

# Association of pulmonary arterial pressure with volume status in patients with acute respiratory distress syndrome receiving extracorporeal membrane oxygenation

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**Background:** Data on pulmonary hemodynamic parameters in patients with acute respiratory distress syndrome (ARDS) receiving extracorporeal membrane oxygenation (ECMO) are scarce.

**Methods:** The associations between pulmonary artery catheter parameters for the first 7 days of ECMO, fluid balance, and hospital mortality were investigated in adult patients (aged  $\geq 19$  years) who received venovenous ECMO for refractory ARDS between 2015 and 2017.

**Results:** Twenty patients were finally included in the analysis (median age, 56.0 years; interquartile range, 45.5–68.0 years; female,  $n=10$ ). A total of 140 values were collected for each parameter (i.e., 7 days $\times$ 20 patients). Net fluid balance was weakly but significantly correlated with systolic and diastolic pulmonary arterial pressures (PAPs;  $r=0.233$  and  $P=0.011$ ;  $r=0.376$  and  $P<0.001$ , respectively). Among the mechanical ventilation parameters, above positive end-expiratory pressure was correlated with systolic PAP ( $r=0.191$  and  $P=0.025$ ), and static compliance was negatively correlated with diastolic PAP ( $r=-0.169$  and  $P=0.048$ ). Non-survivors had significantly higher systolic PAPs than in survivors. However, in multivariate analysis, there was no significant association between mean systolic PAP and hospital mortality (odds ratio, 1.500; 95% confidence interval, 0.937–2.404;  $P=0.091$ ).

**Conclusions:** Systolic PAP was weakly but significantly correlated with net fluid balance during the early ECMO period in patients with refractory ARDS receiving ECMO.

**Key Words:** body fluids; extracorporeal membrane oxygenation; pulmonary artery; respiratory distress syndrome

## INTRODUCTION

Acute respiratory distress syndrome (ARDS) is frequently complicated by pulmonary hypertension [1,2], and many studies have documented the changes in pulmonary hemodynamic parameters in patients with ARDS. Some have reported that systolic pulmonary arterial pressure (PAP) or mean PAP is a significant indicator of patient outcome [3,4], whereas others did not find any associations or did not specifically evaluate the associations [2,5,6]. However, there is still uncertainty about the underlying pathophysiology between the degree of pulmonary hypertension (or pulmonary vascular dysfunction) and patient outcome.

Routine use of a pulmonary artery catheter (PAC) is not currently recommended because

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of the lack of clinical benefit and possible complications [7,8]. However, PACs provide unique and various information to intensivists and often change therapy, particularly regarding fluid management and vasopressor use in critically ill patients. In particular, fluid balance has been considered important in terms of patients' outcomes [8-10].

Recently, extracorporeal membrane oxygenation (ECMO) has been widely used as salvage therapy for patients with severe ARDS. Many authors investigated mechanical ventilation (MV) parameters associated with patient outcomes [11-13]. However, data on pulmonary hemodynamic parameters are very scarce for these patients. Therefore, in this retrospective study, we investigated the association between PAP, fluid balance, and in-hospital mortality in patients in whom a PAC was inserted after initiating venovenous (VV) ECMO for refractory ARDS.

## MATERIALS AND METHODS

### Study Population and Design

This was a retrospective study using data collected from adult patients (age  $\geq 19$  years) who received VV ECMO for refractory ARDS between January 2015 and January 2017. This study was performed in a single center (tertiary hospital) where annual ECMO volume was 60 cases (VV ECMO, 20 cases). During the study period, a PAC was inserted for hemodynamic monitoring in patients for whom written consent was obtained. The Berlin definition was used for diagnosing ARDS [14]. The indications for VV ECMO were severe hypoxemia (e.g.,  $\text{PaO}_2/\text{FiO}_2 < 150$ ) with a high positive end-expiratory pressure (PEEP  $> 10$  cm  $\text{H}_2\text{O}$ ), uncompensated severe hypercapnia ( $\text{pH} < 7.20$ ), or excessively high peak inspiratory pressure or plateau pressure, despite standard of care management with a MV [15-17]. The exclusion criteria were patients with cardiopulmonary resuscitation; do-not-resuscitate order; ECMO treatment for respiratory failure other than ARDS; incomplete data on PAC parameters; and those who were transferred to other hospitals during the ECMO treatment.

This study was approved by the Institutional Review Board of Hallym University (IRB No. 2020-06-22) and conducted in accordance with the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

### ECMO and MV Strategies

We used Capiox EBS (Terumo, Tokyo, Japan) or PLS (Maquet, Hirrlingen, Germany) equipment. Both femoral veins were percutaneously cannulated using the Seldinger technique

### KEY MESSAGES

- Net fluid balance was weakly but significantly correlated with systolic and diastolic pulmonary arterial pressure (PAP) in patients with refractory acute respiratory distress syndrome receiving extracorporeal membrane oxygenation.
- Systolic PAP was higher in non-survivors than in survivors, but was not associated with hospital mortality in multivariable analysis.

under fluoroscopic guidance. The 17- to 19-Fr (for return) and 21-Fr (for drainage) cannulas were placed (DLP and Bio-Medicus, Medtronic, Minneapolis, MN, USA; RMI, Edward's Life sciences, Irvine, CA, USA). After ECMO was initiated, the pump flow was adapted (3-5 L/min) to maintain adequate oxygen ( $\text{SpO}_2 > 88\%$ ), and the sweep gas flow was titrated to maintain a  $\text{PaCO}_2$  of 40 mm Hg (usually 1:1 to blood flow). During ECMO support, heparin was used for anticoagulation, with a target activated partial thromboplastin time of 1.5 times the normal range. MV settings were adjusted to enable lung-protective ventilation after the initiation of ECMO, according to general recommendations [18,19]: tidal volume  $< 6$  ml/kg predicted body weight, PEEP  $\geq 5$  cm  $\text{H}_2\text{O}$ , and peak inspiratory pressure  $< 30$  cm  $\text{H}_2\text{O}$ . ECMO weaning was considered when the patient became hemodynamically stable and showed evidence of pulmonary improvement. The pump flow was first tapered to 2 L/min, and the sweep gas to 0 L/min; decannulation was indicated if the patient tolerated these settings [15-17]. ECMO weaning was considered successful when the patient remained stable for 24 hours without ECMO support. MV weaning was undertaken in accordance with the general recommendations [20].

### PAC Insertion and Fluid Management

PACs (7.5-Fr; Edwards Lifesciences, Irvine, CA, USA) were inserted, using a balloon-flotation catheter in bedside, through the internal jugular vein within the first 2 hours following initiation of ECMO. Correct positioning of the catheter tip (i.e., in the pulmonary artery) was verified by chest radiography. Systolic and diastolic PAP was monitored continuously, and cardiac output was measured by the thermodilution method using 10 mL of injected cold saline. The cardiac output value was the mean of four cardiac output measurements without artifacts on the temperature curves; the cardiac index (CI) was the ratio of cardiac output to the patient's body surface area. Daily PAC

data were collected between 9–10 AM. However, in our cohort, pulmonary artery occlusion pressure (PAOP) was not measured for safety reasons; instead, we used diastolic PAP values (for PAOP) to calculate pulmonary vascular resistance (PVR). A stable relationship exists between diastolic PAP and PAOP [1,21]. We used a target diastolic PAP of <20 cm H<sub>2</sub>O for fluid management during ECMO treatment. Mean arterial pressure (MAP) was maintained at >65 mm Hg and urine output >0.5 ml/kg/hr; vasopressors were used if required. The decision to remove the PAC was at the discretion of the physician. The formulas for the PAC parameters were as follows:

$$\text{Mean PAP} = (\text{systolic PAP} + 2 \times \text{diastolic PAP}) / 3$$

$$\text{PVR (i.e., modified PVR)} = (\text{mean PAP} - \text{diastolic PAP}) \times 80 / \text{cardiac output}$$

$$\text{Systemic vascular resistance} = (\text{MAP} - \text{central venous pressure}) \times 80 / \text{cardiac output}$$

### Data Collection and Analysis

The following data were obtained: demographic characteristics (age and sex); comorbidities; causes of ARDS; laboratory parameters and severity-of-illness scores (Sequential Organ Failure Assessment [SOFA]) before implementing ECMO; and data on MV parameters and fluid balance (input/output) during the first 7 days of ECMO. Systolic and diastolic PAPs, the CI, systemic vascular resistance, PVR (i.e., modified PVR), and central venous pressure were collected during the first 7 days of ECMO. The rates of successful weaning from ECMO and hospital death were investigated as patient outcomes. The primary outcome was the association between systolic and diastolic PAPs and hospital mortality, and the secondary outcomes were the associations between systolic and diastolic PAPs and daily net fluid balance (i.e., a total fluid balance during the early seven ECMO days).

### Statistical Analysis

All results are presented as numbers with percentages for categorical variables, and as medians with interquartile ranges for continuous variables. The Mann-Whitney U-test was used to compare continuous variables, and the chi-square or Fisher's exact test was employed to compare categorical variables. A multivariable logistic regression analysis, adjusted for age, SOFA, fluid balance, and tidal volume, was performed to investigate an independent association of a PAC parameter (i.e., systolic PAP) with hospital mortality. All probability values were two-sided and a  $P < 0.05$  was considered statistically significant. IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA)

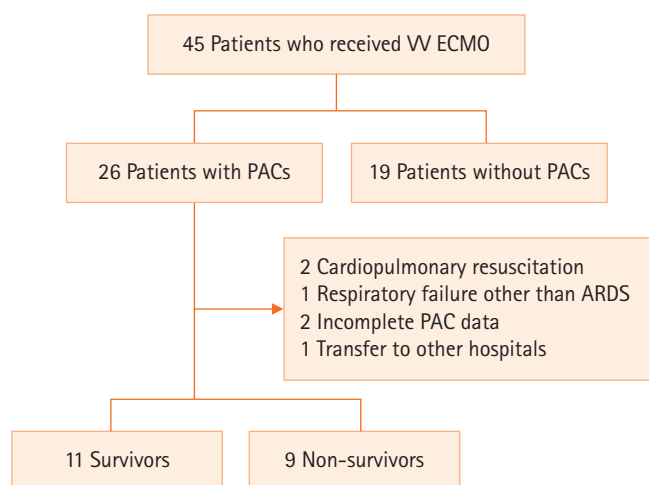
was used for all statistical analyses.

## RESULTS

### Study Population

During the study period, 45 patients received ECMO for refractory ARDS; of these, 26 patients received a PAC (Figure 1). Twenty patients were finally included in the analysis. Their median age was 56.0 years (interquartile range [IQR], 45.5–68.0 years), and 10 patients were female. The median SOFA score was 9.5 (IQR, 7.0–11.0), and 16 (80.0%) of the patients had ARDS of pulmonary origin. Hypertension (20.0%) and heart diseases (20.0%) were the most common comorbidities (Table 1).

One patient had a history of cor pulmonale, and pre-ECMO right systolic ventricular pressure was documented only in six patients (48.0 mm Hg; IQR, 46.0–55.0). The median systolic blood pressure, heart rate, and respiratory rates before initiating ECMO were 134.0 mm Hg (IQR, 117.3–148.3 mm Hg), 115.0 beats/min (IQR, 101.0–131.5 beats/min), and 26.0 breaths/min (IQR, 21.3–31.5 breaths/min), respectively. The median duration of MV before initiating ECMO was 1.0 days (IQR, 0.5–2.0 days). The initial PAC parameters (ECMO day 1) are presented in Supplementary Table 1; the mean PAP was 22.8 mm Hg (IQR, 20.1–27.8 mm Hg), and eight patients had pulmonary hypertension (i.e., mean PAP >25 mm Hg). None of the patients underwent prone positioning before and during ECMO treatment.



**Figure 1.** Flowchart of patients enrolment. VV: venovenous; ECMO: extracorporeal membrane oxygenation; PAC: pulmonary arterial catheter; ARDS: acute respiratory distress syndrome.

**Table 1.** Baseline characteristics before ECMO treatment

Variable	Survivor (n=11)	Non-survivor (n=9)	P-value
Age (yr)	49.0 (45.0–61.0)	68.0 (49.5–72.5)	0.112
Sex (male:female)	6:5	4:5	1.000
Comorbidity			
Diabetes	2 (18.2)	1 (11.1)	1.000
Hypertension	3 (27.3)	1 (11.1)	0.591
Heart disease	1 (9.1)	3 (33.3)	0.285
Chronic kidney disease	0	1 (11.1)	0.450
Liver cirrhosis	1 (9.1)	0	1.000
Cancer	0	1 (11.1)	0.450
Reason for ECMO			0.591
Pulmonary origin	8	8	
Non-pulmonary origin	3	1	
SOFA score at admission	10.0 (8.0–14.0)	8.0 (7.0–10.0)	0.084
Respiratory SOFA score	4.0 (4.0–4.0)	4.0 (4.0–4.0)	0.668
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	85.6 (77.7–98.9)	98.9 (82.8–99.0)	0.208
White blood cell counts (10 <sup>3</sup> /μl)	13.2 (9.0–21.0)	16.7 (9.5–17.9)	0.882
Hemoglobin (g/dl)	11.9 (9.8–13.8)	11.0 (9.9–12.4)	0.503
Platelet (10 <sup>3</sup> /μl)	109.0 (59.0–163.0)	256.0 (147.5–281.0)	0.007
Bilirubin (mg/dl)	1.5 (0.3–2.8)	0.2 (0.2–1.1)	0.020
Albumin (g/dl)	3.0 (2.8–3.5)	2.8 (2.5–3.0)	0.131
Creatinine (mg/dl)	1.2 (0.8–1.3)	0.8 (0.5–1.3)	0.370
C-reactive protein (mg/L)	191.6 (160.4–292.3)	196.9 (108.1–209.5)	0.331
Brain natriuretic peptide (pg/ml)	342.0 (22.9–2898.0)	235.8 (61.6–489.7)	0.551
Vasopressor use	9 (81.8)	2 (22.2)	0.024
Ejection fraction (%)	60.0 (60.0–66.0)	60.0 (55.0–65.5)	0.969
MV setting before ECMO			
Above PEEP (cm H <sub>2</sub> O)	15.0 (12.0–20.0)	18.0 (14.0–19.0)	0.878
PEEP (cm H <sub>2</sub> O)	10.0 (6.0–12.0)	14.0 (12.0–15.0)	0.083
Respiratory rate (breaths/min)	18.0 (12.0–26.0)	20.0 (18.0–28.0)	0.180

Values are presented as median (interquartile range) or number (%).

ECMO: extracorporeal membrane oxygenation; SOFA: Sequential Organ Failure Assessment; MV: mechanical ventilation; PEEP: positive end-expiratory pressure.

## Treatments and Outcomes

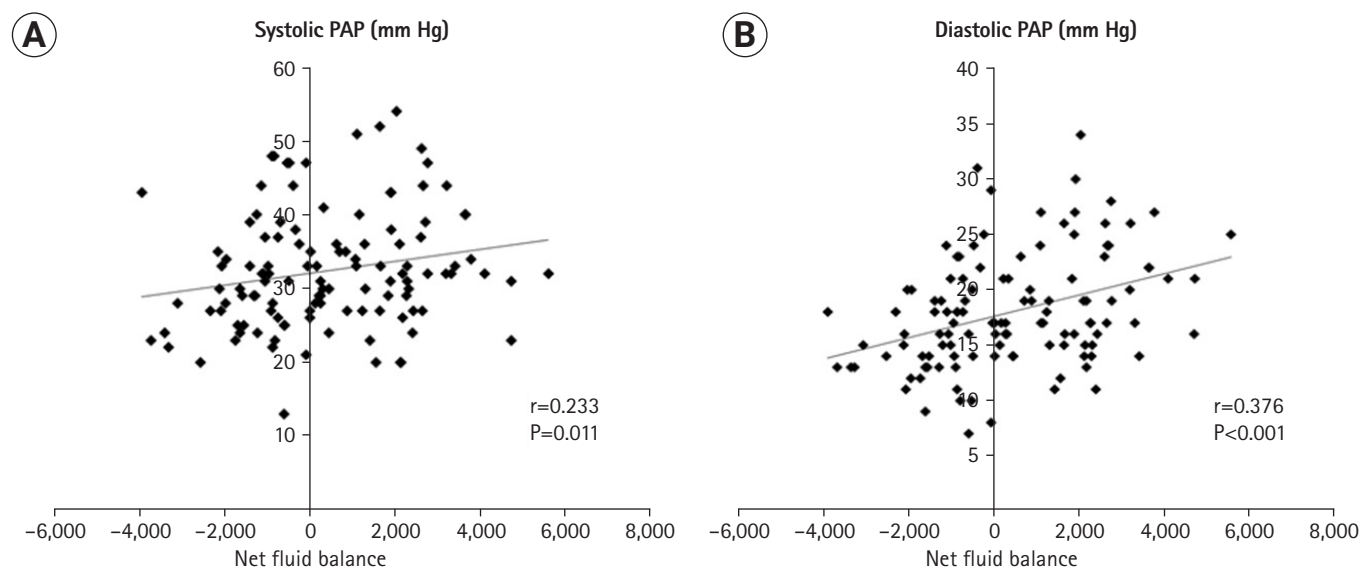
The initial ECMO flow was 4.2 L/min (IQR, 3.9–4.5 L/min) with a sweep gas flow of 4.0 L/min (IQR, 4.0–4.0 L/min). The median numbers of packed red blood cells and platelets transfused were 12.5 units (IQR, 8.0–15.5 units) and 28.5 units (IQR, 0.0–63.5 units), respectively, with no difference between survivors and non-survivors (data not shown). The MV settings before initiating ECMO did not differ between the two groups (Table 1). Fourteen patients (70.0%) were successfully weaned from ECMO and 11 (55.0%) survived to discharge; the median ECMO duration was 18.5 days (IQR, 10.0–27.0 days). The lengths of the intensive care unit (ICU) and hospital stays were 32.0 days (IQR, 26.0–42.8 days) and 42.5 days (IQR, 28.5–53.8 days). None of the patients underwent lung transplantations.

## Correlation Analyses

A total of 140 samples were collected per parameter (i.e., 7 days×20 patients). Net fluid balance was weakly but significantly correlated with systolic and diastolic PAPs ( $r=0.233$  and  $P=0.011$ ;  $r=0.376$  and  $P<0.001$ , respectively) (Figure 2, Table 2) and was negatively correlated with the CI ( $r=-0.205$  and  $P=0.025$ ). Among the MV parameters, above PEEP was correlated with systolic PAP ( $r=0.191$  and  $P=0.025$ ) (Table 3), and static compliance (i.e., tidal volume/above PEEP in pressure-controlled ventilation mode) was negatively correlated with diastolic PAP ( $r=-0.169$  and  $P=0.048$ ).

## Univariate and Multivariate Analyses

Among the PAC parameters, systolic PAP was significantly



**Figure 2.** Correlation analyses between pulmonary arterial pressures (PAPs) and net fluid balance during the first 7 extracorporeal membrane oxygenation (ECMO) period. (A) Correlation between systolic PAP and net fluid balance and (B) correlation between diastolic PAP and net fluid balance. Gray line indicates trend line.

**Table 2.** Correlation of net fluid balance with PAC parameters during the early 7 ECMO days

Net fluid balance	Cardiac index	Systolic PAP	Diastolic PAP	PVR	SVR	CVP
r	-0.205	0.233	0.376	0.038	0.048	0.213
P-value	0.025	0.011	<0.001	0.684	0.599	0.020

Formulas for PAC parameters: (1) mean PAP=(systolic PAP+2×diastolic PAP)/3; (2) PVR (i.e., modified PVR)=(mean PAP–diastolic PAP)×80/cardiac output; (3) systolic vascular resistance=(MAP–CVP)×80/cardiac output; (4) cardiac index=cardiac output/body surface area.

PAC: pulmonary artery catheter; ECMO: extracorporeal membrane oxygenation; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; CVP: central venous pressure.

**Table 3.** Correlation of mechanical ventilation with PAC parameters during the early seven ECMO days

Variable	Above PEEP	PEEP	Tidal volume	Static compliance
<b>Systolic PAP</b>				
r	0.191	-0.042	-0.038	-0.120
P-value	0.025	0.622	0.655	0.161
<b>Diastolic PAP</b>				
r	0.162	0.162	-0.079	-0.169
P-value	0.058	0.058	0.356	0.048
<b>Mean PAP</b>				
r	0.175	0.095	-0.061	-0.153
P-value	0.041	0.266	0.473	0.073
<b>PVR</b>				
r	0.049	-0.123	-0.110	-0.040
P-value	0.568	0.152	0.194	0.645
<b>SVR</b>				
r	-0.111	0.155	-0.324	-0.171
P-value	0.195	0.070	<0.001	0.044
<b>Cardiac index</b>				
r	-0.013	-0.139	-0.021	-0.006
P-value	0.884	0.105	0.806	0.946

PAC: pulmonary artery catheter; ECMO: extracorporeal membrane oxygenation; PEEP: positive end-expiratory pressure; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance.



higher in non-survivors than in survivors (Table 4, Figure 3). However, no significant differences were observed in daily fluid balance (Supplementary Table 2) or MV parameters (Supplementary Table 3) between the two groups. In the multivariable model, five variables (age, SOFA, fluid balance, tidal volume, and systolic PAP) were included (Table 5), and mean systolic PAP was not significantly associated with hospital mortality (odds ratio, 1.500; 95% confidence interval, 0.937–2.404).

## DISCUSSION

This retrospective study revealed that net fluid balance was weakly but significantly correlated with systolic and diastolic

PAPs in patients receiving VV ECMO for severe ARDS. Besides, systolic PAP was significantly higher in non-survivors than survivors. However, the mean systolic PAP value during the first 7 days of ECMO was not significantly associated with hospital mortality.

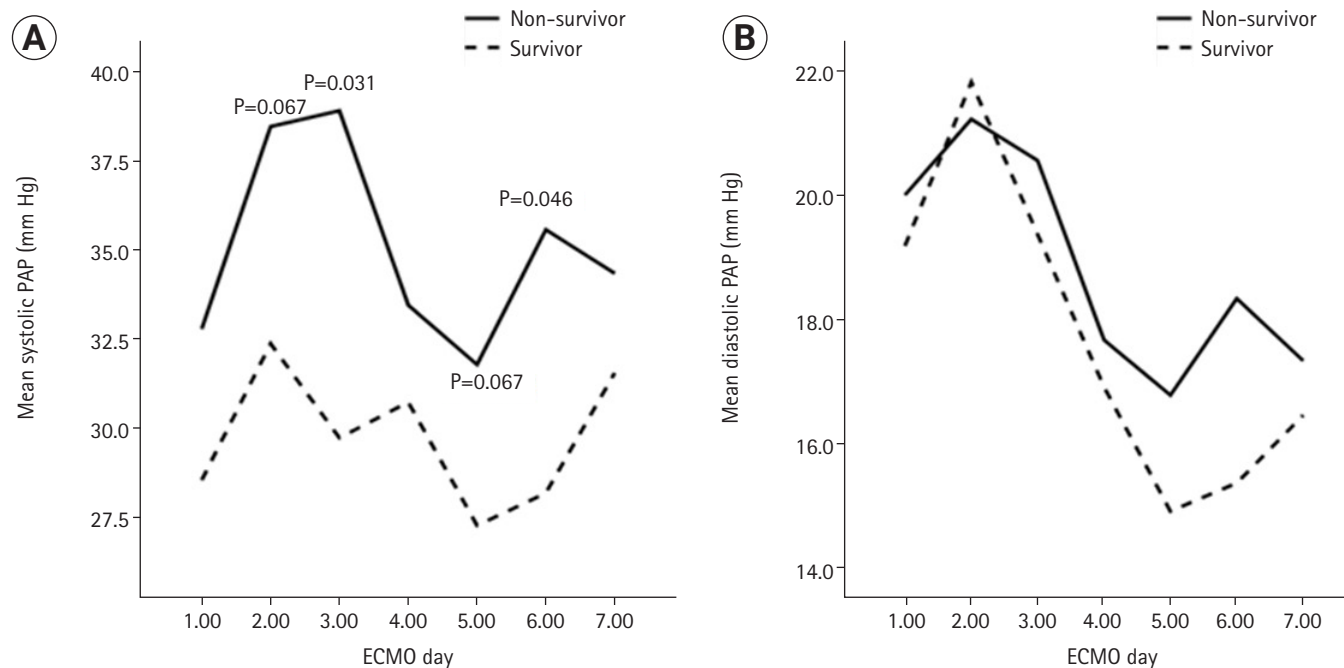
Previous large-scale randomized trials have demonstrated no survival benefit of PAC-guided therapy compared to standard care (in surgical patients) or central venous catheter-guided therapy in those with acute lung injury [7,22,23]. In particular, the PAC-guided therapy was associated with a two-fold risk of catheter-related complications compared to central venous catheter-guided therapy [7]. Since then, the routine use of PAC has not been recommended. However, our

**Table 4.** PAC parameters between survivors and non-survivors during the early 7 days of ECMO (140 samples for each variable per group)

Variable	Survivor		Non-survivor		P-value <sup>a</sup>
	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	
Cardiac index (L/min/m <sup>2</sup> )	5.5 (4.1–6.8)	5.7±2.3	4.9 (4.0–5.9)	5.5±2.5	0.344
Systolic PAP (mm Hg)	29.0 (25.0–33.5)	29.8±7.2	33.0 (30.0–40.0)	35.0±7.8	<0.001
Diastolic PAP (mm Hg)	17.0 (14.5–20.5)	17.7±4.8	19.0 (14.0–23.0)	18.8±5.8	0.221
PVR (dyn·sec/cm <sup>5</sup> )	55.0 (44.0–74.0)	58.7±27.3	65.0 (55.0–98.0)	73.4±34.4	0.006
SVR (dyn·sec/cm <sup>5</sup> )	985.0 (790.0–1152.5)	1,007.3±320.5	838.0 (551.0–1183.0)	887.9±363.3	0.034
CVP (mm Hg)	10.0 (8.0–13.0)	10.6±3.4	10.0 (7.0–15.0)	10.7±4.9	0.875

PAC: pulmonary arterial catheter; ECMO: extracorporeal membrane oxygenation; IQR: interquartile range; SD: standard deviation; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; CVP: central venous pressure.

<sup>a</sup>Mann-Whitney U-test (between survivors and non-survivors).



**Figure 3.** Comparison of mean (A) systolic and (B) diastolic pulmonary arterial pressures (PAPs) between survivors and non-survivors. ECMO: extracorporeal membrane oxygenation.

**Table 5.** Univariable and multivariable analysis for hospital death<sup>a</sup>

Variable	Univariable analysis			Multivariable analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.506	0.978–1.140	0.167	1.053	0.914–1.214	0.475
SOFA	0.710	0.481–1.047	0.084	0.585	0.294–1.164	0.126
Fluid balance <sup>b</sup>	1.122	0.999–1.260	0.051	1.000	1.000–1.000	0.222
Tidal volume	1.000	1.000–1.000	0.106	0.986	0.949–1.025	0.481
Systolic PAP <sup>c</sup>	1.234	0.992–1.536	0.060	1.500	0.937–2.404	0.091

OR: odds ratio; CI: confidence interval; SOFA: Sequential Organ Failure Assessment; PAP: pulmonary artery pressure; ECMO: extracorporeal membrane oxygenation.

<sup>a</sup>Hosmer-Lemeshow test, chi-square=8.044 and P=0.420; <sup>b</sup>Net fluid balance during the 7 ECMO days; <sup>c</sup>Mean value of systolic PAP for each patient.

aim in this retrospective study was not to evaluate the usefulness of PAC but to investigate the therapeutic or prognostic role of PAP in patients receiving ECMO for refractory ARDS. We inserted PACs in patients undergoing VV ECMO to monitor hemodynamics and guide conservative fluid management. A relatively large volume of fluid was given to patients during the early period (e.g., days 1–3) (Supplementary Table 2), but we tried to maintain a conservative strategy while monitoring diastolic PAP and using diuretics. Although we did not find any strong associations due to small sample size, PAP may reflect fluid balance, and a higher systolic PAP might be associated with higher mortality in patients receiving VV ECMO for severe ARDS. These results are consistent with those reported previously [3,4].

As noted above, we did not inflate the balloon of the PAC to measure PAOP in our patients for safety reasons; occluding the proximal pulmonary artery may be associated with an increased risk of thromboembolism or rupture of the pulmonary artery in critically ill patients. Previous studies have reported that the incidence rates of catheter-related infections or embolization in patients with a PAC are 0%–4.6% or 1%–11%, respectively [22–24]. No case of thromboembolic complications was detected in our cohort, but one patient (5.0%) had PAC-related bacteremia; however, the duration of PAC indwelling was longer than that reported in previous studies [22].

ARDS elevates PAP and consequently increases right ventricular afterload, and this elevated pressure harms patient outcomes. Although data are still conflicting [2,5,6], some previous studies have reported the prognostic significance of PAP in patients with ARDS [1,3,4,25]. In a secondary analysis of 501 patients from the Fluid and Catheter Treatment Trial by the ARDS Network, the largest trial in the era of lung-protective ventilation, a high transpulmonary gradient or PVR was significantly associated with a poor outcome [1]; however, no difference was detected in PAP between survivors and

non-survivors in the study. Of importance, PVR is affected mainly by factors that are intrinsic to the lung (e.g., lung injury in ARDS), whereas PAP is affected not only by factors that are intrinsic to the lung (e.g., PVR) but also by extrinsic factors (e.g., right ventricular function). This may have contributed to the different mortality results between the two parameters [2]. In our analysis, diastolic PAP was used instead of PAOP to calculate PVR. Although we cannot conclusively state that the PVR values in our study were correct, the PVRs were significantly higher in non-survivors than in survivors during the first 7 days of ECMO (Table 4), which is consistent with previous data [1,26]. However, the presence of pulmonary vascular dysfunction is likely to be a simple marker of lung injury severity. The causal relationship, as well as the exact mechanism, between pulmonary vascular dysfunction and patient outcomes remains unclear.

Previous studies have demonstrated that conservative fluid management is important to the outcomes of patients with ARDS, including those receiving ECMO [8,9]. In our cohort, net fluid balance did not differ during the early ECMO days between survivors and non-survivors. However, interestingly, systolic and diastolic PAPs were weakly but significantly correlated with net fluid balance (Table 2). These results suggest that if a new noninvasive method is validated in the future [27,28], systolic PAP could be a useful parameter for optimizing fluid management or predicting patient outcomes. However, systolic PAP did not show any correlations with oxygenation (initial PaO<sub>2</sub>/FiO<sub>2</sub> ratio) and other outcomes (i.e., durations of ECMO and MV, and ICU and hospital length of stay).

Regarding ventilator settings, above PEEP was correlated with systolic PAP (Table 3). This implies that together with fluid balance, above PEEP may be a determining factor for PAP. However, notably, lung compliance was also correlated with diastolic PAP. When considering the association of diastolic PAP with fluid balance (Table 2), we may say that a negative (or

less) fluid balance can induce an increase in lung compliance. However, contrary to a previous study [11], neither lung compliance nor diastolic PAP was associated with hospital mortality in our study population. More research is needed to clarify this point.

To date, data on PAC parameters in patients receiving ECMO for severe ARDS are very scarce. Hemmila et al. [6] reported no difference in pre-ECMO systolic and diastolic PAPs between survivors and non-survivors. In contrast, Lazzeri et al. [29] found that survival is significantly associated with lower pre-ECMO systolic PAP. We collected and analyzed PAC data obtained after initiating VV ECMO (during the first 7 days of ECMO), which is one of the strengths of our study. Although our study was underpowered to verify a significant association between systolic PAP and hospital mortality due to its small sample size, the investigation of the role of PAPs seems reasonable in patients receiving ECMO, when considering many factors affecting pulmonary vascular function, such as volume overload, vasopressors, and MV.

This study had several limitations. First, because of the small sample size and retrospective nature of the study, the results may reflect unintended bias. In particular, half of the patients did not receive a PAC during the study period. Second, as aforementioned, we did not measure PAOP directly but used diastolic PAP to calculate PVR. Third, mean values for PAC parameters (for 7 days) were used in the present study. However, daily values might be more valuable in clinical practice. Fourth, although we followed the Extracorporeal Life Support Organization guidelines, ECMO management practices have not been standardized. Fifth, we did not investigate long-term outcomes including quality of life in our study population. However, this is the first study to show the potential usefulness of PAPs obtained during the early ECMO period for predicting outcomes in patients with severe ARDS. Therefore, despite several limitations, our results merit further consideration.

In conclusion, systolic PAP was weakly but significantly correlated with net fluid balance during the early ECMO period among patients with refractory ARDS. Despite no significant association in multivariable analysis, systolic PAP may be a potential parameter for optimizing fluid management or predicting patient outcomes.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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## AUTHOR CONTRIBUTIONS

Conceptualization: THH, SP. Data curation: all authors. Formal analysis: all authors. Methodology: all authors. Project administration: SP. Visualization: THH, HSK. Writing—original draft: THH, SP. Writing—review & editing: all authors.

## SUPPLEMENTARY MATERIALS

Supplementary materials can be found via <https://doi.org/10.4266/acc.2021.00927>.

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