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Original Article

Comparison of prone positioning and extracorporeal membrane oxygenation in acute respiratory distress syndrome: A multicenter cohort study and propensity-matched analysis

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Background/Purpose: Both prone positioning and extracorporeal membrane oxygenation (ECMO) are used as rescue therapies for severe hypoxemia in patients with acute respiratory distress syndrome (ARDS). This study compared outcomes between patients with severe influenza pneumonia-related ARDS who received prone positioning and those who received ECMO.
Methods: This retrospective cohort study included eight tertiary referral centers in Taiwan. All patients who were diagnosed as having influenza pneumonia-related severe ARDS were enrolled between January and March 2016. We collected their demographic data and prone positioning and ECMO outcomes from medical records.
Results: In total, 263 patients diagnosed as having ARDS were included, and 65 and 53 of them received prone positioning and ECMO, respectively. The baseline PaO_2/FiO_2 ratio, Acute Physiology and Chronic Health Evaluation II score and Sequential Organ Failure Assessment score did not significantly differ between the two groups. The 60-day mortality rate was significantly higher in the ECMO group than in the prone positioning group (60% vs. 28%, $p = 0.001$). A significantly higher mortality rate was still observed in the ECMO group after propensity score matching (59% vs. 36%, $p = 0.033$). In the multivariate Cox regression analysis, usage of prone positioning or ECMO was the single independent predictor for 60-day mortality (hazard ratio: 2.177, $p = 0.034$).
Conclusion: While the patients receiving prone positioning had better outcome, the causality between prone positioning and the prognosis is unknown. However, the current data suggested that patients with influenza-related ARDS may receive prone positioning before ECMO support.

Introduction

Acute respiratory distress syndrome (ARDS), diagnosed on the basis of Berlin definition,[1] may be associated with several etiological factors.[2] Although several treatment strategies for ARDS have been examined, only low tidal volume ventilation,[3] high positive end-expiratory pressure (PEEP),[4] neuromuscular blocker agent use,[5] and prone positioning[6] have demonstrated a survival benefit.

Prone positioning can improve gas exchange and oxygenation in patients with ARDS possibly by resulting in homogeneous aeration[7] and reducing shunt fraction[8] and ventilator-induced lung injury.[9,10] The PROSEVA study conducted in 2013 reported that the early application of prolonged prone positioning reduced 28- and 90-day mortality in patients with severe ARDS.[6] Moreover, some meta-analyses have indicated the efficacy of prone positioning in reducing mortality when applied early and used for a long term along with a lung protective strategy in patients with severe ARDS.[11–13]

Extracorporeal membrane oxygenation (ECMO) may serve as an ultra-protective lung ventilation strategy by reducing tidal volume and airway pressure, thus minimizing ventilator-induced lung injury.[14] The CESAR trial conducted in 2009 suggested that the use of ECMO at referred centers could improve the outcomes of severe adult respiratory failure.[15] Furthermore, the EOLIA study performed in 2018 reported that 60-day mortality was not significantly lower in patients with very severe ARDS who received ECMO than in those who received conventional mechanical ventilation that included ECMO as a rescue therapy.[16] A meta-analysis demonstrated that ECMO could reduce 60-day mortality in patients with severe ARDS.[17]

Influenza pneumonia, a crucial etiological factor of ARDS,[18] may result in a high mortality rate.[19] In Taiwan, an influenza epidemic spread between January 2016 and March 2016.[20] The present study evaluated and compared the effects of prone positioning and ECMO on patients who developed severe influenza pneumonia-related ARDS during this epidemic.

Methods

Patients and data collection

We conducted a multicenter retrospective cohort study of patients at eight referral hospitals (four in Northern Taiwan, two in Central Taiwan, and two in Southern Taiwan). All patients admitted to the intensive care units (ICUs) of these hospitals during the epidemic wave were screened between October 1, 2015, and March 31, 2016. Influenza pneumonia was diagnosed in patients with or without mechanical ventilation by collecting their nasal and oral swabs or sputum samples and testing these

samples by using the rapid test or polymerase chain reaction. Patients were diagnosed as having ARDS if they met the following Berlin definition criteria[1]: acute onset of respiratory failure within 1 week, bilateral lung opacities, no evidence of cardiac failure-related hydrostatic edema on echocardiography, and a PaO_2/FiO_2 ratio of $<$300 mmHg with a PEEP of $\geq$5 cm H_2O. All patients with influenza pneumonia-related moderate to severe ARDS who were treated with prone positioning or ECMO were included in this study. Patients were followed up until discharge from the hospital, death, or up to 60 days after the onset of ARDS. The local institutional review board for human research approved this study (CGMH IRB No. 201600632B0), and the need for informed consent was waived due to the retrospective nature of the study.

We collected patient data from medical records and the standard care report form. Baseline characteristics and treatment-related data regarding ARDS development and ICU evolution collected daily during ICU admission were obtained. The following data were recorded and compared between the prone positioning and ECMO groups: age, gender, body mass index, comorbidity, influenza type, pneumonia severity index (PSI),[21] Acute Physiology and Chronic Health Evaluation II score,[22] Sequential Organ Failure Assessment score,[23] laboratory data, other interventions, mechanical ventilator settings, and lung mechanics and duration from ARDS diagnosis to prone positioning or ECMO. The indeterminate influenza type included patients who diagnosed as influenza by rapid antigen test. The chronic liver disease included patients with liver cirrhosis or chronic abnormal liver function in the previous medical record. In terms of outcomes, we compared 30-day mortality, 60-day mortality, and hospital mortality rates; lengths of ICU and hospital stay; and ventilation-free days between the prone positioning and ECMO groups.

Ventilator settings

All patients included in this study were administered the pressure-control mode of mechanical ventilation. Ventilator settings were adjusted according to the lung protective strategy provided by the Acute Respiratory Distress Syndrome Clinical Research Network.[3] PEEP was set according to a lower $PEEP/FiO_2$ combination table.[3] Dynamic driving pressure is calculated as the difference between peak inspiratory pressure and PEEP, and compliance is calculated as tidal volume divided by dynamic driving pressure.

Prone positioning

Prone positioning was initiated on the basis of the decisions of critical care doctors and if a patient's PaO_2/FiO_2 ratio was $<$150 mmHg. According to the PROSEVA study,[6] prone positioning was performed for at least 16 h in a day. Hemodynamic instability is the main contraindication for prone positioning.

ECMO

The initiation of ECMO was decided by critical care doctors and cardiovascular surgeons, and ECMO was administered by cardiovascular surgeons. Venovenous ECMO was used for patients with no improvement of refractory hypoxemia despite optimal ventilator settings or severe hypercapnia. The venoarterial ECMO was used for patients with no improvement of refractory hypoxemia despite optimal ventilator settings combined with severe shock status despite high dose inotropic agent treatment usage.

Statistical analysis

Nominal variables are presented as numbers (percentages), and continuous variables are presented as the mean $\pm$ standard deviation. The chi-square test or Fisher's exact test were used to compare nominal variables, and Student's t test or Mann–Whitney U test was used to comparing continuous variables depending on the underlying distribution. The Kaplan–Meier curve with log-rank statistic was used to compare survival between the prone positioning and ECMO groups. In addition, we used the propensity score to match the prone positioning and ECMO groups by using the PSI, SOFA score and P/F ratio as predictors and a cutoff of 0.10 for match tolerance. We used the univariate and multivariate Cox regression to analyze the predictive factors of survival, and the variables with p value less than 0.10 in univariate analysis were included for multivariate analysis. A p value of $<$0.05 was considered statistically significant. We used SPSS (version 22.0; SPSS Inc., Chicago, IL), for statistical analyses and database management.

Results

In total, 336 patients with virology-proven severe influenza pneumonia were admitted to the ICU during the study period (Fig. 1). Of these 336 patients, 263 were diagnosed as having severe influenza pneumonia-related ARDS. On the basis of the Berlin definition, 28 (10.6%), 79 (30.1%), and 156 (59.3%) patients were classified as having mild, moderate, and severe ARDS, respectively. The 30-day mortality rates in patients with mild, moderate, and severe ARDS was 7.1% (2/28), 19.0% (15/79), and 28.2% (44/156), respectively. Of 263 patients with ARDS, 65 (24.7%) and 53 (20.2%) who received prone positioning and ECMO, respectively, were included in the further analysis. Of 65 patients who received prone positioning, 8 were shifted to ECMO because the initial prone positioning failed, resulting in the deterioration of patients' hypoxemia. These eight patients were excluded in both groups for analysis. In total, 40 patients (including 6 with prone positioning failure) received venovenous ECMO and 13 patients (including 2 patients with prone positioning failure) received venoarterial ECMO.

The characteristics of included patients at admission were similar between the prone positioning group and ECMO group, except for the total bilirubin level (0.8 $\pm$ 0.8 mg/dL

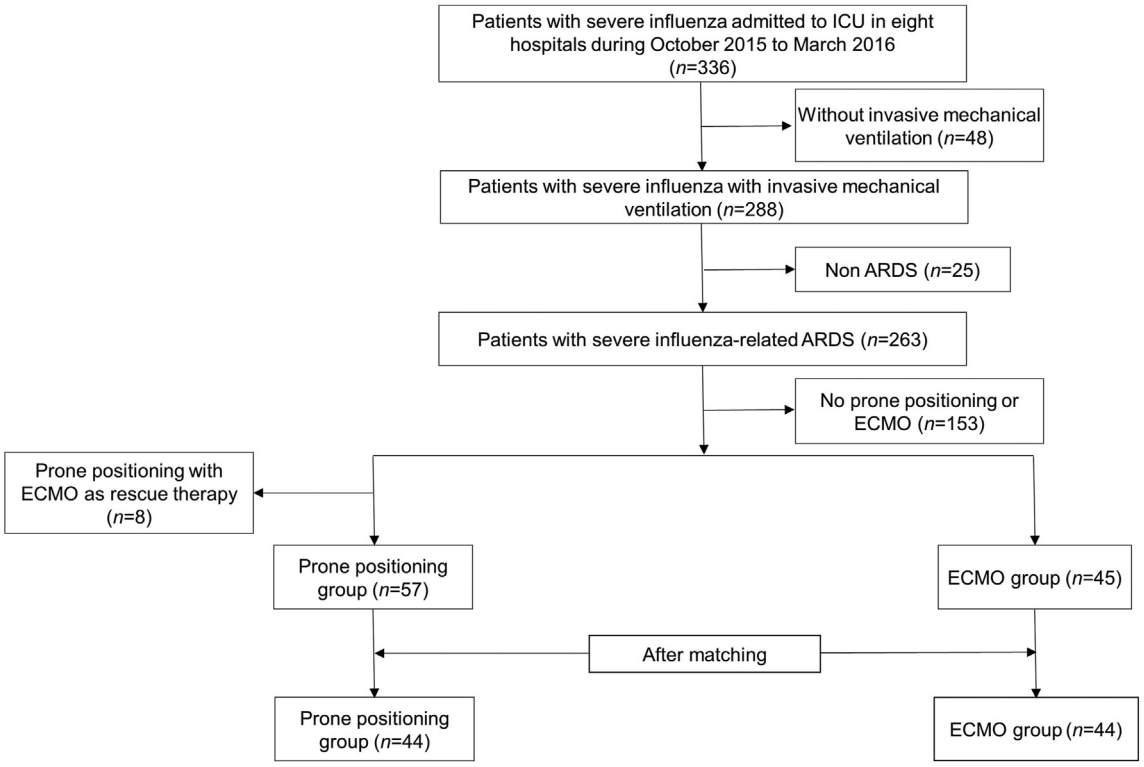

Figure 1 Flow chart of the study; ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit.

in the prone positioning group and 1.9 ± 1.9 mg/dL in the ECMO group, $p = 0.002$; Table 1). Influenza A virus infection was the main cause of severe ARDS, and nonsignificant difference was observed in terms of the cause of severe ARDS between the two groups (79% in the prone positioning group and 82% in the ECMO group).

Table 2 shows oxygenation, ventilator settings, and lung mechanics before initiating prone positioning or ECMO. The PaO_2/FiO_2 ratio, peak airway pressure and PEEP did not significantly differ between the two groups (98.0 ± 55.2 vs. 101.3 ± 70.7 mmHg, $p = 0.652$, 30.4 ± 4.4 vs. 32.4 ± 5.3 cm H_2O, $p = 0.066$, and 13.4 ± 3.3 vs. 12.5 ± 3.9 cm H_2O, $p = 0.293$). The average PaO_2/FiO_2 ratio in venovenous ECMO patients was 93.0 ± 52.2 mmHg, and in venoarterial ECMO patients was 126.7 ± 109.8 mmHg. Moreover, no difference in lung compliance was observed between the groups. In all patients, the duration of receiving prone positioning and ECMO from ARDS diagnosis was 1.9 ± 3.4 and 2.1 ± 3.5 days, respectively.

Clinical outcomes

The 60-day mortality rate was significantly lower in the prone positioning group than in the ECMO group (28% vs. 60%, $p = 0.002$; Table 3), and the statistical power was 0.919. Fig. 2A shows the cumulative survival rate between the prone positioning and ECMO groups from the beginning of the follow-up period until day 60, and Fig. 2B shows the cumulative survival rate between the prone positioning, venovenous ECMO groups and venoarterial ECMO groups. In eight patients who developed prone positioning failure and were subsequently shifted to ECMO, 60-day mortality and in-hospital mortality rates were 50% and 63%, respectively. For survivors, the period of the prone positioning or ECMO usage was 4.1 ± 3.1 and 11.5 ± 7.0 days, respectively. The length of ICU and hospital stay did not significantly differ between the two groups. However, ventilation-free days at day 60 were higher in the prone positioning group than in the ECMO group (25.8 ± 22.1 vs. 13.7 ± 20.1 days, $p = 0.004$). No fatal complication related to prone positioning or ECMO was recorded in all patients during the study period.

Propensity score matching

After matching, baseline characteristics and lung mechanics did not significantly differ between the two groups; however, the 60-day mortality rate was still significantly lower in the prone positioning group than in the ECMO group (36% vs. 59%, $p = 0.033$; Table 3). Fig. 2C shows the cumulative survival rate from the beginning of the follow-up period until day 60 between the matching prone positioning and ECMO groups.

Comparison of prone positioning group and venovenous ECMO group

We also compared the prone positioning group with the venovenous ECMO group (Table 4). The baseline severity index, arterial blood gas data, ventilator settings, and lung mechanics before prone positioning or venovenous ECMO were no significant difference. The P/F ratio in venovenous ECMO was 93.0 ± 52.2 mmHg. However, the venovenous

Table 1 Characteristics of patients with severe influenza pneumonia-related ARDS receiving prone positioning or ECMO at admission.

Characteristics	Before matching			After matching		
	Prone positioning group (n = 57)	ECMO group (n = 45)	*p*	Prone positioning group (n = 44)	ECMO group (n = 44)	*p*
Age (years)	57.8 ± 11.6	56.5 ± 15.6	0.633	57.0 ± 11.1	56.5 ± 15.8	0.852
Gender (male/female)	34/23	29/16	0.621	27/17	28/16	0.826
BMI (kg/m^2)	26.6 ± 4.7	26.2 ± 5.4	0.663	26.9 ± 5.0	26.3 ± 5.4	0.603
Comorbidity						
Malignancy	6 (11%)	6 (13%)	0.662	6 (14%)	5 (11%)	0.747
Chronic liver disease	8 (14%)	9 (20%)	0.422	8 (18%)	8 (18%)	>0.999
Heart failure	2 (4%)	4 (9%)	0.401	2 (5%)	4 (9%)	0.676
Hypertension	28 (49%)	18 (40%)	0.358	21 (48%)	17 (39%)	0.389
End stage renal disease	6 (11%)	1 (2%)	0.130	5 (11%)	1 (2%)	0.202
Diabetes Mellitus	17 (30%)	12 (27%)	0.726	14 (32%)	11 (25%)	0.478
Chronic steroid usage	3 (5%)	2 (4%)	>0.999	3 (7%)	2 (5%)	>0.999
Autoimmune disease	4 (7%)	5 (11%)	0.503	4 (9%)	5 (11%)	>0.999
Severity index						
PSI	115.8 ± 43.8	134.1 ± 49.8	0.051	120.3 ± 47.1	130.5 ± 44.0	0.309
APACHE II score	24.6 ± 8.7	25.5 ± 8.2	0.601	27.2 ± 8.0	25.1 ± 7.8	0.225
SOFA score	11.8 ± 2.9	12.2 ± 2.9	0.501	12.5 ± 2.7	12.3 ± 3.0	0.765
Influenza type			0.850			0.576
Influenza A	45 (79%)	37 (82%)		36 (82%)	37 (84%)	
Influenza B	4 (7%)	2 (4%)		3 (7%)	1 (2%)	
Indeterminate	8 (14%)	6 (14%)		5 (11%)	6 (14%)	
Laboratory data						
White blood cell count (1000/μL)	9.8 ± 6.8	10.9 ± 6.8	0.276	9.9 ± 7.1	11.0 ± 6.9	0.295
Hemoglobin (g/dL)	12.4 ± 2.6	12.3 ± 2.5	0.800	12.5 ± 2.8	12.4 ± 2.4	0.781
Platelet count (1000/μL)	160.3 ± 97.2	140.4 ± 60.9	0.576	153.1 ± 97.1	139.5 ± 61.3	0.861
Albumin (mg/dL)	2.9 ± 0.5	2.7 ± 0.6	0.127	2.9 ± 0.6	2.7 ± 0.6	0.124
Creatinine (mg/dL)	1.7 ± 2.3	1.8 ± 1.4	0.195	1.9 ± 2.6	1.6 ± 1.1	0.472
Total bilirubin (mg/dL)	0.8 ± 0.8	1.9 ± 1.9	<0.001*	0.8 ± 0.8	1.9 ± 1.9	<0.001*
Intervention						
Muscle relaxant usage	56 (98%)	41 (91%)	0.098	44 (100%)	40 (91%)	0.116
Need vasopressor support	40 (70%)	31 (69%)	0.888	35 (80%)	31 (71%)	0.325

APACHE: Acute Physical and Chronic Health Evaluation; ARDS: acute respiratory distress syndrome; BMI: body mass index; ECMO: extracorporeal membrane oxygenation; PSI: pneumonia severity index; SOFA: sequential organ failure assessment.
All values are expressed as number (percentage) or mean ± SD.
*$p < 0.05$: Prone positioning vs ECMO.

ECMO group had significant higher 60-day mortality rate than prone positioning group (62% vs 28%, $p = 0.002$).

Mortality predictors for patients with prone positioning or ECMO

The predictors of 60-day mortality in patients with prone positioning or ECMO are shown in Table 5. In the univariate Cox regression analysis, the PSI (hazard ratio: 1.013, *p* value = <0.001), APACHE II score (hazard ratio: 1.063, *p* value = 0.001), SOFA score (hazard ratio: 0.117, *p* value = 0.031), hemoglobin (hazard ratio: 0.860, *p* value = 0.022), creatinine (hazard ratio: 1.204, *p* value = 0.002, and usage of prone positioning or ECMO (hazard ratio: 2.612, *p* value = 0.002) were significant predictors. However, in the multivariate analysis, only the usage of prone positioning or ECMO was the independent predictor for 60-day mortality (hazard ratio: 2.177, *p* value = 0.034).

Discussion

The results of this multicenter retrospective cohort study revealed that patients with severe influenza pneumonia-related ARDS who received prone positioning had lower mortality rates than did those receiving ECMO at day 60 (28% vs. 60%, $p = 0.001$), and usage or prone positioning or ECMO was an independent predictor for 60-day mortality. Since further randomized controlled trial is needed to elucidate the causality between prone positioning and better clinical outcomes, prone positioning can be considered an adjunct therapy for refractory hypoxemia before administering ECMO in patients with influenza pneumonia complicated by moderate to severe ARDS.

Table 2 Results of artery blood gas, ventilator settings, and lung mechanics at the time of before prone positioning or ECMO.

Characteristics	Before matching			After matching		
	Prone positioning group (n = 57)	ECMO group (n = 45)	*p*	Prone positioning group (n = 44)	ECMO group (n = 44)	*p*
PaO_2/FiO_2 (mm Hg)	98.0 ± 55.2	101.3 ± 70.7	0.698	96.3 ± 56.6	100.0 ± 71.0	0.854
PaO_2 (mm Hg)	79.9 ± 36.8	85.8 ± 70.6	0.414	88.3 ± 18.5	90.4 ± 17.8	0.729
FiO_2	0.9 ± 0.2	0.9 ± 0.2	0.330	0.9 ± 0.2	0.9 ± 0.2	0.606
$PaCO_2$ (mm Hg)	47.5 ± 17.6	47.4 ± 16.8	0.847	47.7 ± 14.6	47.9 ± 16.9	0.959
pH	7.3 ± 0.5	7.3 ± 0.5	0.994	7.2 ± 0.6	7.3 ± 0.5	0.820
Tidal volume/PBW (ml/Kgw)	7.8 ± 2.0	8.3 ± 2.3	0.262	7.8 ± 1.9	8.3 ± 2.3	0.262
PEEP (cm H_2O)	13.8 ± 3.2	12.5 ± 3.9	0.232	13.6 ± 3.2	12.5 ± 3.9	0.201
Peak airway pressure (cm H_2O)	30.4 ± 4.4	32.4 ± 5.3	0.066	30.9 ± 4.3	32.4 ± 5.3	0.186
Dynamic compliance (ml/cm H_2O)	27.6 ± 8.9	26.1 ± 12.0	0.522	27.0 ± 8.2	26.1 ± 12.0	0.718
Duration from ARDS to prone positioning or ECMO (days)	1.9 ± 3.4	2.1 ± 3.5	0.430	2.0 ± 3.7	2.2 ± 3.6	0.323

ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; PBW: predicted body weight; PEEP: positive end expiratory pressure.
All values are expressed as mean ± SD.

Table 3 Outcomes between the prone positioning group and ECMO group.

Outcomes	Before matching			After matching		
	Prone positioning group (n = 57)	ECMO group (n = 45)	*p*	Prone positioning group (n = 44)	ECMO group (n = 44)	*p*
Mortality — no. (%)						
At day 30	13 (23%)	16 (36%)	0.156	13 (30%)	15 (34%)	0.647
At day 60	16 (28%)	27 (60%)	0.001*	16 (36%)	26 (59%)	0.033*
Hospital	17 (30%)	28 (62%)	0.001*	17 (39%)	27 (61%)	0.033*
Duration of prone positioning or ECMO usage in survival (days)	4.1 ± 3.1	11.5 ± 7.0	<0.001*	3.5 ± 1.9	11.5 ± 7.0	<0.001*
Ventilation-free days						
At day 30	8.1 ± 8.8	3.7 ± 7.2	0.009	6.9 ± 8.8	3.8 ± 7.2	0.087
At day 60	25.8 ± 22.1	13.7 ± 20.1	0.004*	22.2 ± 22.6	14.0 ± 20.2	0.065
Length of ICU stay in survival (days)	28.0 ± 24.2	26.8 ± 18.8	0.617	29.4 ± 26.4	26.8 ± 18.8	0.772
Length of hospital stay in survival (days)	45.0 ± 42.2	48.5 ± 29.0	0.219	42.8 ± 40.4	48.5 ± 29.0	0.173
Need renal replacement therapy	9 (16%)	9 (20%)	0.580	9 (21%)	9 (21%)	>0.999

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit.
All values are expressed as number (percentage) or mean ± SD.
*$p < 0.05$: Prone positioning vs ECMO.

Pneumonia, the most common ARDS risk factor, is associated with a high mortality.[24] Influenza (H1N1)-related ARDS can rapidly progress, resulting in life-threatening hypoxemia. The clinical course of influenza (H1N1)-related ARDS appears to be substantially different from that of non—influenza-related ARDS, involving a prolonged recovery of pulmonary gas exchange, a frequent demand for ECMO, and a prolonged ICU stay. In the LUNG SAFE study, the overall 28-day mortality rate of patients with ARDS was 34.8% (29.6%, 35.2%, and 40.9% with mild, moderate, and severe ARDS, respectively) without focusing on any specific risk factor.[2] However, in this study, the 30-day mortality rate of patients with severe influenza pneumonia-related ARDS was relatively low (23.2%)—with it being 7.1%,19.0%, and 28.2% in patients with mild, moderate, and severe ARDS, respectively. Compared with no treatment, neuraminidase inhibitor treatment was associated with a reduction in mortality in patients with H1N1 influenza admitted to hospitals (adjusted odds ratio, 0.81; 95% confidence interval, 0.70—0.93; $p = 0.0024$).[25] In this study, the relatively low mortality rate in patients with severe influenza pneumonia with ARDS might partially be attributed to early recognition of ARDS and the administration of empiric neuraminidase inhibitor treatment to most patients, particularly during the epidemic. Considering easy progression to severe ARDS but with a relatively low mortality rate in some patients with severe influenza pneumonia, we must select an adequate adjunct therapy, such as prone positioning or ECMO, earlier, if required.

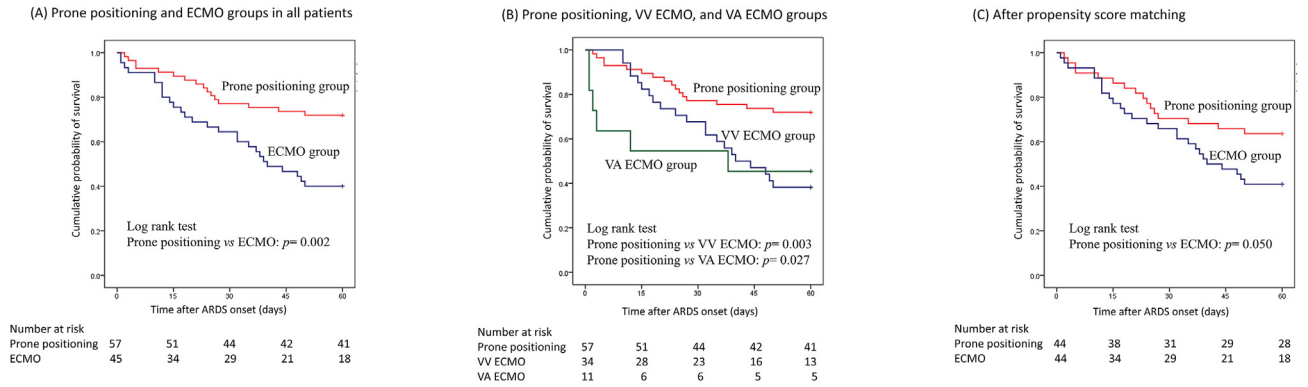

Figure 2 Kaplan–Meier survival curve (A) for prone positioning and ECMO groups in all patients, (B) for prone positioning, VV ECMO, and VA ECMO groups, and (C) for prone positioning and ECMO groups after propensity score matching; ECMO: extracorporeal membrane oxygenation; VV: venovenous; VA: venoarterial.

Current guidelines suggest both prone positioning and ECMO as rescue therapies for refractory hypoxia in patients with severe ARDS.[26,27] However, the guidelines suggest the use of these therapies in different conditions; for example, prone positioning and ECMO may be used when the PaO_2/FiO_2 ratio is < 150 mmHg and <80 mmHg, respectively.[26] In the PROSEVA study,[6] the 28- and 90-day mortality rates of patients who received prone positioning were 16.0% and 23.6%, respectively; these values were lower than real-world data observed in our study (30- and

Table 4 Characteristics of patients with severe influenza pneumonia-related ARDS receiving prone positioning or VV ECMO at admission.

Characteristics	Prone positioning group (n = 57)	VV ECMO group (n = 34)	*p*
Age (years)	57.8 ± 11.6	57.2 ± 15.6	0.821
Gender (male/female)	34/23	20/14	0.938
Severity index			
PSI	115.8 ± 43.8	123.3 ± 42.0	0.422
APACHE II score	24.6 ± 8.7	24.2 ± 7.3	0.786
SOFA score	11.8 ± 2.9	12.3 ± 2.9	0.470
Intervention			
Muscle relaxant usage	56 (98%)	34 (100%)	>0.999
Need vasopressor support	40 (70%)	24 (71%)	0.967
PaO_2/FiO_2 (mm Hg)	98.0 ± 55.2	93.0 ± 52.2	0.560
PaO_2 (mm Hg)	79.9 ± 36.8	81.5 ± 74.6	0.101
FiO_2	0.9 ± 0.2	0.9 ± 0.2	0.291
$PaCO_2$ (mm Hg)	47.5 ± 17.6	48.8 ± 16.6	0.758
pH	7.3 ± 0.5	7.2 ± 0.6	0.791
Tidal volume/PBW (ml/Kgw)	7.8 ± 2.0	8.7 ± 2.6	0.110
PEEP (cm H_2O)	13.8 ± 3.2	12.9 ± 3.7	0.509
Peak airway pressure (cm H_2O)	30.4 ± 4.4	32.4 ± 5.1	0.094
Dynamic compliance (ml/cm H_2O)	27.6 ± 8.9	27.8 ± 12.6	0.687
Mortality – no. (%)			
At day 30	13 (23%)	11 (32%)	0.317
At day 60	16 (28%)	21 (62%)	0.002*
Hospital	17 (30%)	22 (65%)	0.001*
Duration of prone positioning or ECMO usage in survival (days)	4.1 ± 3.1	13.5 ± 7.9	<0.001*
Ventilation-free days			
At day 30	8.1 ± 8.8	2.6 ± 5.7	0.003*
At day 60	25.8 ± 22.1	11.3 ± 18.1	0.001*
Need renal replacement therapy	9 (16%)	6 (18%)	0.817

APACHE: Acute Physical and Chronic Health Evaluation; ARDS: acute respiratory distress syndrome; BMI: body mass index; VV ECMO: venovenous extracorporeal membrane oxygenation; PSI: pneumonia severity index; SOFA: sequential organ failure assessment.
All values are expressed as number (percentage) or mean ± SD.
*$p < 0.05$: Prone positioning vs VV ECMO.

Table 5 Predictive factors for 60 days mortality in patients with prone positioning or ECMO.

	Univariate		Multivariate	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Gender				
Female	1 (Reference)			
Male	1.592 (0.830−3.053)	0.161		
Age, per 1 year increment	1.006 (0.984−1.029)	0.596		
PSI, per 1 increment	1.013 (1.007−1.020)	<0.001*	1.004 (0.996−1.013)	0.288
APACHE II score, per 1 increment	1.063 (1.025−1.101)	0.001*	1.037 (0.981−1.096)	0.201
SOFA score, per 1 increment	1.117 (1.010−1.236)	0.031*	0.952 (0.820−1.104)	0.514
Laboratory data				
Hemoglobin, per 1 g/dL increment	0.860 (0.756−0.979)	0.022*	0.906 (0.784−1.048)	0.183
Creatinine, per 1 mg/dL increment	1.204 (1.068−1.357)	0.002*	1.083 (0.886−1.324)	0.437
Total bilirubin, per 1 mg/dL increment	1.082 (0.893−1.310)	0.420		
Blood gas analysis and respiratory mechanism				
PaO_2/FiO_2 ratio, per 1 mm Hg increment	0.995 (0.988−1.001)	0.090	0.994 (0.987−1.002)	0.146
$PaCO_2$, per 1 mm Hg increment	1.005 (0.989−1.023)	0.525		
Positive end expiratory pressure, per 1 cm H_2O increment	0.983 (0.890−1.085)	0.733		
Peak airway pressure, per 1 cm H_2O increment	1.061 (0.982−1.146)	0.136		
Tidal volume/predicted body weight, per 1 mL/kg increment	1.017 (0.861−1.201)	0.840		
Intervention				
Need vasopressor support				
No	1 (Reference)			
Yes	1.550 (0.764−3.146)	0.225		
Prone positioning vs Extracorporeal membrane oxygenation				
Prone positioning	1 (Reference)		1 (Reference)	
Extracorporeal membrane oxygenation	2.612 (1.405−4.855)	0.002*	2.177 (1.060−4.471)	0.034*

APACHE: Acute Physical and Chronic Health Evaluation; ECMO: extracorporeal membrane oxygenation; PSI: pneumonia severity index; SOFA: sequential organ failure assessment.
*$p < 0.05$.

60-day mortality rates were 26% and 31%, respectively, in our study). However, we focused on patients with severe influenza pneumonia, and the mean PaO_2/FiO_2 ratio of patients in our study was lower than that of patients in the PROSEVA study (95.9 vs. 100 mmHg). Moreover, the mortality rate reported in Cochrane meta-analysis data[28] was higher than that observed in our study both in the short term (33.4%) and long term (41.7%). By contrast, the mortality rate of the ECMO group in our study was higher (30- and 60-day mortality rates were 36% and 60%, respectively) than that reported in the EOLIA study (60-day mortality rate was 35%)[16] or other studies including patients with influenza.[29,30] These differences are potentially attributable to different viral characteristics, early ECMO usage (mean PaO_2/FiO_2 ratio = 101.3 mmHg), or the nonuse of an efficient ultra-protective ventilator strategy with a low tidal volume according to the current suggestion.[14] To the best of our knowledge, no study has compared the outcomes of patients with severe ARDS receiving prone positioning and those receiving ECMO, especially those with severe influenza-related ARDS. According to the results of the present study, prone positioning should be considered before ECMO as a rescue therapy in patients with severe influenza pneumonia-related ARDS. Additional prospective randomized controlled trials are warranted to compare the efficacy between prone positioning and ECMO in patients with severe ARDS.

The current guidelines[31] recommend ECMO only after other strategies such as prone positioning, neuromuscular blockers, or high PEEP cannot reverse refractory hypoxemia. However, a trial of prone positioning may delay the initiation of ECMO. A study reported that patients with influenza who received late cannulation (after >7 days) had significantly high mortality.[32] A previous study compared patients who received ECMO with or without a prone positioning trial before the ECMO was initiated.[33] The 30-day mortality in patients who received prone positioning before ECMO was not significantly higher than that in patients who did not receive prone positioning (21% vs. 41%, $p = 0.098$). In our study, eight patients received prone positioning before ECMO, and the mortality rate of these patients who received prone positioning before ECMO did not have a significantly higher 60-day mortality rate than did those who did not receive prone positioning before ECMO (50% vs. 60%, $p = 0.597$). Therefore, a trial of prone positioning before ECMO implementation is a suitable consideration in clinical practice.

In the real-world, however, prone positioning may be underused in clinical practice for ARDS management. In this study that the choice of prone positioning or ECMO was mainly by the duty doctors' decision, or the equipment or experience in the unit or hospital, 24.7% (65/263) of patients with severe influenza pneumonia-related ARDS received prone positioning. However, in the LUNG SAFE study, only 16.3% (95% CI, 13.7%—19.2%) of patients with severe ARDS had received prone positioning.[2] The infrequent use of prone positioning in patients with severe ARDS reflects the under recognition of indications, appearance of contraindications, the unavailability of experienced staff, and the absence of strong evidence supporting this intervention. Furthermore, before initiating ECMO, only 31% of patients with severe ARDS received a trial of prone positioning, which is a simple and cost-effective technique that demonstrated a survival benefit.[34] During an epidemic, handling a suddenly increasing number of patients with severe ARDS requiring ECMO is considerably challenging for the health care system. Because of the effectiveness of prone positioning and limited facility for administering ECMO, patients with severe influenza pneumonia-related ARDS should receive a trial of prone positioning before ECMO.

This study has some limitations that should be addressed. First, because it was a retrospective study, standardizing the protocols of prone positioning and ECMO in different hospitals was difficult. Bias existed regarding the choice of adjunct therapy and the time to initiate it because both these factors depended on the available facility, staff experience, and physician's decision. Nevertheless, this multicenter study is valuable because it included a large sample size from different regions in Taiwan. Second, only patients who developed severe ARDS due to influenza were included in this study. Thus, this might limit the applicability of results to patients with severe ARDS caused by other risk factors. Whether these rescue therapies can result in the same outcomes in patients with various causes of ARDS should be examined in the future. Third, we did not analyze ECMO or ventilator settings after starting ECMO support, and this might have affected the mortality of patients who received ECMO. Additional studies are required to analyze optimal ECMO or ventilator settings in these patients.

Conclusions

While the patients receiving prone positioning had better outcome, the causality between prone positioning and the prognosis is unknown. However, the current data suggested that patients with influenza-related ARDS may receive prone positioning before ECMO support.

Declaration of competing of interest

The authors have no conflicts of interest relevant to this article.

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Abbreviations

ARDS	acute respiratory distress syndrome
PEEP	positive end-expiratory pressure
ECMO	extracorporeal membrane oxygenation
ICU	intensive care unit
PSI	pneumonia severity index

Authors' contributions

KWC drafted the manuscript. KCK revised the manuscript and conceived the study and was responsible for its coordination. KWC, LCC, MCC, WCC, YMC, WAC, and YCC helped with data curation. SJL, HCW, YCC, and CKP helped with the formal analysis. HCH, LCC, KYY, WFF, CCS, and CLW helped with the validation. All authors critically revised the manuscript and have seen and approved the final draft of the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The local institutional review boards for human research of all participating hospitals approved this study (Linkou Chang-Gung Memorial Hospital IRB No. 201600632B0, Taichung Veterans General Hospital CE16093A, National Taiwan University Hospital 201605036RIND, Taipei Veterans General Hospital 2016-05-020CC, Tri-Service General Hospital 1-105-05-086, China Medical University Hospital 105-REC2-053(FR), Kaohsiung Medical University Hospital KUMHIRB-E(I)-20170097, and Kaohsiung Chang-Gung Memorial Hospital 201600988B0). The need for informed consent was waived due to the retrospective nature of the study.

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