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Outcome and prognostic factors of interstitial lung disease patients with acute respiratory failure in the intensive care unit

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Abstract

Background: There are few studies reporting the clinical characteristics and outcomes of interstitial lung disease (ILD) patients with acute respiratory failure (ARF). The goal of this study is to investigate the clinical features, management, mortality, and associated factors in ILD patients with ARF requiring mechanical ventilation (MV).

Methods: This was a retrospective, observational study conducted in a 24-bed intensive care unit (ICU) of a medical center in Taiwan during a 3-year period. Patients admitted to the ICU with a diagnosis of ILD with ARF needing MV were included for analysis. Patient characteristics, including demographics, critical-illness factors, and outcome data, were collected and analyzed.

Results: A total of 82 patients with ILD who developed ARF were admitted to the ICU during the study period. At the onset of ARF, 38 patients received invasive MV, while 44 patients were treated with noninvasive MV. Overall in-hospital mortality was 65.9%, and 90-day and 1-year mortality were 69.5% and 76.8%, respectively. The independent risk factors for in-hospital mortality were worse oxygenation on days 5 and 7 after the onset of ARF. Invasive MV patients had significantly lower albumin levels, had higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores at the onset of ARF, and received more vasopressors, sedatives, and corticosteroid pulse therapy during hospitalization compared with noninvasive MV patients.

Conclusion: High in-hospital and long-term mortality rates were observed in ILD patients with ARF requiring MV. Poor oxygenation during hospitalization could serve as a predictive factor of poor prognosis.

The reviews of this paper are available via the supplemental material section.

Keywords: acute respiratory failure, intensive care unit, interstitial lung disease, mechanical ventilation, mortality

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Background

Interstitial lung disease (ILD) is a group of disorders that contains more than 200 entities characterized histopathologically by diffuse fibrotic and inflammatory abnormalities of the lung parenchyma.[1] Although the exact epidemiological data are not known, an earlier study indicated that the overall prevalence of ILD in New Mexico, United States, is 80.9 per 100,000 males and 67.2 per 100,000 females, corresponding with annual incidence rates of 31.5 per 100,000 males and 26.1 per 100,000 females.[2] The outcomes of various forms of ILD are quite different, with the highest 5-year survival rate of up to 91.6% observed in sarcoidosis compared with only 35.4% in idiopathic pulmonary fibrosis (IPF).[3]

Acute respiratory failure (ARF) is one of the major complications of ILD and may result from acute exacerbation of ILD, infection, heart

failure, or pulmonary venous thromboembolism.[4] Severe patients must be admitted to an intensive care unit (ICU). There are limited studies reporting the clinical features and outcomes of ILD patients developing ARF. A prediction model incorporating male sex, interstitial pulmonary fibrosis diagnosis, use of invasive mechanical ventilation (MV), extracorporeal life support, no ambulation within 24 h of ICU admission, higher body mass index, and higher severity scoring has been created for prediction of in-hospital mortality in patients with ILD admitted to an ICU.[5] The optimal strategy to manage ILD patients with ARF is not well established. However, among patients with idiopathic pulmonary fibrosis (IPF) and respiratory failure, MV is not recommended in the majority of patients.[6]

The aim of the current study was to analyze the clinical features, mortality, and risk factors in ILD patients with ARF requiring MV.

Methods

This is a retrospective observational study conducted in the medical ICU of a tertiary medical center in Taiwan. Patients admitted to the ICU with a past history or new diagnosis of ILD with ARF needing MV between January 2014 and December 2016 were included for analysis. Patient characteristics, including demographics, critical-illness factors and outcome data, were recorded and analyzed. The study was approved by the institutional review board of Taipei Veterans General Hospital (TPEVGH IRB No. 2017-09-010AC).

Patients

All patients admitted to the ICU with ARF requiring MV during the study period were enrolled if they had a past history of ILD or a new diagnosis of ILD during the ICU stay. We excluded patients with age less than 20 years, pregnancy, repeated ICU admission at the same hospitalization, or MV use for more than 48 h before ICU admission.

ILD classification

One pulmonologist (WCC) carefully reviewed all medical records and clinical data and images for each study subject whenever available. Hypersensitivity pneumonitis was diagnosed according to the diagnostic criteria by American Thoracic Society (ATS).[7] A diagnosis of connective tissue disease (CTD)–related ILD was made when the patient had an established autoimmune disease known to cause ILD based on published criteria.[8–12] Unclassified ILD was diagnosed when there was not enough information to make a specific diagnosis of ILD, according to ATS/European Respiratory Society (ERS) guidelines.[1]

Data collection and measurement

Data were extracted from the medical record database. These variables included age, sex, body mass index, smoking status, and comorbidities. We also recorded critical-illness data, such as the cause of respiratory failure, laboratory values, and arterial blood gas at the onset of ARF. Acute exacerbation (AE) of ILD was defined as rapid worsening of respiratory symptoms with increased dyspnea by new radiologic abnormalities within 1 month without evidence of other causes, such as myocardial infarction, pulmonary embolism, or fluid overload.[13] Clinical management, including the type of mechanical ventilation, vasopressor use, sedative use, corticosteroid pulse therapy and steroid dosage, oxygenation, and fluid balance, was recorded. The primary outcomes were in-hospital mortality and its risk factors. Secondary outcomes included ICU stay and hospital stay.

Statistical analysis

The results are presented as mean ± standard deviation, median with interquartile range, or number with percentage, as appropriate. We used the Kolmogorov–Smirnov and Shapiro–Wilk tests to examine the normality of continuous variables. The independent t test was used to compare normally distributed continuous variables, and the Mann–Whitney U test was used to compare nonnormally distributed continuous variables. We used the Pearson χ^2 test or Fisher's exact test to compare categorical variables. Variables showing significant differences between survivors and nonsurvivors were entered into univariate and multivariate logistic regression analyses using the enter method to determine factors independently associated with mortality. Odds ratio (OR) and 95% confidence interval (CI) were also calculated. A p value < 0.05 was considered to be statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows/Macintosh, Version 22.0 (IBM Corp., Armonk, NY, USA).

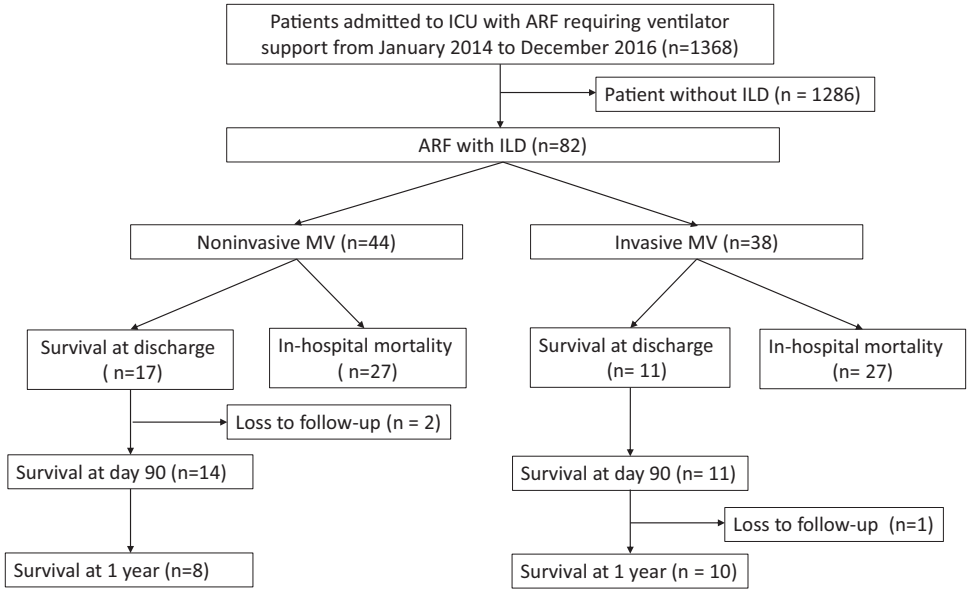

Figure 1. Flow chart of the study.
ARF, acute respiratory failure; ICU, intensive care unit; ILD, interstitial lung disease; MV, mechanical ventilation.

Results

During the study period, 1368 patients were admitted to the ICU with ARF requiring MV. Of them, 1286 patients without a diagnosis of ILD were excluded. The remaining 82 patients were included in our study. Among them, 38 patients (46%) received invasive MV and 44 patients (54%) received noninvasive MV for ARF. Overall, the in-hospital mortality was 65.9%. The 90-day and 1-year mortality rates were 69.5% and 76.8%, respectively (Figure 1). There was no mortality difference between the invasive and noninvasive MV groups (Supplemental Figure S1).

Baseline characteristics are summarized in Table 1. In all, 5 patients (6.1%) were diagnosed with hypersensitivity pneumonitis, 30 patients (36.6%) with CTD-related ILDs, 18 patients (22.0%) with idiopathic pulmonary fibrosis, and 29 patients (35.4%) with unclassified ILD. Most patients (89.0%) had at least one pre-existing comorbidity other than ILD. Survivors had significantly better oxygenation at the onset of ARF, less need for vasopressors and sedatives, and better oxygenation during the critically ill period, as shown in Table 2. In addition, survivors stayed longer in the hospital, but not in the ICU, compared with nonsurvivors.

We also used general and clinical features to compare the invasive and noninvasive MV groups (Tables 3 and 4). The invasive MV groups had a lower albumin level and higher APACHE II score at the onset of ARF. In addition, the invasive MV group received more vasopressors and more sedation during hospitalization. The invasive MV group spent more days in the ICU than the noninvasive MV group. However, both groups had similar hospital stays, ICU mortality, and in-hospital mortality.

To further elucidate clinical predictors of in-hospital mortality among ILD patients with ARF requiring MV, we used univariate and multivariate logistic regression analyses (Table 5). Significant variables included vasopressor use, sedation use, PF ratio (PaO_2/FiO_2, partial pressure of oxygen *versus* fraction of inspired oxygen) at the onset of ARF, and PF ratio at days 3, 5, and 7. After multivariate logistic regression analysis, better PF ratio at day 5 [OR 0.971, CI (0.946–0.996), $p = 0.024$] and better PF ratio at day 7 [OR 0.986, CI (0.974–0.999), $p = 0.033$] remained independent good prognostic factors. Survivors also had persistently better oxygenation status in the first week of ARF compared with nonsurvivors (Figure 2).

Discussion

The aim of this study was to explore the in-hospital mortality of ILD patients with ARF requiring MV and its risk factors. The in-hospital

Table 1. Baseline characteristics of the 82 subjects with ILD developing ARF.

Variable	Survivors ($n = 28$)	Nonsurvivors ($n = 54$)	*p* value
Age (years)	80.8 ± 13.0	78.9 ± 11.1	0.493
Male	23 (82.1%)	44 (81.5%)	0.941
BMI (kg/m^2)	22.0 ± 5.2	22.3 ± 3.7	0.836
Ever-smoker	5 (17.9%)	12 (22.2%)	0.644
Comorbidities			
Hypertension	15 (53.6%)	34 (63.0%)	0.411
Congestive heart failure	6 (21.4%)	21 (38.9%)	0.111
COPD	5 (17.9%)	7 (13.0%)	0.533
Type 2 diabetes mellitus	6 (21.4%)	14 (26.4%)	0.621
Chronic liver disease	2 (7.1%)	3 (5.7%)	1.0
Chronic kidney disease	2 (7.1%)	4 (7.4%)	1.0
Lung cancer	2 (7.1%)	6 (11.1%)	0.709
Other neoplastic disease	6 (21.4%)	12(22.2%)	0.934
Degenerative neurologic disease	3 (11.1%)	6 (11.1%)	1.0
Classification of ILD			0.61
Hypersensitivity pneumonitis	3 (10.7%)	2 (3.7%)	
CTD-related ILD	10 (35.7%)	20 (37.0%)	
Idiopathic pulmonary fibrosis	5 (17.9%)	13 (24.1%)	
Unclassified	10 (35.7%)	19 (35.2%)	

ARF, acute respiratory failure; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; ILD, interstitial lung disease.

mortality among the study subjects was 65.8%. Worse oxygenation on days 5 and 7 independently predicted in-hospital mortality. Although survivors had longer hospital stay, the duration of ICU stay was similar between survivors and nonsurvivors.

A meta-analysis reported that the in-hospital mortality in mixed ILD studies was 52%, though half of these patients had IPF.[14–26] Both the in-hospital and ICU mortality rates seem to have decreased in the past 10 years with advancements in critical care and supportive management.[14] The in-hospital mortality was higher in our study for two reasons. First, we enrolled only ILD patients with ARF requiring MV. Second, our patients were older and had more comorbidities.

The risk factors for mortality in ILD patients with ARF have been reported by several studies. More severe patients according to APACHE II score,[15,17,21] use of MV,[15,20,21,24] and hypoxemia[17,25] were identified as poor prognostic factors. Fernandez-Perez and coworkers reported that each 10-unit increase in the PF ratio was protective against both in-hospital and 1-year mortality in ILD patients with ARF requiring invasive MV.[17] In another study focusing on rapidly progressive interstitial pneumonia patients receiving noninvasive MV, survivors had a significantly higher PF

Table 2. Clinical features during hospitalization of the 82 subjects with ILD developing ARF.

Variable	Survivors ($n = 28$)	Nonsurvivors ($n = 54$)	*p* value
At the onset of ARF			
Cause of respiratory failure			0.527
ILD with AE	3 (10.7%)	10 (18.5%)	
Other cause	25 (89.3%)	44 (81.5%)	
WBC (cells/mm^3)	11,805.4 ± 4529.4	13,065.4 ± 5096.6	0.274
Hemoglobin (g/dl)	11.9 ± 2.3	11.4 ± 2.1	0.298
Albumin (g/dl)	3.0 ± 0.8	2.7 ± 0.6	0.168
BUN (mg/dl)	27.5 ± 19.9	29.4 ± 25.5	0.744
Creatinine (mg/dl)	1.2 ± 0.7	1.5 ± 1.0	0.156
Total bilirubin(mg/dl)	0.8 ± 0.4	0.6 ± 0.6	0.29
ALT (U/l)	57.6 ± 136.5	46.7 ± 99.6	0.681
AST (U/l)	77.8 ± 214.4	92.1 ± 324.8	0.871
Glucose (mg/dl)	156.1 ± 43.9	167.8 ± 57.5	0.377
LDH (U/l)	379.4 ± 269.6	390.7 ± 179.4	0.871
CRP (mg/dl)	9.1 ± 8.2	10.4 ± 9.2	0.52
Lactate (mg/dl)	23.3 ± 34.6	27.2 ± 25.1	0.794
NT-pro-BNP (pg/ml)	1946.3 ± 2241.7	2797.0 ± 2973.9	0.178
APACHE II	14.0 ± 5.8	15.9 ± 6.4	0.173
Arterial blood gas			
pH	7.4 ± 0.1	7.4 ± 0.1	0.835
$PaCO_2$ (mmHg)	46.2 ± 19.7	39.8 ± 9.8	0.056
HCO_3^-(mEq/l)	26.1 ± 7.4	24.0 ± 5.5	0.17
PaO_2/FiO_2	208.4 ± 125.9	146.1 ± 95.7	0.019
Management and follow up			
Type of MV			0.356
Noninvasive	17 (60.7%)	27 (50.0%)	
Invasive	11 (39.3)	27 (50.0%)	
Vasopressor	5 (17.9%)	37 (68.5%)	< 0.001
Sedation	11 (39.3%)	36 (66.7%)	0.017
Corticosteroid pulse therapy	26 (92.9%)	50 (92.6%)	1.0
PaO_2/FiO_2 Day 3	227.1 ± 73.1	180.4 ± 98.1	0.042
PaO_2/FiO_2 Day 5	256.3 ± 98.4	190.2 ± 96.8	0.018
PaO_2/FiO_2 Day 7	289.5 ± 90.6	188.4 ± 97.0	0.003

(Continued)

Table 2. (Continued)

Variable	Survivors ($n = 28$)	Nonsurvivors ($n = 54$)	*p* value
Mean steroid dosage (mg/kg/day)	1.0 ± 0.7	1.2 ± 0.7	0.103
Cumulative IO	1709.1 ± 3130.9	2578.2 ± 3349.5	0.258
Outcome			
ICU days	11.6 ± 8.4	12.4 ± 9.9	0.705
Hospital days	39.2 ± 25.6	22.4 ± 23.2	0.004

AE, acute exacerbation; ALT, alanine aminotransferase; APACHE II, Acute Physiology and Chronic Health Evaluation II; ARF, acute respiratory failure; AST, aspartate aminotransaminase; BUN, blood urea nitrogen; CRP, C-reactive protein; FiO_2, fraction of inspired oxygen; $HCO3^-$, bicarbonate; ICU, intensive care unit; ILD, interstitial lung disease; IO, intake and output; LDH, lactate dehydrogenase; MV, mechanical ventilation; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; WBC, white blood cells.

Table 3. Baseline characteristics between patients receiving noninvasive and invasive MV.

Variable	Noninvasive ($n = 44$)	Invasive ($n = 38$)	*p* value
Age (years)	78.7 ± 12.0	80.5 ± 11.6	0.505
Male	35 (79.5%)	32 (84.2%)	0.586
BMI (kg/m^2)	22.8 ± 4.5	21.5 ± 3.8	0.187
Ever smoker	12 (27.3%)	5 (13.2%)	0.116
Comorbidities			
Hypertension	24 (54.5%)	25 (65.8%)	0.301
Congestive heart failure	15 (34.1%)	12 (31.6%)	0.809
COPD	9 (20.5%)	3 (7.9%)	0.109
Type 2 diabetes mellitus	11 (25%)	9 (24.3%)	0.944
Chronic liver disease	1 (2.3%)	4 (10.5%)	0.181
Chronic kidney disease	2 (4.5%)	4 (10.5%)	0.408
Lung cancer	6 (13.6%)	2 (5.3%)	0.275
Other neoplastic disease	11 (25%)	7 (18.4%)	0.473
Degenerative neurologic disease	3 (6.8%)	6 (16.2%)	0.288
Classification of ILD			0.3
Hypersensitivity pneumonitis	4 (9.1%)	1 (2.6%)	
CTD-related ILD	17 (38.6%)	13 (34.2%)	
Idiopathic pulmonary fibrosis	11 (25%)	7 (18.4%)	
Unclassified	12 (27.3%)	17 (44.7%)	

ARF, acute respiratory failure; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; ILD, interstitial lung disease; MV, mechanical ventilation.

Table 4. Clinical features during hospitalization between patients receiving noninvasive and invasive MV.

Variable	Noninvasive ($n = 44$)	Invasive ($n = 38$)	*p* value
At the onset of ARF			
Cause of respiratory failure			0.071
ILD with AE	4 (9.1%)	9 (23.7%)	
Other cause	40 (90.9%)	29 (76.3%)	
WBC (cells/mm^3)	12282.5 ± 5165.9	13043.4 ± 4651.5	0.488
Hemoglobin (g/dl)	11.7 ± 1.9	11.4 ± 2.5	0.484
Albumin (g/dl)	3.1 ± 0.6	2.7 ± 0.4	0.003
BUN (mg/dl)	26.4 ± 18.9	31.2 ± 27.7	0.373
Creatinine (mg/dl)	1.3 ± 1.0	1.5 ± 0.9	0.254
Total bilirubin(mg/dl)	0.8 ± 0.5	0.7 ± 0.4	0.368
ALT (U/l)	38.5 ± 65.9	64.3 ± 149.8	0.304
AST (U/l)	31.6 ± 29.4	134.8 ± 392.9	0.177
Glucose (mg/dl)	153.3 ± 46.3	173.2 ± 57.3	0.118
LDH (U/l)	379.4 ± 231.6	396.2 ± 175.7	0.783
CRP (mg/dl)	8.3 ± 7.1	11.8 ± 10.3	0.083
Lactate (mg/dl)	21.5 ± 17.6	31.4 ± 36.2	0.139
NT-pro-BNP (pg/ml)	2272.0 ± 2738.0	2805.4 ± 2795.0	0.42
APACHE II	12.3 ± 4.4	18.7 ± 6.3	< 0.001
Arterial blood gas			
pH	7.4 ± 0.1	7.4 ± 0.1	0.797
$PaCO_2$(mmHg)	43.2 ± 10.4	40.9 ± 17.7	0.486
HCO_3^-(mEq/l)	27.7 ± 6.5	25.5 ± 7.4	0.154
PaO_2/FiO_2	173.5 ± 92.7	159.0 ± 127.0	0.569
Management and follow-up			
Vasopressor	15 (34.1%)	26 (68.4%)	0.002
Sedation	13 (29.5%)	34 (89.5%)	< 0.001
Corticosteroid pulse therapy	4 (9.3%)	14 (37.8%)	0.002
PaO_2/FiO_2 Day 3	195.3 ± 95.6	199.3 ± 90.0	0.857

(Continued)

Table 4. (Continued)

Variable	Noninvasive ($n = 44$)	Invasive ($n = 38$)	*p* value
PaO_2/FiO_2 Day 5	213.3 ± 118.3	214.3 ± 82.3	0.973
PaO_2/FiO_2 Day 7	229.9 ± 107.9	209.6 ± 104.1	0.539
Mean steroid dosage (mg/kg/day)	1.2 ± 0.7	1.1 ± 0.7	0.913
Cumulative IO	1930.1 ±2 987.3	2688.2 ± 3593.4	0.3
Outcome			
ICU days	9.9 ± 9.2	14.6 ± 9.2	0.023
Hospital days	26.8 ± 22.1	30.2 ± 28.2	0.55
ICU mortality	18 (40.9%)	17 (44.7%)	0.727
In-hospital mortality	27 (61.4%)	27 (71.1%)	0.356

AE, acute exacerbation; ALT, alanine aminotransferase; APACHE II, Acute Physiology and Chronic Health Evaluation II; ARF, acute respiratory failure; AST, aspartate aminotransaminase; BUN, blood urea nitrogen; CRP, C-reactive protein; FiO_2, fraction of inspired oxygen; $HCO3^-$, bicarbonate; ICU, intensive care unit; ILD, interstitial lung disease; IO, intake and output; LDH, lactate dehydrogenase; MV, mechanical ventilation; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; WBC, white blood cells.

Table 5. Multivariate logistic regression analysis for risks of in-hospital mortality.

Variables	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Vasopressor user	9.2	3–28.21	< 0.001	1.665	0.237–11.724	0.609
Sedation user	3.091	1.2–7.962	0.019	1.187	0.154–9.172	0.869
PF ratio at the onset of ARF	0.995	0.99–0.999	0.027	0.998	0.989–1.007	0.696
PF ratio Day 3	0.994	0.989–1.0	0.049	1.029	0.999–1.059	0.058
PF ratio Day 5	0.993	0.987–0.999	0.025	0.971	0.946–0.996	0.024
PF ratio Day 7	0.99	0.982–0.997	0.009	0.986	0.974–0.999	0.033

ARF, acute respiratory failure; CI, confidence interval; OR, odds ratio; PF ratio, partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2).

ratio at the start of noninvasive MV but not on admission compared with nonsurvivors. In our study, we also found that worse oxygenation, especially on day 3 and day 5 after the onset of ARF, was a poor prognostic sign for in-hospital mortality. Although poor oxygenation at the onset of ARF had an impact on survival on univariate analysis, its effect diminished after adjustment for other variables.

Before this, there were no direct comparisons of the characteristics between invasive and noninvasive MV users among ILD patients with ARF. Our study is the first to report these findings. At the onset of ARF, invasive MV users had significantly lower albumin levels and higher APACHE II scores. This reflects the need for invasive MV in more severe patients. Additionally, invasive MV users received more vasopressors, more sedatives,

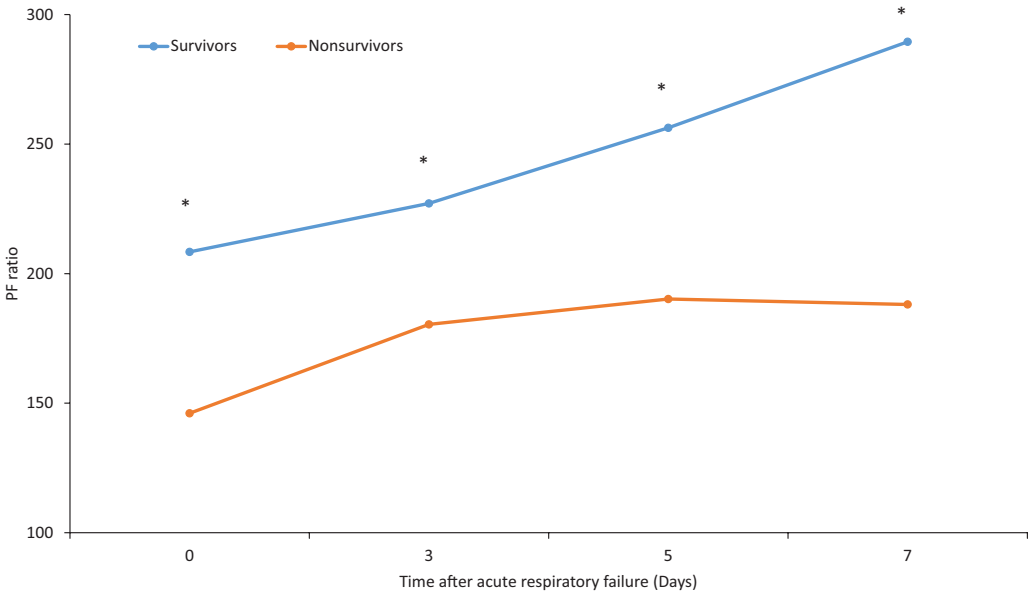

Figure 2. Oxygenation among survivors and nonsurvivors.
Survivors had significantly better oxygenation compared with non-survivors at the onset of acute respiratory failure and through the first 7 days. *$p < 0.05$. PF ratio, partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2).

and more steroid pulse therapy, possibly for the management of side effects of MV and underlying diseases. The ICU and in-hospital mortality rates between invasive and noninvasive MV users were similar, and were in accordance with previous findings.[26] Some studies found that invasive MV users might have higher mortality than noninvasive MV users.[20,21] The ventilator setting might be the true culprit. Positive end-expiratory pressure (PEEP) greater than 10 cmH_2O in the first 24 h of invasive MV has been associated with hospital mortality (OR 17.26) and even 12-month mortality (hazard ratio 4.72) compared with physiological PEEP.[17]

There are important limitations that should be addressed in this study. First, the study cohort was collected retrospectively in a single center, and the diagnosis of ILD was based mainly on clinical features. Definite pathological diagnosis of ILD was lacking. Second, the case number was relatively small, and some patients were lost to follow up. Third, some patients had "Do-Not-Resuscitate" orders in our study. However, most of our patients signed non-resuscitation notices after initial stabilization of the acute stage, and the medical decision to choose the initial type of mechanical ventilation was not influenced by the request.

In conclusion, in patients with ILD developing ARF requiring MV, the in-hospital mortality rate was high and long-term outcome was poor. Of note, poor PF ratio on day 3 and day 5 after the onset of ARF are risk factors for in-hospital mortality.

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Author contribution(s)
Wei-Ling Lain: Data curation; Formal analysis; Investigation; Methodology; Writing-original draft; Writing-review & editing.

Shi-Chuan Chang: Conceptualization; Formal analysis; Methodology; Supervision; Writing-review & editing.

Wei-Chih Chen: Formal analysis; Investigation; Methodology; Supervision; Writing-review & editing.

Availability of data and materials
Available from the corresponding author on reasonable request.

Conflict of interest statement
The authors declare that there is no conflict of interest.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study was approved by the institutional review board of Taipei Veterans General Hospital (TPEVGH IRB No. 2017-09-010AC). The requirement for written informed consent was waived because all patient information was anonymized and deidentified during data recording.

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Supplemental material
The reviews of this paper are available via the supplemental material section.

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