

Prognostic factors and outcome of mechanically ventilated interstitial lung disease patients

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Background The prognosis of mechanically ventilated interstitial lung disease (ILD) patients was controversial in previous studies. Identifying the factors associated with mortality could guide therapy and allow good use of ICU resources.

Aim The aim was to study the outcome of ILD mechanically ventilated patients admitted to the respiratory ICU and to demonstrate the possible factors associated with mortality in these patients.

Patients and methods The observational prospective study was carried out on ILD patients undergoing mechanical ventilation, either invasive mechanical ventilation (IMV) or noninvasive ventilation (NIV). Clinical, radiological, and outcome assessments were done for all enrolled patients. For outcome assessment, patients were classified into either survivors or nonsurvivors.

Results Twenty-one (70%) of the patients were subjected to NIV, whereas nine (30%) of them were subjected to IMV. The overall mortality rate was 53.3%. However, the mortality rate was 35% in patients with NIV, but 100% in patients with IMV. Severity assessment scores were significantly higher in nonsurvivors compared with survivors. Nonsurvivors also presented significantly with lower pH and higher PaCO₂

compared with survivors. Acute Physiology and Chronic Health Evaluation-II score greater than or equal to 18.5, Simplified Acute Physiology Score greater than or equal to 27.5, Glasgow coma scale score less than 12.5 and PaO₂/FiO₂ less than 161.5 were associated with increased risk of mortality of ILD patients.

Conclusion Mechanically ventilated ILD patients had a poor outcome. However, the survival rate of ILD patients was better on NIV than IMV. Severity assessment scores and PaO₂/FiO₂ could predict the risk of mortality in ILD patients. *Egypt J Bronchol* 2018 12:226–232

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Introduction

Interstitial lung diseases (ILDs) are a group of diseases having different etiologies and various histopathologic patterns that could impair the respiratory function. When progressive disease inflammation and extensive fibrosis of pulmonary parenchyma occur, clinical deterioration with derangement of gas exchange appears [1].

Acute or acute-on-chronic respiratory failure is a common presentation of critically ill patients with ILD admitted to the ICU. Acute deterioration may occur secondary to infections, pulmonary embolism, pneumothorax, or heart failure [1]. In about 50% of patients, the cause could not be detected and the term of acute exacerbation is used [2,3]. Either invasive or noninvasive mechanical ventilation (non-IMV) can be considered as a therapeutic option. Several studies have reported a poor prognosis for patients with idiopathic pulmonary fibrosis (IPF) admitted to the ICU [2–7]; some suggested that these patients should not receive MV [2,7]. Others suggested noninvasive ventilation (NIV) as a beneficial alternative tool [6–8].

This study aimed to study the outcome of ILD with respiratory failure in mechanically ventilated patients admitted to the respiratory ICU of the Chest

Department of Assiut University Hospital and to demonstrate the possible factors associated with mortality in these patients.

Patients and methods

That observational prospective study was carried out on ILD patients with acute respiratory failure admitted to the Respiratory Intensive Care Unit of the Chest Department of Assiut University Hospital, undergoing mechanical ventilation, either IMV or NIV over a period of 8 months. ILD patients associated with chronic obstructive pulmonary disease, and other significant respiratory and cardiovascular diseases were excluded from the study. An informed consent was obtained from the patient or his relatives for inclusion in the study. This study was approved by the medical ethics committee of Faculty of Medicine, Assiut University. Clinical, radiological, and outcome assessment were done for all enrolled patients.

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Clinical assessment

A detailed medical history was taken and physical examination was done for all patients. Baseline clinical presentation, patients' blood pressure, and baseline arterial blood gas were all recorded. Diagnosis of the ILD disease was based on diagnostic criteria of the disease. Idiopathic interstitial pneumonias were diagnosed based on the American Thoracic Society diagnostic criteria [9]. Collagen vascular diseases associated ILD was diagnosed based on the diagnostic criteria of each disease [10–17].

The reasons for acute respiratory failure were evaluated and identified as acute exacerbation of ILD [5], pneumonia [18], acute heart failure [19], pulmonary embolism [20], or pneumothorax [21]. The commonly used severity assessment scores [Acute Physiology and Chronic Health Evaluation (APACHE II), Simplified Acute Physiology Score-II (SAPS II), and MSOFA (modified-sequential organ failure assessment)] were applied for the evaluation of severity of illness on admission [22–24]. Glasgow coma scale (GCS) [25] was applied for evaluating the patient's conscious level. Patients with acute exacerbation of ILD and with acute heart failure received intravenous corticosteroids. Other patients were maintained on their previous dose of steroids.

Radiological assessment

After reviewing their high-resolution computed tomography, the patients were classified into either usual interstitial pneumonia or nonusual interstitial pneumonia pattern [26].

Assessment of treatment with mechanical ventilation

A total of 21 patients of the study population were subjected to NIV as initial therapy, whereas nine patients were subjected to IMV. NIV was applied in the presence of $\text{PaO}_2/\text{FiO}_2$ ratio of less than 200, respiratory rate of more than 30 breaths/min, or other signs of respiratory distress in the absence of respiratory acidosis ($\text{pH} < 7.35$, $\text{PaCO}_2 \geq 45$ mmHg) [6]. IMV was used with any of the following criteria: signs of respiratory exhaustion on physical examination (use of the accessory muscles of respiration with paradoxical abdominal or thoracic motion), hemodynamic instability, disturbed conscious level, cardiac arrest, or refractory hypoxemia or the presence of contraindications to NIV [6].

Mechanical ventilation settings

Both IMV and NIV were performed by Puritan Bennett 840 Ventilator (NPB 840, Puritan-Bennett/Covidien, Carlsbad, California, USA). In patients who are candidates for NIV [6], NIV was performed in

pressure support mode using oronasal mask (Respironics AF531 oronasal mask) as an interface for patients. Positive end expiratory pressure (PEEP) and inspiratory pressure were adjusted to improve gas exchange and to relieve respiratory distress and were further on modified on the basis of gasometric data [27]. Patients indicated for IMV were initially ventilated with the pressure control ventilation mode. Inspiratory pressure was adjusted to get the tidal volume from 6 to 8 ml/kg and the plateau pressure did not exceed 30 cm H_2O . Initially PEEP was adjusted to 5–7 cm H_2O as the ILD patients are at a high risk of pneumothorax. Further change on PEEP was reset in order to obtain an oxygen saturation of not less than 90% [6].

Outcome assessment

The study population was classified into one of the two groups (survivors and nonsurvivors). ICU survival was identified as the discharge of the patient from the ICU [6].

Statistical analysis

Statistical package for the social sciences (SPSS, version 16; SPSS Inc., Chicago, USA) software was used for the analysis of results. Results in this study were presented in number and percentage or mean \pm SD. The qualitative data were compared between the survivor and the nonsurvivor group using χ^2 -test, whereas independent sample *t*-test was used for comparison of quantitative data between the two groups. To assign the best cutoff for mortality-associated factors in ILD patients, collected data were analyzed using receiving operating characteristic curve. Results with a *P* value of less than 0.05 were considered significant.

Results

A total of 30 patients with ILD who were admitted to the Respiratory Intensive Care Unit during the study period were included in the study analysis, out of whom 21 (70%) patients were subjected to NIV, whereas nine (30%) patients were subjected to IMV. Patients received antibiotics according to culture and sensitivity, systemic steroids, and treatment of heart failure and other managements according to their cause of admission. The demographic and clinical characteristics data of the study group are shown in Tables 1 and 2. Among the study people, the overall mortality rate was 53.3%. Mortality rate was 35% in patients with NIV, but 100% in patients with IMV (Fig. 1).

Demographic data of survivors and nonsurvivors are shown in Table 3. No significant differences were observed between the two groups regarding the type of

Table 1 Demographic criteria of 30 patients with interstitial lung diseases

Items	n (%)
Age	40.31±14.91
Sex	
Male	6 (20)
Female	24 (80)
Smoking habit	
Smoker	6 (20)
HRCT pattern	
UIP	6 (20)
Non-UIP	24 (80)
Diagnosis	
IPF	9 (30)
Collagen vascular disease	4 (13.3)
Acute interstitial pneumonia	8 (26.7)
Extrinsic allergic alveolitis	7 (23.3)
others	2 (6.6)
Cause of ICU admission	
Pneumonia	18 (60)
Acute exacerbation	6 (20)
Pulmonary embolism	3 (10)
Heart failure	7 (23.3)
Pneumothorax	1 (3.3)
Initial mode of MV	
NIV	21 (70)
IMV	9 (30)

HRCT, high-resolution computed tomography; IMV, invasive mechanical ventilation; IPF, idiopathic pulmonary fibrosis; MV, mechanical ventilation; NIV, noninvasive ventilation; UIP, usual interstitial pneumonia.

Table 2 Baseline clinical criteria of 30 patients with interstitial lung diseases

Items	Mean±SD
Duration of ICU admission (days)	4.83±2.46
Assessment severity scores	
APACHE II score	18.83±7.3
MSOFA score	9.1±7.39
SAPS score	31.1±16.75
GCS	10.7±4.1
Baseline clinical parameters	
RR	37.7±8.8
HR	112.3±23.17
SBP	106.7±23.39
DBP	67±13.43
Baseline ABG	
pH	7.4±0.11
PaO ₂ /FiO ₂	138.1±68.9
PaCO ₂	48.33±23.68
SaO ₂	73.47±10.12

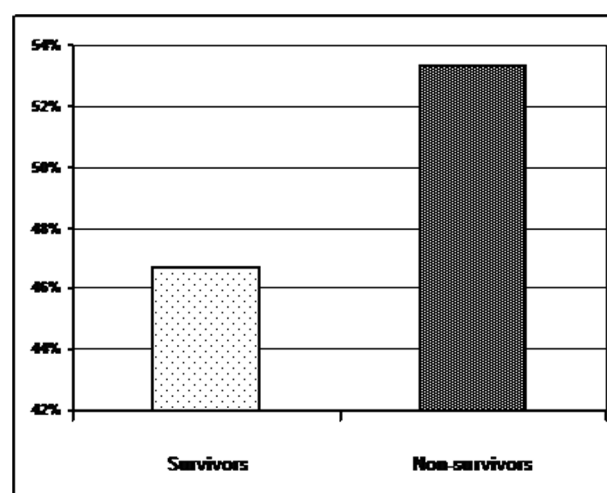
ABG, arterial blood gas; APACHE II, acute physiology and chronic health evaluation-II; DBP, diastolic blood pressure; GCS, Glasgow coma scale; HR, heart rate; MSOFA, modified-sequential organ failure assessment; PaCO₂, partial arterial carbon dioxide tension; PaO₂, partial arterial oxygen tension; RR, respiratory rate; SaO₂, arterial oxygen saturation; SAPS II, simplified acute Physiology Score-II; SBP, systolic blood pressure.

the disease or the cause of ICU admission. However, the mortality rate among patients with IMV (100%) was

Table 3 Demographic criteria of survivors and nonsurvivors group of interstitial lung disease patients (N=30)

Items	Survivors [n (%)]	Nonsurvivors [n (%)]	P value
Age	39.79±11.21	40.8±18.08	0.857
Sex			
Male	3 (18.8)	3 (21.4)	0.091
Female	13 (81.2)	11 (78.6)	
Smoking habit			
Smoker	0.000	6 (28.6)	0.092
HRCT pattern			
Non-UIP	4 (28.6)	10 (71.4)	0.272
UIP	2 (12.5)	14 (87.5)	
Diagnosis			
IPF	4 (28.6)	5 (31.2)	0.756
Collagen vascular disease	2 (14.3)	2 (12.5)	
Acute interstitial pneumonia	3 (21.4)	5 (31.2)	
Extrinsic allergic alveolitis	4 (28.6)	3 (18.8)	
Others	1 (7.1)	1 (6.2)	
Cause of ICU admission			
Pneumonia	9 (64.3)	9 (56.2)	0.540
Acute exacerbation	1 (7.1)	5 (31.2)	
Pulmonary embolism	1 (7.1)	2 (12.5)	
Heart failure	4 (28.6)	3 (18.8)	
Pneumothorax	0	1 (6.2)	
Initial mode of MV			
NIV	14 (100)	7 (43.8)	0.001*
IMV	0.00	9 (56.2)	

IMV, invasive mechanical ventilation; IPF, idiopathic pulmonary fibrosis; MV, mechanical ventilation; NIV, noninvasive ventilation; UIP, usual interstitial pneumonia; *Significant.

Figure 1

Overall outcome of ILDs patients.

significantly higher compared with patients on NIV (35%) ($P=0.001$). It was also noted that about 62.4% of nonsurvivors had IPF (31.2%) and acute interstitial pneumonia (31.2%). Furthermore APACHE II, SAPS

II, and MSOFA severity assessment scores were significantly higher in nonsurvivors compared with survivors (22.94±6.69 vs. 14.14±4.802, $P=0.002$; 39.38±17.36 vs. 21.64±9.88, $P\leq 0.001$; 12.38±8.523 vs. 5.36±3.128, $P=0.006$, respectively) and the GCS was significantly lower in nonsurvivors compared with survivors (8±3.795 vs. 13.93±1.072, $P\leq 0.001$). Regarding, gasometric parameters, nonsurvivors had significantly lower PH and higher PaCO₂ compared with survivors (7.45±0.74 vs. 7.36±0.127, $P=0.018$; 56.66±28.076 vs. 38.57±12.24 mmHg, $P=0.005$, respectively). It was also observed that the nonsurvivors have a lower PaO₂/FiO₂ ratio compared with survivors (119±48.89 vs. 159.64±83.193, $P=0.111$) (Table 4).

To determine the optimum cutoff of factors that could predict mortality among ILD patients, the data were analyzed using the receiving operating characteristic curve. An APACHE II score greater than or equal to 18.5 showed 81.2% sensitivity, 78.6% specificity with an area under the curve (AUC) of 0.859 (CI: 0.685–0.985) (Fig. 2a). MSOFA score greater than or equal to 6.5 was associated with 81.2% sensitivity, 71.4% specificity with an AUC of 0.83 (CI: 0.685–0.985) (Fig. 2b). SAPS score greater than or equal to 27.5 showed 87.5% sensitivity, 78.6% specificity with an AUC of 0.812 (CI: 0.647–0.978) (Fig. 2c). GCS less than 12.5 is associated with 87.5%

Table 4 Clinical criteria of survivors and nonsurvivors of interstitial lung disease patients (N=30)

Items	Survivors	Nonsurvivors	P value
Duration of ICU admission (days)	5.14±2.931	4.56±2.032	0.529
Assessment severity scores			
APACHE II score	14.14±4.802	22.94±6.69	<0.001*
MSOFA score	5.36±3.128	12.38±8.523	0.006*
SAPS score	21.64±9.88	39.38±17.36	0.002*
GCS	13.93±1.072	8±3.795	<0.001*
Baseline clinical parameters			
RR	36.79±8.903	38.56±8.974	0.591
HR	109.36±19.634	115±26.240	0.515
SBP	112.86±16.838	101.25±27.29	0.180
DBP	70.71±10.716	63.75±15	0.160
Baseline ABG			
pH	7.45±0.74	7.36±0.127	0.018*
PaO ₂ /FiO ₂	159.64±83.193	119±48.89	0.111
PaCO ₂	38.57±12.24	56.66±28.076	0.028*

Data were presented as mean±SD; ABG, arterial blood gas; APACHE II, acute physiology and chronic health evaluation-II; DBP, diastolic blood pressure; GCS, Glasgow coma scale; HR, heart rate; MSOFA, modified-sequential organ failure assessment; PaCO₂, partial arterial carbon dioxide tension; PaO₂, partial arterial oxygen tension; RR, respiratory rate; SaO₂, arterial oxygen saturation; SAPS II, simplified acute physiology score II; SBP, systolic blood pressure; *Significant.

sensitivity and 92.9% specificity with AUC 0.962 (CI: 0.903–1.021) (Fig. 2d). Furthermore, PaO₂/FiO₂ less than 161.5 is associated with risk of mortality of ILD patients giving 81.2% sensitivity and 50% specificity with an AUC of 0.614 (CI: 0.404–0.824) (Fig. 2e).

Discussion

Patients with ILDs may have a variable course ranging from mild symptoms that required just monitoring to advanced symptoms that required NIV or IMV [28]. However, the effectiveness of MV on the prognosis of IPF patients presenting with ARF is controversial [29,30].

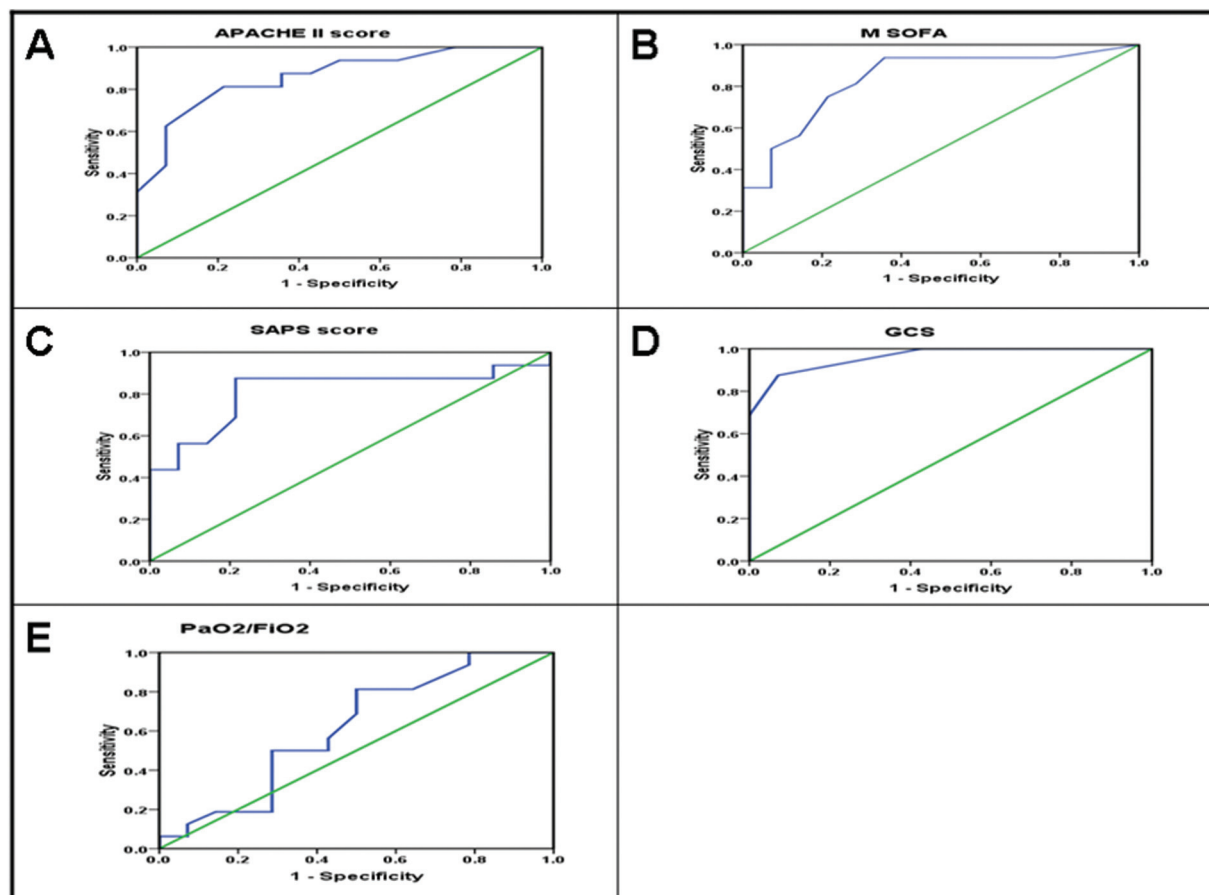
Identifying the prognostic factors as clinical disease characteristics, comorbidities, ILD patterns, reason for admission, and gasometric parameters as well as severity of the disease may be helpful in guiding therapy and allowing good use of ICU resources [28].

This study aimed to study the outcome of ILD mechanically ventilated patients admitted to the respiratory ICU of Chest Department of Assiut University Hospital and to demonstrate the possible factors associated with mortality in these patients. The most common cause of admission in the ICU in our study was pneumonia in 63.33% of cases followed by heart failure (23.3%) and acute exacerbation of IPF (20%). That was similarly reported in previous studies [31–33].

Among the study the overall mortality rate was 53.3%. Güngör *et al.* [6] and Saydain *et al.* [32] have found a mortality rate of about 60% in hospitalized ILDs patients. However, Zafrani *et al.* [34] have found a hospital mortality rate of 54%. Differences in the rate of mortality might differ according to the ILD pattern and severity of illness on admission. Furthermore, mortality rates differ with the method of ventilation used. In our study, the mortality rate was 35% in patients with NIV and 100% in patients with IMV. NIV had been found to be a viable option for the respiratory management of acute exacerbation of IPF [30]. It also could be successful in diffuse interstitial lung disease patients undergoing NIV [35]. Güngör *et al.* [6] also found that the mortality rate was 61.7% for continuous NIV versus 89.7% for invasive ventilation. Small, retrospective studies have reported survival rate in patients treated with NIV to be around 40% [30,36,37].

Although MV was considered a supportive tool for patients with acute respiratory failure, it can initiate or

Figure 2



Receiving operating curve (ROC) analysis of parameters that could predict mortality of ILDs patients. (A) ROC analysis of APACHE II score to predict mortality of ILDs patients. The optimum cut off level of APACHE II was ≥ 18.5 with 81.2% sensitivity, 78.6% specificity and an AUC of 0.859 [CI (0.647–0.978)]. (B) ROC analysis of MSOFA score to predict mortality of ILDs patients. The optimum cut off level of MSOFA score ≥ 6.5 associated with 81.2% sensitivity, 71.4% specificity and an AUC of 0.83 [CI (0.685–0.985)]. (C) ROC analysis of SAPS score to predict mortality of ILDs patients. The optimum cut off level of SAPS score ≥ 27.5 showed 87.5% sensitivity, 78.6% specificity with an AUC 0.812 [CI (0.647–0.978)]. (D) ROC analysis of GCS to predict mortality of ILDs patients. The optimum cut off level of GCS < 12.5 is associated with 87.5% sensitivity, 92.9% specificity and AUC 0.962 [CI (0.903–1.021)]. (E) ROC analysis of $\text{PaO}_2/\text{FiO}_2$ to predict mortality of ILDs patients. The optimum cut off level of $\text{PaO}_2/\text{FiO}_2 < 161.5$ giving 81.2% sensitivity, 50% specificity and AUC 0.614 [CI (0.404–0.824)].

worsen lung injury [6,34]. All nine patients who received IMV in our study eventually died. Most studies have shown that most of the patients died during MV or shortly after discharge from the ICU [38–40].

The type of ILD could affect prognosis of the disease. It was also noted that about 62% of nonsurvivors had IPF and acute interstitial pneumonia. Advanced IPF disease caused a marked decrease in dynamic and static compliance of the lungs [41]. The expected hazardous effects of intubation on IPF has suggested that NIV should replace IMV wherever possible in IPF patients [3,42].

During the last 30 years, scoring systems have been developed for use in the ICU. The most commonly applied scores are the MSOFA score [24], acute physiology and APACHE II [22] and SAPS II [23].

They allow assessment of the degree of severity of illness and the risk of mortality [43]. In our study, we suggested that higher APACHE II (≥ 18.5), MSOFA (≥ 6.5), and SAPS II (≥ 27.5) scores were associated with high risk of mortality. Previous studies have suggested that the survival of ILD patients was higher in patients with APACHE II scores of less than 20 [34,44]. APACHE II score had also been evaluated in other critically ill pulmonary diseases. In ventilator-associated pneumonia, APACHE II score greater than 25 had 84.6% sensitivity and 78.1% specificity in predicting mortality [45]. In chronic obstructive pulmonary disease, APACHE II score is also an independent factor associated with mortality [46]. Furthermore, both mean SOFA scores and an increase in SOFA score during the first 48 h in the ICU were useful predictors of outcome of patients with sepsis syndrome [47,48].

We also suggested that patients with PaO₂/FiO₂ less than 161.5 was associated with risk of mortality. The presence of refractory hypoxemia referred to the end stage of the ILD [6]. PaO₂/FiO₂ ratio, corticosteroids use, and the use of MV were significantly associated with the risk of death in ILD patients [49].

Conclusion

Mechanically ventilated ILD patients had a poor outcome. However, the survival rate of ILD patients was better on NIV than IMV. Severity assessment scores and PaO₂/FiO₂ could predict risk of mortality in ILD patients. We recommended early application of NIV in critically ill ILD patients. Expectation of poor prognosis of those patients should be discussed with their relatives. Priority of ICU admission should be given to those with better prognostic factors.

Limitations

First, the sample size of the study was small and so we could not generalize our results to all critically ill ILD patients. Second, the predictors for risk of mortality were assessed at the time of admission only without serial follow-up of those scores.

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Conflicts of interest

There are no conflicts in interest.

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