Acute exacerbations of idiopathic pulmonary fibrosis: Does clinical stratification or steroid treatment matter?

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Abstract

Acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) is defined as a sudden acceleration of the disease with the appearance of pulmonary infiltrates superimposed on the characteristic pattern of IPF that leads to a significant decline in lung function. It has high in-hospital mortality rates, despite medical treatment with systematic steroids. We sought to investigate whether there were in-hospital mortality differences according to clinical stratification (AE, suspected AE, or AE of known cause) and/or treatment with systemic steroids. We reviewed the clinical characteristics and outcomes of patients with IPF admitted to our hospital during the years 2003–2014 due to a worsening of their clinical status. We identified 50 IPF patients, 9 with AE (18%), 12 with suspected exacerbation (24%), and 29 with AE of known cause (58%), mostly respiratory infections. In-hospital mortality was similar in the three groups (33% vs. 17% vs. 34%, respectively). Likewise, we did not find differences between them with respect to the use of systemic steroids (length of treatment duration or total dose). Nevertheless, there was an independent association between in-hospital mortality and high average daily steroid dose. We did not observe significant differences in prognosis or use of systemic steroids according to current diagnostic stratification groups in patients hospitalized because of an exacerbation of IPF.

Keywords

Idiopathic pulmonary fibrosis, usual interstitial pneumonia, acute exacerbation, corticosteroid therapy

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive disease with an estimated prevalence of 13–20 cases/100,000 inhabitants[1] and a high in-hospital mortality rate (50% at 5 years after the diagnosis).[2] Exacerbations of IPF can occur at any stage during the evolution of the disease, have an incidence of 5–10% per year, and are associated with an in-hospital mortality rate that ranges between 50% and 80%.[3,4]

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Because the biological mechanisms underlying IPF exacerbations are unknown, there are no specific diagnostic biomarkers. In 2007, a consensus statement proposed the following diagnostic criteria for IPF exacerbations: (1) a previous or concurrent diagnosis of IPF; (2) unexplained worsening of dyspnea within the past 30 days; (3) high-resolution computed tomography (HRCT) showing the appearance of new pulmonary infiltrates in addition to usual interstitial pneumonia (UIP) radiological pattern, in the absence of lung infections or alternative causes of clinical deterioration; and (4) exclusion of alternative causes, including pulmonary infection by endotracheal aspirate or bronchoalveolar lavage. Yet, because in clinical practice these criteria are sometimes difficult to fulfill, some experts proposed an alternative diagnostic category (suspected acute exacerbation (SAE)) for those patients who do not meet all four criteria, but in whom no other known cause could be established. This definition was in fact tested in a cohort of patients from the Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF) clinical trial, and it was observed that patients with SAE were clinically indistinguishable from those with a definitive diagnosis of acute exacerbation (AE) of IPF.[5] Recently, an international working group report[6] has proposed a new definition where "etiology" is no longer requested among these criteria in the diagnosis, so there may be AE of known etiology (AEKE). The applicability and impact of these new definitions have not yet been tested in a "real" clinical setting.

High doses of systemic corticosteroids is the recommended treatment for AEs of IPF.[2] Yet this recommendation is not based on any randomized clinical trials.[2,3] Furthermore, given that corticosteroids increase in-hospital mortality in stable IPF patients,[7] the treatment has been criticized.[8]

This study sought to: (1) compare the clinical characteristics and in-hospital mortality rates of hospitalized patients with AE, SAE, or AEKE and (2) investigate potential differential effects of systemic steroid treatment in these three groups of IPF patients.

Materials and methods

Study design and ethics

This is a retrospective, observational, uncontrolled analysis of electronic medical records (EMR) of patients hospitalized in the Hospital Clinic (Barcelona, Spain) due to exacerbation of IPF (see diagnostic criteria below). This analysis was approved by the Ethics Committee of our institution.

Population studied

Patients were identified by reviewing the discharge EMRs of our hospital from 2003 until 2014 using three different International Classification of Diseases (ICD) codes for IPF: 515 (post-inflammatory pulmonary fibrosis), 516.3 (idiopathic interstitial pneumonia), and 516.8 (alveolar lung disease or other interstitial pneumonia). Patients with planned hospital admissions were excluded from analysis. Likewise, patients with an active malignant neoplasm at admission, HIV infection, severe immunosuppression resulting from bone marrow transplantation or solid organ transplant, and severe hematological diseases were also excluded. HRCT scans and lung pathology samples were reviewed by the authors, and diagnosis of IPF was confirmed following the multidisciplinary international guidelines of IPF.[2]

Patient stratification

On the basis of clinical information, HRCT findings, pathological diagnosis, and following multidisciplinary consensus, patients were stratified in three groups[3,5]: (1) AE (previous or concurrent diagnosis of IPF, unexplained worsening dyspnea within 30 days prior to admission, and the appearance of new pulmonary infiltrates added to UIP radiological pattern with the absence of lung infections or alternative causes of clinical deterioration of the patient condition), (2) SAE (worsening or unexplained dyspnea within 30 days prior to admission but without the fulfillment of all the criteria of AE), and (3) AEKE (appearance or worsening of dyspnea within 30 days prior to admission that is associated to an identified cause of deterioration (respiratory infection, heart failure, and pulmonary embolism). Lower respiratory infection was defined as patients who presented fever, cough, and sputum with purulent characteristics and/or a positive respiratory microbiological culture during the first 48 hours of admission. Based on the clinical condition that hampered the performance of the fibrobronchoscopy in patients, the procedure was only performed in 2 of the 50 patients; therefore, it is possible that the proportion of exacerbation due to infectious disease could be underestimated in the study.
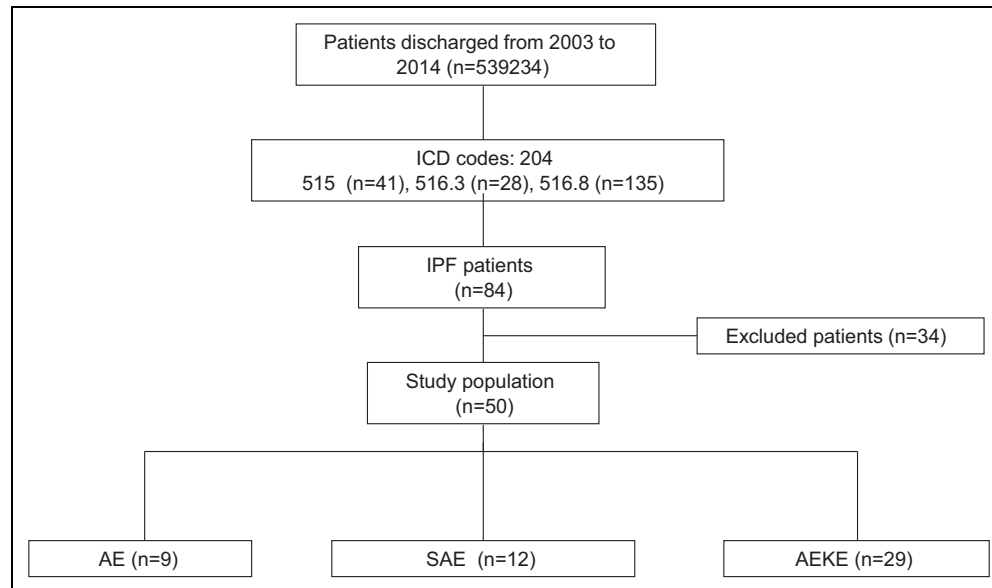
Figure 1. Schematic representation of the studied population. The main reasons for excluding patients were planned hospital admission without worsening of the respiratory symptoms ($n = 21$), patients with severe immunosuppression resulting from bone marrow transplantation or solid organ transplant ($n = 2$), severe hematological diseases ($n = 6$), and active malign neoplasm ($n = 5$). ICD: International Classification of Diseases.

Measurements

Relevant clinical, physiological, and biochemical data were collected and analyzed from the EMR of all included patients.

Statistical analysis

Categorical variables were summarized by total number and percentages, whereas in continuous variables we first performed a Kolmogorov test, those of them which followed a normal distribution were summarized by their mean and standard deviation, while those of them that did not meet this condition were expressed by their median and percentiles.

Continuous variables were compared across different groups using one-way analysis of variance, with Tukey's post hoc comparisons. In the case of continuous variables which did not follow a normal distribution, we used a nonparametric test (Mann–Whitney U). Categorical variables were contrasted using the χ^2 test or Fisher's exact tests.

To rule out factors that could affect the association between in-hospital mortality and corticosteroids dose, a multivariate logistic regression analysis was performed (conditional stepwise forward model, $p_{in} < 0.10$, $p_{out} < 0.05$), the results being adjusted for the following variables: age, gender, forced vital capacity (FVC), pulmonary gas exchange (PaFiO$_2$)

before exacerbation, average daily dose of corticosteroids, and antibiotic therapy received during the patients hospital stay.

In-hospital mortality was analyzed during the hospital stay and 1 year after discharge. Receiver operating characteristics (ROC) curves were used to determine the optimal cutoff values of daily corticosteroids dose in relation to in-hospital mortality. Multivariate analyses of 1-year survival were performed with Cox proportional hazard regression. A conditional stepwise forward model ($p_{in} < 0.10$, $p_{out} < 0.05$) was used to correct for colinearity, and adjusted odds ratios and 95% confidence intervals were computed for variables independently associated with these events in all multivariate analyses. The value of $p < 0.05$ was considered statistically significant.

Results

Figure 1 presents the consort diagram of the study. We finally included in the analysis a total of 50 patients, 9 of whom had AE (18%), 12 SAE (24%), and 29 AEKE (58%). In the latter group, 28 patients (48%) fulfilled the criteria for respiratory infection as the cause of the acute episode. In these patients, cultures were positive in only four cases (two sputum, one broncoaspirate, and one blood), with the following microbiological results: *Mycobacterirum*

Table 1. Baseline characteristics of patients (n = 50).

	AE (*n* = 9)	SAE (*n* = 12)	AEKE (*n* = 29)
Age (years), mean $\pm$ SD	77 $\pm$ 10	75 $\pm$ 9	74 $\pm$ 11
Gender female/male, *n*	4/5	4/8	8/21
Smoking status, *n* (%)			
Never smoker	4 (44)	3 (25)	12 (41)
Ex-smoker	5 (56)	9 (75)	16 (56)
Current smoker	0 (0)	0 (0)	1 (3)
Underlying diseases, *n* (%)			
Diabetes mellitus	2 (22)	2 (17)	6 (21)
Liver disease	0 (0)	1 (8)	3 (10)
Chronic heart disorders[a]	3 (33)	5 (42)	13 (45)
PFT nearest to hospitalization, mean $\pm$ SD			
FVC % predicted	59 $\pm$ 23	50 $\pm$ 13	56 $\pm$ 20
DL_{CO} % predicted	45 $\pm$ 7	32 $\pm$ 9	38 $\pm$ 15
Arterial blood gases nearest to hospitalization, mean $\pm$ SD			
PaO_2 (mmHg)	67 $\pm$ 14	66 $\pm$ 12	64 $\pm$ 14
$PaCO_2$ (mmHg)	39 $\pm$ 4	37 $\pm$ 4	38 $\pm$ 5
IPF drug therapy before hospitalization, *n* (%)			
Corticosteroids	5 (56)	8 (67)	22 (76)
Immunosuppression therapy	3 (33)	3 (25)	10 (34)

IPF: idiopathic pulmonary fibrosis; PFT: pulmonary function test; FVC: forced vital capacity; DL_{CO}: lung diffusing capacity for carbon monoxide; AE: acute exacerbation; SAE: suspected acute exacerbation; AEKE: acute exacerbation of known etiology.
[a]Chronic heart disorders include coronary artery disease, hypertensive or valvular heart diseases, and dilated myocardial disease of any cause.

tuberculosis, *Pseudomonas aeruginosa*, *Candida* spp., *Streptococcus hominis*. In one patient cardiac failure was the established cause of AEKE.

We did not find any significant difference between groups in relation to their clinical characteristics (Table 1), hospital admission-related data (Table 2), outcomes (Table 3), or 1-year survival (Figure 2), except for the fact that the number of days with respiratory symptoms before hospitalization as well as antibiotics use was higher in patients with AEKE (Table 2).

Role of corticosteroid treatment

There were no significant differences between groups with regard to the use of corticosteroids, length of treatment, total dose, or daily average dose (Table 2). However, we observed (Table 4) that higher doses of corticosteroids received during hospitalization were associated with higher in-hospital mortality (odds ratio (OR) 1.044, 95% confidence interval (CI; 1.006–1.085), $p = 0.024$). ROC curve of daily corticosteroids dose in relation to in-hospital mortality was performed (Figure 3(a)). A daily corticosteroid dose $\geq$55 mg/day had the best discriminative capacity to predict hospital

survival. Interestingly, 1 year in-hospital mortality was also higher in patients who received a daily corticosteroid dose of 55 mg/day or higher while in hospital (Figure 3(b)). Likewise, Cox regression analysis identified an association between 1-year in-hospital mortality and hospital daily corticosteroid dose (OR 1.075, 95% CI (1.044–1.107), $p <$ 0.001).

Conclusions and discussion

The main observations of this study are the following: (1) contrary to previous consensus recommendations,[3] we could not identify clinically relevant differences between AE, SAE, and AEKE and (2) there is a relationship between higher doses of systemic steroids and both during admission and 1-year in-hospital mortality.

Previous studies and interpretation of findings

Our results, in a real-world setting, showed that the relative proportion of the combined group of AE and SAE (as well as in-hospital mortality, Figure 2) was similar to that reported in the analysis of the STEP-IPF clinical trial (42% in our group vs. 51% of the STEP-IPF trial).[9] The percentage of survival was

Table 2. Hospitalization characteristics (*n* = 50).

	AE (*n* = 9)	SAE (*n* = 12)	AEKE (*n* = 29)
Days of previous respiratory symptoms before hospitalization, mean ± SD	17 ± 7	19 ± 16	9 ± 9
Arterial blood gases on admission, mean ± SD			
PaO_2 (mmHg)	63 ± 13	68 ± 23	73 ± 23
PaO_2/FiO_2	270 ± 50	239 ± 71	258 ± 88
Laboratory data on admission, mean ± SD			
C-reactive protein (mg/dL)	5.70 ± 3.10	3.10 ± 3.81	8.13 ± 7.56
White blood cell count × 10^9/L	9.62 ± 2.88	10.84 ± 3.58	11.42 ± 4.93
Bronchoscopy performed, *n* (%)	0 (0)	0 (0)	2 (7)
Drug therapy during hospitalization, *n* (%)			
Corticosteroids	8 (89)	12 (100)	27 (93)
Length of treatment (days), mean ± SD	5 ± 3	7 ± 4	7 ± 5
Total dose (mg), mean ± SD	237 ± 141	355 ± 202	289 ± 307
Average daily dose (mg/day), mean ± SD	47 ± 17	49 ± 13	40 ± 24
Antibiotics, *n* (%)			
None	7 (78)	10 (83)	2 (7)
Amoxicillin	0 (0)	1 (8)	2 (7)
Ciprofloxacin	0 (0)	0 (0)	1 (3)
Levofloxacin	2 (22)	0 (0)	14 (48)
Ceftriaxone + azithromycin	0 (0)	1 (8)	9 (31)
Tuberculosis treatment	0 (0)	0 (0)	1 (3)
Mechanical ventilation, *n* (%)			
None	9 (100)	11 (92)	26 (90)
NIV	0 (0)	1 (8)	2 (7)
Invasive MV	0 (0)	0 (0)	1 (3)

NIV: noninvasive ventilation; MV: mechanical ventilation; AE: acute exacerbation; SAE: suspected acute exacerbation; AEKE: acute exacerbation of known etiology.

Table 3. Outcome variables (*n* = 50).

	AE (*n* = 9)	SAE (*n* = 12)	AEKE (*n* = 29)	*p* Value[a]	*p* Value[b]
Months from IPF diagnosis to first hospitalization, median (range)	20 (5–67)	13 (3–44)	20 (5–49)	0.59	0.91
Hospitalization days, median (range)	4 (3–8)	7 (4–10)	6 (3–8)	0.78	0.90
Oxygen therapy at discharge, *n* (%)	4 (44)	9 (75)	19 (65)	0.34	>0.99
Palliative care at discharge, *n* (%)	1 (11)	5 (42)	8 (28)	0.30	>0.99
Hospital mortality, *n* (%)	3 (33)	2 (17)	10 (34)	0.51	0.62
New hospitalizations after 6 months from discharge, *n* (%)	3 (33)	5 (42)	12 (41)	> 0.99	>0.99

AE: acute exacerbation; SAE: suspected acute exacerbation; AEKE: acute exacerbation of known etiology; IPF: idiopathic pulmonary fibrosis.
[a]Comparisons between the three groups of the study.
[b]Comparisons between idiopathic and suspected idiopathic acute exacerbations versus acute exacerbations of known cause.

also similar compared to the study of Song et al.[4] (50% survival with steroid pulses + cytotoxic agent and 53% with steroid pulses alone) compared to our group. These observations raise questions concerning the clinical usefulness of the "old" classification.[3]

High doses of systemic corticosteroids are recommended and often prescribed in clinical practice for patients with AE of IPF, despite the fact that only a few uncontrolled studies have explored their impact.[10–14] It is noteworthy that, so far, none of them investigated its potential effect on prognosis. These recommendations have been criticized[6,8] because, first, corticosteroids are not recommended in stable IPF, where they can even increase in-hospital mortality[2] and, second, because diffuse alveolar damage
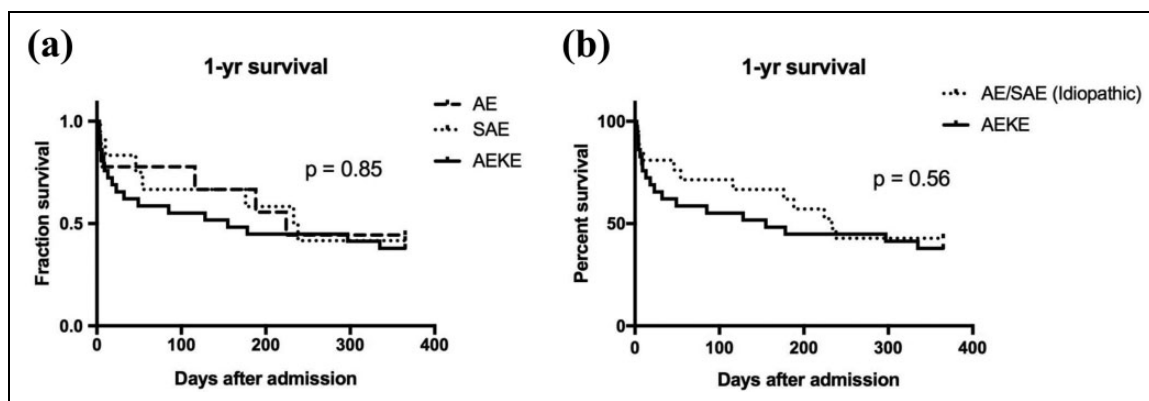
Figure 2. Survival analysis for the three definition groups. (a) Survival analysis comparing AE, SAE and AEKE (b) Survival analysis comparing idiopathic excerbation (combined AE/SAE patients) and AEKE. AE: acute exacerbation; SAE: suspected acute exacerbation; AEKE: acute exacerbation of known etiology.

Table 4. Association between corticosteroids dose and in-hospital mortality.

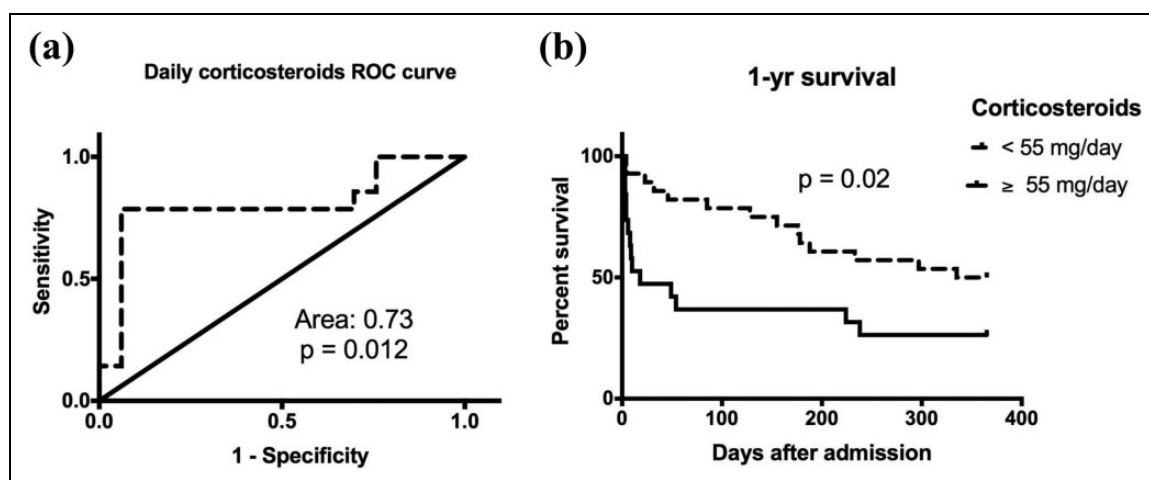|	Dead	Alive	p Value
Average daily dose (mg/day), median (25th–75th percentile)	60 (52.5–60)	40 (25–55)	0.010
Length of treatment (days), mean ± SD	5.78 ± 4.33	7.30 ± 4.90	0.32
Total corticosteroid dose (mg), median (25th–75th percentile)	280 (110–450)	240 (9.5–410)	0.584

Figure 3. (a) ROC curves of daily corticosteroids dose in relation to in-hospital mortality and (b) survival analysis between patients with high and low doses of corticosteroids. ROC: receiver operating characteristics.

(DAD) is the usual histological substrate of AE of IPF 6 and corticosteroids have proved ineffective in acute lung injury, also characterized by DAD.[8,15] In concordance with our study, in a recent observational study, patients treated previously to an AE of IPF with corticosteroids have a worst prognosis.[16] Our results lend support to the conclusion that systemic corticosteroids may be ineffective in the treatment of IPF exacerbation. In fact, despite being a relatively small size study, we observed that those patients who received higher dose of corticosteroids had higher in-hospital mortality and 1 year mortality after discharge from hospital (Figure 3). Of course, these findings may simply indicate bias by indication, since higher doses of steroids are likely to have been used in more severely ill patients; however, in the multivariate analysis, we corrected the results for the possible variables that might have influenced the

outcomes such as age, gender, and respiratory function (FVC and PaFiO$_2$).

Potential limitations

Our study has several clear limitations, most notably its retrospective, descriptive, and uncontrolled design. However, to the best of our knowledge, it is the first to explore the potential clinical relevance of the recently suggested patient stratification (AE, SAE, and AEKE), as well as the potential effects of systemic steroid treatment in both in-hospital and 1-year after discharge from hospital mortality. Likewise, our study represents the experience of a single center and has therefore a relatively small sample size. Nevertheless, our center is a national reference in intensive and specialized respiratory care of interstitial lung diseases,[17–20] so these results represent state-ofthe-art management of acute IPF exacerbation during the last 10 years.

Conclusions

Our results indicate that (1) the clinical stratification of patients in AE, SAE, and AEKE does not really identify different patient subpopulations and (2) intensive systemic steroid treatment is associated with higher in-hospital and 1-year after discharge from hospital mortality. Until novel and more specific therapies are developed and tested rigorously, our results suggest that the daily dose of prednisone in these patients should be carefully monitored during AE of IPF.

Author contributions

Dra Cuerpo and Dr Moisés had full access to all of the data related to the patients included in the study and takes responsibility for the integrity of the data analysis. Dra Hernández-González, Dra Benegas, Dr Ramirez, and Dr Sánchez contributed to the assessment of the patients included as committee members of the Interstitial Disease Unit of our hospital. Dr Agustí and Dr Sellarés contributed to the study design, data analysis, and interpretation of the results as well as the writing of the text. All co-authors reviewed and approved the submitted manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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