Characteristics and Outcomes of Severe ARDS Patients Receiving ECMO in Southern Thailand

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ABSTRACT: Extracorporeal membrane oxygenation (ECMO) is a treatment option considered for acute respiratory distress syndrome (ARDS) patients who are refractory to conventional treatments. However, treatment with ECMO has not shown significant reduction of mortality which may be due to inappropriate selection criteria. Thus, we aim to evaluate the treatment outcomes of patients treated with ECMO in our center and determine an optimal cutoff level of the Respiratory ECMO Survival Prediction (RESP) score for case selection. This was a retrospective case-control study conducted at Songklanagarind Hospital, Thailand, from January 2014 to August 2018. ECMO patients were randomly matched to a control group of patients with severe ARDS within the same time period. There were 19 cases diagnosed with ARDS and treated with ECMO and 57 controls with ARDS. The patients in both groups had an average APACHE II score of 30.2 (SD = 4.7) and mainly had bacterial pneumonia. The in-hospital mortality was not significantly different between the cases and controls (68.4% vs 63.2%, respectively); however, the ECMO cases had a significantly longer length of intensive care unit stay and cost of hospitalization. Active malignancy, male gender, PaO_2/FiO_2 ratio, and hypotension needing vasopressors were the risk factors for mortality. The RESP score did not discriminate between the survivors and nonsurvivors. Thus, more patient is needed to construct a better selection criterion.

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Introduction

According to the Berlin definition,[1] severe acute respiratory distress syndrome (ARDS) is defined by a PaO_2/FiO_2 (PF) ratio ⩽ 100 mm Hg which has high mortality rates of 37.8% and 66%.[2,3] This group of patients is usually refractory to conventional treatments and there are limited effective options available for rescue therapy.[4,5] Extracorporeal membrane oxygenation (ECMO) is a treatment strategy that can improve oxygenation and reduce ventilator-associated lung injury.[6,7] However, previous studies have shown conflicting results regarding reduction of mortality.[8-10]

The ECMO program in our hospital, Songklanagarind, the major tertiary care hospital and largest referral center in southern Thailand, was initiated in 2014. From then until August 2018, the time this study concluded, 49 adult patients received ECMO which includes 19 pulmonary cases. The ECMO cases were selected primarily on the judgment of the attending intensivist. No specific criteria had been established during those early years; thus, there might have been some cases for which ECMO was not appropriate or other cases that might have had better outcomes had they been treated with ECMO.

For this study, we hypothesized that the survival rate of ECMO cases could be improved by applying the Respiratory ECMO Survival Prediction (RESP) score[11] to assist with case selection. This score was chosen from the various scores available because it was derived from the largest global cohort of ECMO patients and it has also been validated in many cohorts and found to be superior to other scoring systems.[12-15] The RESP score consists of 12 pre-ECMO variables which have been found to be independently associated with hospital survival at the initiation of ECMO.[11]

The primary objective of this study was to illustrate the characteristics of the severe ARDS patients in our institute during the study period according to the RESP survival prediction score. We also aim to evaluate the treatment outcomes of the 19 patients treated with ECMO in comparison with 57 controls and determine the optimal cutoff level of the RESP score for case selection.

Materials and Methods

Study design and setting

This was a retrospective case-control study conducted at Songklanagarind hospital, Thailand. Data collection and analyses were in accordance with the ethical standards of the Ethics Committee for Research in Human Beings of the Faculty of Medicine, Prince of Songkla University, and with the Helsinki declaration and the International Conference on Harmonization in Good Clinical Practice standards (Approval No. REC.61-273-14-1). The nature of the study was a retrospective chart review; therefore, an informed consent was wavied by the ethics committee. All data were obtained from the electronic

medical records system and scanned intensive care unit (ICU) record charts. The medical ICU in our institute is a closed ICU, and treatment decisions are made by three rotating board-certified intensivists. The surgical ICU is an open ICU with anesthesiologists conducting ventilator rounds; however, the treatment decisions are made by the attending surgeons.

There is no established ECMO protocol in our hospital; thus, case selection for ECMO treatment is based on the attending physician's judgment. All the cannulations are made by a cardiovascular-thoracic surgeon using a single venous drainage catheter. The ECMO devices available are the Maquet Rotaflow and the Xenios AG Novalung.

Study population

The cases selected for the study were adult patients who received ECMO support for ARDS from January 2014 to August 2018. The controls were patients who were admitted to the ICU during the same time period and fulfilled the diagnosis of ARDS according to the Berlin definition.[1] In addition, to be comparable with the ECMO group, they had to have severe ARDS as defined by arterial blood gas records with PaO_2/FiO_2 ratio $\leqslant$ 100 mm Hg for 3 consecutive hours after the diagnosis of ARDS. The records of patients who died within 6 hours after admission to the ICU were excluded. The cases were randomly matched with the controls using age and gender.

Variables

The main outcomes were ICU mortality defined as death during admission in the ICU, hospital mortality defined as death before hospital discharge, and length of stay defined as duration from admission to discharge in days. Treatment with ECMO was the main independent variable. Other demographic and clinical characteristics recorded were age, gender, BMI, APACHE II score, RESP score, and laboratory parameters.

Sample size calculation and statistical analysis

The sample size was limited by the number of actual cases that were treated with ECMO during the study period, following which the number of controls was calculated for a matched case-control study design with a 1:3 ratio using the formula for comparing two independent proportions.[16] The in-hospital mortality rate of ARDS patients treated with ECMO used for the calculation of the power was 37.7% from a meta-analysis,[17] while the in-hospital mortality of the general ARDS patients was taken from another meta-analysis[2] at 46%.

Independent variables were shown as mean with standard deviation or median with interquartile range (IQR) or percentage as appropriate. Independent variables were compared between the two groups of patients, ECMO and non-ECMO, using tests appropriate to the data distribution. Regression analysis for predictors of mortality in the ARDS patients and ECMO patients was performed using stepwise simple logistic regression analysis. The level of significance was set at 0.05. Data were analyzed using the R program version 3.5.1[18] (R Core Team) with the Epicalc package.[19]

Results

There were 19 cases that received ECMO for severe ARDS and 141 non-ECMO patients diagnosed with ARDS who had a PaO_2/FiO_2 ratio $\leqslant$ 100 mm Hg for 3 consecutive hours, of which 57 cases were matched with the ECMO cases. However, some of the control patients were slightly older than their matches because there were no enough cases for matching in some age strata so a replacement was taken from the age strata above.

Characteristics of cases and controls

The ECMO cases had a mean age of 45.9 years (SD = 18 years) which was younger than the controls (55.7 years, SD = 15.2). The patients in both groups were predominantly male (73.7% in both groups) with similar underlying diseases. Most patients had at least one underlying disease, the most prevalent being related to chronic cardiac conditions (coronary artery disease, atrial fibrillation, and congestive heart failure) followed by diabetes and chronic lung conditions (chronic obstructive pulmonary disease or asthma). There were more patients with chronic kidney disease (CKD) in the cases group, and more patients in the control group had an active malignancy. The APACHE II and Sequential Organ Failure Assessment (SOFA) scores were calculated at ICU admission, and the average was slightly higher in the control group. The causes of ARDS were mainly community-acquired bacterial pneumonia and influenza pneumonia. In the ECMO group, there were 3 trauma patients with lung contusion, and one each with transfusion-related acute lung injury, diffuse alveolar hemorrhage, massive hemoptysis, and acute interstitial pneumonitis. Patients with bacterial pneumonia received antibiotics according to the sputum culture sensitivity while patients with influenza pneumonia received oseltamivir. The ECMO cases had a significantly lower average PF ratio and higher $paCO_2$ at baseline. All of the patients required a mechanical ventilator which was set with a low tidal volume protocol not exceeding 8 mL/kg of predicted body weight (PBW). However, the actual mean tidal volume per body weight that both groups received during the first day of ICU admission was slightly higher than 8 mL/kg PBW. A neuromuscular blocking agent was used in 94.1% of the cases but only for 40.4% of the controls, and more bicarbonate infusion was given among the ECMO cases. None of the patients in this study received prone positioning or nitric oxide therapy; recruitment maneuvers were not documented. Seventy-three percent of all the patients received either norepinephrine, dopamine, or epinephrine as a continuous infusion at ICU admission with patients in the control group receiving higher dose. More patients in the ECMO group received continuous renal replacement therapy during their admission (Table 1).

Table 1. Characteristics and outcomes of ECMO cases and severe ARDS controls.

	CASE	CONTROL	*P*
	N = 19	N = 57	
Age, mean (SD)	45.9 (18)	55.7 (15.2)	.023
Male, n (%)	14 (73.7%)	42 (73.7%)	1
APACHE II score, mean (SD)	30.4 (5)	33.3 (5.2)	.037
SOFA score, mean (SD)	11.3 (3.4)	12.3 (3.2)	.24
Nonpulmonary SOFA score, mean (SD)	7.3 (3.4)	8.3 (3.2)	.24
RESP score, mean (SD)	–1.7 (4.1)	–2.3 (4.1)	.607
Underlying disease, n (%)			
Diabetes mellitus	4 (21.1)	14 (24.6)	1
Chronic kidney disease	6 (31.6)	7 (12.3)	.077
COPD, asthma	2 (10.5)	12 (21.1)	.496
CAD, AF, CHF	3 (15.8)	11 (19.3)	1
Cirrhosis	2 (10.5)	7 (12.3)	1
Malignancy	3 (15.8)	15 (26.3)	.535
Immunocompromised status, n (%)	8 (42.1)	23 (39.7)	1
ARDS etiology, n (%)			.014
Influenza A/B pneumonia	1 (5.3)	8 (14.0)	
Bacterial pneumonia	11 (57.9)	43 (75.4)	
Asthma	0 (0)	1 (1.8)	
Trauma	3 (15.8)	0 (0.0)	
Other	4 (21.1)	5 (8.8)	
Gas exchange parameters in the first day of ICU admission			
PF ratio, mean (SD)	56.8 (12.9)	72.9 (16.6)	<.001
$paCO_2$, median (IQR)	46.3 (40.1, 55.6)	40.2 (33.8, 8.49)	.026
pH, median (IQR)	7.4 (7.2, 7.4)	7.3 (7.2, 7.4)	.164
Ventilatory parameters in the first day of ICU admission			
VT, mean (SD), mL/kg of PBW	8.3 (2.5)	8.9 (2.4)	.401
Maximum PIP, median (IQR)	29.7 (20.5,40.8)	35 (23.3,46.7)	.271
PEEP, median (IQR)	8 (5.3, 12.7)	6 (5, 9)	.065
MV, mean (SD)	11.7 (3.7)	12.6 (3.8)	.374
Treatment, n (%)			
NMB usage	18 (94.7)	23 (40.4)	<.001
CRRT	10 (52.6)	15 (26.3)	.067
Vasoactive agents used	12 (63.2)	44 (77.2)	.367
VIS, median (IQR)	9.3 (0, 24.3)	27.5 (6.6, 64,8)	.077
Bicarbonate infusion, n%	15 (78.9)	24 (42.1)	.012

Table 1. (Continued)

	CASE N = 19	CONTROL N = 57	*P*
Outcomes			
In-hospital mortality, n (%)	13 (68.4)	36 (63.2)	.89
ICU mortality, n (%)	12 (63.2)	27 (47.4)	.37
Length of ICU stay Median, (IQR) in days	19.7 (12.2, 30.6)	7.4 (2.9, 9.9)	.001
Length of hospital stay Median, (IQR) in days	27.8 (18.1,51.1)	16.9 (7.8, 32.8)	.035
Total cost of current hospitalization Median, (IQR) in US dollars[a]	25 395 (16 511, 32 810)	5849 (3018, 10 326)	<.001

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disorder; CRRT, continuous renal replacement therapy; IQR: interquartile range; MV, minute ventilation; NMB: neuromuscular blocking agent; PBW, predicted body weight, PEEP, positive end-expiratory pressure; PF ratio, PaO_2/FiO_2; PIP, peak inspiratory pressure; RESP, Respiratory ECMO Survival Prediction; SOFA, Sequential Organ Failure Assessment; VIS, vaso-inotropic score; VT, tidal volume.
[a]1 USD = 35 THB.

Outcomes of treatment

The overall in-hospital mortality rate in our study was 64.5% and was not different between the cases and controls. However, the length of ICU stay was longer among cases that were treated with ECMO, and the total cost for hospitalization was 4 times higher among the ECMO cases (Table 1). There was a trend toward a gradual increased of survival rate in both the ECMO cases and the controls from 2014 to 2018. However, the number of cases per year in the ECMO group was not large enough to make a statistical comparison (range = 1-7 cases).

ECMO cases

Among the 19 ECMO cases, 16 cases were treated with a venovenous circuit; in three cases with refractory hypotension due to septic shock a venoarterial circuit was used.

There was no difference in demographics data, severity scoring, or other pre-ECMO variables between the survivors and those who did not survive. The patients were ventilated with a mean tidal volume of 7.59 mL/kg PBW (SD = 2.28) which was significantly reduced to 5.13 mL/kg PBW (SD = 2.03) post ECMO initiation. The positive end-expiratory pressure (PEEP) was also reduced but not as significantly. The survivors did have higher initial $paCO_2$ and used initially significantly higher PEEP before ECMO initiation. The median duration of mechanical ventilation before ECMO was 87 hours (IQR = 24.48, 255.88), with survivors having a slightly shorter period of mechanical ventilation before ECMO (Table 2). The average duration of ECMO run was 10 days (IQR = 3.79, 17.77), with a maximum of 23 days. In the cases that did not survive to ICU discharge, the cause of death was refractory hypotension due to concurrent septic shock; 2 cases had cardiogenic shock from cardiomyopathy and 2 cases had severe neurological dysfunction. In the septic shock cases, there were no signs of lung recovery so conversion to a hybrid circuit was not considered. There were 4 cases that died after successful decannulation, of which 3 developed another episode of septic shock and the other case developed severe central nervous system vasculitis related to the underlying disease. There was bleeding at the cannulation site that required blood component transfusion in 4 cases and no other complications were encountered.

Scores for prediction of survival and actual survival

When the RESP scores were examined, it was found that most of the patients fell into class III or above. There was no difference in the score by treatment group or treatment outcome. The survival rates in both of the case and control groups were both below the predicted survival rates. The factor that most contributed to the high RESP class in both groups was central nervous system dysfunction. In the ECMO case group, additional bicarbonate infusion, having a PIP $\geqslant$ 42 cmH_2O and a nonpulmonary infection contributed to the high RESP class while in the control group it was having a prior cardiac arrest. Compared within the same RESP class, only patients in RESP classes III and IV had a slightly higher chance of survival when treated with ECMO, but the difference was not statistically significant (Table 3).

We compared the RESP score with the SOFA and APACHE II score for predicting in-hospital mortality using a receiver operating characteristic curve (ROC). We found the area under the curve (AUC) of the RESP score to predict in-hospital mortality of 0.65 (95% confidence interval [CI] = 0.64-0.66). This was not significantly different from the

Table 2. Characteristics of ECMO survivors and nonsurvivors.

	SURVIVORS N = 6	NONSURVIVORS N = 13	*P*
Age, mean (SD)	45 (16.2)	46.3 (19.4)	.888
Male, n (%)	4 (66.7)	10 (76.9)	1
APACHE II score, mean (SD)	29.7 (5.8)	30.6 (4.8)	.811
SOFA score, mean (SD)	10.2 (4.9)	11.8 (2.7)	.361
Nonpulmonary SOFA score, mean (SD)	6.2 (4.9)	7.8 (2.7)	.361
RESP score, mean (SD)	−0.2 (3.5)	−2.5 (4.2)	.263
Immunocompromised status, n (%)	2 (33.3)	6 (46.2)	1
Active malignancy, n (%)	0 (0)	3 (23.1)	.517
ARDS etiology, n (%)			.358
Influenza A/B pneumonia	1 (16.7)	0 (0)	
Bacterial pneumonia	3 (50)	8 (61.5)	
Trauma	0 (0)	3 (23.1)	
Other	2 (33.3)	2 (15.4)	
Gas exchange parameters in the first day of ICU admission			
PF ratio, mean (SD)	48.6 (13.7)	60.6 (11.2)	0.058
$paCO_2$, mean (SD)	61.3 (19.8)	44.8 (11.7)	0.034
pH, median (IQR)	7.3 (7.2, 7.4)	7.4 (7.3, 7.4)	0.629
Ventilatory parameters in the first day of ICU admission			
VT, mean (SD), mL/kg of PBW	7.8 (2.1)	8.5 (2.7)	0.563
PIP, mean (SD)	34.9 (11.1)	29.6 (13.1)	0.401
PEEP, mean (SD)	11.9 (3.8)	7.6 (2.9)	0.014
MV, mean (SD)	11.4 (3.2)	11.9 (4)	0.818
Treatment, n (%)			
NMB usage	6 (100)	12 (92.3)	1
CRRT	2 (33.3)	8 (61.5)	0.35
Vasoactive agents used	2 (33.3)	10 (76.9)	0.129
VIS, median (IQR)	0 (0, 11.2)	9.3 (5.2, 33.3)	0.261
Duration of MV before ECMO, median, IQR), hours	60.8 (36, 188.9)	112.3 (39.9, 280.9)	0.456
Duration of ECMO run, mean (SD), days	14.1 (7.8)	9.4 (8.1)	0.25

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disorder; CRRT, continuous renal replacement therapy; IQR, interquartile range; MV, minute ventilation; NMB, neuromuscular blocking agent; PBW, predicted body weight; PEEP, positive end-expiratory pressure; PF ratio, PaO_2/FiO_2; PIP, peak inspiratory pressure; RESP, Respiratory ECMO Survival Prediction; SOFA, Sequential Organ Failure Assessment; VT, tidal volume.

SOFA (AUC = 0.60, 95% CI = 0.59-0.62) and APACHE II (AUC = 0.59, 95% CI = 0.57-0.60) scores.

Factors associated with mortality

The univariate logistic regression analysis found the factors significantly associated with increased mortality were arterial lactate ⩾ 5 mmol/L at ICU admission and vasoactive agent usage. Variables that were selected for multivariate logistic regression were based on having a *P*-value < .3 in the univariate analysis. These variables were age, gender, SOFA score, PF ratio, active malignancy, continuous renal replacement therapy (CRRT) use during admission, mean arterial pressure < 65 mm Hg, bicarbonate infusion, vasoactive agent usage,

Table 3. Distribution of RESP scores and actual in-hospital survival in case and control, comparison with other studies.

	RESP CLASS, N (% SURVIVAL)					*P* VALUE	AUC (95% CI)
	I	II	III	IV	V		
Ours							
Overall (N = 76)	1 (0)	7 (57.1)	31 (29)	20 (35)	17 (41.2)	0.402	0.65 (0.64-0.66)
Case (N = 19)	0 (0)	2 (50)	9 (33.3)	4 (50)	4 (0)		
Controls (N = 57)	1 (0)	5 (60)	22 (27.3)	16 (31.2)	13 (53.8)		
Schmidt[11] (Derivation Cohort)	164 (92)	563 (76)	1033 (57)	449 (33)	146 (18)	Not reported	0.73 (0.71-0.75)
Klinzing et al[14]	3 (100)	18 (38.8)	23 (56.5)	7 (28.5)	0 (0)	0.07	0.65 (0.5-0.8)
Huang et al[20]	2 (100)	8 (75)	4 (75)	4 (50)	5 (0)	0.044	0.835 (0.66-1.01)
Brunet et al[15]	0 (0)	6 (50)	14 (43)	5 (20)	2 (50)	Not reported	0.60 (0.41-0.78)
Baek et al[12a]	68	53	42	19	24	Not reported	0.66 (0.58-0.73)

Abbreviations: AUC, area under the curve; CI, confidence interval; RESP, Respiratory ECMO Survival Prediction.
[a]Number of cases in each score class not reported.

Table 4. Results of multivariate analysis of factors associated with increased hospital mortality.

VARIABLE	CRUDE OR (95% CI)	ADJUSTED OR (95% CI)	*P* VALUE
Male gender	2.29 (0.81-6.53)	4.24 (1.21-14.89)	.024
Active malignancy	2.3 (0.67-7.86)	4.79 (1.02-22.43)	.047
Usage of NE, DA or ADR	3.06 (1.06-8.77)	5.18 (1.41-19)	.013
PF[a] < 80 mm Hg	1.9 (0.7-5.15)	3.42 (1.05-11.14)	.041

Abbreviations: ADR, epinephrine; CI, confidence interval; DA, dopamine; NE, norepinephrine; OR, odds ratio.
[a]PF ratio, PaO_2/FiO_2.

mechanical ventilator duration before ECMO > 7 days, lactate level ⩾ 5 mmol/L, white blood cell count < 3000 cells/mm^3, pH < 7.15, and Glascow Coma Scale < 8. Multivariate analysis was performed using a backward stepwise regression method and found that the usage of vasoactive agents was the strongest predictor of in-hospital death followed by active malignancy, male gender, and PF ratio (Table 4).

Discussion

We report 76 cases of severe ARDS patients in which 19 cases were treated with ECMO. The overall in-hospital mortality rate in these patients was 64.5% and the mortality rate was not lower among the patients treated with ECMO (68.4%). Most of our patients fell above class III of the RESP score. However, the RESP score was not superior to the SOFA or APACHEII scores, and it did not have adequate discriminatory power to predict mortality. The risk factors for mortality in our study were male gender, an active malignancy, PF ratio, and hypotension needing a vasopressor.

The overall mortality rate for severe ARDS in our study was higher than those reported in both ECMO studies and non-ECMO studies. For the severe ARDS cases that were not treated with ECMO, the in-hospital mortality rates in other studies have varied between 37.8% and 47.9%.[3,8-10,21,22] However, for patients in developing countries, a higher mortality rate for ARDS has been reported.[23-25] The higher mortality rate in our setting could be explained by the patient's factor and the quality of ARDS treatment. Our patients had higher nonpulmonary SOFA score at day 1 of ARDS diagnosis (mean = 8, 95% CI = 7.3-8.8) compared with the previously reported cohort study (mean = 7, 95% CI = 6.7-7.4)[21] that had a lower mortality rate. There were also a more than half of our patients who had concurrent hypotension needing high dose of vasoactive agents. We hypothesize that in our setting, a delay in recognition of ARDS may have resulted in intercepting the patient at a worser condition. Although we have a protocol to ventilate ARDS patients with low tidal volume in our ICU, only 38.2% received a mean tidal volume less than 8 mL/kg PBW in the first day after the diagnosis of ARDS. In addition, there was limited use of neuromuscular blocking agents in the control group which may have resulted in the higher tidal volume; there was also a lack of other rescue therapies apart from ECMO. These combined factors resulted in the high mortality rate and in our opinions also reflects the inadequacy of adherence to evidenced-based treatment which has to be improved in our hospital.

We found an in-hospital mortality rate of 68.4% for severe ARDS patients treated with ECMO which was higher than in previous observational studies which reported in-hospital mortality of ECMO cases between 24% and 62%.[11-15,20,26] The mortality rate was even lower in randomized controlled trials.[8,9] The demographics of the patient in those studies were similar to ours with most being male patients and aged 40 to 65 years. However, they had slightly lower SOFA and APACHE II scores which could indicate a less severe cohort.[12-15,22,27] The etiology of ARDS was mainly pneumonia with some studies having higher rates of influenza pneumonia.[14,22] There was one study conducted in Germany that reported similar mortality rate of 62%; they had higher SOFA score of 14 (12-16) and had a high portion of patients with bacterial pneumonia similar to our study.[13] Interestingly, all of the reported studies had shorter interval between mechanical ventilator and ECMO initiation. In most studies, this interval did not exceed 2 days,[12-14,20,28] and 3 studies found that this interval was an independent predictor of mortality.[11,13,26] Our median interval was 87 hours (IQR = 34-255), and there was a nonsignificant trend of survivors having shorter interval than those who did not survive. The ECMO survivors in our study also had a significantly higher PEEP than the nonsurvivors. All previously reported studies used a PEEP level of more than 10 cmH_2O highlighting the benefit of an open-lung strategy in severe ARDS.[12-15,22,27]

There was not enough sample size in the ECMO group to perform reliable logistic regression modeling; thus, the whole cohort was used. The main risk factors for mortality in our study were usage of vasoactive agents, male gender, active malignancy, and PF ratio < 80 mm Hg. Treatment with ECMO did not have an impact on mortality. We had 73.7% of the whole study that had continuous infusion of norepinephrine, epinephrine, or dopamine at ICU admission with survivors using lower dose in both the ECMO and non-ECMO group. This agrees with the German study that also found significantly higher dose of norepinephrine in the nonsurvivors.[13] There was no study that reported an active malignancy as a risk factor for mortality, even though the proportion of cases with an active malignancy is similar to ours.[13,14] This may be due to the difference in severity of the malignancy. Our cases mostly had ARDS from pneumonia as a result of post-chemotherapy immune suppression or surgery for tumor removal. Other commonly reported risk factors for mortality were use of CRRT,[22,28] age,[12,22,26] high lactate level,[13,29] and high SOFA or high APACHE II scores.[22,26,27]

Being able to predict which patients with severe ARDS will benefit from ECMO treatments is an important concern in a resource-limited setting due to the high cost of the treatment. We found that treatment with ECMO resulted in more days and higher costs of hospitalization. Prior to the study, our hypothesis was that RESP scores could aid in selection of cases for ECMO who would be most likely to benefit from this treatment. However, the RESP scores did not have a high power of prediction of mortality in our study when compared with the initial derivation cohort.[11] We found an AUC of only 0.65 (95% CI = 0.64-0.66) which was within the same range as other validation cohorts[12-15,20] (Table 3). Our patients were slightly older than the derivation cohort and the proportion of patients having each pre-ECMO support variable that were included in the RESP score were also different. We had higher proportion of bacterial pneumonia, more immunocompromised patients, no nitric oxide uses, and longer mechanical ventilation initiation to ECMO initiation duration than the derivation cohort. Although the derivation cohort was from the ELSO registry, most of the patients in the registry were from higher income countries which may not be applicable to our settings. A larger cohort is needed to establish our set of static parameters to predict ECMO outcomes; parameters based on continuous factors such as changes in lung mechanics or hemodynamics over time may be more promising to predict survival.

ECMO may seem like a revolutionary therapy in ARDS; however, the survival rate still depends on timely recognition of ARDS and standardized management of ARDS and sepsis with current evidence-based treatments. Early application of ECMO before the development of full-blown lung injury and selection of cases with least morbidity and most hemodynamics stability may improve survival. The strength of this study is the completeness of the electronic medical records that made all the required data available. The main limitation is the number of cases that underwent ECMO, resulting in a power of 5.5% to detect mortality differences. Continuous calculation of SOFA and APACHE score was not done and continuous records of lung mechanics variables was also not available. These dynamics variables may have predicted survival better.

In conclusion, this is the first report from Thailand from a large regional referral center providing data on the characteristics of patients with severe ARDS and examining the implications of an ECMO program in the region. We have shown that treatment with ECMO is feasible in out setting and have resulted in good outcome in a selected group of patients. However, more prospective data and case volume are needed to construct better selection criteria.

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Author Contributions

NA and RB conceived and designed the study. NA collected the data and performed data analysis. PV planned and contributed to the data analysis. NA drafted the manuscript with contribution from all the authors.

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REFERENCES

1. The ARDS Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307:2526-2533.
2. Maca J, Jor O, Holub M, et al. Past and present ARDS mortality rates: a systematic review. *Respir Care*. 2017;62:113-122.
3. Pham T, Rubenfeld GD. Fifty years of research in ARDS: the epidemiology of acute respiratory distress syndrome. A 50th birthday review. *Am J Respir Crit Care Med*. 2017;195:860-870.
4. Alessandri F, Pugliese F, Ranieri VM. The role of rescue therapies in the treatment of severe ARDS. *Respir Care*. 2018;63:92-101.
5. Bein T, Grasso S, Moerer O, et al. The standard of care of patients with ARDS: ventilatory settings and rescue therapies for refractory hypoxemia. *Intensive Care Med*. 2016;42:699-711.
6. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. *N Engl J Med*. 2017;377:562-572.
7. Hardin CC, Hibbert K. ECMO for severe ARDS. *N Engl J Med*. 2018;378:2032-2034.
8. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374:1351-1363.
9. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018;378:1965-1975.
10. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA*. 2011;306:1659-1668.
11. Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *Am J Respir Crit Care Med*. 2014;189:1374-1382.
12. Baek MS, Chung CR, Kim HJ, et al. Age is major factor for predicting survival in patients with acute respiratory failure on extracorporeal membrane oxygenation: a Korean multicenter study. *J Thorac Dis*. 2018;10:1406-1417.
13. Hilder M, Herbstreit F, Adamzik M, et al. Comparison of mortality prediction models in acute respiratory distress syndrome undergoing extracorporeal membrane oxygenation and development of a novel prediction score: the PREdiction of Survival on ECMO Therapy-Score (PRESET-Score). *Crit Care*. 2017;21:301.
14. Klinzing S, Wenger U, Steiger P, et al. External validation of scores proposed for estimation of survival probability of patients with severe adult respiratory distress syndrome undergoing extracorporeal membrane oxygenation therapy: a retrospective study. *Crit Care*. 2015;19:142.
15. Brunet J, Valette X, Buklas D, et al. Predicting survival after extracorporeal membrane oxygenation for ARDS: an external validation of RESP and PRESERVE scores. *Respir Care*. 2017;62:912-919.
16. Rosner B. Estimation of sample size and power for comparing two binomial proportions. In: Rosner B, ed. *Fundamentals of Biostatistics*. 7th ed. Boston, MA: Cengage Learning; 2010:725-810.
17. Vaquer S, de Haro C, Peruga P, Oliva JC, Artigas A. Systematic review and meta-analysis of complications and mortality of veno-venous extracorporeal membrane oxygenation for refractory acute respiratory distress syndrome. *Ann Intensive Care*. 2017;7:51.
18. *R: A Language and Environment for Statistical Computing* [Computer Program]. Vienna, Austria: R Foundation for Statistical Computing; 2018.
19. *Epicalc: Epidemiological Calculator* [Computer Program]. Songkhla, Thailand: Prince of Songkla University; 2018.
20. Huang L, Li T, Xu L, et al. Performance of multiple risk assessment tools to predict mortality for adult respiratory distress syndrome with extracorporeal membrane oxygenation therapy: an external validation study based on Chinese single-center data. *Chin Med J (Engl)*. 2016;129:1688-1695.
21. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315:788-800.
22. Munoz J, Santa-Teresa P, Tomey MJ, et al. Extracorporeal membrane oxygenation (ECMO) in adults with acute respiratory distress syndrome (ARDS): a 6-year experience and case-control study. *Heart Lung*. 2017;46:100-105.
23. Kiatboonsri S, Vathesatogit P, Charoenpan P. Adult respiratory distress syndrome in Thai medical patients. *Southeast Asian J Trop Med Public Health*. 1995;26:774-780.
24. Amin Z, Afifah H, Mamudi CO. Short-term survival of acute respiratory distress syndrome patients at a single tertiary referral centre in Indonesia. *Acta Med Indones*. 2016;48:300-306.
25. Bhadade R, de'Souza R, Harde M, Asgaonkar D, Tuplondhe N. Mortality predictors of ARDS in medical intensive care unit of a tertiary care centre in a tropical country. *J Assoc Physicians India*. 2015;63:16-22.
26. Chiu L-C, Tsai F-C, Hu H-C, et al. Survival predictors in acute respiratory distress syndrome with extracorporeal membrane oxygenation. *Ann Thorac Surg*. 2015;99:243-250.
27. Tsai H-C, Chang C-H, Tsai F-C, et al. Acute respiratory distress syndrome with and without extracorporeal membrane oxygenation: a score matched study. *Ann Thorac Surg*. 2015;100:458-464.
28. Panholzer B, Meckelburg K, Huenges K, et al. Extracorporeal membrane oxygenation for acute respiratory distress syndrome in adults: an analysis of differences between survivors and non-survivors. *Perfusion*. 2017;32:495-500.
29. Lazzeri C, Bonizzoli M, Cianchi G, et al. Body mass index and echocardiography in refractory ARDS treated with veno-venous extracorporeal membrane oxygenation. *J Artif Organs*. 2017;20:50-56.