Reclassifying severity after 48 hours could better predict mortality in acute respiratory distress syndrome

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Abstract

Background: Disease severity may change in the first week after acute respiratory distress syndrome (ARDS) onset. The aim of this study was to evaluate whether the reclassification of disease severity after 48 h (i.e. day 3) of ARDS onset could help in predicting mortality and determine factors associated with ARDS persistence and mortality.

Methods: We performed a secondary analysis of a 3-year prospective, observational cohort study of ARDS in a tertiary care referral center. Disease severity was reclassified after 48 h of enrollment, and cases that still fulfilled the Berlin criteria were regarded as nonresolving ARDS.

Results: A total of 1034 ARDS patients were analyzed. Overall hospital mortality was 57.7% (56.7%, 57.5%, and 58.6% for patients with initial mild, moderate, and severe ARDS, respectively, $p = 0.189$). On day 3 reclassification, the hospital mortality rates were as follows: resolved (42.1%), mild (47.9%), moderate (62.4%), and severe ARDS (76.1%) ($p < 0.001$). Patients with improving severity on day 3 had lower mortality (48.8%), whereas patients with the same or worsening severity on day 3 had higher mortality (62.7% and 76.3%, respectively). Patients who were older, had lower PaO_2/FiO_2, or higher positive end-expiratory pressure on day 1 were significantly associated with nonresolving ARDS on day 3. A Cox regression model with ARDS severity as a time-dependent covariate and competing risk analysis demonstrated that ARDS severity was independently associated with hospital mortality, and nonresolving ARDS had significantly increased hazard of death than resolved ARDS ($p < 0.0001$). Cumulative mortality curve for ARDS severity comparisons demonstrated significantly different (overall comparison, $p < 0.001$).

Conclusions: Reclassification of disease severity after 48 h of ARDS onset could help to divide patients into subgroups with greater separation in terms of mortality.

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

Keywords: acute respiratory distress syndrome, reclassification, prediction, outcome, mortality

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Introduction

Acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome with complex patho-physiologic mechanisms characterized by severe hypoxemia and high mortality.[1] Lung-protective mechanical ventilation with low tidal volume and low airway pressure has been shown to improve the outcomes among ARDS patients.[1–3] LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) was a recent large-scale study with the objective of obtaining epidemiologic data of

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ARDS patients, and reported hospital mortality rates ranging from 35% to 46%, depending on the initial categorization of severity.[4]

The definition of ARDS has evolved over the past few decades; however, the diagnostic criteria remain nonspecific, and not a prognostication tool for ARDS. Previous studies also concluded that second assessment of disease severity after 24 h greatly improved risk stratification of ARDS patients.[5–15] The LUNG SAFE study reported that over half of ARDS patients had resolving or decreasing in severity after 24 h.[4] Therefore, the severity of ARDS may change significantly during first few days after onset and initial classifications of ARDS may not reflect the evolution of disease severity and permit accurate predictions of clinical outcomes and mortality.

We hypothesized that patients presenting with ARDS initially constitute heterogenous groups with distinct disease severity evolutions, and the evolution in the first few days after ARDS onset may be associated with clinical outcome.

The LUNG SAFE study concluded that ARDS reclassification 24 h after onset was of relatively limited predictive value for mortality.[8] However, one recent analysis of two large cohorts of intensive care unit (ICU) patients enrolled critically ill patients receiving mechanical ventilator for at least 48 h and demonstrated that one ventilation variable (i.e. mechanical power) is independently associated with higher in-hospital mortality. This study suggested that more severely ill patients would be selected after 48 h, including ARDS patients, and also guaranteed that patients were exposed to invasive ventilation and the primary exposure of interest for a sufficient period of time.[16] Therefore, the rationale of our study was to verify whether reclassification 48 h later would improve prediction of mortality and ensure that ARDS patients were exposed to a sufficient time for response to clinical therapy and adjusted mechanical ventilator settings.

The primary outcome of this secondary analysis of a 3-year prospective study in Taiwan[17,18] was to determine whether the reclassification of disease severity after 48 h of ARDS onset (i.e. day 3 rather than the initial 24 h) would improve the accuracy of predictions pertaining to clinical outcomes. The secondary outcome was to identify the risk factors associated with nonresolving ARDS at day 3 and hospital mortality.

Methods

Study design and participants

This was a retrospective analysis of the prospective observational study conducted from September 2012 to September 2015 at Chang Gung Memorial Hospital, the tertiary care referral center in Taiwan with 3700 ward beds and 278 adult ICU beds (9 medical ICUs, 7 surgical ICUs, and 1 burn ICU).[17,18] All patients admitted to the ICUs with invasive mechanical ventilation were screened, and patients that met the Berlin criteria for ARDS were included.[19] Exclusion criteria were as follows: (1) age $<$ 18 years and (2) ARDS diagnosis and referral from other hospitals. The local Institutional Review Board for Human Research approved this study (CGMH IRB No. 102-1729B) and waived the need for informed consent.

Definitions

The term day 1 refers to the day on which the patient first met the Berlin definition of ARDS, irrespective of ICU admission and intubation day, whereas day 3 was defined as 48 h after ARDS onset. Clinical variables that did not fulfill the Berlin criteria on day 3 were deemed to be resolved, whereas clinical variables that still fulfilled the Berlin criteria on day 3 were regarded as nonresolving ARDS. Continuous change of ARDS severity was regarded as a time-varying covariate. If the patients were extubated and alive during the follow-up period, the ARDS severity was deemed to be resolved. The term ventilator-free days was defined as the number of days between day 1 and day 28 in which the patient breathed without assistance for at least 48 consecutive hours. Patients who did not survive to 28 days were assigned zero ventilator-free days. The term hospital mortality refers to all-cause death during the hospital stay. Patients who remained alive for 90 days after discharge from the hospital were regarded as survivors.

Data collections

Demographic variables, baseline clinical variables, and the etiology of ARDS were recorded from hospital charts at study entry. Arterial blood gas, mechanical ventilator settings including tidal volume, positive end-expiratory pressure (PEEP), peak inspiratory pressure, total respiratory rate, and FiO_2, Acute Physiology and Chronic Health

Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, and lung injury score (LIS) were prospectively collected at around 10 a.m. on the day of ARDS onset as well as on days 3, 7, and 14 after the initial diagnosis. Rescue therapies included prone positioning and extracorporeal membrane oxygenation (ECMO). All enrolled ARDS patients were followed up until death in the hospital or discharge from the hospital.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range), and categorical variables were reported as numbers (percentages). A Student's *t* test or the Mann–Whitney *U* test was used to compare continuous variables between groups. Categorical variables were tested using the chi-squared test for equal proportions or Fisher's exact test. Risk factors associated with hospital mortality or nonresolving ARDS on day 3 were analyzed using univariate analysis in the first step. While considering ARDS severity variability over time, Cox proportional hazards regression model with continuous change of ARDS severity as a time-varying covariate and multivariable logistic regression model with stepwise selection procedure were performed. The results were presented as hazard ratio (HR) or odds ratio (95% confidence interval). While considering that patients who were liberated from the mechanical ventilator and still alive as the competing event, competing-risks regression based on Fine-Gray proportional subdistribution hazards model was performed. The results were presented as subdistribution hazard ratio (SHR) (95% confidence interval).[20] Cumulative mortality curves were generated as a function of time using the Kaplan–Meier approach, and compared using the log-rank test. All statistical analysis was performed using SPSS 22.0 and Stata 14.2 statistical software, and a two-sided p value < 0.05 was considered statistically significant.

Results

Study population

A total of 1034 patients who fulfilled the Berlin definition of ARDS were included for analysis (Figure 1). The overall all-cause in-hospital mortality was 57.7%. Among ARDS patients on day 1, the mortality rates were as follows: mild ARDS (56.7%), moderate ARDS (57.5%), and severe ARDS (58.6%), and no significant difference was observed across the three groups ($p = 0.189$). At day 3 after ARDS onset, 96 patients (9.3%) had died, had been discharged from the ICU, or had missing data. Among the 938 ARDS patients remaining on day 3, the mortality rate showed significant difference between resolved and nonresolving ARDS patients (42.1% *versus* 59.9%, $p < 0.001$). In addition, prone positioning was applied to three patients, and ECMO was used in 61 patients.

Baseline variables between groups

Table 1 demonstrates that nonsurvivors were older, had a lower body mass index (BMI), higher APACHE II score, higher SOFA score, and higher LIS. Almost all ARDS patients received pressure-controlled ventilation, and there were no significant differences in terms of baseline ventilator settings or arterial blood gas, except for higher peak inspiratory pressure among nonsurvivors ($p = 0.013$). Table 2 showed that the etiologies of ARDS were not associated with the persistence of ARDS on day 3. Compared with patients with nonresolving ARDS, those with resolved ARDS tended to be younger and had lower LIS, higher PaO_2/FiO_2 ratios, lower PEEP, lower peak inspiratory pressure, lower total respiratory rates, and lower FiO_2 values on day 1 (all $p < 0.05$). The APACHE II and SOFA scores on day 1 did not present significant differences.

Evolution of ARDS severity and clinical variables over first 48 h

Among the 938 ARDS patients who were reassessed at 48 h post-diagnosis, nearly half (48.2%) of the cases had resolved or improving severity (mortality rate: 48.8%), 31.1% presented the same severity (mortality rate: 62.7%), and 11.4% had worsening severity (mortality rate: 76.3%). The actual hospital mortality rates of patients reclassified on day 3 were as follows: resolved ARDS (42.1%), mild ARDS (47.9%), moderate ARDS (62.4%), and severe ARDS (76.1%) ($p < 0.001$).

In terms of organ dysfunction, patients with resolved ARDS had significantly lower APACHE II scores, lower SOFA scores, and lower LIS on day 3 than on day 1 (all $p < 0.001$), whereas

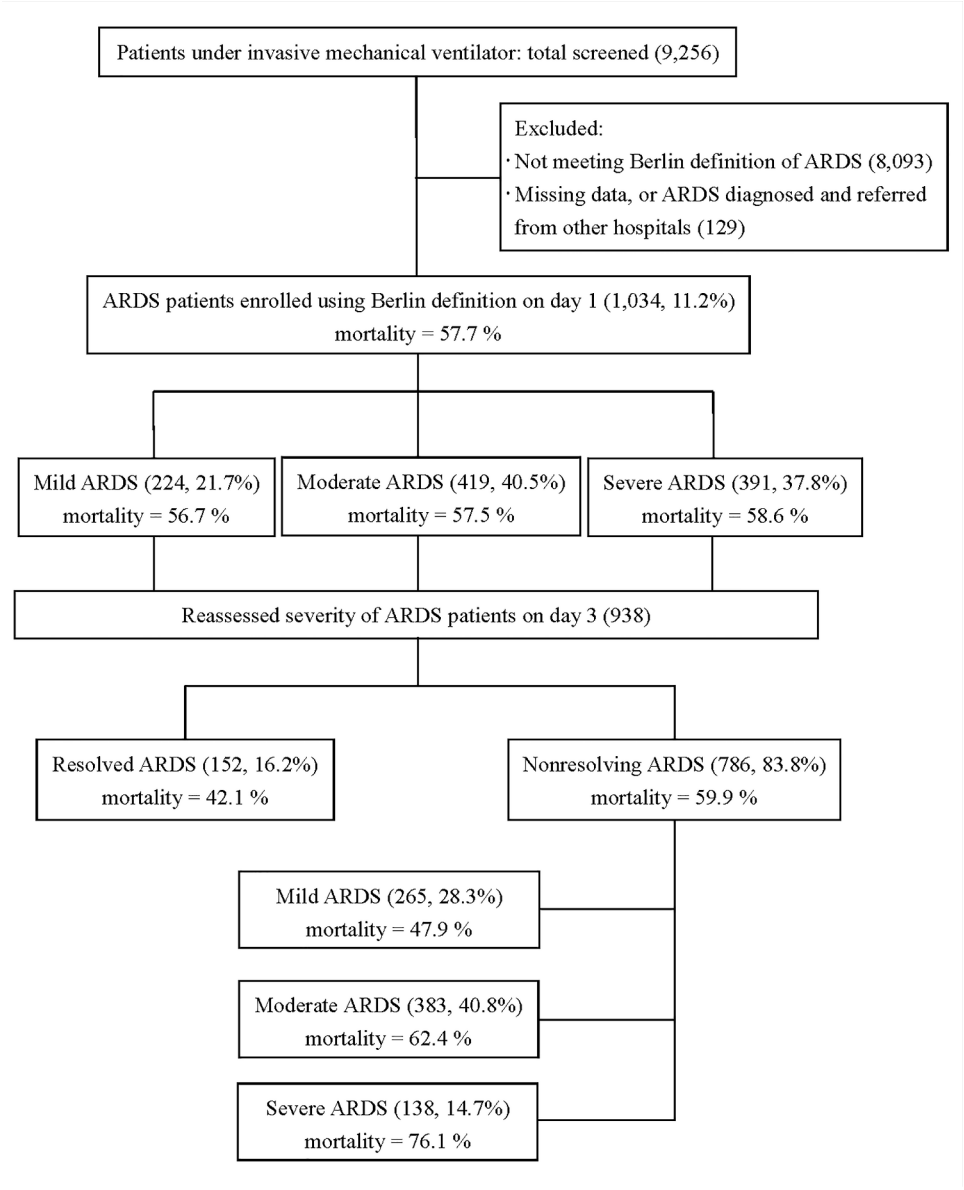

Figure 1. Flow chart showing enrollment of patients with acute respiratory distress syndrome (ARDS) and outcomes. Day 1 was defined as the day the patient first met the Berlin criteria of ARDS, and day 3 was defined as 48 h after ARDS onset.

nonresolving ARDS patients had significantly lower APACHE II scores and lower LIS but slightly higher SOFA scores on day 3 than on day 1 (Table 2).

In terms of ventilator settings, resolved ARDS patients had significantly lower peak inspiratory pressure and lower total respiratory rate on day 3 than on day 1 ($p < 0.001$ and $p = 0.005$, respectively), whereas nonresolving ARDS patients had significantly higher PEEP and higher total respiratory rates on day 3 than on day 1 ($p < 0.001$ and $p = 0.001$, respectively) (Table 2).

Comparisons of variables between resolved and nonresolving ARDS on day 3

Following reassessment on day 3, resolved ARDS patients had significantly lower APACHE II scores, lower SOFA scores, and lower LIS, as well as higher PaO_2/FiO_2 ratio, higher tidal volumes, lower PEEP, lower peak inspiratory

Table 1. Background characteristics: ARDS patients, survivors, and nonsurvivors.

Characteristic	All patients (*n* = 1034)	Survivors (*n* = 437)	Nonsurvivors (*n* = 597)	*p* value
Age (years)	63.1 ± 16.1	60.2 ± 16.9	65.1 ± 15.1	<0.001
Gender (male)	715 (69.1%)	302 (69.1%)	413 (69.2%)	0.98
Body mass index (kg/m^2)	23.8 ± 4.5	24.4 ± 4.8	23.3 ± 4.2	<0.001
ARDS etiologies				
Bacterial pneumonia	682 (66.0%)	285 (65.2%)	397 (66.5%)	0.667
Extrapulmonary sepsis	142 (13.7%)	52 (11.9%)	90 (15.1%)	0.143
Aspiration pneumonia	70 (6.8%)	32 (7.3%)	38 (6.4%)	0.545
Influenza pneumonia	39 (3.8%)	23 (5.3%)	16 (2.7%)	0.031
Pulmonary contusion	21 (2.0%)	16 (3.7%)	5 (0.8%)	0.001
Other causes	80 (7.7%)	29 (6.6%)	51 (8.5%)	0.257
APACHE II score	23.5 ± 7.2	21.8 ± 7.1	24.7 ± 7.1	<0.001
SOFA score	9.9 ± 3.5	8.9 ± 3.0	10.7 ± 3.7	<0.001
Lung injury score	2.89 ± 0.51	2.85 ± 0.53	2.92 ± 0.49	0.031
Ventilator settings				
PaO_2/FiO_2 (mmHg)	138.6 ± 70.9	138.5 ± 70.5	138.6 ± 71.1	0.839
Tidal volume (ml/kg PBW)	8.3 ± 2.1	8.2 ± 2.0	8.4 ± 2.1	0.387
PEEP (cmH_2O)	9.9 ± 2.1	9.8 ± 2.2	9.9 ± 2.1	0.707
Peak inspiratory pressure (cm H_2O)	29.1 ± 5.8	28.6 ± 5.6	29.5 ± 5.9	0.013
Total respiratory rate (breaths/min)	21.6 ± 5.9	21.4 ± 6.2	21.6 ± 5.6	0.533
FiO_2 (%)	78.5 ± 23.2	78.6 ± 23.2	78.5 ± 23.1	0.975
Arterial blood gas				
pH	7.35 ± 0.13	7.36 ± 0.12	7.34 ± 0.13	0.027
$PaCO_2$ (mmHg)	45.4 ± 16.4	44.7 ± 15.1	45.9 ± 17.2	0.23
PaO_2 (mmHg)	99.4 ± 49.3	99.6 ± 49.4	99.2 ± 49.3	0.901
HCO_3 (mEq/l)	23.7 ± 6.2	23.9 ± 5.7	23.6 ± 6.5	0.380
Saturation (%)	93.2 ± 9.4	93.2 ± 9.7	93.2 ± 9.2	0.584
Mechanical ventilation(days)	14 (8–28)	12 (7–24.5)	16 (8–29)	0.013
ICU length of stay (days)	16.0 (9.0–31.0)	16.0 (10.0–32.0)	16.0 (8.0–30.0)	0.088
Hospital length of stay (days)	26.0 (14.0–46.0)	37.0 (23.0–61.0)	18.0 (8.0–34.0)	<0.001

Values are presented as mean ± standard deviation, count or median (interquartile range).
APACHE, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; PBW, predicted body weight; PEEP, positive end-expiratory pressure; SOFA, sequential organ failure assessment.

Table 2. Characteristics of patients with resolved and nonresolving ARDS on day 3 after diagnosis.

Characteristic	All patients (*n* = 938)	Resolved (*n* = 152)	Nonresolving (*n* = 786)	*p* value
Age (years)	63.0 ± 16.2	60.3 ± 17.8	63.6 ± 15.8	0.025
Gender (male)	649 (69.2%)	101 (66.4%)	548 (69.7%)	0.424
Body mass index (kg/m^2)	23.8 ± 4.5	23.2 ± 4.3	23.9 ± 4.5	0.098
ARDS etiologies				
Bacterial pneumonia	626 (66.7%)	107 (70.4%)	519 (66.0%)	0.296
Extrapulmonary sepsis	119 (12.7%)	20 (13.2%)	99 (12.6%)	0.849
Aspiration pneumonia	61 (6.5%)	5 (3.3%)	56 (7.1%)	0.079
Viral pneumonia	36 (3.8%)	4 (2.6%)	32 (4.1%)	0.495
Pulmonary contusion	20 (2.1%)	5 (3.3%)	15 (1.9%)	0.281
Other causes	76 (8.1%)	11 (7.2%)	65 (8.3%)	0.669
Organ failure score on day 1				
APACHE II score	23.2 ± 7.1	23.0 ± 7.3	23.3 ± 7.0	0.668
SOFA score	9.8 ± 3.4	9.4 ± 3.4	9.8 ± 3.4	0.134
Lung injury score	2.89 ± 0.51	2.65 ± 0.55	2.94 ± 0.48	<0.001
Ventilator settings on day 1				
PaO_2/FiO_2 (mmHg)	139.7 ± 71.7	165.7 ± 76.4	135.2 ± 69.8	<0.001
Tidal volume (ml/kg PBW)	8.3 ± 2.1	8.5 ± 2.1	8.3 ± 2.1	0.246
PEEP (cmH_2O)	9.9 ± 2.1	9.2 ± 1.9	10.0 ± 2.1	<0.001
Peak inspiratory pressure (cm H_2O)	29.3 ± 5.7	28.3 ± 5.8	29.5 ± 5.7	0.024
Total respiratory rate (breaths/min)	21.5 ± 5.9	20.6 ± 5.5	21.7 ± 5.9	0.036
FiO_2 (%)	78.6 ± 23.1	73.8 ± 24.6	79.6 ± 22.7	0.009
Arterial blood gas on day 1				
pH	7.35 ± 0.12	7.34 ± 0.13	7.35 ± 0.12	0.114
$PaCO_2$ (mmHg)	45.4 ± 16.6	45.5 ± 21.2	45.4 ± 15.5	0.952
PaO_2 (mmHg)	100.3 ± 50.1	109.6 ± 50.3	98.5 ± 49.8	0.012
HCO_3 (mEq/l)	24.0 ± 6.2	22.6 ± 6.2	24.2 ± 6.1	0.003
Saturation (%)	93.3 ± 9.7	94.0 ± 10.6	93.3 ± 8.9	0.342
Organ failure score on day 3				
APACHE II score	21.4 ± 7.4	18.1 ± 5.8	22.1 ± 7.5	<0.001

(Continued)

Table 2. (Continued)

Characteristic	All patients (*n* = 938)	Resolved (*n* = 152)	Nonresolving (*n* = 786)	*p* value
SOFA score	9.6 ± 3.8	7.1 ± 3.4	10.0 ± 3.7	<0.001
Lung injury score	2.72 ± 0.63	1.94 ± 0.41	2.87 ± 0.55	<0.001
Ventilator settings on day 3				
PaO_2/FiO_2 (mmHg)	203.8 ± 109.5	389.2 ± 105.4	168.7 ± 65.7	<0.001
Tidal volume (ml/kg PBW)	8.3 ± 2.3	8.7 ± 2.5	8.2 ± 2.2	0.009
PEEP (cm H_2O)	10.8 ± 2.6	9.3 ± 1.9	11.0 ± 2.7	<0.001
Peak inspiratory pressure (cm H_2O)	28.4 ± 6.7	24.3 ± 6.0	29.2 ± 6.6	<0.001
Total respiratory rate (breaths/min)	22.1 ± 5.6	19.2 ± 5.1	22.6 ± 5.5	<0.001
FiO_2 (%)	53.3 ± 19.3	38.4 ± 7.6	56.1 ± 19.6	<0.001
Arterial blood gas on day 3				
pH	7.40 ± 0.10	7.44 ± 0.07	7.40 ± 0.11	<0.001
$PaCO_2$ (mmHg)	43.3 ± 13.8	37.2 ± 8.1	44.4 ± 14.3	<0.001
PaO_2 (mmHg)	96.1 ± 37.5	149.1 ± 47.6	85.9 ± 24.3	<0.001
HCO_3 (mEq/l)	26.0 ± 5.8	24.7 ± 5.1	26.3 ± 5.9	<0.001
Saturation (%)	95.5 ± 4.6	98.8 ± 0.5	94.8 ± 4.7	<0.001
Ventilator-free days on day 28	0.0 (0.0–16.0)	17.5 (0.0–21.0)	0.0 (0.0–14.0)	<0.001
ICU length of stay (days)	17.0 (10.0–32.0)	13.5 (9.0–25.0)	18.0 (11.0–33.0)	0.002
Hospital length of stay (days)	28.0 (16.0–47.0)	30.5 (19.0–52.0)	27.0 (14.8–47.0)	0.148

Values are presented as mean ± standard deviation, count or median (interquartile range).
APACHE, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; PBW, predicted body weight; PEEP, positive end-expiratory pressure; SOFA, sequential organ failure assessment.

pressure, lower total respiratory rates, and lower FiO_2 values than did the nonresolving ARDS patients (all $p < 0.05$). Resolved ARDS patients also had more ventilator-free days ($p < 0.001$) and a shorter length of stay in the ICU ($p = 0.002$) (Table 2).

Factors associated with hospital mortality and ARDS persistence on day 3

After adjusting for significant confounding variables, both Cox regression model with ARDS severity as a time-varying covariate and competing risk analysis showed that ARDS severity was significantly associated with hospital mortality. Nonresolving ARDS had significantly higher mortality than resolved ARDS during the study period (mild *versus* resolved ARDS, HR 2.007, SHR 3.462; moderate *versus* resolved ARDS, HR 2.700, SHR 4.653; severe *versus* resolved ARDS, HR 6.963, SHR 11.648, all $p < 0.0001$). The hospital mortality rate also showed significant difference between moderate and mild ARDS patients (HR 1.346, $p = 0.01$; SHR 1.344, $p = 0.007$), and between severe and moderate ARDS patients (HR 2.578, $p < 0.0001$;

Table 3. Factors associated with hospital mortality using Cox regression model with ARDS severity as a time-dependent covariate and incorporating time-dependent covariate in competing risk analysis.

Variables	Time-dependent covariate model		Competing risk model	
	HR (95% CI)	*p* value	SHR (95% CI)	*p* value
ARDS severity				
Mild *versus* resolved	2.007 (1.527–2.638)	<0.0001	3.462 (2.576–4.652)	<0.0001
Moderate *versus* resolved	2.700 (2.095–3.481)	<0.0001	4.653 (3.530–6.135)	<0.0001
Severe *versus* resolved	6.963 (5.023–9.650)	<0.0001	11.648 (8.197–16.553)	<0.0001
Age	1.010 (1.004–1.016)	0.001	1.011 (1.005–1.017)	<0.0001
Body mass index (kg/m^2)	0.944 (0.925–0.964)	<0.0001	0.941 (0.923–0.961)	<0.0001
Influenza pneumonia	0.418 (0.220–0.795)	0.008	0.414 (0.220–0.779)	0.006
SOFA score on day 3	1.132 (1.103–1.162)	<0.0001	1.142 (1.113–1.171)	<0.0001

ARDS, acute respiratory distress syndrome; CI, confidence interval; HR, hazard ratio; SHR, subdistribution hazard ratio; SOFA, sequential organ failure assessment.

Table 4. Factors associated with nonresolving ARDS on day 3 after diagnosis using multivariable logistic regression model.

Clinical variables	Odds ratio (95% CI)	*p* value
Age	1.014 (1.002–1.025)	0.020
PaO_2/FiO_2 (mmHg) on day 1	0.995 (0.993–0.998)	< 0.001
PEEP (cm H_2O) on day 1	1.160 (1.048–1.284)	0.004

ARDS, acute respiratory distress syndrome; CI, confidence interval; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in arterial blood; PEEP, positive end-expiratory pressure.

SHR 2.503, $p<0.001$). Age, BMI, influenza pneumonia, SOFA score on day 3 were also independently associated with hospital mortality (Table 3). Patients who were older, had lower PaO_2/FiO_2, and had higher PEEP on day 1 were significantly associated with nonresolving ARDS on day 3 (Table 4).

Continuous change of ARDS severity and hospital mortality

Cumulative mortality curve using the Kaplan–Meier approach for ARDS categorical comparisons without and with accounting for ARDS severity as a time-dependent covariate and competing risk analysis demonstrated significant difference (Figure 2(a) and (b)). Log-rank test for ARDS category comparisons: overall comparison, $p<0.001$ (Figure 2(a)); $p<0.001$ (Figure 2(b)).

Discussion

This is the secondary analysis of the prospective observational 3-year cohort study in patients with ARDS in Taiwan. No significant differences in hospital mortality rates were observed among the ARDS severity groups as diagnosed on day 1. However, among the 938 remaining ARDS patients on day 3 (48 h later), there was a significant difference in hospital mortality rates between resolved and nonresolving ARDS patients (42.1% *versus* 59.9%, $p<0.001$). Continuous change of ARDS severity was significantly associated with hospital mortality and mortality rates among the distinct ARDS severity was significantly different.

The hospital mortality rate of this study was 57.7%, which was higher than the figures reported in recent epidemiologic studies.[4,21] Our hospital is the tertiary care referral center in Taiwan and we did not exclude patients with malignancy and severe comorbidities, such as chronic heart failure, advanced liver disease, chronic lung or kidney diseases, or terminal illness in the present study. The LUNG SAFE study reported that

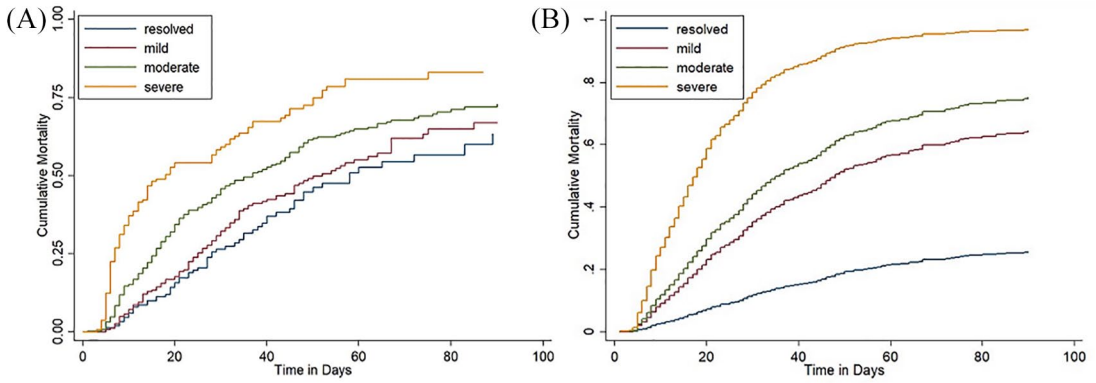

Figure 2. Cumulative mortality curve using the Kaplan–Meier approach among patients with acute respiratory distress syndrome (ARDS) without (a) and with (b) accounting for ARDS severity as a time-dependent covariate and competing risk analysis. Log-rank test for ARDS category comparisons: overall comparison, (a) $p < 0.001$; (b) $p < 0.001$.

overall hospital mortality was 38%, and 24% patients no longer fulfilled ARDS definition after 24 h (i.e. resolved ARDS) with mortality rate of 31%. Compared with patients with the LUNG SAFE study,[4] our enrolled ARDS patients were older, had more chronic diseases, and receiving higher airway pressure, and these factors may cause higher mortality in our study.

Lung-protective mechanical ventilation strategies using lower tidal volumes, optimal PEEP values, and lower airway pressure have been shown to decrease ARDS-related mortality,[1–3] mitigate the effects of ventilator-induced lung injury (VILI), and reduce multiple organ failure.[22,23] Most ARDS patients did not receive low tidal volume ventilation in clinical practice. The mean tidal volume was 7.6 ml/kg predicted body weight in the LUNG SAFE study[4] and 8.3 ml/kg in the present study. Both values exceeded the recommended 6 ml/kg but were far below levels deemed injurious (12 ml/kg).[2] However, tidal volume in this study was not significantly associated with ARDS persistence on day 3 or with hospital mortality.

On day 1, the PEEP value, peak inspiratory pressure, and total respiratory rate of nonresolving ARDS patients were significantly higher than those of resolved ARDS patients (all $p < 0.05$). Gattinoni *et al.* identified these three parameters as aspects of mechanical power, which has been linked to the development of VILI.[24] One recent study reported that high mechanical power is independently associated with higher in-hospital mortality rates among critically ill patients receiving invasive ventilation for at least 48 h.[16] In the current study, there was a significant difference in the mortality rates of resolved ARDS and nonresolving ARDS patients at 48 h after ARDS onset (42.1% *versus* 59.9%, $p < 0.001$). It is reasonable to assume that higher mechanical power on day 1 could increase the risk of VILI and would therefore be associated with ARDS persistence on day 3 and hospital mortality.

On day 3, the PEEP value, peak inspiratory pressure, and total respiratory rate of nonresolving ARDS patients were still higher than those of resolved ARDS patients (all $p < 0.001$). We also compared the changes in ventilator settings from day 1 to day 3. The peak inspiratory pressure and total respiratory rate of resolved ARDS patients were significantly lower on day 3 than on day 1, whereas the PEEP values and total respiratory rate of nonresolving ARDS patients were significantly higher on day 3 than on day 1. These changes may be indicative of oxygenation levels, the severity of lung damage, and the corresponding adjustments of the ventilator settings.

The most common cause of death among ARDS patients is multiorgan failure,[1] and previous studies have shown that the degree of systemic organ failure is correlated with ARDS outcome.[6,8,21,25] Secondary analysis of the LUNG SAFE study revealed that the SOFA score is independently associated with hospital mortality in ARDS patients.[8,25] In our study, the APACHE II and SOFA scores of survivors were significantly lower than those of nonsurvivors on day 1 ($p < 0.001$).

On day 1, there was no significant difference between resolved and nonresolving ARDS patients in terms of APACHE II or SOFA scores; however, on day 3, there was a significant difference in these scores ($p < 0.001$) as well as hospital mortality (42.1% *versus* 59.9%; $p < 0.001$). This indicates that organ dysfunction was correlated with clinical outcome. Moreover, SOFA scores on day 3 were independently associated with hospital mortality in a multivariable Cox model.

Villar *et al.* reported significant differences in mortality among ARDS patients classified by responses to standard ventilatory settings (PEEP $\geq$ 10 cm H_2O and FiO2 $\geq$ 0.5) at 24 h after ARDS onset.[7,9,10,12,13] Several studies have also reported that reassessing disease severity and clinical parameters at 24–72 h after ARDS diagnosis might have a significant effect on predicting mortality.[6–15] A persistently low PaO_2/FiO_2 ratio is associated with poor outcomes and could potentially indicate a failure to respond to conventional therapy.[14] No significant difference in hospital mortality was observed between patients with different severity levels at ARDS onset in the present study, it indicates that initial PaO_2/FiO_2 ratio cannot discriminate subphenotype of ARDS patients precisely in terms of mortality in our study. However, patients with resolved or mild ARDS 48 h later faced a relatively lower risk of mortality (42.1% and 47.9%, respectively), whereas those with moderate or severe ARDS at 48 h faced a higher risk of mortality (62.4% and 76.1%, respectively). In addition, mortality according to the evolution of ARDS severity between day 1 and day 3 demonstrated that patients with resolved or improving severity on day 3 had lower mortality (48.8%), whereas patients with the same or worsening severity on day 3 had higher mortality (62.7% and 76.3%, respectively).

The main objective of this study was to assess prognostic factors and factors associated with nonresolving ARDS, not to evaluate the effect of factors associated with nonresolving ARDS (i.e. mediator) on mortality outcome. Therefore, we used multivariable regression models, including a Cox regression model with ARDS severity as a time-varying covariate and competing risk analysis that do not provide any estimate of causal relationship (even if this link could exist). Our results demonstrated that serial change of ARDS severity was significantly associated with hospital mortality, and nonresolving ARDS had significantly increased hazard of death than resolved ARDS. Cumulative mortality curve demonstrated significant differences in hospital mortality rates among the distinct ARDS severity groups.

In all the studies mentioned previously, it appears that the initial definition of ARDS is insufficient to obtain an accurate assessment of disease severity or derive reliable predictions of mortality. We therefore recommend the reclassification at some point after ARDS onset (e.g. 24–48 h) to categorize more homogeneous subpopulations of patients according to disease prognosis and mortality.

This study was hindered by several limitations. First, this study was conducted in one tertiary care referral center with retrospective analysis, and we did not exclude patients with malignancy or severe comorbidities, which cause higher mortality in the present study, thereby limiting generalizability to other ICUs or hospitals. Second, there was no standard protocol for ventilator settings among the enrolled ICUs, and our enrolled ARDS patients received higher tidal volume and higher FiO_2 than other studies. These two limitations make external validation of our study to other ARDS cohorts problematic to perform. Furthermore, throughout the ICU stay, ventilator settings were recorded only once a day (at around 10 a.m.) and therefore do not necessarily manifest dynamic changes in ventilator status. Third, during the first 48 h after ARDS onset, we analyzed only the ventilator settings, arterial blood gas, and organ dysfunction score. Other clinical variables that could be used to predict hospital mortality or nonresolving ARDS on day 3 have yet to be confirmed. Fourth, we did not exclude the 96 patients (9.3%) who had died, had been discharged from the ICU, or had missing data within first 48 h for survival predictors analysis. Fifth, causes of mortality were not reported, and patients may not die from ARDS, but from the underlying diseases. Finally, there may be unmeasured residual (i.e. confounding) variables, such as daily fluid balance, that were not included in this study. Finally, prone positioning and ECMO were underutilized as these rescue therapies might have saved many of the patients with persistent severe ARDS.

Conclusion

Our findings indicated that the reclassification of ARDS severity after 48 h could improve the accuracy of clinical outcome predictions. Continuous

change of ARDS severity was significantly associated with hospital mortality and mortality rate was significantly different among distinct ARDS severity. Our study is valuable for clinical trials in the future to include more homogeneous ARDS patients in terms of mortality and help to identify severe cases warranting aggressive clinical intervention or additional rescue therapies.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

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

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