Original Article

Age is major factor for predicting survival in patients with acute respiratory failure on extracorporeal membrane oxygenation: a Korean multicenter study

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Background: The proportion of elderly patients in the intensive care unit population is increasing. Although the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score is widely used for survival prediction of extracorporeal membrane oxygenation (ECMO) patients, it is questionable whether the RESP score is applicable to older patients. The aim of this study was to investigate the applicability of the RESP score in Korean cohort.

Methods: Data were retrospectively analyzed from 209 acute respiratory failure (ARF) patients treated with ECMO from 2014 to 2015 at 11 hospitals. A comparison of outcome prediction models was conducted and multivariate logistic regression analysis was performed to identify independent risk factors for hospital mortality.

Results: In all patients, the median age was 58 (IQR, 45–65) years. Overall survival at hospital discharge was 45.9%, and veno-venous ECMO was used in 82.3% of patients. Patients older than 65 years treated with ECMO support were 51 with 31.4% of hospital survival. The PRedicting dEath for SEvere ARDS on VV-ECMO (PRESERVE) and RESP scores significantly predicted mortality in patients, with areas under the curve (AUCs) of 0.63 [95% confidence interval (CI), 0.54–0.72] and 0.66 (95% CI, 0.58–0.73), respectively. In multivariate logistic regression analysis, age is independent risk factor for hospital mortality [odds ratio 1.044 (95% CI, 1.020–1.068), P<0.001] with AUC of 0.67 (95% CI, 0.59–0.74). The RESP score was modified using reclassified age and the modified RESP score obtained AUC of 0.71 (95% CI, 0.63–0.78).

Conclusions: The RESP score is significant model for predicting outcomes in a Korean ECMO

population. Elderly patients had higher mortality, and age alone showed similar discrimination ability for prediction of mortality compared to the RESP score.

Keywords: Extracorporeal membrane oxygenation (ECMO); acute respiratory failure (ARF); survival; age

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Introduction

Despite use of lung-protective ventilation strategies (1) and advanced adjunctive therapies (2) mortality of acute respiratory distress syndrome (ARDS) remains high at 40% (3). Since the 2009 H1N1 influenza pandemic, extracorporeal membrane oxygenation (ECMO) has emerged as a salvage therapy for severe ARDS (4,5), with a randomized controlled trial demonstrating a survival benefit from ECMO therapy (6). However, incremental hospital costs associated with ECMO (6), or complications such as bleeding (4,6) remain important issues. Therefore, appropriate patient selection is important prior to the initiation of ECMO. Several outcome prediction scoring systems have recently been developed, such as the ECMOnet score (7), the PRedicting dEath for SEvere ARDS on VV-ECMO (PRESERVE) score (8), and the Respiratory ECMO Survival Prediction (RESP) score (9). The RESP score is widely accepted survival prediction model at ECMO initiation for severe acute respiratory failure (ARF).

Overall hospital mortality rates were associated with increasing age (10) and the proportion of elderly patients in the intensive care unit (ICU) population is increasing (11). Mendiratta *et al.* reviewed patients older than 65 years treated with ECMO support in the Extracorporeal Life Support Organization (ELSO) registry between 1990 and May 2013. According to the study, the number of elderly patients receiving ECMO increased significantly recent years. Although survival at hospital discharge is low in elderly ECMO patients compared to the all adults, they emphasized that age should not be a firm contraindication for the initiation of ECMO (12).

In Korea, the use of ECMO in elderly patients is increasing also, and we wondered whether the RESP score could help to predict the survival in the population with large elderly patients. The aim of this study was to investigate the applicability of the RESP score in Korean cohort.

Methods

Study design

This retrospective multicenter study was conducted in ARF patients who did not respond to conventional treatment. From January 2014 to December 2015, patients who received ECMO therapy with acute respiratory and/or circulatory failure were included from 11 hospitals in Korea. This study was approved by the institutional review board of Asian Medical Center (approval No. 2016-0269), and each participating center approved the protocol. The requirement for informed consent was waived due to the retrospective design.

ECMO management

ECMO can provide both respiratory and circulatory support. VV ECMO to maintain gas exchange was primarily implemented for ARF patients. Veno-arterial (VA) ECMO was performed in patients with severe heart failure, hemodynamic instability, or pulmonary hypertension. Both types of ECMO involve inserting two cannulas following: one for draining the blood from venous system (superior vena cava/inferior vena cava) to ECMO circuit, the other one for returning the oxygenated blood either to right atrium (VV) or to arterial system (VA) (13). Cannulations were performed percutaneously. The standard configuration for VV ECMO was femoral vein and internal jugular vein, and femoral vein and femoral artery were preferred for VA ECMO.

Although indications for the use of ECMO have yet to be standardized between participating centers, decisions for ECMO initiation were based on the ELSO guidelines. ECMO therapy is recommended in patients with severe but potentially reversible respiratory failure with persistent hypoxemia or hypercapnia. According to the ELSO guidelines, ECMO is indicated when the risk of mortality is 80% or greater. This mortality risk is associated with a PaO_2/FiO_2 <100 on FiO_2 >90% and/or a Murray score

3–4 despite optimal care for 6 hours or more. It can also be considered for patients with CO_2 retention on mechanical ventilation despite high Pplat (>30 cmH_2O). Relative contraindications for ECMO therapy were mechanical ventilation at high settings (FiO_2 >0.9, Pplat >30) for 7 days or more, absolute neutrophil count <400/mm^3, recent central nervous system hemorrhage, or terminal malignancy.

Data collection

Patients older than 19 years who received ECMO therapy in tertiary care centers were screened. After a review of electronic medical records, clinical data were recorded on the registry form. The ECMO registry form comprises baseline demographic data, ARF etiology, ventilation and hemodynamic parameters, and the results of arterial blood gas analysis (ABGA) prior to initiation of ECMO therapy. Any adjunctive therapy was also recorded, such as use of vasopressor, steroid, neuromuscular blockade, NO, polymyxin B-immobilized fiber column hemoperfusion, prone positioning, continuous renal replacement therapy (CRRT), and bicarbonate infusion. Acute physiology and chronic health evaluation (APACHE) II and sequential organ failure assessment (SOFA) scores were calculated using the worst value within 24 hours of ICU admission. Data for the ventilation and hemodynamic parameters, ABGA, and SOFA score were collected immediately, 4 hours, and 24 hours after ECMO cannulation. We also collected ECMO parameters including ECMO mode, equipment, membrane oxygenator, number of membrane changes, duration of ECMO support, and duration of mechanical ventilation prior to ECMO initiation. The primary outcome of the study was hospital survival and successful ECMO weaning (survival within 48 hours after weaning from ECMO) was recorded.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Version 22.0 (IBM Corporation, Armonk, NY, USA), and differences with a P value <0.05 were considered statistically significant. Kolmogorov-Smirnov and Shapiro-Wilk tests for normal distribution were conducted. Continuous variables are reported as the mean ± standard deviation or median [interquartile range (IQR)]. Categorical variables are reported as numbers (percentages). For continuous variables, either a Student's *t*-test or Mann-Whitney U test was performed depending on their distribution. For categorical variables, either a Chi-square test or the Fisher exact test was used to investigate comparisons between survivor and non-survivor groups. Discrimination of outcome prediction scores was evaluated by receiver operating characteristic (ROC) curve analysis. Sensitivity and specificity for the scores were determined and the cutoff point corresponded to the maximum of the Youden's index. Univariate and multivariate logistic regression analyses were performed to identify the factors associated with hospital mortality. Variables with P<0.1 in the univariate analyses were included in the multivariate model and considered significant by forward stepwise selection at P<0.05.

Results

Baseline and clinical characteristics of the study population

During the study period, 223 ARF patients received ECMO therapy. Among 14 patients (6.3%) who performed ECMO as a bridge to lung transplantation, 3 patients were underwent lung transplantation. After the exclusion of the 14 patients, 209 patients were analyzed (*Figure 1*). The successful weaning rate was 65.5% and 96 patients (45.9%) were alive at hospital discharge. The survival rates of VV ECMO and VA ECMO were 47.7% and 37.8%, respectively. Elderly patients older than 65 years were 51 with 31.4% of hospital survival.

Data on baseline characteristics and pre-ECMO parameters are presented in *Tables 1,2*. In all patients, the median age was 58 (IQR, 45–65) years and pneumonia was the most common cause of ARF (40.2%). There were 58 (27.8%) immunocompromised patients and 31 patients (14.8%) were receiving steroids. Before ECMO initiation, the following rescue therapies were applied: prone positioning, 98 patients (48.8%); neuromuscular blockade, 134 patients (64.1%); and nitric oxide, 50 patients (23.9%). The median PaO_2/FiO_2 ratio was 69 (IQR, 55–99) mmHg with a high positive end-expiratory pressure level [10 (IQR, 7–12) cmH_2O and peak inspiratory pressure level 27 (IQR, 23–30) cmH_2O]. Pre-ECMO blood gases analyses showed that the PaO_2 was 65 (IQR, 52–83) mmHg and the $PaCO_2$ was 50 (IQR, 38–65) mmHg. VV ECMO was used for 82.3% of patients, and the median duration of ECMO support was 7 (IQR, 3–14) days.

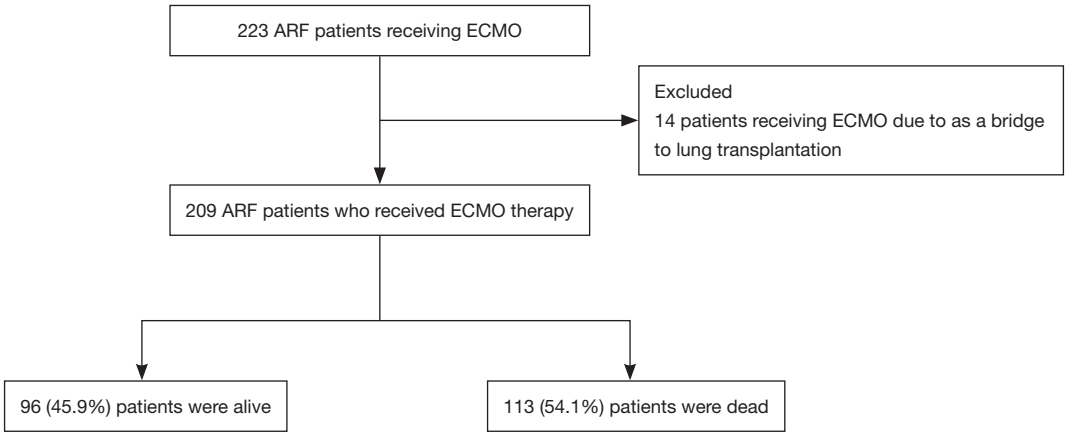

Figure 1 Flow chart of the ARF patients receiving ECMO. ARF, acute respiratory failure; ECMO, extracorporeal membrane oxygenation.

Characteristics of survivors and non-survivors

The median age of survivors was lower than that of non-survivors [52 (IQR, 37–62) *vs.* 61 (IQR, 52–68) years, P<0.001]. There were no significant differences in sex, body mass index, and ARF etiology between survivors and non-survivors. Use of steroids and NO as a rescue therapy of ARF was significantly different between the two groups (9.4% *vs.* 19.5%, P<0.041; 16.7% *vs.* 30.1%, P=0.023). However, prone positioning, use of neuromuscular blockade, and bicarbonate infusion were not significantly different between the survivors and non-survivors.

Ventilator settings such as FiO_2 and positive end-expiratory pressure were not significantly different, whereas peak inspiratory pressure was lower in survivors [26 (IQR, 22–30) *vs.* 28 (IQR, 24–31), P=0.026]. Before ECMO initiation, lactic acid, mean blood pressure, and heart rate were significantly different between the two groups: lactic acid [1.8 (IQR, 1.1–4.9) *vs.* 3.2 (IQR, 1.7–6.6), P=0.009], mean blood pressure [71 (IQR, 59–87) *vs.* 62 (IQR, 53–77), P=0.017], and heart rate [103 (IQR, 80–125) *vs.* 110 (IQR, 96–128), P=0.036].

Serial changes in the SOFA score and parameters after ECMO cannulation

There were no differences between survivors and non-survivors in the initial lactic acid level, but it was lower in survivors after 4 hours [2.7 (IQR, 1.7–5.8) *vs.* 5.6 (IQR, 2.7–9.2), P<0.001; *Table 3*]. After 24 hours, the SOFA score was significantly different between survivors and non-survivors [9 (IQR, 7–12) *vs.* 10 (IQR, 8–14), P=0.008].

Predictors for hospital mortality in patients with ECMO support

In the logistic regression analyses, hospital mortality was associated with the following variables: age, APACHE II score, SOFA score, acute exacerbation of interstitial lung disease, CRRT, use of steroid, use of NO, positive end-expiratory pressure, peak inspiratory pressure, pH, and hospital stay before ECMO initiation. Multivariate analysis showed that age [odds ratio (OR) =1.044; 95% confidence interval (CI), 1.020–1.068; P<0.001], use of NO (OR =2.322; 95% CI, 1.045–5.161; P=0.039), and pH (OR =0.069; 95% CI, 0.008–0.625; P=0.017) were significant independent prognostic factors (*Table 4*).

A comparison of the areas under the curves (AUCs) for pre-existing outcome prediction models is shown in *Table 5*. The AUC (*c*-statistic) of each outcome prediction score was as follows: RESP score, 0.66 (95% CI, 0.58–0.73); PRESERVE score, 0.63 (95% CI, 0.54–0.72); score proposed by Roch and colleagues, 0.56 (95% CI, 0.47–0.64); age, 0.67 (95% CI, 0.59–0.74); APACHE II score, 0.57 (95% CI, 0.49–0.64); and SOFA score, 0.62 (95% CI, 0.54–0.70). The optimal cutoff points for the RESP and PRESERVE scores were 0 (sensitivity of 75.6% and specificity of 47.6%) and 5 (sensitivity of 73.5% and specificity of 48.6%), respectively.

Modification of the RESP score

Survival rate declined with increasing patient age, and mortality was over 50% in patients over 50 years of age (*Figure 2*). The RESP score was calculated for our 209

Table 1 Clinical characteristics of the study patients according to the survival status for acute respiratory failure

Characteristic	All patients (n=209)	Status at hospital discharge		P
		Alive (n=96)	Dead (n=113)	
Age (years)	58 [45–65]	52 [37–62]	61 [52–68]	<0.001
Sex, male	138 (66.0)	64 (66.7)	74 (65.5)	0.858
Body mass index (kg/m^2)	23.4±3.7	23.6±3.7	23.2±3.8	0.404
APACHE II score	20 [14–27]	19 [13–25]	21 [14–29]	0.080
SOFA score	11 [8–14]	10 [7–13]	12 [8–15]	0.003
Etiology of ARF				
Viral pneumonia	27 (13.0)	15 (15.8)	12 (10.6)	0.269
Bacterial pneumonia	57 (27.3)	24 (25.3)	33 (29.2)	0.526
COPD/asthma	3 (1.4)	2 (2.1)	1 (0.9)	0.593
Trauma/burn	14 (6.7)	9 (9.5)	5 (4.4)	0.148
Asphyxia	4 (1.9)	0 (0.0)	4 (3.5)	0.127
Acute exacerbation of ILD	16 (7.7)	3 (3.2)	13 (11.5)	0.024
Chronic respiratory failure	5 (2.4)	3 (3.2)	2 (1.8)	0.662
Other respiratory failure	82 (39.4)	39 (41.1)	43 (38.1)	0.659
Immunocompromised*	58 (27.8)	24 (25.0)	34 (30.1)	0.413
CNS dysfunction†	21 (10.0)	7 (7.3)	14 (12.4)	0.222
Vasopressor	154 (75.5)	67 (73.6)	87 (77.0)	0.625
Steroid	31 (14.8)	9 (9.4)	22 (19.5)	0.041
Bicarbonate infusion	31 (14.8)	11 (11.5)	20 (17.7)	0.206
Cardiac arrest	41 (19.8)	16 (16.7)	25 (22.5)	0.292
CRRT	34 (16.3)	11 (11.5)	23 (20.4)	0.082
PMX	4 (1.9)	2 (2.1)	2 (1.8)	1.000

Values are expressed as a median [interquartile range], mean ± SD, or n (%). *, "Immunocompromised" includes hematological malignancies, solid tumors, solid-organ transplantation, high-dose or long-term corticosteroid and/or immunosuppressant use, or HIV infection; †, "CNS dysfunction" diagnosis combines neurotrauma, stroke, encephalopathy, cerebral embolism, and seizure and epileptic syndrome. APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; CNS, central nervous system; CRRT, continuous renal replacement therapy; PMX, polymyxin B-immobilized fiber column hemoperfusion.

patients and each risk class showed lower survival rate except for risk class V (*Figure 3*). Due to the discrepancy between the ELSO data and our cohort, we sought to develop for our cohort-specific prediction model. To improve the discriminative power of the RESP score, we added candidate variables that were independent risk factors according to multivariate logistic regression analysis. A final model was derived from the RESP score and reclassified age, and the predicted hospital survival according to the modified RESP score is described in *Tables 6*,7. Cumulative predicted hospital survivals were 70%, 57%, and 27 for the three risk classes, namely, I (0 to 3), II (4 to 7), and III (8 to 24.5), respectively. Internal validation of the modified RESP score exhibited reasonable discrimination [*c*=0. 71 (IQR, 0.63–0.78)] (*Figure 4*).

Discussion

This multicenter study involved a retrospective analysis of 209 patients receiving ECMO support for ARF refractory

Table 2 Physiologic variables and pre-ECMO parameters according to the survival status for acute respiratory failure

Characteristic	All patients (n=209)	Status at hospital discharge		P
		Alive (n=96)	Dead (n=113)	
Vital signs				
MBP (mmHg)	68 [55–84]	71 [59–87]	62 [53–77]	0.017
Heart rate (min^{-1})	107 [87–126]	103 [80–125]	110 [96–128]	0.036
Respiratory rate (min^{-1})	20 [16–25]	20 [15–25]	22 [16–25]	0.162
Rescue therapy				
Prone positioning	98 (48.8)	44 (47.3)	54 (50.0)	0.704
Nitric oxide	50 (23.9)	16 (16.7)	34 (30.1)	0.023
Neuromuscular blockade	134 (64.1)	56 (58.3)	78 (69.0)	0.108
Arterial blood gases				
pH	7.26 [7.16–7.36]	7.27 [7.18–7.36]	7.24 [7.13–7.35]	0.081
PaO_2 (mmHg)	65 [52–83]	65 [49–82]	65 [53–83]	0.823
$PaCO_2$ (mmHg)	50 [38–65]	48 [38–63]	52 [39–69]	0.251
HCO_3^- (mEq/L)	22 [18–27]	22 [18–28]	21 [18–27]	0.317
SaO_2 (%)	88 [79–93]	90 [79–93]	88 [77–93]	0.350
Lactic acid (mmol/L)	2.8 [1.4–5.8]	1.8 [1.1–4.9]	3.2 [1.7–6.6]	0.009
Ventilation parameters				
PaO_2/FiO_2	69 [55–99]	69 [55–98]	68 [55–101]	0.828
FiO_2	100 [80–100]	100 [80–100]	100 [80–100]	0.485
PEEP (cmH_2O)	10 [7–12]	10 [8–12]	10 [6–11]	0.063
PIP (cmH_2O)	27 [23–30]	26 [22–30]	28 [24–31]	0.026
MAP (cmH_2O)	15 [14–17]	15 [13–16]	15 [14–17]	0.528
Minute ventilation (L/min)	9.1 [6.8–11.1]	8.8 [6.2–11.1]	9.3 [7.4–11.1]	0.439
ECMO mode				
Veno-venous	172 (82.3)	82 (85.4)	90 (79.6)	0.276
Veno-arterial	30 (14.4)	11 (11.5)	19 (16.8)	0.271
Veno-arteriovenous	7 (3.3)	3 (3.1)	4 (3.5)	1.000
Duration or length of stay (d)				
MV-ECMO	1 [0–4]	1 [0–2]	1 [0–4]	0.021
ECMO	7 [3–14]	6 [2–12]	7 [4–22]	0.052
Hospital	35 [16–58]	39 [16–73]	32 [15–53]	0.080
ICU	18 [7–32]	16 [5–31]	22 [8–36]	0.063

Values are expressed as median [interquartile range] or n (%). ECMO, extracorporeal membrane oxygenation; MBP, mean blood pressure; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; HCO_3^-, bicarbonate; SaO_2, oxygen saturation; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; MAP, mean airway pressure; MV, mechanical ventilation; ICU, intensive care unit.

Table 3 Serial changes in SOFA score and ventilation parameters during ECMO support according to the survival status

Variables	After ECMO initiation			After 4 hours			After 24 hours		
	Alive (n=96)	Dead (n=113)	P	Alive (n=96)	Dead (n=113)	P	Alive (n=96)	Dead (n=113)	P
SOFA score	11 [8–13]	11 [9–14]	0.123	10±4	11±4	0.016	9 [7–12]	10 [8–14]	0.008
Vital signs									
MBP (mmHg)	82±21	76±24	0.079	87±17	79±20	0.003	85±15	85±15	0.881
Heart rate (min^{-1})	108±24	109±23	0.805	100±19	102±26	0.428	95±19	99±23	0.217
Respiratory rate (min^{-1})	15 [11–20]	15 [12–18]	0.693	13 [10–16]	14 [12–18]	0.292	13 [10–16]	14 [12–18]	0.139
Arterial blood gases									
pH	7.40 [7.32–7.50]	7.38 [7.29–7.46]	0.097	7.41±0.10	7.39±0.12	0.088	7.45 [7.39–7.49]	7.43 [7.38–7.49]	0.130
PaO_2, mmHg	125 [78–365]	123 [78–288]	0.804	92 [77–159]	99 [75–151]	0.974	95 [77–138]	90 [72–131]	0.461
$PaCO_2$ (mmHg)	32 [25–36]	32 [26–37]	0.666	32 [27–38]	31 [26–35]	0.063	34 [30–40]	33 [30–38]	0.319
HCO_3^- (mEq/L)	20±6	19±7	0.078	21±5	19±5	0.013	23 [21–26]	22 [20–25]	0.008
SaO_2 (%)	98 [95–100]	99 [94–100]	0.563	97 [94–100]	98 [94–99]	0.594	97 [95–99]	97 [94–99]	0.376
Lactic acid (mmol/L)	2.9 [1.9–4.8]	3.8 [2.4–6.8]	0.105	2.7 [1.7–5.8]	5.6 [2.7–9.2]	<0.001	1.9 [1.3–2.8]	2.9 [1.7–4.7]	0.002
Ventilation parameters									
PaO_2/FiO_2	196 [127–535]	242 [143–452]	0.654	204 [142–349]	228 [131–340]	0.622	210 [169–322]	210 [147–347]	0.645
FiO_2	60 [50–80]	60 [40–83]	0.529	50 [40–60]	50 [40–60]	0.743	40 [38–60]	40 [40–60]	0.504
PEEP (cmH_2O)	10 [6–10]	8 [6–10]	0.077	9 [6–10]	8 [6–10]	0.715	9 [5–10]	8 [6–10]	0.488
PIP (cmH_2O)	22 [20–25]	22 [19–26]	0.535	21 [20–26]	22 [19–26]	0.629	20 [18–23]	20 [18–24]	0.251
MAP (cmH_2O)	15 [14–17]	15 [14–17]	0.948	14 [12–16]	14 [12–16]	0.448	14 [12–15]	14 [12–15]	0.865
Minute ventilation (L/min)	6.0 [4.2–9.2]	4.6 [2.6–7.8]	0.026	4.5 [3.1–6.4]	4.4 [2.5–6.9]	0.574	4.5 [3.0–6.3]	3.8 [2.2–5.8]	0.102

Values are expressed as median [interquartile range] or mean ± SD. ECMO, extracorporeal membrane oxygenation; MBP, mean blood pressure; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; MAP, mean airway pressure.

Table 4 Univariate and multivariate analysis of pre-ECMO variables for hospital mortality

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.040 (1.020–1.061)	<0.001	1.044 (1.020–1.068)	<0.001
APACHE II score	1.033 (1.002–1.064)	0.036		
SOFA score	1.107 (1.034–1.185)	0.003		
Acute exacerbation of ILD	3.987 (1.101–14.438)	0.035		
CRRT	1.975 (0.908–4.296)	0.086		
Steroid	2.337 (1.020–5.356)	0.045		
Nitric oxide	2.152 (1.100–4.208)	0.025	2.322 (1.045–5.161)	0.039
PEEP	0.935 (0.866–1.010)	0.087		
PIP	1.066 (1.007–1.128)	0.028		
pH	0.199 (0.034–1.153)	0.072	0.069 (0.008–0.625)	0.017
Hospital stay before ECMO initiation	1.026 (1.001–1.052)	0.043		

ECMO, extracorporeal membrane oxygenation. OR, odds ratio; CI, confidence interval. APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; ILD, interstitial lung disease; CRRT, continuous renal replacement therapy; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure.

Table 5 Comparison of outcome prediction models

Prediction model	All patients (n=209)		VV ECMO (n=172)	
	AUC (95% CI)	n	AUC (95% CI)	n
RESP score	0.66 (0.58–0.73)	189	0.66 (0.57–0.74)	151
PRESERVE score	0.63 (0.54–0.72)	153	0.65 (0.55–0.74)	121
Score by Roch *et al.*	0.56 (0.47–0.64)	180	0.52 (0.43–0.61)	144
Age	0.67 (0.59–0.74)	209	0.63 (0.55–0.71)	170
APACHE II score	0.57 (0.49–0.64)	205	0.58 (0.49–0.66)	168
SOFA score	0.62 (0.54–0.70)	190	0.61 (0.52–0.70)	155

AUC, area under the curve; CI, confidence interval; VV, veno-venous; RESP, Respiratory Extracorporeal Membrane Oxygenation Survival Prediction; PRESERVE, predicting death for severe ARDS on VV ECMO; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

to conventional treatment and was conducted to investigate the applicability of the recently proposed outcome prediction models. Our result shows that the RESP score is significant model for predicting outcomes in a Korean ECMO population. In addition, age is an important factor in the survival of patients treated with ECMO. Age alone showed similar discrimination ability for prediction of mortality compared to the RESP score and elderly patients had higher mortality rate. Therefore, further studies are needed to guide decision making for ECMO initiation in elderly patients.

In our present study, we validated three outcome prediction-scoring models: the score by Roch and colleagues, the PRESERVE score, and the RESP score. The Roch score, which includes age, SOFA score, and influenza pneumonia, was developed to predict prognosis in ARDS patients who underwent cannulation in a distant hospital (14). Application of this prediction model in our cohort is difficult because only 8.1% of patients were transferred from a referring hospital and the ROC curve analysis showed no discriminative power in predicting hospital mortality in our data set (c=0.56).

Comparing our baseline characteristics to the PRESERVE study (8), the incidence of immunocompromised patients was similar, whereas the median SOFA score and the incidence of steroid use, NO inhalation, prone positioning, and CRRT were lower in our study population. The reason for this difference is that the PRESERVE and Roch scores were designed for pre-ECMO mortality prediction in patients with ARDS (a more specific population than ARF). The AUC of the PRESERVE score in our cohort demonstrated significant performance but weaker discriminative power than in the original data (c=0.63 *vs.* c=0.89). We postulate that the poor discriminatory ability of the PRESERVE score is because our population tended to be older with a lower incidence of

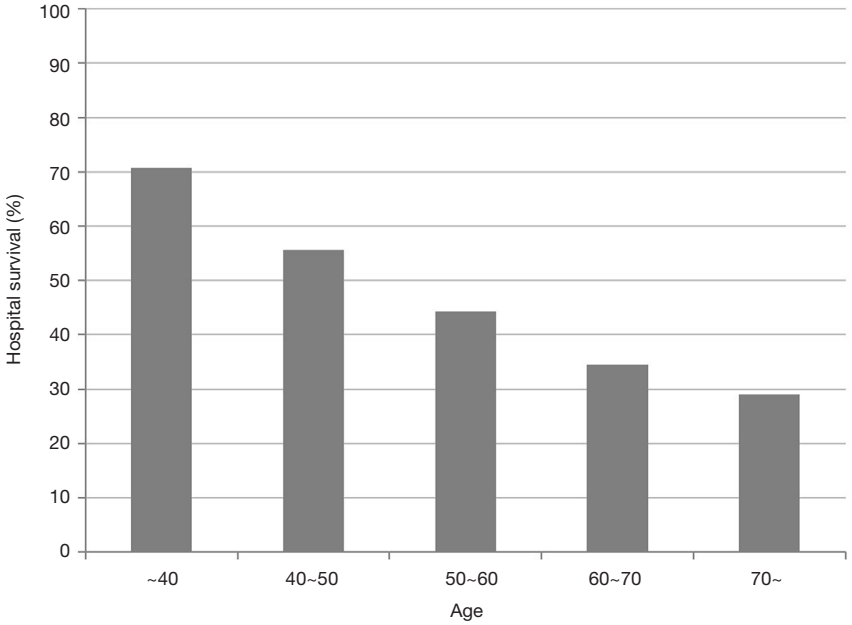

Figure 2 Hospital survival percentage of patients receiving ECMO in respect of the age. ECMO, extracorporeal membrane oxygenation.

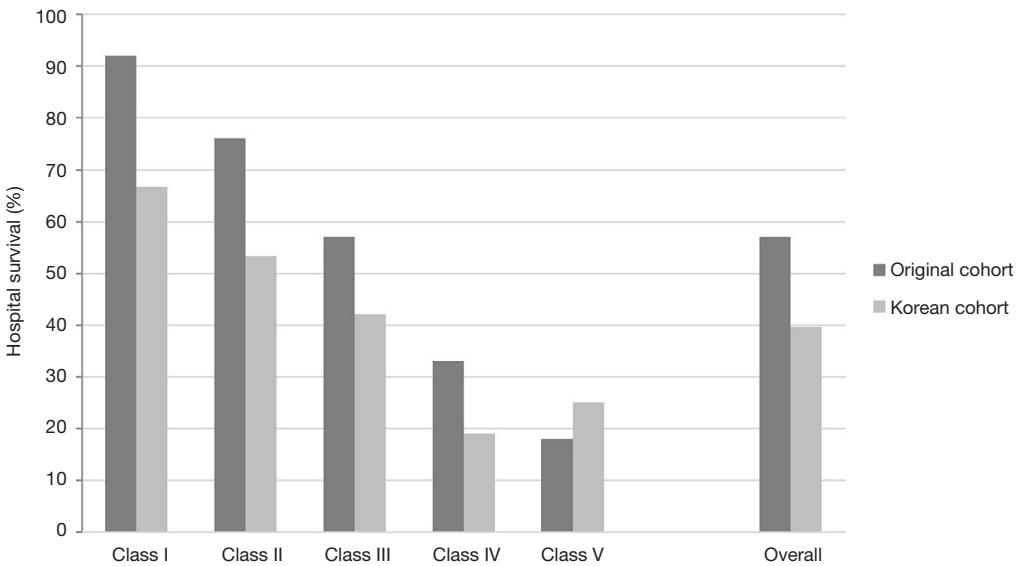

Figure 3 Comparison of hospital survival percentage in original and Korean cohorts according to the RESP score at ECMO initiation for severe acute respiratory failure. RESP score is divided into five risk classes, referred to as I (≥6), II (3 to 5), III (–1 to 2), IV (–5 to –2), and V (≤–6). RESP, respiratory extracorporeal membrane oxygenation survival prediction; ECMO, extracorporeal membrane oxygenation.

prone positioning and body mass index, all variables of the score calculation associated with worse prognosis.

The RESP score (9), which was constructed from 2,355 ECMO-treated patients with severe ARF, was a discriminatory survival model (c=0.73). However, in our population, the RESP score also showed average discrimination ability to predict survival from ECMO therapy (c=0.66). This result is presumably due to the

Table 6 The modified RESP score

Variable	Score	Grouping
RESP	≥6	0
	3 to 5	3
	–1 to 2	5
	–5 to –2	10
	≤–6	21
Age (year)	<50	0
	50–59	2
	60–69	3
	≥70	3.5
Total score		0 to 24.5

RESP, Respiratory Extracorporeal Membrane Oxygenation Survival Prediction.

Table 7 Hospital survival by the modified RESP score

The modified RESP score	Risk class (N=189)	Survival
0 to 3	I (n=30)	70%
4 to 7	II (n=74)	57%
≥8	III (n=85)	27%

RESP, Respiratory Extracorporeal Membrane Oxygenation Survival Prediction.

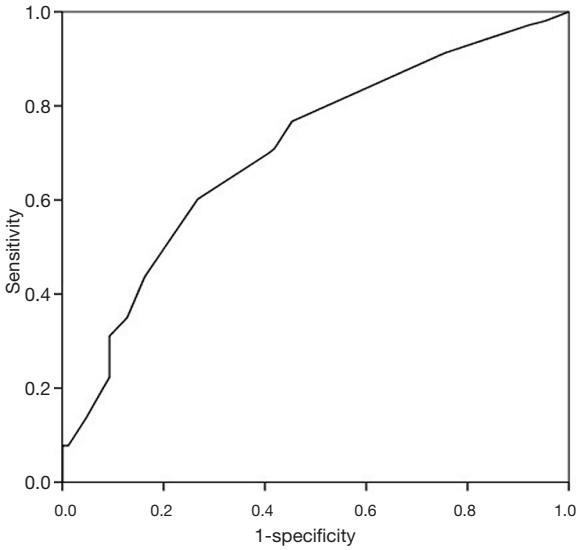

Figure 4 Receiver operating characteristic curves of the modified RESP score (n=189). The modified RESP score had better discrimination [(AUC of 0.71 (95% CI, 0.63–0.78)] than the RESP score [AUC of 0.66 (0.58–0.73)]. RESP, Respiratory Extracorporeal Membrane Oxygenation Survival Prediction; AUC, area under the curve; CI, confidence interval.

difference in the RESP score parameters between study populations. In other words, our cohort included older patients with a higher incidence of immunocompromised status and cardiac arrest than the RESP study. Recently, Klinzing *et al.* (15) performed external validation of these outcome prediction models on a dataset of 51 patients with severe ARDS. Interestingly, although there was no similarity between the study populations, the discrimination of each outcome prediction model was comparable (c=0.67 for the PRESERVE score, c=0.65 for the RESP score, and c=0.55 for the Roch score). They concluded that the PRESERVE and RESP scores were useful tools, particularly in the subgroup of patients who receive VV ECMO (c=0.75 and c=0.81, respectively). However, in our study, there was no better predictive ability in patients treated with VV ECMO. Therefore, we believe that modification of the RESP or PRESERVE scores for each study population would help to predict survival for ECMO therapy.

In the PRESERVE study (8), 60% of patients treated with ECMO were alive 6 months after ICU discharge, and the survival rate was at least 50% in most studies (4,6,7,9,15-17). According to the ELSO registry, the hospital survival rates of ECMO patients were 50.3% from 1986 to 2006 (16) and 56.8% from 2002 to 2012 (9). Despite this steady improvement in the survival rate and major technological advances in devices (18-21), our study showed a 45.9% survival rate. Mortality is influenced by pre-ECMO variables such as older age, organ dysfunction, immunocompromised status, and impaired lung compliance (21).

Many countries are faced with ageing populations and elderly patients consume a high proportion of intensive care (10,11). Although there was no specific age contraindication in the ELSO guideline, it is necessary to consider increasing risk with increasing age (22). Mendiratta *et al.* reported that survival rate of patients older than 65 years treated with ECMO was 41% (12), which was 10% higher compared with our cohort. However, they reviewed only 368 patients in the ELSO registry, which was including more than 40,000 patient-cases. Previous other studies demonstrated that age is an independent risk factor for survival in patients treated with ECMO (8,9,14,17). In the RESP study (9), age over 50 years was associated with

increased mortality and the lowest score was assigned to patients aged 60 and over. However, we needed adjustment of the RESP score because 15% of our patients were aged 70 and over. Moreover, median age of 58 in our cohort was much higher than 41 years in the RESP study based on the ELSO registry. Therefore, reclassification of age group in the RESP score is convincing and the modified RESP score might be helpful for triage of ECMO initiation in the countries with the elderly population.

The SOFA score is a good prognostic model to assess organ dysfunction or failure over time and correlated with mortality in the ICU (23). Roch *et al.* (14) demonstrated that the SOFA score immediately before ECMO was an independent risk factor for mortality (OR 1.267, P=0.01), and Enger *et al.* (17) reported that the SOFA score showed better discrimination than the PRESERVE and ECMOnet scores. In accordance with previous studies, the SOFA score was a significant outcome prediction model in our analysis. Moreover, we speculated that serial evaluation of the SOFA score would be a good indicator of prognosis in patients on ECMO therapy because the SOFA scores at 24 hours after ECMO cannulation were significantly lower in survivors than in non-survivors.

Immunosuppression was associated with reduced functional reserves and mortality (8,9,17). Although the results of the present study did not correspond with those of previous studies, immunocompromised status is a valuable parameter used in both the PRESERVE and RESP scores. Another distinctive characteristic in our cohort was a higher incidence of non-VV cannulation. Non-VV cannulation was applied in our study in 17.7% of patients, whereas it was applied in 5% and 2% of patients in the PRESERVE and ECMOnet studies (7,8), respectively. Although non-VV cannulation was not a significant risk factor for mortality in our analysis, a number of studies showed that VA cannulated patients tended to have worse prognosis (15,16,24,25). Generally, non-VV cannulation was performed in patients with cardiogenic dysfunction or hemodynamic instability (7,8). In addition, the incidence of cardiac arrest in our study was higher than in the RESP study (19.8% *vs.* 9%) (9). Therefore, we postulated that non-VV cannulation was an indirect indicator of a poor outcome.

There were some limitations to our study of note. First, because this was a retrospective study and included only a Korean population, there is a limitation in terms of the general applicability of the results. Second, we failed to evaluate long-term outcomes because our study lacked data such as mortality at 6 months after ICU discharge or long-term quality of life. Third, external validation of the modified RESP score was not conducted due to the small study population. Thus far, the RESP score has been the most recommended outcome prediction model to identify specific populations who could benefit from ECMO therapy (21). Although further validation of our modified RESP score is necessary by other study populations, our study suggests that reclassification of age in the RESP score might be helpful.

In conclusion, the RESP score is significant model for predicting outcomes in a Korean ECMO population. Elderly patients had higher mortality, and age alone showed similar discrimination ability for prediction of mortality compared to the RESP score.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the institutional review board of Asan Medical Center, Samsung Medical Center, Pusan National University Yangsan Hospital, Seoul National University Bundang Hospital, Hallym University Sacred Heart Hospital, Chonbuk National University Hospital, Ulsan University Hospital, Bundang CHA Hospital, Kyung Hee University Hospital at Gangdong, Dongguk University Ilsan Hospital, and Hallym University Kangnam Sacred Heart Hospital. The need for informed consent was waived due to the retrospective design.

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