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Outcome of patients with interstitial lung diseases admitted to the intensive care unit

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Abstract. *Introduction:* The outcome of acute respiratory failure (ARF) affecting patients with various interstitial lung diseases (ILD) is poorly defined particularly in those with drug-induced ILD (DI-ILD). We investigated this issue focusing on fibrosing idiopathic interstitial pneumonitis (FIIP) and DI-ILD. *Methods:* We carried out a retrospective study of patients with ILD admitted in a single center ICU. The primary end-point was in-hospital mortality. *Results:* We included 72 subjects who fell into 3 diagnostic groups: DI-ILD (*n*=20), FIIP (*n*=28) and miscellaneous (M-ILD) (*n*=24). In-hospital mortality rates were 40% (*n*=8/20), 68% (*n*=19/28), and 25% (n=6/24) for DI-ILD, FIIP and M-ILD, respectively, (*p*=0.006). It reached, 64% (*n*=7/11), 100% (*n*=17/17) and 60% (*n*=6/10), respectively, in subjects on mechanical ventilation (*p*=0.007). In multivariate analysis, the need for mechanical ventilation (OR= 35; [95% CI, 5-255]), the type of ILD (FIIP *vs* miscellaneous) (OR=22; [95% CI, 3-147]) and high-dose steroids during ICU stay (OR=0.19; [95% CI, 0.04-0.99]) were independent determinants of in-hospital mortality. *Conclusion:* This study, while confirming the poor prognosis of FIIP patients in ICU, highlights the better prognosis of DI-ILD and M-ILD even though severity criteria on admission are similar in these 3 groups. These data impact on the management of these patients in ICU in whom a proper diagnostic of the underlying condition is crucial. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 134-142)*

Key words: Interstitial lung disease, fibrosing idiopathic interstitial pneumonitis, drug-induced interstitial lung disease

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Abbreviation

ARF: Acute respiratory failure
ATS: American Thoracic Society
CPFE: Combined pulmonary fibrosis and emphysema.
CVD: Collagen vascular diseases
DI-ILD: Drug-induced interstitial lung disease
ERS: European Respiratory Society
FIIP: Fibrosing idiopathic interstitial pneumonitis
HELA: High emergency lung allocation

AVD participated in the study design and the data collection and performed the statistical analysis. OS and DIB conceived the study and participated in its design and coordination. They made major contributions to the writing of the manuscript. BD, LG, DW, EG made substantial contributions to the clinical management of the patients and to the data collection. All authors read and approved the final manuscript.

ICD: International classification of diseases
ICU: Intensive care unit
ILD: Interstitial lung disease
IMV: Invasive mechanical ventilation
IPF: Idiopathic pulmonary fibrosis
M-ILD: Miscellaneous interstitial lung disease
MV: Mechanical ventilation
NIV: Non invasive ventilation
NSIP: Non specific interstitial pneumonia
PMSI: *Progamme de Médicalisation des Systèmes d'Information*
UIP: Usual interstitial pneumonia

Introduction

Interstitial lung diseases (ILDs) are heterogeneous in their etiologies, clinico-radiological presentations, histological patterns and clinical courses (1). Affected patients deteriorate because of acute exacerbations and superimposed infection; invariably in some cases acute respiratory failure (ARF) may ensue (2-6). Several studies have reported a poor prognosis for patients with idiopathic pulmonary fibrosis (IPF) patients admitted to ICU (7-12); it is suggested that these patients should not receive mechanical ventilation (MV) (7, 12). However, the situation remains unclear for ILDs other than IPF, since few studies have failed to distinguish ILD subtypes who survive from those who succumb to respiratory decompensation.

In order to identify non selected ILD patients who were likely to survive ARF, it is important to analyze the outcome of these patients admitted to ICU and describe the risk factors. It is important to distinguish between the subset of ILD patients likely to survive ARF, advocating aggressive management of those likely to have a better outcome and avoiding ventilating those patients with a poor prognosis. We investigated these issues here.

Methods

Study population

In this retrospective observational study, we reviewed all consecutive patients admitted to our ICU between July 1993 and December 2009 for ILD-associated acute respiratory failure. This study was approved by the Institutional Review Board of the *Société de Pneumologie de Langue Française*. Patients were identified from the hospital electronic PMSI (*Progamme de Médicalisation des Systèmes d'Information*) database, on the basis of ICD-10 classification. All data were retrieved from the medical records. We considered only the first ICU stay for patients with multiple admissions. The exclusion criteria were 1) primary infectious ILD (intracellular bacteria or virus-related pneumonia) and 2) incomplete medical records that prevented the verification of the diagnosis of ILD-associated ARF. All medical records were reviewed by an adjudication committee blind to the ICU outcome. ILD diagnosis was based on published criteria (1), with certain specific features used to identify drug- or radiation-induced ILD (DI-ILD) (13), collagen vascular disease (CVD)-associated ILD or vasculitis (14, 15). Fibrosing idiopathic interstitial pneumonia (FIIP) was diagnosed according to the ATS/ERS consensus definition (16-18). ILD was considered unclassifiable if the specific diagnosis was not possible on the basis of histological findings (16). For the purpose of this study, we assigned patients to three diagnostic categories: fibrosing idiopathic interstitial pneumonitis (FIIP), drug-induced ILD (DI-ILD) and miscellaneous ILD (M-ILD).

Data collection

We obtained the following data from the patients' medical records: age, sex, smoking history, comorbid conditions. PaO_2/FiO_2 ratios were calculated for all patients within the first 24 h of admission. For patients not on ventilation support (mechanical or non invasive ventilation), we used correspondence tables for oxygen rate flow/FiO_2. In order to evaluate the clinical severity and calculate predicted mortality rates at admission, we used the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (19) and the Simplified Acute Physiology Score (SAPS II) (20). ARF was considered to be post-operative or post-bronchoscopic if it occurred shortly (≤48 h) after a surgical lung biopsy or fibreoptic bronchoscopy. Acute exacerbation of ILD was diagnosed as per published criteria (2, 4).

Statistical analysis

Data are presented as means ± SD for continuous variables or counts and percentages for categori-

cal variables. For univariate analysis of the characteristics of the patients, we compared the three groups (FIIP, DI-ILD and M-ILD). We took the M-ILD group as the reference group because this group had the best prognosis and was highly heterogeneous; the other two groups were relatively homogeneous. We used Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables, to compare the three groups.

We analyzed survival by univariate analysis, using all-cause in-hospital mortality as the primary outcome. Fisher's exact test, Kaplan-Meier survival curves and the logrank test were used to compare mortality in the three groups. We then used Student's *t*-test or the Mann-Whitney *U* test and Fisher's exact test, as appropriate for continuous and categorical variables, to compare the characteristics of survivors and non-survivors. Variables considered clinically relevant and yielding p values ≤ 0.1 in univariate analysis were included in a forward multivariate logistic regression analysis taking colinearity into account, to identify the factors remaining predictive for hospital mortality. Likelihood ratio statistics were used as criteria for selection in a backward stepwise procedure. All tests were two-tailed, with p <0.05 considered statistically significant. Statistic analysis was performed with the STATA v. 11 package for Windows (StataCorp., Texas, USA).

Results

Characteristics of the study population

We identified 88 patients with ILD who were admitted to the ICU for acute respiratory failure during the study period. In total, 16 patients were excluded from the study: three had primary infection-related ILD (influenza: n=2; *Mycoplasma pneumoniae*: n=1) and 13 had incomplete medical records. The remaining 72 patients fulfilled all the inclusion criteria and were therefore included in the analysis. We assigned these patients to three groups on the basis of diagnosis: fibrosing idiopathic interstitial pneumonitis (FIIP, n=28), drug-induced ILD (DI-ILD, n=20) and miscellaneous ILD (M-ILD, n=24). The drug-induced ILD group consisted of acute drug-induced pneumonia (n=16) and chronic drug-induced ILD with a superimposed cause of ARF (n=4). The clinical characteristics of the patients and their medical management in the ICU are summarized in Tables 1 and 2.

In-hospital mortality in the three groups

Predicted mortality rates, based on APACHE II and SAPS II scores, were 26.2% and 11.7%, respectively, for the overall population. Overall all-cause in-hospital mortality was 46% (n=33/72), reaching 79% (n=30/38) in patients requiring invasive mechanical ventilation (IMV) (Table 3). Mortality was high in patients with FIIP (68% (n=19/28)) and significantly less in those with DI-ILD and M-ILD, (40% (n=8/20) and 25% (n=6/25), respectively) (p=0.006) (Table 3). Within the FIIP group, no particular CT scan pattern was indicative of outcome. Indeed, the UIP, NSIP and CPFE patterns were associated with

Table 1. Types of ILDs in the total study population

Types of ILDs	N (%)
Fibrosing idiopathic interstitial pneumonitis (FIIP)	28 (39)
UIP	16
NSIP	9
CPFE	3
Drug-induced ILD (DI-ILD)	20 (28)
Amiodarone	5
Statin	3
Docetaxel	2
Methotrexate	2
Cyclophosphamide	1
Cyclophosphamide/busulphan	1
Nitrofurantoin	1
Gemcitabine	1
Hydrochlorothiazide	1
Flutamide	1
Lenalidomide	1
Rapamycin	1
Miscellaneous ILD: (M-ILD)	24 (33)
CVD-ILD	6
Vasculitis*	5
Sarcoidosis	3
Hypersensitivity pneumonitis	3
Unclassifiable interstitial pneumonia	3
Pneumoconiosis	1
Alveolar proteinosis	1
Cryptogenic organizing pneumonia	1
Radiation-induced ILD	1

Data are expressed as the number of patients (%). ILD: interstitial lung disease; UIP: usual interstitial pneumonia; NSIP: non specific interstitial pneumonia; CPFE: combined pulmonary fibrosis and emphysema. CVD-ILD: collagen vascular disease-associated interstitial lung disease. *vasculitis includes systemic lupus erythematosus-associated vasculitis and ANCA-associated vasculitis

Table 2. Clinical characteristics and medical management of the acute episode

	Total population (n=72)	FIIP (n=28)	DI-ILDs (n=20)	M-ILDs (n=24)	*P*
Age in years, m ± SD	63 ± 17	67 ± 18	65 ± 18	58 ± 14	0.02
Male, n (%)	51 (71)	22 (79)	13 (65)	16 (67)	ns
Smokers, n (%)	40 (55)	18 (67)	9 (60)	13 (57)	ns
Known history of ILD, n (%)	44 (61)	23(82)	5 (25)	16 (67)	<0.0001**
Cause of ARF, n (%)					
AE of fibrotic ILD	12 (17)	10 (36)	0 (0)	2 (8)	<0.0001**
Pneumotoxic drug	16 (22)	0 (0)	16 (80)	0 (0)	
Superinfection with underlying ILD	18 (25)	11 (39)	2 (10)	5 (21)	
Post-biopsy or -bronchoscopy	7 (10)	4 (14)	2 (10)	1 (4)	
Other**	19 (26)	3 (11)	0 (0)	16 (67)	
HRCT pattern (n=68)					
Honeycombing, n (%)	37 (54)	24 (89)	4 (22)	9 (39)	<0.0001**
Consolidation	34 (50)	7 (26)	14 (78)	13 (57)	0.002
Ground Glasses	63 (93)	24 (89)	17 (95)	22 (96)	0.62
PaO_2/FiO_2 on admission, m ± SD	149 ± 78	141 ± 71	115 ± 44	185 ± 95	0.02*
APACHE II score, m ± SD	17 ± 7	17 ± 4	17 ± 5	18 ± 9	ns
SAPS II score, m ± SD	31 ± 15	29 ± 9	32 ± 15	32 ± 19	ns
Corticosteroid treatment, n (%)	57 (79)	20 (71)	18 (90)	19 (79)	ns
Antibiotic treatment, n (%)	60 (83)	23 (82)	17 (85)	20 (83)	ns
Intubation (MV), n (%)	38 (53)	17 (61)	11 (55)	10 (42)	ns
Ventilator support (MV or NIV)	50 (69)	18 (64)	14 (70)	18 (75)	ns
ICU stay in days, m ± SD	16 ± 19	13 ± 21	18 ± 18	19 ± 19	ns
Post ICU stay in days, m ±SD	15 ± 14	16 ± 13	17 ± 18	14 ± 12	ns

Data are expressed as the number of patients (%) or as mean ± standard deviation. ILD: interstitial lung disease; FIIP: fibrosing idiopathic interstitial pneumonitis; DI-ILD: drug-induced ILD; M-ILD: miscellaneous ILD; ICU: intensive care unit; ARF: acute respiratory failure; AE: acute exacerbation. MV: mechanical ventilation; NIV: non invasive ventilation. ns: not significant (p>0.05).
*significant p value obtained in Kruskal-Wallis test comparing the 3 groups **significant p value obtained in Fisher's exact test comparing the 3 groups.
** other causes of ARF were as followed: acute pulmonary vascularitis (n=4), corticosteroid treatment interruption (n=3), hypersensitivity pneumonitis (n=3), radiation induced pneumonia (n=1), pulmonary hypertension (n=1), pulmonary embolism (n=1), aggravation of chronic ILD such as sarcoidosis, organized pneumonia, asbestosis, alveolar proteinosis (n=7).

similar in-hospital mortality rates (68% (n=10/16), 78% (n=7/9) and 67% (n=2/3), respectively; p=0.84). The requirement for invasive mechanical ventilation was associated with an extremely poor prognosis in FIIP patients, for whom 100% mortality was observed (n=17/17), whereas it was significantly lower in the other two groups (64% (n=7/11) and 60% (n=6/10) in DI-ILD and M-ILD, respectively, p=0.007) (Table 3). All but one of the FIIP patients initially on non invasive mechanical ventilation (NIV) subsequently required intubation. The remaining patient in this group underwent lung transplantation after seven days of NIV, through an emergency procedure. All FIIP patients on invasive mechanical ventilation died in the ICU.

Kaplan-Meier analysis confirmed that survival rates were significantly higher for the DI-ILD and M-ILD groups than for the FIIP group (p=0.007; Figure 1). Finally, even after stratification of the total population for well known disease severity criteria, such as the need for ventilator support, PaO_2/FiO_2 ratio < 200 mmHg and APACHE II score > 17, FIIP patients had a higher relative risk of death in hospital than the other two groups of patients (Table 4).

Risk factors for mortality in the total population

In univariate analysis, ARF etiology, PaO_2/FiO_2 ratio, the use of mechanical ventilation and the use of corticosteroids were significantly associated with the risk of in-hospital death (Table 5). Mortality rates did not depend on the period of admission to the ICU (p=0.57).

Table 3. In-hospital mortality

	Total population (n=72)	FIIP (n=28)	DI-ILDs (n=20)	M-ILDs (n=24)	*P*
Hospital mortality, n (%, [95%CI])	33 (46,[34-58])	19 (68,[49-86])	8 (40, [16-63])	6 (25, [6-44])	0.006*
Hospital mortality in intubated patients, n (%, [95%CI]) (n=38)	30 (79,[65-92])	17 (100,[100-100])	7 (64,[30-98])	6 (60,[23-97])	0.007*
Causes of death, n (%) (n=33)					0.02*
Refractory hypoxemia	12 (36)	8 (42)	3 (38)	1 (17)	
Septic shock	14 (42)	6 (32)	5 (63)	3 (50)	
Multiple organ failure	7 (22)	5 (26)	0 (0)	2 (33)	

Data are expressed as numbers of patients (%). FIIP: fibrosing idiopathic interstitial pneumonitis; DI-ILD: drug-induced ILD; M-ILD: miscellaneous ILD; ILD: interstitial lung Disease.
*significant *p* value obtained in Fisher's exact test comparing the 3 groups.

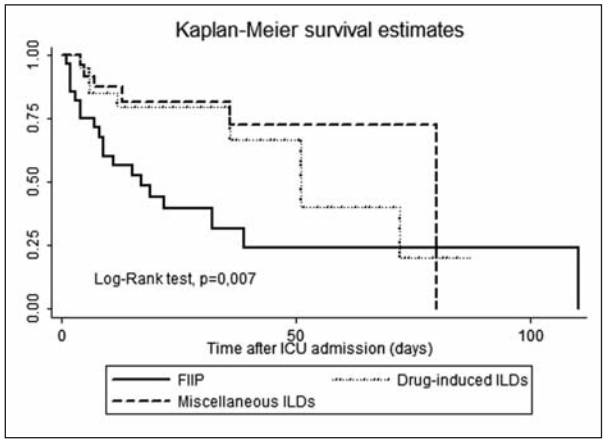

Fig. 1. Survival analysis.
In-hospital survival analyses: global logrank test, *p*=0.007; logrank test comparing FIIP and drug-induced ILDs, *p*=0.04; logrank test comparing FIIP and miscellaneous ILDs, *p*=0.007; logrank test comparing drug-induced ILDs and miscellaneous ILDs, *p*=0.41.

Multivariate logistic regression analysis identified three independent predictors of in-hospital mortality (Table 6): 1) the type of ILD (*p*=0.0002), with FIIP having the worst prognosis (OR=25; 95% CI, 4-160); DI-ILD (OR=3.8; 95%CI, 0.8-17.8) had similar prognosis to M-ILD 2) the need for mechanical ventilation (OR= 31; 95% CI, 5- 206; *p*<0.0001) and 3) the use of steroids during the acute episode. Steroid use was found to be protective (OR=0.2; 95% CI, 0.03-0.9; *p*=0.033). Despite the fact that the superinfection and the mortality rates were higher in the FIIP group, the overall cause of acute respiratory failure (acute exacerbation of fibrotic ILD, pneumotoxic drug, superinfection of underlying ILD, post-biopsy or post–bronchoscopy deterioration as well as other causes) was not an independent predictive factor for in-hospital mortality in multivariate analysis.

Discussion

The overall prognosis of patients with ILD admitted to the ICU for acute respiratory failure is widely recognized to be very poor. Most studies have

Table 4. Relative risk of death in hospital after stratification for severity criteria

	FIIP (n=28)	DI-ILDs (n=20)	M-ILDs (n=24)	*p*
If need for MV or NIV	RR= 2.8 [1.5-5.5]	RR=1.5 [0.6-3.5]	RR=1 (reference)	0.0001*
If PaO_2/FiO_2<200	RR=3.9 [1.4-11.0]	RR=2.1 [0.7-6.6]	RR=1 (reference)	0.001*
If APACHE 2 score >17 (median)	RR=3.5 [1.3-9.7]	RR=1.8 [0.5-6.0]	RR=1 (reference)	0.016*

RR: relative risk [95 % confidential interval]. FIIP: fibrosing idiopathic interstitial pneumonitis; DI-ILD: drug-induced ILD; M-ILD: miscellaneous ILD; ILD: interstitial lung disease; MV: mechanical ventilation; NIV: non invasive ventilation.
*significant *p* value obtained in Fisher's exact test comparing the 3 groups.

Table 5. Characteristics of survivors and non survivors

	Survivors (n=39)	Non survivors (n=33)	*p*
Age, years, m ± SD	61 ± 17	66 ± 17	ns
Male, n (%)	24 (61)	27 (82)	ns
Before admission			
Smokers, n (%) (n=65)	21 (58)	19 (65)	ns
Pre-existing comorbid disease, n (%)	23 (59)	26 (79)	ns
Known history of ILD, n (%)	20 (51)	24 (73)	ns
During ICU stay			
Cause of ARF, n (%)			0.024**
AE of fibrotic ILD	7 (18)	5 (15)	
Superinfection with underlying ILD	5 (13)	13 (40)	
Post-biopsy or -bronchoscopy	2 (5)	5 (15)	
Drug-induced ILD	11 (28)	5 (15)	
Others	14 (36)	5 (15)	
HRCT pattern (n=68)			
Honeycombing, n (%)	17 (47)	20 (63)	ns
Consolidation	22 (61)	12 (38)	ns
Ground Glasses	34 (94)	29 (91)	ns
PaO_2/FiO_2 ratio on admission, m ± SD	175 ± 84	118 ± 58	0.0017*
APACHE II score, m ± SD	16 ± 6	19 ± 7	ns
IGS II score, m ± SD	28 ± 12	34 ± 17	ns
Corticosteroid treatment, n (%)	35 (90)	22 (67)	0.021**
Antibiotic treatment, n (%)	30 (77)	30 (91)	ns
Intubation (MV), n (%)	8 (20)	30 (91)	<0.0001**
Ventilator support (MV or NIV), n (%)	20 (51)	30 (91)	<0.0001**
ICU stay, m ± SD	14 ± 12	19 ± 25	ns

The data are expressed as numbers of patients (%), or as means ± standard deviation. ILD: interstitial lung disease. ICU: intensive care unit. AE: acute exacerbation. MV: mechanical ventilation. NIV: non invasive ventilation. ns: not significant (p>0.05). *P values for Student's t tests or Mann Whitney U tests are indicated, as appropriate. **P values for Fisher's exact test.

Table 6. Multiple logistic regression analysis of variables associated with in-hospital mortality

Variable	Odds ratio	95% CI	*P*
Type of ILD			0.0002*
Miscellaneous ILDs	Reference		
Drug-induced ILDs	3.8	[0.8-17.8]	
Fibrosing idiopathic interstitial pneumonitis	25.0	[3.9-159.8]	
Ventilator support (MV or NIV)	31.0	[4.7-205.9]	<0.0001*
Corticosteroids	0.2	[0.03-0.9]	0.033*

ILD: interstitial lung disease. CI: confidence interval. MV: mechanical ventilation. NIV: non invasive ventilation. ICU: intensive care unit. *Significant p value for likelihood ratio statistics.

focused on IPF and very little is known about the prognosis of patients with other types of ILDs presenting with acute respiratory failure. The need for mechanical ventilation is associated with an extremely poor prognosis, with 80-100% mortality in IPF and CVD-associated ILD patients (7-12, 21-23). This has led to suggestions that mechanical ventilation should not be used in such patients (7, 12). However, not all ILD patients prone to ARF have IPF and patients with other types of ILDs may have a different prognostic outcome. We investigated this possibility, by analyzing the outcome and risk factors

for death in a large cohort of unselected patients with ILDs admitted to the ICU.

The overall mortality rate was high (46%), largely exceeding predictions based on APACHE 2 and SAPS 2 scores. This suggests that these scores, which were developed for assessment of the severity of acute multiple organ failure, may not be reliable indicators of severity in respiratory diseases, and should therefore not be used as criteria for ICU admission in this context.

The type of ILD, the need for ventilator support (IMV or NIV) and the use of corticosteroids during ICU stay were independent predictors of in-hospital mortality. FIIP patients had the worst prognosis, even after stratification for the usual severity criteria and in Kaplan-Meier analysis of in-hospital mortality. Consistent with previous studies (5), most of the patients with FIIP presented with either an acute exacerbation of their underlying fibrosis or a superinfection. Prognosis in this context has frequently been found to be very poor, with mortality rates of 68% to 100% reported for cases in which mechanical ventilation is required (2, 3, 5, 7-12, 23). Consistent with these previous findings, we recorded mortality rates of 68% for the total FIIP group and 100% for ventilated subjects with FIIP. Given the well known severely deleterious effects of intubation on FIIP, it has been suggested that NIV should replace IMV wherever possible in IPF patients (10, 23). In our cohort, all but one of the FIIP patients initially ventilated by NIV methods subsequently required intubation. The remaining patient underwent lung transplantation after seven days of NIV. Several studies have highlighted the possible effect of ventilator settings on the outcome of intubated IPF patients (24). However, the retrospective nature of our study and changes in the ventilation settings used during the course of the study period made any reliable analysis of the effect of these settings impossible in this study. A prospective study specifically designed to evaluate optimal ventilation settings in IPF patients is clearly required. The recent development of a high emergency lung allocation (HELA) system, making emergency transplantation possible in IPF patients, has made it necessary to define these optimal conditions. Indeed, mechanical ventilation for less than seven days for acute exacerbation is now considered one of the highly restrictive criteria governing this procedure in IPF subjects with no contraindication to transplantation (25). Invasive ventilation should, therefore, no longer be ruled out systematically for IPF patients, provided that the possibility of lung transplantation has been anticipated and the appropriate work-up performed. One study has highlighted the importance of mechanical ventilation in this context (12) and it should be noted that the only subject with IPF in our series who survived NIV was the patient who underwent successful lung transplantation through the HELA procedure. It is not possible to draw firm conclusions based on a single case, but our findings are consistent with current recommendations to carry out all the necessary examinations for transplantation early in the course of the disease. The use of mechanical ventilation only in subjects in which transplantation is possible might be a reasonable approach.

Our data for the D-ILD group are quite original as no report on a large group (n=20) of patients with drug-related acute respiratory failure is currently available. Indeed, most previous studies have reported either few case reports or very small series (26-28). The severity of clinical presentation was not associated with any drug in particular. The most common CT scan patterns were diffuse ground-glass opacities or consolidation. It is noteworthy that the HRCT pattern was not an independent predictive factor of mortality in our population. Mortality was high in this group (40% overall, and as high as 64% in those requiring MV), but remained significantly lower than that of FIIP patients (p=0.006) even though both groups presented similar criteria of severity at entry. Indeed, D-ILD and FIIP patients exhibited comparable and low PaO_2/FiO_2 ratios (115±44 and 141±71 respectively, NS) and comparable and high SAPS2 score (32±15 and 29±9, respectively, NS). Noticeably, 55% of the patients with D-ILD required mechanical ventilation. Overall, these data support the aggressive clinical management of patients presenting with diffuse ground-glass opacities or with an NSIP pattern in which drug-induced toxicity cannot be ruled out.

Our reference group, the M-ILD group, which contained mostly patients with various types of CVD-ILD or vasculitis, had survival rates similar to those of the D-ILD group and significantly better than that of the FIIP group. Despite having similar severity criteria to the other groups at admission

(PaO_2/FiO_2=185±95, APACHE2=18±9, SAPS2=32±19), overall mortality in this group was low (25%) and 40% of the ventilated patients survived. Little is known about acute exacerbations of connective tissue disease-associated ILD (4, 6, 21, 29), but our data are consistent with the paucity of reports on this subject. Given that ARF is occasionally the first sign of underlying CVD-ILD has a satisfactory prognostic outcome, our data again provide support for the aggressive management of these patients, including the use of MV. The protective effect of corticosteroids should also be highlighted here. Multivariate logistic regression analysis showed their use was protective (adjusted OR=0.2; 95% CI = [0.03-0.9]), even after adjustment for confounding factors such as the type of ILD and the cause of ARF.There is currently no consensus regarding the use of corticosteroids for the treatment of acute exacerbations of IPF or other types of ILD-associated ARF. Corticosteroids are generally used, although they are reported to have only moderate, often transient beneficial effects (30) or even considered to be deleterious. Our data favor the use of steroids, once infection has been ruled out, in acute presentations of ILD. Further studies will provide definitive conclusions concerning their efficiency, safety and tolerability in this context.

Our study has several limitations. The major one is due to the length of the study period (1993-2009) during which clinical practice clearly underwent modifications. These mainly concerned the mechanical ventilation settings used in ILD patients. Other aspects of their clinical management have only been moderately impacted (antibiotics, steroids) as, in the absence of any recommendation on their use in these settings, they have been left so far to the clinicians' appreciation. We should underline here the second limitation of our study; i. e. its monocentric nature. Our choice in this matter was based upon our decision to limit differences in clinical practice frequently observed between centers. Due to the retrospective nature of our study, several data were occasionally lacking particularly the ventilator settings. However, as we stated in the results section, an extensive statistical analysis of our data showed that the outcome was not different according to the time of admission in ICU. This argues for a poor role of differences in clinical pratice in our conclusions. Finally, the limited size of this series may have resulted in a lack of power for identifying other predictive factors. However, we think that our data provide a good rationale for a prospective, multicentric study which will help to better delineate the latter.

In conclusion, this study while confirming the poor prognosis of FIIP patients in ICU highlights the better prognosis of other ILDs, namely DI-ILDs, even though severity criteria on admission are similar in all groups. Our data might suggest that ILD-associated ARF should be aggressively managed until a diagnosis of DI-ILD or of CVD-ILD has been ruled out. They might also help to provide recommendations about limitation of care in ARF occurring in IPF patients, highlighting the need to anticipate this situation with patients themselves and their care-givers during stable periods of their disease.

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