Prognostic Factors to Predict ICU Mortality in Patients with ARDS Who Received Early and Prolonged Prone Positioning Therapy

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Research

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Prognostic Factors to Predict ICU Mortality in Patients with ARDS Who Received Early and Prolonged Prone Positioning Therapy

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Abstract

Background: Early and prolonged prone positioning (PP) could reduce the mortality in patients with moderate to severe ARDS, however, factors associated with mortality in the intensive care unit (ICU) remain unclear. The aim of this study is to identified factors associated with mortality and create the prognostic score in patients with ARDS who underwent early and prolonged PP.

Methods: This retrospective study included patients with moderate to severe ARDS admitted to the intensive care unit (ICU) from January 2015 to June 2018 in a tertiary referral center in Taiwan and who received early and prolonged PP. Demographic data, disease severity score, comorbidities, and clinical outcomes were recorded. Univariate and multivariate regression models were used to estimate the odds ratio (OR) of ICU mortality. Receiver operating characteristic (ROC) curve analysis were performed to identify the cutoff value of parameters.

Results: A total of 116 patients were enrolled. In the multivariate analysis, three factors were significantly associated with mortality: renal replacement therapy (RRT; OR: 3.38, 1.55–7.36), malignant comorbidity (OR: 7.42, 2.06–26.70), and noninfluenza-related ARDS (OR: 3.78, 1.07–13.29). Age, RRT, noninfluenza-related ARDS, malignant comorbidity, and APACHE II score were included in a composite prone score, which demonstrated an area under the curve of 0.816 for predicting mortality risk. The mortality risk in ICU was 27.1% in the low-risk group (prone score: 0–2) and 84.2% in the high-risk group (prone score: 3–5).

Conclusions: For patients with moderate to severe ARDS even receiving early and prolonged PP in ICU, poor prognostic factors were age, RRT, malignant comorbidity, noninfluenza-related ARDS, and higher APACHE II score. High mortality should be informed to the family of patient if their prone score was more than 3 points.

Keywords

Acute respiratory distress syndrome, Prone positioning, Prognostic factors, ICU mortality

Background

The prevalence of acute respiratory distress syndrome (ARDS) in patients admitted to the intensive care units (ICU) is approximately 10%, [1] and the mortality rate ranges from 30% to 50% because of the high heterogeneity in ARDS. [2, 3] Although pharmaceutical treatment is limited, prone positioning (PP) improves the outcomes of patients with ARDS. [3-5] In 1976, Piehl and Brown proposed that PP therapy could improve oxygenation in patients with ARDS. [6] Since 2001, several randomized control trials have demonstrated the survival benefit of PP therapy in patients with ARDS. [7-20] In 2013, The PROSEVA trial demonstrated that early application and prolonged duration of PP significantly reduced mortality in patients with moderate to severe ARDS. [7] Since then, five meta-analyses have recommend that in patients with ARDS requiring PP therapy, early introduction of PP accompanied by lung protective strategy and prolonged PP to ≥10–12 h per day were associated with lower mortality. [21-29]

PP has become a standard treatment in ARDS, and numerous studies have revealed factors associated with lower mortality. [4, 5, 30] However, few studies have discussed the poor prognostic factors in patients with ARDS who received early and prolonged PP therapy. [30, 31] Modrykamien et al. analyzed 43 patients with severe ARDS treated with PP and found that only three parameters were significant predictors of survival in ICU: APACHE II score, plateau pressure (Pplat), and driving pressure. [30] Kao et al. enrolled 65 patients with severe influenza-related pulmonary ARDS and found three factors to be independently associated with 60-day mortality: pneumonia severe index, renal replacement therapy (RRT), and dynamic change in driving pressure. [31] However, these prognostic factors are of limited clinical utility in predicting which patients will benefit from PP therapy because of the lack of standardized the PP protocol, only on influenza-related ARDS, lack of consideration of ICU mortality, and lack of a scoring system for clinical application. [30, 31] In the current study, we identified factors associated ICU mortality in 116 patients with ARDS who received early and prolonged PP therapy and developed

a prognostic score (prone score) to predict ICU mortality.

2. Methods

2.1. Study design and patients

This retrospective cohort study was conducted in the medical ICUs of Taichung Veterans General Hospital (TCVGH), a 1200-bed tertiary referral center in Taiwan, from January 2015 to June 2018. We enrolled patients diagnosed as having ARDS who received mechanical ventilation in ICUs and were treated with PP for moderate to severe hypoxemia despite a positive end-expiratory pressure (PEEP) of >10 cmH_2O. Moderate to severe hypoxemia was defined as a PaO_2/fraction concentration of inspired oxygen (FiO_2) ratio <150 mmHg according to previous clinical trials [32, 33] and the Berlin definition of ARDS. [33] We excluded patients who received PP therapy for <6 h and those who received extracorporeal membrane oxygenation due to failed PP therapy. Data related to demographics, laboratory examination, period from hypoxemia to PP, duration of PP therapy, ventilator settings, comorbidities, and clinical outcomes were extracted from the electronic medical records. The study protocol was reviewed and approved by the Institutional Review Board of TCVGH (IRB number, CE19379A; date of approval, October 25, 2019); the need for patient consent was waived due to the retrospective study design and anonymization and deidentification of patient data prior to analysis.

2.2 Mechanical ventilator setting, recruitment maneuver, and protocol of PP therapy in medical ICUs

Patients diagnosed ARDS were treated with lung protective strategy to maintain Pplat ≤ 30 cm H_2O by using lower tidal volume ventilation (goal of tidal volume: 4–8 mL/kg predicted body weight). The setting of PEEP in our ICUs was followed by a lower PEEP strategy according to previous research and meta-analysis. [34-36] FiO_2 in the ventilator was adjusted to keep oxyhemoglobin saturation by pulse oximetry (SpO_2) > 90%. The PEEP-FiO_2 combinations were the following: 5–8/0.5, 8–10/0.6, 10–12/0.7, 12–14/0.8, 14–16/0.9, and 16–18/1.0. [37] For

patients who failed to maintain the goal of $SpO_2 \geq 90\%$ even using FiO_2 of >0.6, recruitment maneuvers (RMs) were indicated through brief application of a high level of continuous positive airway pressure (CPAP) to correct hypoxemia. In our hospital, RMs include sustained inflation by abruptly raising the CPAP to 40 cmH_2O for 40 s. [38, 39] PP was initiated as rescue therapy for patients with ARDS who experienced refractory hypoxemia within 24 h, provided the following criteria were met: $PaO_2/FiO_2 < 150$ mmHg, $FiO_2 \geq 0.6$, and PEEP ≥ 10 cmH_2O.

The protocol of PP therapy was according to previous publication. [37] In brief, patients lied in a prone position on a silicone pad, with their dependent parts supported by silicone cushions. Patients received PP continuously for 48–72 h and even longer until PaO_2/FiO_2 remained <150. During PP therapy, patients were turned right or left alternately every 2 h to avoid pressure sore formation. After hypoxemia improved and clinical condition stabilized (i.e., when $SpO_2 > 90\%$ and $FiO_2 < 60\%$ for >24 h after at least 48–72 h of PP therapy), patients lied in the supine position.

2.3 Data collection, assessment, and outcome measures

Data were collected on age, sex, body mass index (BMI), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and major comorbidities. The major comorbidities were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code, such as congestive heart failure (CHF), coronary artery disease (CAD), interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), chronic kidney disease (CKD), liver cirrhosis, autoimmune disease, and malignancy. Patients who received RRT during PP therapy were identified and analyzed. Parameters of ventilator settings extracted from electronic medical records included the following: mode of ventilation, tidal volume, peak inspiratory pressure (PIP), PEEP, and Pplat. The primary outcome was ICU mortality, which was defined as death in the ICU.

2.4 Statistical analysis

Statistical analyses and database management were performed using SPSS (version 22.0; IBM, Armonk, NY, USA). Categorical variables are presented as frequencies and percentages and were analyzed with the chi-square test. Nonparametric data were assessed using the Mann–Whitney U test and are presented as the median and interquartile range (IQR). Univariate and multivariate logistic regression models were used to estimate the odds ratio (OR). Receiver operating characteristic (ROC) curve analysis were performed for all the parameters measured and the cut-off points were decided to maximize the sum of sensitivity and specificity values of the respective ROC curves. In this study, we used the two-tailed test, and significance was set at $P < 0.05$.

3. Results

3.1 Patients' clinical and demographic characteristics

From January 2015 to June 2018, 116 patients with ARDS received mechanical ventilation in ICUs and were treated with PP for moderate to severe hypoxemia despite using PEEP of >10 cmH_2O (Figure 1). Table 1 presents the patients' demographic characteristics, etiology of ARDS, comorbidities, protocol of PP therapy, ventilator parameters, and ICU mortality (Table 1). The time from diagnosis of ARDS to initiation of PP therapy was 18.3 (IQR, 8.4–33.4) h, and the duration of continuous PP therapy was 66.1 (44.4–84.5) h, which fit the current treatment concept of early and prolonged PP in ARDS (Table 1). In this cohort, the major cause of ARDS was noninfluenza-related ARDS (n = 83, 71.6%), followed by influenza-related ARDS (n = 20, 17.2%) and extrapulmonary ARDS (n = 13, 11.2%). The median APACHE II score was 31, indicating high clinical severity in this cohort. The ICU mortality was 55.2% (n = 64). Figure 1 presents the details of enrollment and follow-up.

3.2 Clinical and demographic characteristics between surviving and nonsurviving patients

Clinicodemographic parameters were compared between surviving and nonsurviving patients (Table 2). The nonsurviving patients were older, had a malignant comorbidity, had a higher

APACHE II score, noninfluenza-related pulmonary ARDS and received RRT more frequently (all $P < 0.05$). Other variables were not significantly different between the surviving and nonsurviving groups (Table 2).

3.3 Factors associated with ICU mortality for patients with ARDS who received PP therapy

Table 3 summarizes the results of logistic regression analysis for determining factors associated with ICU mortality. Univariate analysis identified five factors associated with mortality: male sex (OR, 1.04; 95% CI, 1.01–1.07, $P = 0.003$), APACHE II score (OR, 1.07; 95% CI, 1.01–1.14; $P = 0.029$), noninfluenza-related pulmonary ARDS (OR, 3.78 compared with extrapulmonary ARDS; 95% CI, 1.07–13.29; $P = 0.039$), RRT (OR, 3.38; 95% CI, 1.55–7.36; $P = 0.002$), and active malignant disease (OR, 7.42; 95% CI, 2.06–26.7; $P = 0.002$). Multivariate analysis indicated that noninfluenza-related pulmonary ARDS (OR: 5.17 compared with extrapulmonary ARDS, 95% CI: 1.16–23.16), RRT (OR, 4.05; 95% CI, 1.54–10.67; $P = 0.005$), and active malignant disease (OR, 8.86; 95% CI, 2.22–35.41; $P = 0.003$) were significant predictive factors of ARDS-related mortality.

3.4 Composition of prone score and its prediction of ICU mortality with PP therapy

A "prone score" was generated to predict the risk of ICU mortality. Receiver operating curves (ROC) were plotted to identify the optimal cutoff threshold in each parameter for predicting ICU mortality (Figure 2). The cutoffs were the following: age, 53 years (AUC = 0.668) and APACHE II score, 33 points (AUC = 0.623) (Figure 2 and Table 4). The composite "prone score" to predict poor prognosis included five parameters: (1) age ≥ 53 years, (2) APACHE II ≥ 33, (3) receiving RRT in the ICU, (4) noninfluenza-related pulmonary ARDS, and (5) malignancy. Each item was assigned 1 point, and the total prone score ranged from 0 to 5 points. The cutoff value of the prone score with the best predictive power of ICU mortality was ≥3 points (AUC = 0.816), which was better than the APACHE II score (Table 4). The ICU mortality in the low-risk group (prone score: 0–2 points) was 27.1%; however, the ICU mortality in the high-risk group (prone score 3–5) was

84.2%. Univariate analysis revealed that prone score ≥3 points had a significantly higher risk of ICU mortality (OR, 14.33; 95% CI, 5.74–35.77; $P < 0.001$; Table 3). As shown in Table 4, the sensitivity of prone score to predict ICU mortality was 75.0 % and the specificity was 82.7 %.

Discussion

The current study had three major findings. First, we identified five factors associated with ICU mortality in patients with moderate to severe ARDS who received PP therapy: age, higher APACHE II score, noninfluenza-related pulmonary ARDS, RRT, and malignant comorbidity. Second, we developed a new clinical scoring tool—the prone score—to predict refractoriness to PP therapy and high risk of ICU mortality due to advanced ARDS. Third, our data revealed that the ICU mortality was 84.2% in the high-risk group (prone score 3–5) and 27.1% in the low-risk group (prone score 0–2). This is the first real-world study to evaluate the treatment outcomes of PP therapy in patients with moderate to severe ARDS and develop a prediction score of ICU mortality in them.

Factors associated with good outcomes for these patients are early PP initiation, prolonged PP treatment sessions, and combinations with lung protective strategies. [7, 13] However, how early should PP therapy be initiated to reduce mortality in ARDS remains unclear. Guérin et al. (2004) proposed that PP therapy should be initiated "as early as possible" in patients with ARDS,[7] which has been widely followed, with PP being initiated between 6 and 72 h after ARDS diagnosis. [3, 7, 9, 12, 13, 17, 18] In 2013, the PROSEVA trial clarified that PP therapy should be initiated within 36 h of ARDS diagnosis.[3] In our medical ICUs, the protocol is PP initiation within 24 h of the diagnosis of moderate to severe ARDS. In the current study, the timing of PP initiation was within 36 h (median: 18.3 h, IQR: 8.4–33.4). In addition, no significant difference between the surviving and nonsurviving groups regarding the timing of PP initiation was noted (15.6 vs. 21.3 h, $P = 0.084$). Therefore, the timing of PP therapy is less likely to be a confounder in ICU mortality in this cohort.

Prolonged PP therapy may be a critical factor associated with mortality. [7, 9, 17, 18] In the PROSEVA trial, the goal of PP therapy was >20-h duration, and the actual dose was 17 h on average, which reduced mortality in patients with moderate to severe ARDS. [7] Two meta-analyses stated that the PP therapy >12 h/day significantly reduced mortality in patients with ARDS having refractory hypoxemia. [21, 25] In our medical ICUs, patients received PP continuously for 48–72 h and even longer if PaO_2/FiO_2 persisted to be <150. [37] A recent prospective study performed 231 PP sessions with a mean length of 21.5 ± 5 h per session in patients with ARDS and recommended that the duration of PP therapy should be ≥24 h, depending on whether PaO_2/FiO_2 remains <150. [40] In the current study, PP therapy was significantly longer than 20 h (median: 66.1 h, IQR: 44.4–85.4), with no significant difference between the surviving and nonsurviving groups (69.3 vs. 61.1 h, $p = 0.170$). Therefore, the dose of PP therapy is less likely to be a confounder in ICU mortality in this cohort.

Lung protective strategy in conjunction with PP appeared to be a useful approach. Two meta-analyses revealed that the benefit of PP therapy in reducing mortality was only found in combination with the lung protective strategy. [21, 22] At our ICUs, the lung protective strategy is the standard of care. Therefore, in the current study, ventilation settings, including tidal volume, PEEP, and Pplat, were not significantly different between the surviving and nonsurviving groups.

The main strength of this study is the development of a scoring system to evaluate patients with moderate to severe ARDS admitted to the ICUs to determine who will receive greater benefit from early and prolonged PP therapy. Several studies have attempted to determine factors associated with mortality in patients with ARDS, including those receiving PP therapy. Lim et al. found that oxygenation improved faster in patients with extrapulmonary ARDS than pneumonia-related ARDS. [41] Kao et al. retrospectively examined 65 patients with influenza-related ARDS treated with PP and found that 60-day mortality was associated with a higher pneumonia severity index, RRT, and increased dynamic driving pressure. [31] Modrykamien et al. retrospectively

studied 43 patients and identified only three factors—APACHE II score, Pplat, and driving pressure—to be associated with mortality when receiving PP therapy. [30] These studies provided some clues of mortality predictors but were limited in developing a scoring system. In our study, we identified five prognostic factors from 116 patients and used their cutoffs to develop the prone score to predict ICU mortality: age ≥ 53 years, APACHE II score ≥ 33 points, receiving RRT, malignant comorbidity, and noninfluenza-related ARDS.

This study has several limitations. First, because of the retrospective design, heterogeneity may have existed in each patient. Second, the study was conducted at medical ICUs in a single medical center rather than a multicenter study, meaning that the results may not be generalizable. In practice, the protocol of PP therapy, especially timing of initiation and dosage, and combination with other intensive respiratory therapies, such as recruitment maneuver and fluid strategy, vary between ICUs in different hospitals. In our medical ICUs, we followed a standard protocol of early and prolonged PP therapy since 2007.[37] We treated patients with sepsis, pneumonia, and ARDS by using the documented protocol modified from the latest severe sepsis guideline.[42] In addition, our ICUs were serviced by full-time intensivists. Therefore, heterogeneity in ICU care and PP therapy protocols was minimal in the present study. Third, critically ill patients in different countries or ICUs may have different demographic patterns, disease severity, and comorbidities, which can confound ICU mortality. Finally, our results may not be generalizable to patients with ARDS in pediatric, neurosurgical, surgical, and cardiac ICUs, because the current study included only adult patients admitted to the medical ICUs in TCVGH.

Conclusions

We developed the prone score to predict ICU mortality in patients with ARDS receiving early and prolonged PP therapy. The prone score comprises five parameters: age ≥ 53 years, receiving RRT in ICU, noninfluenza-related pulmonary ARDS, malignancy, and APACHE II score ≥ 33. The corresponding mortality rates for low risk (score 0–2) and high risk (score 3–5) were 27.1%

and 84.2%, respectively. To the best of our knowledge, the current study is the first article to develop the prognostic score for patients with ARDS receiving early and prolonged PP therapy.

List of abbreviations

ARDS: Acute respiratory distress syndrome

APACHE II: Acute Physiology and Chronic Health Evaluation II

AUC: Area under the receiver operating characteristic curve

CAD: Coronary artery disease

CHF: Congestive heart failure

CKD: Chronic kidney disease

COPD: Chronic obstructive pulmonary disease

DM: Diabetes Mellitus

ECMO: extracorporeal membrane oxygenation

ICU: Intensive care unit

ILD: Interstitial lung disease

PEEP: Positive end-expiratory pressure

PIP: Peak inspiratory pressure

Pplat: Plateau pressure

ROC: Receiver operating curves

Declarations

Ethics approval and consent to participate: The study protocol was reviewed and approved by the Institutional Review Board of TCVGH (IRB number, CE19379A; date of approval, October 25, 2019); the need for patient consent was waived due to the retrospective study design and anonymization and deidentification of patient data prior to analysis.

Consent for publication: Not applicable

Availability of data and materials: The datasets generated and/or analysed during the current study are not publicly available due to this study was conducted by using deidentified medical records from TCVGH but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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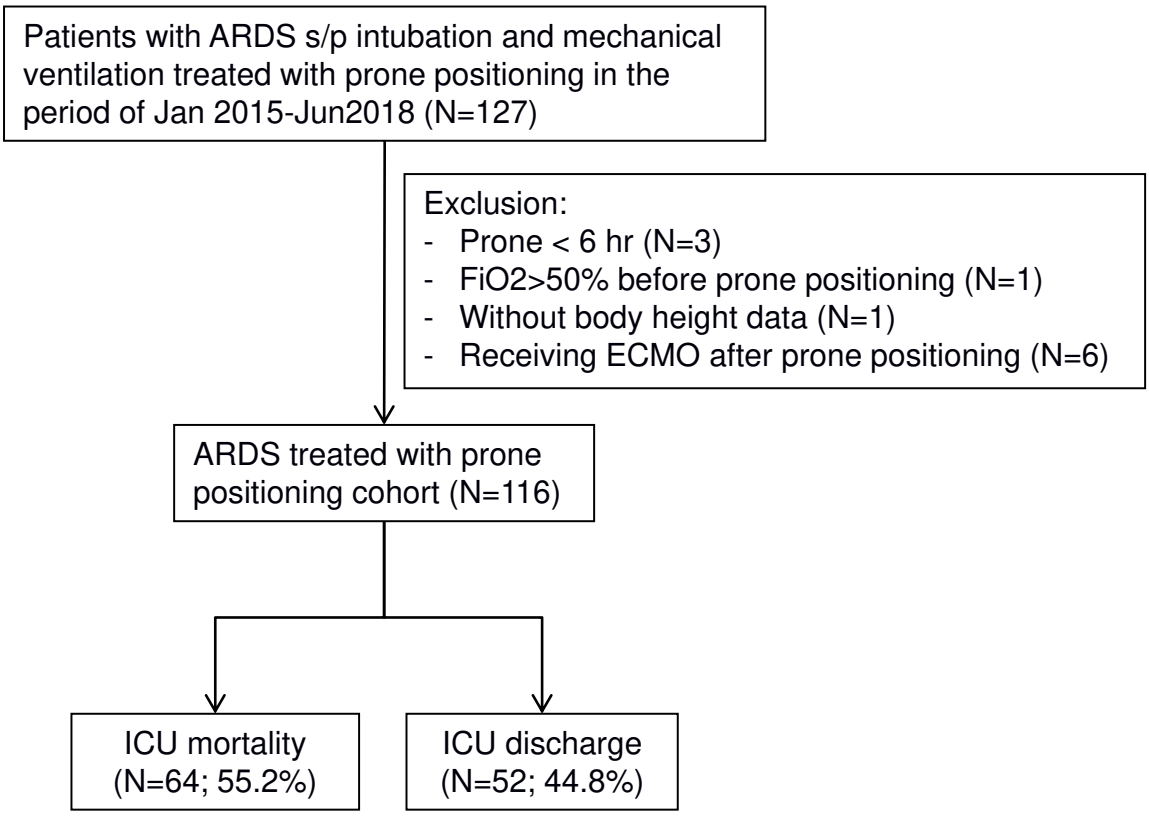

Fig. 1 Enrollment and follow-up of the study participants. ARDS, acute respiratory distress syndrome; FiO2, fraction concentration of inspired oxygen; ECMO, extracorporeal membrane oxygenation; ICU: intensive care unit

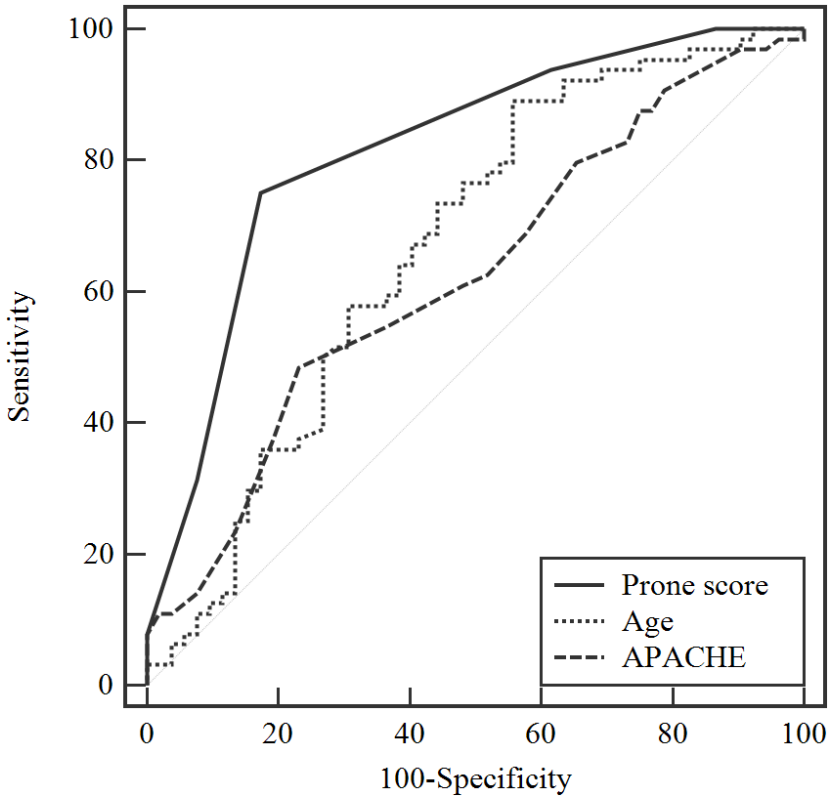

Fig. 2 Receiver operating curves analysis of age, APACHE II score, and prone score for predicting ICU mortality in patients with acute respiratory distress syndrome receiving early and prolonged prone positioning.

Table 1 Patients' clinicodemographic characteristics

	Total (n = 116)	
Demographic data		
Age	62.9	(52.1-74.2)
Gender-Male	70	(60.3%)
BMI (kg/m^2)	24.4	(21.9-27.9)
APACHE II score	31	(27-35)
ICU mortality	64	(55.2%)
Cause of ARDS		
Non-influenza pulmonary ARDS	83	(71.6%)
Influenza	20	(17.2%)
Extrapulmonary ARDS	13	(11.2%)
Renal replacement therapy	52	(44.8%)
Comorbidity		
CHF	6	(5.2%)
CAD	8	(6.9%)
ILD	6	(5.2%)
COPD	10	(8.6%)
DM	40	(34.5%)
CKD	44	(37.9%)
Liver Cirrhosis	10	(8.6%)
Autoimmune disease	18	(15.5%)
Malignancy	23	(19.8%)
Prone information		
Timing from ARDS to prone (h)	18.3	(8.4-33.4)
Total prone duration (h)	66.1	(44.4-84.5)
PF ratio	90.6	(71.0-113.8)
Ventilation setting		
Mode, volume control	114	(95.7%)
Tidal volume (ml/Kg)	6.0	(5.7-6.5)
PEEP (mmHg)	14.0	(14-16)
PIP (mmHg)	32.0	(29-35)
Pplat (mmHg)	29.0	(26.2-31)
Driving Pressure (mmHg)	13.0	(11.8-16.2)
Compliance (ml/mmHg)	25.8	(21.3-32.5)

Continuous data are expressed as median and IQR. Categorical data were expressed number and percentage. CHF, congestive heart failure; CAD, coronary artery disease; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease, DM, diabetes mellitus; CKD, chronic kidney disease; PEEP: positive end-expiratory pressure；PIP, peak inspiratory pressure; Pplat, plateau pressure

Table 2 Characteristics of survivors and nonsurvivors in patients with ARDS receiving prone positioning

	Alive (n = 52)		Death (n = 64)		*p* value
Demographic data					
Age	56.7	(46.2-68.3)	65.7	(57.3-76.0)	0.002**
Gender-Male	34	(65.4%)	36	(56.3%)	0.345
BMI (kg/m^2)	25.5	(22.0-28.3)	24.0	(21.8-27.1)	0.289
APACHE II score	30.0	(25.8-32.0)	32.0	(28-35)	0.022*
Cause of ARDS					0.028*
Non-influenza pulmonary ARDS	31	(59.6%)	52	(81.3%)	
Influenza	12	(23.1%)	8	(12.5%)	
Extrapulmonary ARDS	9	(17.3%)	4	(6.3%)	
Renal replacement therapy	15	(28.8%)	37	(57.8%)	0.003**
Comorbidity					
CHF [f]	4	(7.7%)	2	(3.1%)	0.406
CAD [f]	4	(7.7%)	4	(6.3%)	1.000
ILD [f]	3	(5.8%)	3	(4.7%)	1.000
COPD [f]	6	(11.5%)	4	(6.3%)	0.340
DM	22	(42.3%)	18	(28.1%)	0.121
CKD	17	(32.7%)	27	(42.2%)	0.339
Cirrhosis [f]	3	(5.8%)	7	(10.9%)	0.508
Autoimmune disease	7	(13.5%)	11	(17.2%)	0.617
Malignancy	3	(5.8%)	20	(31.3%)	0.001**
Prone information					
Timing from ARDS to prone (h)	15.6	(7.6-30.2)	21.3	(9.1-46.8)	0.084
Total prone duration (h)	69.3	(52.8-84.2)	61.1	(36.8-84.5)	0.170
PF ratio	93.4	(69.8-118.9)	88.5	(72.2-112.4)	0.363
Ventilation setting					
Mode, volume control	51	(98.1%)	60	(93.7%)	0.378
Tidal volume (ml/Kg)	5.9	(5.7-6.2)	6.2	(5.8-6.6)	0.088
PEEP (mmHg)	16.0	(14-16)	14.0	(14-16)	0.108
PIP (mmHg)	32.0	(29.2-35.0)	32.5	(29-35)	0.953
Pplat (mmHg)	28.0	(26.8-30.3)	29.0	(26-31)	0.765
Driving Pressure (mmHg)	13.0	(11-15.5)	14.0	(12-16.2)	0.349
Compliance (ml/mmHg)	26.4	(22.8-33.5)	25.4	(20-30.8)	0.252

Mann–Whitney U test. Chi-square test. [f]Fisher's exact test. *$p < 0.05$, **$p < 0.01$. Continuous data are expressed as median and IQR. Categorical data are expressed number and percentage.
CHF, congestive heart failure; CAD, coronary artery disease; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease, DM, diabetes mellitus; CKD, chronic kidney disease; PEEP: positive end-expiratory pressure; PIP, peak inspiratory pressure; Pplat, plateau pressure

Table 3 Logistic regression analysis of clinical variables associated with ICU mortality in patients with ARDS receiving early and prolonged prone positioning

	Univariate analysis			Multivariable analysis		
	OR	(95% CI)	p value	OR	(95% CI)	p value
Demographic data						
Age	1.04	(1.01-1.07)	0.003**	1.02	(0.99-1.05)	0.139
Gender-Male	0.68	(0.32-1.45)	0.318			
BMI (kg/m2)	0.97	(0.90-1.05)	0.404			
APACHE II score	1.07	(1.01-1.14)	0.029*	1.05	(0.97-1.14)	0.206
Cause of ARDS						
Extrapulmonary ARDS	ref.			ref.		
Non-influenza pulmonary ARDS	3.78	(1.07-13.29)	0.039*	5.17	(1.16-23.16)	0.032*
Influenza	1.50	(0.34-6.58)	0.591	2.00	(0.36-11.12)	0.428
Renal replacement therapy	3.38	(1.55-7.36)	0.002**	4.05	(1.54-10.67)	0.005**
Comorbidity						
CHF	0.39	(0.07-2.20)	0.285			
CAD	0.80	(0.19-3.37)	0.761			
ILD	0.79	(0.19-3.33)	0.748			
COPD	0.51	(0.14-1.92)	0.320			
DM	0.53	(0.25-1.16)	0.112			
CKD	1.50	(0.70-3.22)	0.296			
Cirrhosis	2.01	(0.49-8.18)	0.332			
Autoimmune disease	1.33	(0.48-3.73)	0.582			
Malignancy	7.42	(2.06-26.70)	0.002**	8.86	(2.22-35.41)	0.003**
Prone information						
Timing from ARDS to prone (h)	1.01	(1.00-1.03)	0.057			
Total prone duration (h)	1.00	(0.99-1.01)	0.995			
PF ratio	0.99	(0.98-1.00)	0.238			
Ventilation setting						
Mode, pressure control	3.40	(0.37-31.40)	0.281			
Tidal volume (ml/Kg)	1.42	(0.95-2.11)	0.084			
PEEP (mmHg)	0.93	(0.81-1.06)	0.257			
PIP (mmHg)	0.99	(0.90-1.09)	0.826			
Pplat (mmHg)	0.99	(0.90-1.10)	0.880			
Driving Pressure (mmHg)	1.04	(0.94-1.15)	0.447			
Compliance (ml/mmHg)	0.98	(0.94-1.02)	0.376			
Prone score high risk (score 3-5)	14.33	(5.74-35.77)	<0.001**			

Logistic regression. *$P < 0.05$, **$P < 0.01$. CHF, congestive heart failure; CAD, coronary artery disease; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease, DM, diabetes mellitus; CKD, chronic kidney disease; PEEP: positive end-expiratory pressure; PIP, peak inspiratory pressure; Pplat, plateau pressure.

Table 4**.** ROC curve analysis of parameters associated with ICU mortality in patients with severe ARDS receiving early and prolonged prone positioning

	AUC	(95% CI)	*p* value	Cut-off point	Sensitivity	Specificity	Accuracy	PPV	NPV
Prone score	0.816	(0.773-0.882)	<0.0001	≥3	75.00	82.69	78.45	84.21	72.88
Age	0.668	(0.574-0.752)	0.001**	≥53	89.06	44.23	68.97	66.28	76.67
APACHE	0.623	(0.529-0.712)	0.018*	≥33	48.44	76.92	61.21	72.09	54.79

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Figures

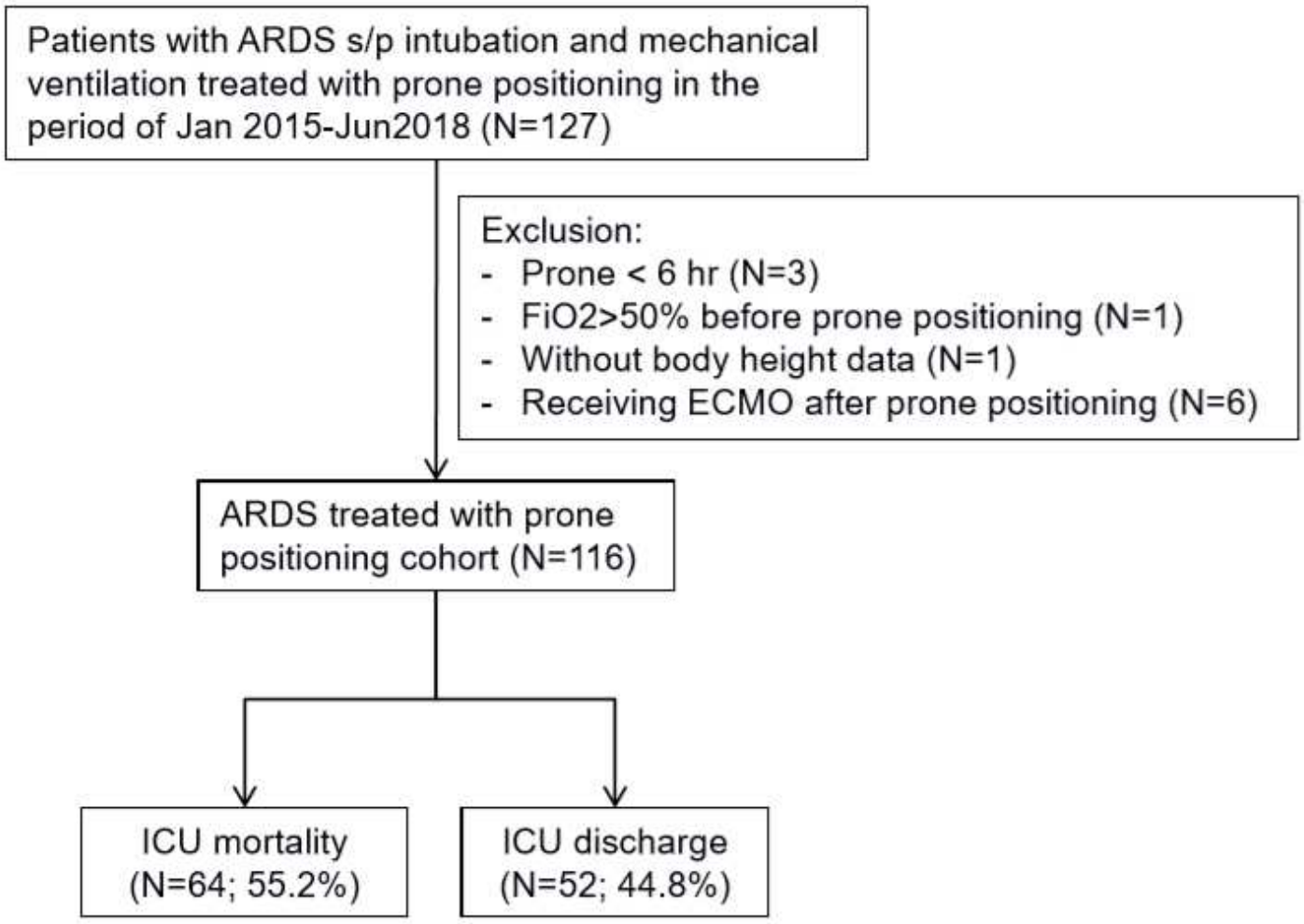

Figure 1

Enrollment and follow-up of the study participants. ARDS, acute respiratory distress syndrome; FiO2, fraction concentration of inspired oxygen; ECMO, extracorporeal membrane oxygenation; ICU: intensive care unit

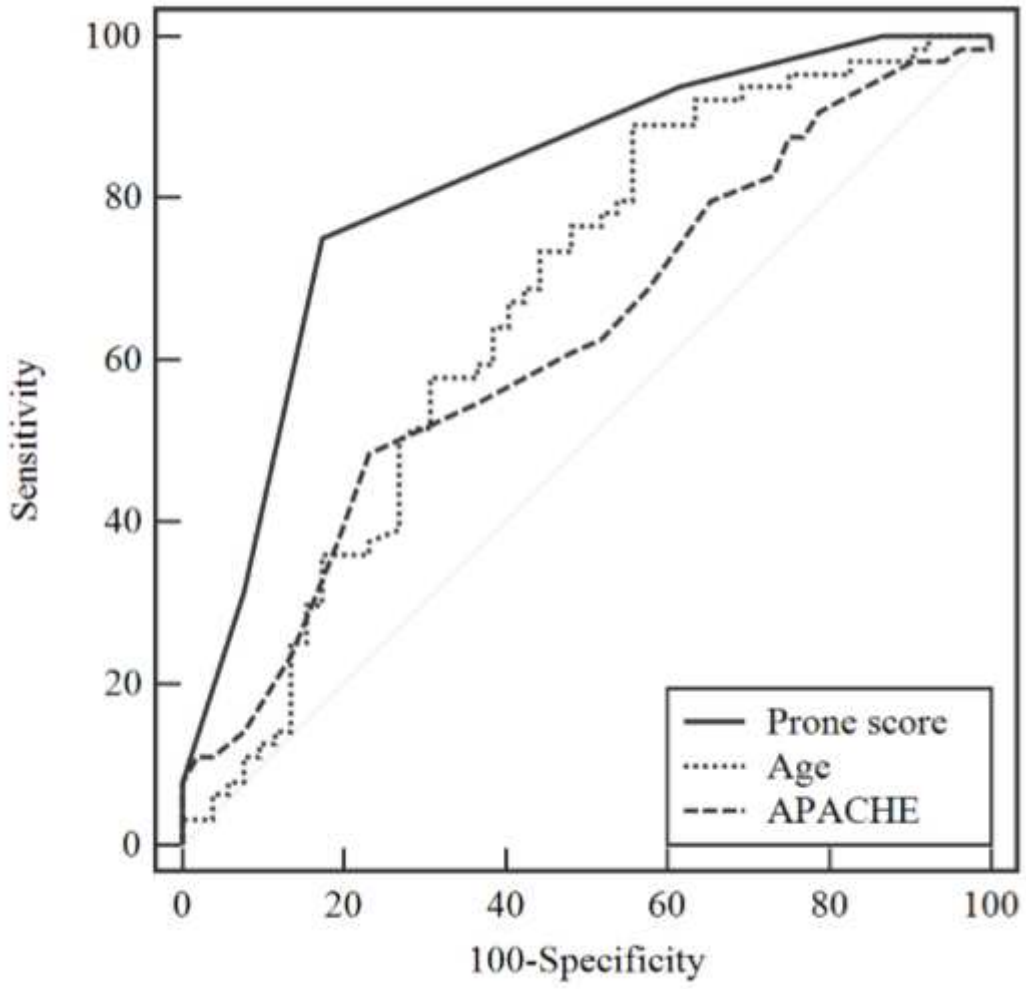

Figure 2

Receiver operating curves analysis of age, APACHE II score, and prone score for predicting ICU mortality in patients with acute respiratory distress syndrome receiving early and prolonged prone positioning.