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The Ratio of Partial Pressure Arterial Oxygen and Fraction of Inspired Oxygen 1 Day After Acute Respiratory Distress Syndrome Onset Can Predict the Outcomes of Involving Patients

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Abstract: The initial hypoxemic level of acute respiratory distress syndrome (ARDS) defined according to Berlin definition might not be the optimal predictor for prognosis. We aimed to determine the predictive validity of the stabilized ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2 ratio) following standard ventilator setting in the prognosis of patients with ARDS.

This prospective observational study was conducted in a single tertiary medical center in Taiwan and compared the stabilized PaO_2/FiO_2 ratio (Day 1) following standard ventilator settings and the PaO_2/FiO_2 ratio on the day patients met ARDS Berlin criteria (Day 0). Patients admitted to intensive care units and in accordance with the Berlin criteria for ARDS were collected between December 1, 2012 and May 31, 2015. Main outcome was 28-day mortality. Arterial blood gas and ventilator setting on Days 0 and 1 were obtained.

A total of 238 patients met the Berlin criteria for ARDS were enrolled, and they were classified as mild (n = 50), moderate (n = 125), and severe (n = 63) ARDS, respectively. Twelve (5%) patients who originally were classified as ARDS did not continually meet the Berlin definition, and a total of 134 (56%) patients had the changes regarding the severity of ARDS from Day 0 to Day 1. The 28-day mortality rate was 49.1%, and multivariate analysis identified age, PaO_2/FiO_2 on Day 1, number of organ failures, and positive fluid balance within 5 days as significant risk factors of death. Moreover, the area under receiver-operating curve for mortality prediction using PaO_2/FiO_2 on Day 1 was significant higher than that on Day 0 ($P = 0.016$).

PaO_2/FiO_2 ratio on Day 1 after applying mechanical ventilator is a better predictor of outcomes in patients with ARDS than those on Day 0.

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Abbreviations: ABG = arterial blood gas, AECC = American and European Consensus Conference, ALI = acute lung injury, APACHE = Acute Physiology and Chronic Health Evaluation, ARDS = acute respiratory distress syndrome, PaO_2/FiO_2 ratio = ratio of partial pressure arterial oxygen and fraction of inspired oxygen, PEEP = positive end expiratory pressure.

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a sudden and catastrophic lung condition associated with low oxygen level in the blood. ARDS is a major cause of acute respiratory failure, and can be caused by a pulmonary insult or an indirect extra-pulmonary insult.[1] In 1994, the American and European Consensus Conference (AECC) established specific clinical criteria for ARDS and acute lung injury, including acute and sudden onset of severe respiratory distress, bilateral infiltrates on chest radiography, the absence of cardiogenic pulmonary edema, and severe hypoxemia.[2] Based on AECC definition, the incidence of ARDS was reported ranging from 5.0 to 33.8 per 100,000 people in several epidemiological studies.[3–6]

Although the mortality of ARDS varies according to differences in study populations, co-morbidities, severity of lung injury, predisposing factors for ARDS, and the setting of mechanical ventilation (MV); the reported mortality of ARDS in adult remains >40% and has not changed with time substantially.[6–8] Because severe hypoxemia is the hallmark of ARDS, various parameters of oxygenation or lung mechanics are assessed as appropriate indicators of disease severity or good predictors of deaths in several studies.[9,10] However, AECC definition may not truly reflect the severity and outcome of this clinical entity due to PaO_2/FiO_2 may vary in response to ventilator settings, especially for the setting of positive end expiratory pressure (PEEP).[11,12]

In 2012, the Berlin definition of ARDS proposed 3 categories of ARDS based on the degree of hypoxemia: mild ($200\,mm\,Hg < PaO_2/FiO_2 \leq 300\,mm\,Hg$), moderate ($100\,mm\,Hg < PaO_2/FiO_2 \leq 300\,mm\,Hg$), and severe ($PaO_2/FiO_2 \leq 100\,mm\,Hg$) with a PEEP $\geq 5\,cm\,H_2O$.[13,14] Despite the fact that the Berlin criteria showed better predictive power of mortality in ARDS than the AECC definition, the absolute value of the area under the receiver-operating characteristic (ROC) curve was only 0.577.[15] It suggests that some significant prognostic factors are still missing, and the initial hypoxemic level may not be the optimal predictor for prognosis. Therefore, we are interested in knowing whether the stabilized PaO_2/FiO_2 ratio following a standard ventilator setting or any other factors are more precise predictors of the prognosis in patients with ARDS. This study aimed to determine whether PaO_2/FiO_2 ratio 24 h (Day 1) after standard ventilator setting would be a better outcome predictor than the PaO_2/FiO_2 ratio on the day patients met ARDS Berlin criteria (Day 0).

PATIENTS AND METHODS

Patients and Hospital Setting

This study was conducted at Chi Mei Medical Center, a 1288-bed tertiary medical center with total 96 intensive care unit (ICU) beds for adults, including 57 medical and 39 surgical beds. The care in the ICU is covered by intensivists, senior residents, nurses, respiratory therapists, dietitians, physical therapists, and clinical pharmacists. The ICU team makes rounds at least once daily, and respiratory therapists are responsible for managing all MV, including weaning processes and spontaneous breathing trials. Patients admitted to ICUs were screened daily to identify who met the Berlin definition of ARDS and were collected prospectively between December 1, 2012 and May 31, 2015. Ethics approval was obtained from the Institution Review Board of Chi Mei Medical Center.

Variables Measurements

The following information of the included patients, including age; gender; co-morbidities; cause of ARDS; clinical features; laboratory data; comorbidities including congestive heart failure, chronic lung diseases, end-stage renal disease, liver cirrhosis, diabetes mellitus, acute or chronic encephalopathy, cancer, and immunocompromised condition; daily intake/output (I/O) ; organs dysfunction; Acute Physiology and Chronic Health Evaluation (APACHE II) score[16]; and Lung Injury Score during the first 24 h in the ICU before and after applying standard MV, were prospectively collected. The primary outcome was 28-day mortality caused by any reasons. In addition, arterial blood gas (ABG) and ventilator setting on the day of enrolling (Day 0) as well as 24 h later (Day 1) were obtained following the mandatory standard ventilator setting—mode: volume assist/control; tidal volume (V_T): 7 mL/kg of predicted body weight (PBW); ventilator rate: to maintain 35 to 50 mm Hg of $PaCO_2$, plus the PEEP and FiO_2 settings described in previous study according to ARDS Clinical Trials Network.[17] After the setting, patients were left undisturbed and blood gases were collected 30 min afterward. Throughout the acute course of ventilatory care, patients were recommended to receive a V_T of 5 to 9 mL/kg PBW at a plateau pressure < 30 cm H_2O with a ventilatory rate to maintain $PaCO_2$ at 35 to 50 mm Hg and PEEP ≥ 5 cm H_2O.

Definitions

Cardiovascular failure was defined as systolic blood pressure (SBP) of $\leq$90 mm Hg or a mean arterial pressure (MAP) $\leq$65 mm Hg for at least 1 h despite adequate fluid resuscitation; or the need for vasoactive agents (dopamine $\geq$5 mg/kg per min) to maintain SBP $\geq$ 90 mm Hg or MAP $\geq$ 65 mm Hg. Metabolic failure was defined as pH $\leq$ 7.30 or base deficit $\geq$ 5.0 mEq/L and a plasma lactate level >3 mmol/L. Hematologic failure was considered as a platelet count <80,000 per mm^3 or 50% decrease in platelet count from the highest value recorded over the past 3 days. Kidney failure was considered as oliguria with an average urine output < 0.5 mL/kg per h for 4 h despite adequate fluid resuscitation or creatinine $\geq$2 mg/dL. Hepatic failure was defined as markedly increased serum bilirubin level $\geq$4 mg/dL.

Statistical Analysis

Continuous variables were reported as mean and standard deviation. Categorical variables were presented as frequency counts with percentages. In addition, the differences of baseline characteristics and clinical variables between the survival and nonsurvival groups were evaluated using Student test (for continuous variables) and Pearson chi-squared test (for categorical variables). Logistic regression analysis was performed to estimate the association between the predictors of mortality and death at Day 28. The variables with significant difference at P value < 0.05 were selected as predictors in the multiple logistic regression analysis. The Cochran–Armitage trend test was used to determine proportions of mortality trend according to the severity of ARDS. SAS 9.4 for Windows (SAS Institute, Cary, NC) was used for all analyses. The ROC curves were plotted using STATA (version 12; Stata Corp., College Station, TX). Significance was set at $P < 0.05$ (2-tailed).

RESULTS

During the 30-month period, a total of 238 cases met the Berlin criteria for ARDS were enrolled, and their demographic characteristics were summarized in Table 1. The mean age of the patients was 62.7 ± 16.5 years and male comprised most of the patients (72.3%). Most of the patients were transferred from emergency department (53.8%), followed by general ward (37.0%). About two-thirds of patients came from medical departments. Pneumonia was the most common etiology of ARDS (n = 168, 70.6%), followed by nonpulmonary sepsis, transfusion-related acute lung injury, and lung contusion. Organ failure in cardiovascular system was the most common systemic failure, followed by hematological, renal, and metabolic failure. The average number of organ failure and comorbidity were 1.8 ± 1.2 and 1.0 ± 0.9, respectively. The APACHE II scores were 21.4 ± 8.7, and the Glasgow coma scale scores were 8.9 ± 4.2. The average lung injury score was 2.6 ± 0.5, and the baseline PaO_2/FiO_2 was 147.5 ± 64.3 mm Hg. Based on Berlin definition, most of the patients were classified as moderate ARDS (n = 125, 52.5%) on Day 0. The average length of ICU and hospital stays were 18.0 ± 11.3 and 32.6 ± 30.9, respectively.

The responses to standard ventilator setting at Days 0 and 1 were shown in Table 2. Twelve (5%) of the 238 cases who originally were classified as ARDS did not continually meet Berlin definition. In addition, a total of 134 (56%) patients had the changes regarding the severity of ARDS from Day 0 to Day 1. According to the criteria for severity determination in Berlin definition, 79 patients had better oxygenation on Day 1 while 55 patients had worse oxygenation on Day 1. Among 50 patients with initial mild ARDS, more than half of them had the PaO_2/FiO_2 ratios changed to within 100 and 200 mm Hg when only 11 (22%) patients remained the ratio within 200 and 300 mm Hg. For 125 patients with initial moderate ARDS, most of their PaO_2/FiO_2 ratios remained within 100 and 200 mm Hg. In 63 patients with initial severe ARDS, about half of their PaO_2/FiO_2 ratios were improved to the level between 100 and 200 mm Hg.

TABLE 1. Demographics of the Patients

Variables	n = 238
Male sex, n (%)	172 (72.3)
Age, y	62.7 ± 16.5
Source	
Emergency department, n (%)	128 (53.8)
Ward, n (%)	88 (37.0)
Other hospital, n (%)	22 (9.2)
Department	
Medicine, n (%)	154 (64.7)
Surgery, n (%)	84 (35.3)
Cause of ARDS	
Pneumonia, n (%)	168 (70.6)
Sepsis other than lung infection, n (%)	48 (20.2)
Transfusion-related acute lung injury, n (%)	10 (4.2)
Lung contusion, n (%)	6 (2.5)
Pancreatitis, n (%)	3 (1.3)
Neurogenic pulmonary edema, n (%)	2 (0.8)
Aspiration pneumonitis, n (%)	1 (0.4)
APACHE II score	21.4 ± 8.7
Glasgow coma scale	8.9 ± 4.2
Lung injury score	2.6 ± 0.5
V_T, mL/kg PBW	8.1 ± 1.9
Arterial blood gas (Day 0)	
pH	7.38 ± 0.08
$PaCO_2$, cm H_2O	33.9 ± 9.6
PaO_2, cm H_2O	95.8 ± 47.2
HCO_3, mEq/L	20.2 ± 5.0
FiO_2	0.70 ± 0.25
PaO_2/FiO_2, mm Hg	147.5 ± 64.3
Oxygenation based on Berlin definition	
Mild ARDS, n (%)	50 (21.0)
Moderate ARDS, n (%)	125 (52.5)
Severe ARDS, n (%)	63 (26.5)
Organ failure	
Cardiovascular, n (%)	161 (67.6)
Hematologic, n (%)	86 (36.1)
Kidney, n (%)	84 (35.3)
Metabolic, n (%)	75 (31.5)
Hepatic, n (%)	20 (8.4)
Numbers of comorbidity	1.0 ± 0.9
Numbers of organ failure	1.8 ± 1.2
Length of ICU stay, d	18.0 ± 11.3
Length of hospital stay, d	32.6 ± 30.9

Values are mean ± SD unless indicated otherwise.
APACHE = Acute Physiology and Chronic Health Evaluation, ARDS = acute respiratory distress syndrome, ICU = intensive care unit, PBW = predicted body weight, SD = standard deviation.

A total of 117 patients died during this study and the rate of 28-day mortality was 49.1%. We further compared the clinical variables between patients with survival and mortality outcomes (Table 3). Significant differences between mortality and survival groups were found as follows: age, disease severity, sepsis relevance, number of organ failure, fluid balance, length of ICU stay, and PaO_2/FiO_2 ratio on Day 1. On the contrary, the following variables, including gender, body mass index, lung injury score, cause of ARDS, V_T/PBW, baseline data of ABG, number of comorbidity, oxygenation, and PaO_2/FiO_2 ratio on Day 0, were not significantly different.

Table 4 shows the crude and adjusted odds ratio (OR) of the predictor for 28-day mortality. This multivariate analysis identified age, PaO_2/FiO_2 on Day 1, number of organ failures, and positive fluid balance within 5 days as significant risk factors of death.

Figures 1 and 2 show the mortality according to the PaO_2/FiO_2 ratio and ARDS severity using Berlin definition on Days 0 and 1. In Figure 1, we found that the mortality rate was increased along with the PaO_2/FiO_2 ratio on Day 1 ($P < 0.0001$) rather than on Day 0 ($P = 0.290$). Moreover, the same trend of increased mortality as well as PaO_2/FiO_2 ratio on Day 1 in patients with initial mild ARDS and in patients with moderate ARDS on Day 0 were shown Figure 2. When we compared the receiver operating curve to predict mortality according to the PaO_2/FiO_2 on Days 0 and 1, we found that the area under curve (AUC) for PaO_2/FiO_2 on Day 1 was 0.657 (95% CI: 0.589–0.726, $P < 0.001$) and 0.557 on Day 0 (95% CI: 0.484–0.630, $P = 0.130$) (Figure 3). Furthermore, AUC for PaO_2/FiO_2 on Day 1 was significant higher than for PaO_2/FiO_2 on Day 0 ($P = 0.0158$).

DISCUSSION

This study investigating 238 cases of ARDS based on Berlin definition have several significant findings. First of all, the initial severity of ARDS on Day 0 according to Berlin definition was not significantly associated with the outcome. It may indicate that current Berlin criteria for ARDS cannot identify a uniform group of patients with a similar severity of lung injury and mortality. By contrast, PaO_2/FiO_2 ratio on Day 1 following standard ventilator setting was found to be significantly associated with the outcome and thus could separate patients into subgroups with different clinical outcomes. It suggests that the 24 h standard ventilator setting application can effectively classify patients into different subgroups with significantly different mortality rates.

In the original study of Berlin definition for ARDS,[14] the mortality proportionally increased with the severity of ARDS (mild ARDS: 27%, 95% CI: 24–30; moderate: ARDS: 32%, 95% CI: 29–34; severe ARDS: 45%, 95% CI: 42–48, $P < 0.001$). However, further study[18] failed to validate this finding. In Hernu et al's prospective observation study, the 28-day mortality rate was 30.9%, 27.9%, and 49.3% in mild, moderate, and severe ARDS, respectively. However, they could not find that ARDS severity was significantly associated with the mortality in the Cox proportional hazard regression analysis ($P = 0.84$).[18] In our study, mortality rates between mild, moderate, and severe ARDS patients (48.0% vs 45.6% vs 57.1%, $P = 0.457$) at the onset of ARDS were not significantly different, and the mortality rates were not found significantly associated with the initial ARDS stage using further multivariate analysis ($P = 0.136$). These findings indicated that PaO_2/FiO_2 at the onset of ARDS might not be an accurate predictor of mortality.[19]

On the contrary, Villar et al[20] showed that a standard ventilatory setting could effectively distinguish the 3 PaO_2/FiO_2 risk categories 24 h after the onset of ARDS ($P = 0.0001$). By using this ventilatory setting, the mortality of patients were classified as mild (17%), moderate (40.9%), and severe ARDS (58.1%) ($P = 0.00001$), separately. Costa and Amato[19] proposed that the use of stabilized PaO_2/FiO_2 ratio (after the first 24 h) might improve the distinguishability of the patients. In their results, the oxygenation level taken 24 h afterward in patients with moderate ARDS had significant higher unadjusted

TABLE 2. Case Number According to Berlin Definition and the Ratio of Partial Pressure Arterial Oxygen and Fraction of Inspired Oxygen Ratio on Day 1

	Day 0		
Day 1	Mild ARDS (200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg) (n = 50)	Moderate ARDS (100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg) (n = 125)	Severe ARDS (PaO_2/FiO_2 ≤ 100 mm Hg) (n = 63)
PaO_2/FiO_2 > 300 mm Hg	7 (14.0)	3 (2.4)	2 (3.2)
200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg	11 (22.0)	28 (22.4)	7 (11.1)
100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg	27 (54.0)	71 (56.8)	32 (50.8)
PaO_2/FiO_2 ≤ 100 mm Hg	5 (10.0)	23 (18.4)	22 (34.9)

ARDS = acute respiratory distress syndrome.

TABLE 3. Comparisons Between Patients With Survival and Mortality

Characteristics	Mortality (n = 117)	Survival (n = 121)	*P* Value
Age	67.3 ± 14.8	58.3 ± 16.9	<0.001
Gender			0.315
Male	81 (69.2)	91 (75.2)	
Female	36 (30.8)	30 (24.8)	
Department			0.499
Medicine	73 (62.4)	81 (66.9)	
Surgery	44 (37.6)	40 (33.1)	
Body mass index	24.2 ± 5.2	24.0 ± 4.7	0.844
APACHE II score	23.7 ± 8.7	19.2 ± 8.0	<0.001
Lung injury score	2.64 ± 0.49	2.58 ± 0.60	0.352
Sepsis related			0.001
Yes	107 (91.5)	90 (74.4)	
No	10 (8.5)	31 (25.6)	
Cause of ARDS			0.661
Pulmonary	85 (72.6)	91 (75.2)	
Nonpulmonary	32 (27.4)	30 (24.8)	
V_T, mL/kg PBW	8.0 ± 1.9	8.3 ± 1.8	0.223
Mean arterial pressure	80.0 ± 19.1	78.3 ± 19.4	0.479
Arterial blood gas			
pH	7.37 ± 0.08	7.38 ± 0.08	0.577
$PaCO_2$, cm H_2O	34.7 ± 11.3	33.1 ± 7.5	0.192
PaO_2, cm H_2O	94.9 ± 50.1	96.7 ± 44.4	0.769
HCO_3, mEq/L	20.5 ± 5.7	19.9 ± 4.1	0.392
FiO_2	0.72 ± 0.25	0.69 ± 0.25	0.254
PaO_2/FiO_2, mm Hg	141.2 ± 63.2	153.7 ± 65.0	0.136
Lab. data			
C-reactive protein	135.1 ± 92.6	154.9 ± 87.2	0.121
Creatinine	2.15 ± 1.66	1.83 ± 1.61	0.147
Oxygenation based on Berlin definition on Day 0			0.457
Mild ARDS	24 (20.5)	26 (21.5)	
Moderate ARDS	57 (48.7)	68 (56.2)	
Severe ARDS	36 (30.8)	27 (22.3)	
PaO_2/FiO_2, mm Hg on Day 1	141.6 ± 66.5	183.5 ± 83.3	<0.001
Oxygenation based on Berlin definition on Day 1			0.001
Mild ARDS	18 (15.4)	40 (33.1)	
Moderate ARDS	65 (55.6)	65 (53.7)	
Severe ARDS	34 (29.1)	16 (13.2)	
Numbers of comorbidity	1.16 ± 0.90	1.00 ± 0.97	0.183
Numbers of organ failure	2.15 ± 1.29	1.44 ± 1.16	<0.001
I/O negative within 5 d			<0.001
Yes	74 (63.2)	106 (87.6)	
No	43 (36.8)	15 (12.4)	
Length of ICU stay, d	14.2 ± 8.3	21.7 ± 12.6	<0.001

Categorical variables are expressed in numbers (%) and continuous variable as mean ± SD.

APACHE = Acute Physiology and Chronic Health Evaluation, ARDS = acute respiratory distress syndrome, ICU = intensive care unit, PBW = predicted body weight, SD = standard deviation.

TABLE 4. Predictors of 28-d Mortality Outcome

Variables	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age (per 10)	1.427 (1.203–1.692)	<0.001	1.478 (1.222–1.788)	<0.001
APACHE II score (per 10)	1.914 (1.381–2.652)	<0.001	1.324 (0.895–1.958)	0.160
PaO_2/FiO_2 on Day 1 (per 100 units)	0.448 (0.300–0.670)	<0.001	0.568 (0.368–0.879)	0.011
Numbers of organ failure	1.602 (1.284–1.998)	<0.001	1.557 (1.220–1.988)	<0.001
Sepsis related				
No	1.00		1.00	
Yes	3.686 (1.713–7.928)	0.001	1.599 (0.662–3.867)	0.297
I/O negative ≤5 d				
Yes	1.00		1.00	
No	4.106 (2.126–7.933)	<0.001	3.379 (1.616–7.067)	0.001

Adjust covariables include age, APACHE II score, sepsis relevance, number of organ failure, fluid balance, and PaO_2/FiO_2 ratio on Day 1. APACHE = Acute Physiology and Chronic Health Evaluation, CI = confidence interval, OR = odds ratio.

and adjusted ORs for mortality (1.65 and 1.49) than in patients with mild ARDS. In our study, oxygenation measurements 24 h after the onset of ARDS among mild, moderate, and severe ARDS could be significantly identified (34.8% vs 50.0% vs 68.0%, $P = 0.001$), and further multivariate analysis also confirmed that PaO_2/FiO_2 ratio after 24 h was significantly associated with mortality ($P < 0.001$). All the findings indicated that the PaO_2/FiO_2 ratio after stabilization might be a more appropriate predictor of death than the initial PaO_2/FiO_2 ratio at the onset of ARDS.

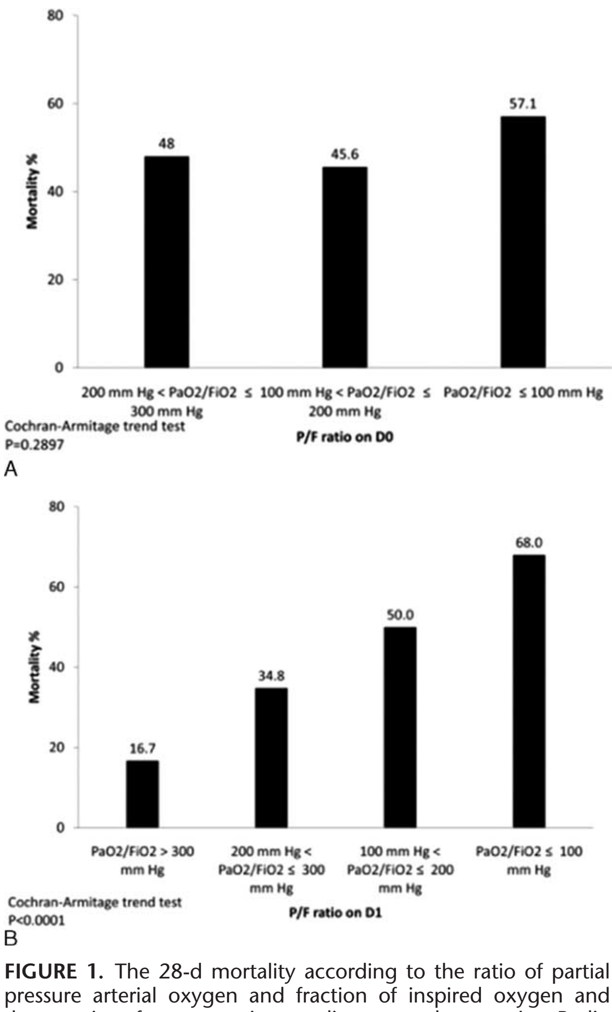

FIGURE 1. The 28-d mortality according to the ratio of partial pressure arterial oxygen and fraction of inspired oxygen and the severity of acute respiratory distress syndrome using Berlin definition on Day 0 (A) and Day 1 (B).

We also found that the increases of PaO_2/FiO_2 from Day 0 to Day 1 were significantly higher among survivors than mortality subgroups (0.3 mm Hg vs 29.8 mm Hg, $P = 0.005$). This finding was consistent with previous study that the increase in PaO_2/FiO_2 was associated with mortality reduction (adjusted OR: 0.80 [95% CI: 0.72–0.89] per 25-mm Hg increase in PaO_2/FiO_2). Moreover, the association was more prominent in patients with severe disease (baseline PaO_2/FiO_2 ≤ 150 mm Hg).[21] Another study investigating the outcome of 216 ARDS patients treated with inhaled epoprostenol had the similar finding that hospital mortality was significantly associated with an incremental change in PaO_2/FiO_2 during the first 24 h of treatment (adjusted OR: 0.99, 95% CI: 0.988–0.994, $P = 0.002$).[22] Therefore, these findings suggest that the change of PaO_2/FiO_2 may be another good predictor of outcome in patients with ARDS.

In addition to PaO_2/FiO_2 ratio on Day 1, we also identified some independent risk factors of death, including age, number of organ failure, and positive fluid balance in this study. Several previous studies published similar findings. In Gong et al,[23] age was a significant predictor of mortality with adjusted OR of 1.96 (95% CI: 1.50–2.53). In Pacheco et al,[22] the addition of cumulative fluid balance of >4 L was an independent predictor (adjusted OR: 2.36, 95% CI: 1.66–3.37, $P = 0.02$). In Zhang and Chen,[24] positive fluid balance in the first 8 days was significantly associated with increased risk of death after stepwise regression analysis (OR: 1.00057; 95% CI: 1.00034–1.00080). In Li et al,[25] the logistic analysis showed that the number of organ dysfunction was related with prognosis in elderly patients with ARDS (OR: 2.328, 95% CI: 1.193–4.520, $P = 0.029$). Even for the young patients with ARDS, the numbers of organ dysfunctions in nonsurvivors were significantly higher than those of the survivors.[25] However, in contrast to most of the above studies[22–25] using AECC criteria for ARDS diagnosis, our study used Berlin definition. Therefore, a further large-scale study using Berlin definition of ARDS is still needed to validate our findings.

This study had several limitations. First, we only measure PaO_2/FiO_2 ratio on Days 0 and 1. It may be possible that at

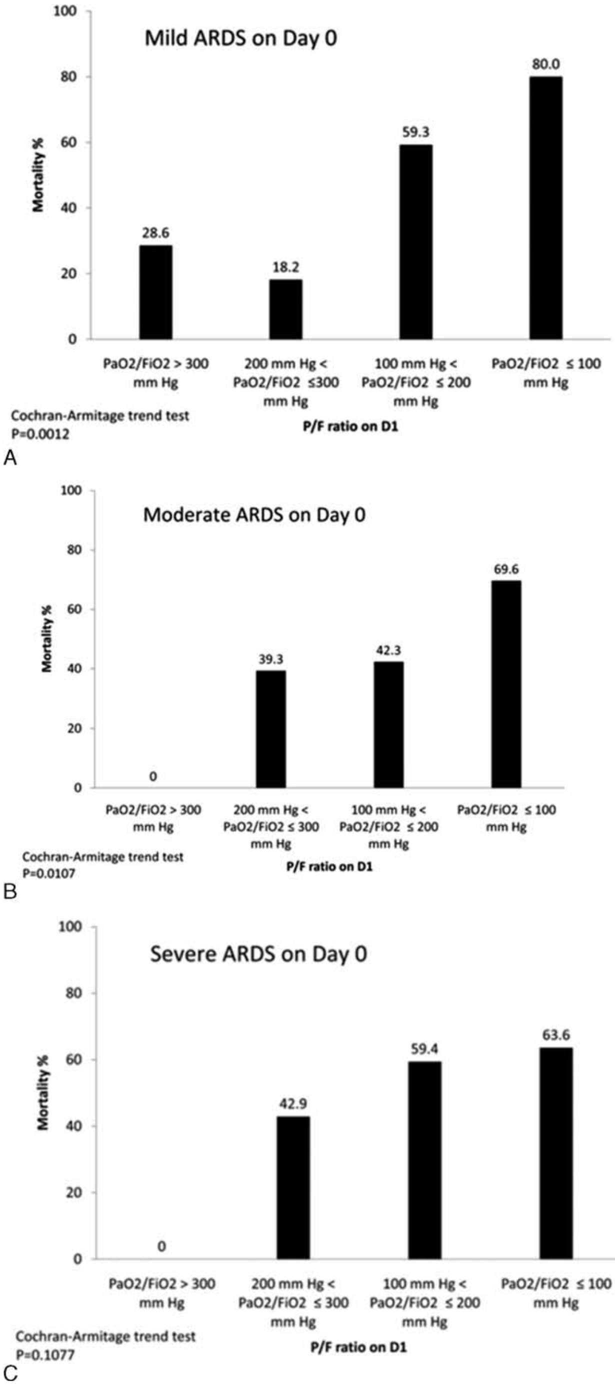

FIGURE 2. The 28-d mortality according to the severity of acute respiratory distress syndrome (mild, A; moderate, B; and severe, C) using Berlin definition on Day 0.

earlier time we are better capable of separating patients into different severity of ARDS. Second, we only followed the lung-protective strategy, but we did not provide a specific protocol for adjusting the setting of mechanical ventilator throughout the all ICU course. However, our study design can truly reflect the situation in the real life. Third, some managements for ARDS such as prone position, high frequency oscillatory ventilation, or lung recruitment maneuver were not recorded. Fourth, this study was conducted in a single medical center, and the patient number was limited. Our findings may not be generalized to other hospital. A large and multicenter study should be warranted to clarify this issue.

In conclusion, PaO_2/FiO_2 ratio on Day 0 is not a good predictor of outcomes in patients with ARDS. In contrast, a stabilized (24-h delayed) PaO_2/FiO_2 ratio after applying mechanical ventilator can accurately predict the outcomes in patients with ARDS. In addition, age, number of organ failure, and the status of fluid balance are found to be independently associated with mortality.

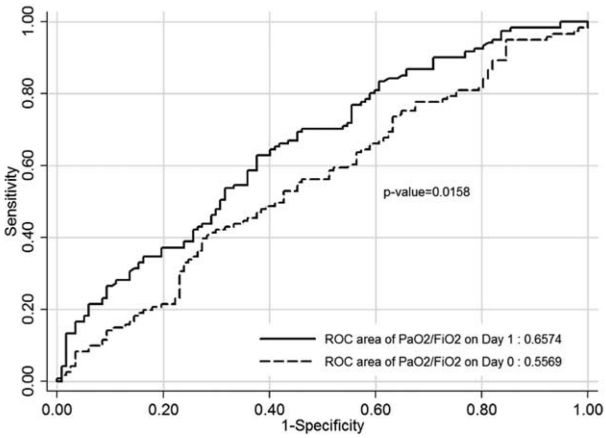

FIGURE 3. Comparisons between the receiver operating curve for predictive validity of mortality according to the ratio of partial pressure arterial oxygen and fraction of inspired oxygen on Days 0 and 1.

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