Coimbra University Hospital Center for exacerbation of fibrosing lung disease between January 2019 and December 2020. These were classified as: idiopathic pulmonary fibrosis (IPF), fibrotic hypersensitivity pneumonitis (fHP) and other fibrosing lung diseases (FLD). This survey resulted in 124 patients, however de following exclusion criteria were applied: patients with fibrosing lung diseases but whose reason for hospitalization was not an exacerbation of the disease; patients with pulmonary thromboembolism; cardiac insufficiency and patients admitted to departments other than pulmonology. The following data were collected: age, sex, days of hospitalization, comorbidities, smoking habits, isolated microorganisms, C-reactive protein (CRP) and gasometric values on admission, if they were taking immunosuppressants, use of non-invasive ventilation (NIV) at admission, peripheral saturation values at admission and deaths. Categorical variables are expressed in frequency (percentage) and proportions were compared using chi-square test. To compare continuous variables, the *One-Way Anova* test was used. The descriptive analysis is represented by the median (interquartile range-IIQ) according to the *Kolmogorov –Smirnov* normality test. To determine predictive factors of mortality and need for NIV during hospitalization, a binary logistic regression was used. In the univariate model to identify predictive factors of death during hospitalization, the following variables were studied: age, gender, other FLD subgroup, immunosuppression, NIV, PaCO2 and CRP at admission, antibiotic therapy, history of obstructive sleep apnea (OSA), cardiac pathology, previous exacerbations and smoking history. In the univariate model to determine predictive factors of need for NIV during hospitalization, the following variables were studied: other FLD subgroup, cardiac pathology, OSA, chronic respiratory failure and immunosuppression. In the multivariate model, variables with $p<0.10$ in the univariate analysis were included. Statistical analysis was performed using SPSS 26.0 considering statically significant $p<0.05$ values.

## Results

The study included 73 patients, with a median age of 76.0 (IIQ 14 years), 27 (37.0%) patients were female and 46 (63.0%) were male, of which 15 (20.5%) had FPI, 15 (20.5%) had fHP and 43 (58.9%) had other FLD: unclassifiable PF (n=17), drug-induced PF (n=2), PF related with autoimmune diseases (n=9), PF secondary to diffuse alveolar hemorrhage (n=1), radiation-induced PF (n=2), organizing pneumonia progressing to fibrosis (n=1), NSIP (n=3), sarcoidosis (n=6), RBILD (n=1), DIP (n=1). Thirty-one patients (42.5%) were on immunosuppressive therapy and 8 (11.0%) on antifibrotics. With regard to personal history, the following stand out: OSA (n=10, 13.7%), heart failure (n=33, 45.2%), chronic respiratory failure (n=51, 69.9%), previous exacerbations (n=32, 43.8 %) and smoking (n=32, 43.8%).

The main reason for hospitalization was infectious exacerbation (n=65, 89.0%), with a median length of stay of 11 (IQI of 11 days). The most frequently isolated microorganisms were Sthaphylococcus aureus (n=5), Klebsiella pneumoniae (n=5), Streptococcus pneumoniae (n=3), Pseudomonas aeruginosa (n=2) and Serratia marcescens (n=2). In 50 patients, no microorganisms were isolated in the sputum.

The results show that IPF is significantly associated with a longer hospital stay for fHP and other FLD mean of 20.93 days (95% CI: 14.69-27.18) vs 11.8 days (95% CI: 1.05-17.22 , p=0.023) vs 12.23 days (95% CI: 2.06-15.34, p=0.007), respectively. With regard to mortality, there was no statistically significant difference between IPF (53.3%), fHP (46.7%) and other FLD (46.9%) as a group (p=0.631). However, looking individually within "other FLD", only 16,6% of patients with sarcoidosis died. Unclassifiable PF had the highest mortality in this group (52.9%), followed by drug-induced PF (50%) and PF secondary to autoimmune diseases (44.4%). Looking at readmissions, it was found that IPF had the highest percentage of patients readmitted within 30 days after discharge (46.2%), followed by fHP (36.4%) and sarcoidosis (20%).

In the multivariate analysis (Table 1), we concluded that NIV during hospitalization is an independent predictor of mortality OR=5.8 (95% CI: 1.1-30.1), p=0.036. The main indication for initiating NIV during hospitalization was respiratory failure, with cases of both hypoxemic (n=44 patients; 60.3%) and hypercapnic (n=24, 32.9%) being observed. For each increase of 1 mmHg in PaO2 on admission there is protection against death during

**Table 1.** Predictive factors of mortality in acute exacerbation.

| ariables | OR – univariate analysis | IC 95% | p | OR – multivariate analysis | IC 95% | p |
|---|---|---|---|---|---|---|
| **Age** | 1,04 | 0,99-1,1 | 0,128 | | | |
| **NIMV** | | | | | | |
| No | Reference | | | | | |
| Yes | 5,77 | 1,43-23,2 | 0,014 | **5,81** | 1,12-30,09 | 0,036 |
| **Gender** | | | | | | |
| Female | Reference | | | | | |
| Male | 2,59 | 0,95-7,10 | 0,064 | | | |
| **Previous exacerbations** | | | | | | |
| No | Reference | | | | | |
| Yes | 2,48 | 0,96-6,42 | 0,061 | | | |
| **Cardiac pathology** | | | | | | |
| No | Reference | | | | | |
| Yes | 1,77 | 0,69-4,52 | 0,231 | | | |
| **Smoking** | | | | | | |
| Não | Reference | | | | | |
| Sim | 1,56 | 0,61-3,98 | 0,349 | | | |
| **Imunossuppressive therapy** | | | | | | |
| No | Reference | | | | | |
| Yes | 0,695 | 0,27-1,78 | 0,449 | | | |
| **IPF** | Reference | | | | | |
| fHP | 0.76 | 0,18-3,21 | 0,715 | | | |
| Other fibrosing lung diseases | 0.57 | 0,18-1,87 | 0,355 | | | |
| **Obstructive sleep apnea** | | | | | | |
| No | Reference | | | | | |
| Yes | 2,135 | 0,55-8,33 | 0,275 | | | |
| **PCO** | 1,01 | 0,97-1,06 | 0,639 | | | |
| **PaO2** | 0,95 | 0,91-0,99 | 0,009 | **0,93** | 0,89-0,99 | 0,020 |
| **PaCO2** | 1,02 | 0,97-1,06 | 0,523 | | | |

A*bbreviations*: NIMV- noninvasive mechanical ventilation; IPF- idiopathic pulmonary fibrosis; HPf- fibrotic hypersensitivity pneumonitis; PaO2- partial pressure of oxygen; PaCO2- partial pressure of carbon dioxide.

hospitalization, adjusted for relevant clinical variables such as age, gender, immunosuppression, subgroup of fibrosing lung disease, cardiac pathology and history of exacerbations (OR=0.9, 95% CI: 0.89-0.99, p=0.020). In the multivariate analysis, cardiac pathology and OSA are predictive factors for NIV during hospitalization (OR= 5.6, 95% CI: 1.2-26.2, p=0.029; OR=12.5, 95% CI: 2.4-63.8, p=0.002), regardless of the FLD subgroup, immunosuppression status or chronic respiratory failure.

## Discussion

IPF is a progressive disease, characterized by episodes of decompensation with accentuated decline in lung function, impaired gas exchange and consequent worsening of symptoms. It has an average survival time from diagnosis of only 3 years (3). This study demonstrated that IPF, compared to fHP and other FLD, is associated with longer hospital stays, probably due to its progressive course despite the

institution of corticosteroid therapy, especially during the decompensation phase (4). IPF also had the highest rate of readmissions, which has already been observed in previous studies conducted in this field, where a respiratory-related readmission was shown to be an independent risk factor for mortality (5). NIV during hospitalization proved to be an independent predictive factor of mortality, perhaps since these patients present with more severe respiratory failure and, therefore, already present a worse prognosis. In a study conducted by Salonen J. et al (2023), it was found that NIV and a low pO2/FiO2 ratio are associated with increased mortality in AE of interstitial lung disease, which is consistent with our findings (5). The coexistence of cardiac pathology and OSA was identified as a predictive factor for the need for NIV, so we can assume that these comorbidities condition more severe decompensations and, indirectly, contribute to mortality in these patients. These results are corroborated by the literature, which states that prolonged hospitalization and need for mechanical ventilation are responsible for a worse prognosis (6). Ba C. et al (2024) stated in a retrospective study that IPF-AE had more respiratory failure on admission and comorbidities such as cardiac pathology, having an in-hospital mortality rate greater than 50% (7). Surprisingly, the state of immunosuppression in patients receiving corticosteroids or biologics, despite the recognized predisposition to complicated infections, did not prove to have any prognostic significance. Faverio P. et al (2021) conducted a study whose results showed that increased inflammatory markers, such as CRP and neutrophils, carry a worse prognosis, supporting that there's a role for inflammation in the pathogenesis of AE (6). In relation to these findings, this work also argues that AE from ILD not IPF have a better prognosis because they have lower levels of inflammation (8). The clinical trials that proved the effectiveness of the antifibrotic nintedanib in delaying the progression of IPF also led to the conclusion that there is also a reduction in the time until the first exacerbation (6). However, nintedanib was not associated with longer survival after exacerbation (9). A limitation of our study is the small number of patients, mainly under antifibrotic treatment (only 8 patients), so it was not possible to assess the real impact of that therapy about ILD-AE.

**Conflict of Interest**: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

**Author Contributions:** writing-original draft: JP; data base and review: AIS; statistical analysis: JC, design, review and approval of the work: SF.

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