

Early trajectories of pulmonary hemodynamics in ARDS patients undergoing V-V ECMO: key determinants and prognostic impact

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Early trajectories of pulmonary hemodynamics in ARDS patients undergoing V-V ECMO: key determinants and prognostic impact

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DECLARATIONS

- **Ethical Approval and Consent to participate**

The prospective data collection for patients admitted to the ICU, and its use for retrospective studies, was approved by the local ethics committee (Comitato Etico Brianza) in July 2016 (Reference No. 714). No additional or study-specific approval was required, as retrospective epidemiological analyses using anonymized administrative or clinical data do not require further committee authorization under local regulations. Informed consent was waived due to the retrospective design of the study and the use of anonymized patient codes.

- **Consent for publication**

Not applicable

- **Availability of supporting data**

The datasets generated and/or analyzed during the current study are available from the corresponding author (M.G.) upon reasonable request.

- **Competing interests**

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None

- **Authors' contributions**

Methodology: MG, ER

Formal analysis: MG, ER

Investigation / Data curation: BF, MR, MG

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None

Abstract

Background

Pulmonary hypertension (PH) frequently complicates acute respiratory distress syndrome (ARDS) and contributes to right ventricular dysfunction and mortality. Veno-venous extracorporeal membrane oxygenation (V-V ECMO) may attenuate PH through improved gas exchange, yet pulmonary pressures often remain elevated. Data on the determinants and prognostic impact of PH in ECMO-supported ARDS are limited.

Methods

We performed a retrospective observational study of adult ARDS patients receiving V-V ECMO at a tertiary referral center between 2003 and 2024. Only patients monitored with a pulmonary artery catheter were included. Daily hemodynamic, ventilatory, and gas exchange data were prospectively collected. Determinants of mean pulmonary artery pressure (mPAP) were analyzed using a linear mixed-effects model. The association of (1) mPAP on the first day of ECMO and (2) the mPAP trajectory over the first 5 ECMO days - expressed as the patient-specific daily slope - with hospital mortality was assessed using logistic regression before and after adjustment for confounders.

Results

Among 240 consecutive V-V ECMO patients, 225 had a pulmonary artery catheter and were analyzed. Median age was 51 years, 33% were female. The median mPAP during ECMO was 27 mmHg [23–32], with 91% of measurements exceeding 20 mmHg. Independent determinants of higher mPAP included intrapulmonary shunt fraction, lower venous pH, higher pulmonary artery occlusion pressure, increased PEEP, reduced respiratory system compliance, and longer ECMO duration. In contrast, higher venous partial pressure of oxygen and mixed venous oxygen saturation were associated with lower mPAP. mPAP on the first day of ECMO was not associated with hospital mortality. In contrast, the trajectory of mPAP during the first 5 days was independently associated with mortality (adjusted OR 1.89 per 1-mmHg/day increase, 95% CI 1.33–2.77, $p < 0.001$).

Conclusions

Pulmonary hypertension is highly prevalent in ARDS patients on V-V ECMO and reflects underlying disease severity. Early upward trajectories in mPAP, rather than the initial mPAP value, independently predicted higher mortality. Serial pulmonary pressure monitoring may provide relevant prognostic information and help guide management of pulmonary hemodynamics in ECMO-supported ARDS.

Introduction

Pulmonary hypertension (PH) is a hemodynamic alteration defined by an increase in mean pulmonary artery pressure (mPAP) above 20 mmHg [1]. PH is a well-recognized complication in patients with acute respiratory distress syndrome (ARDS) [2] and is associated with an increased risk of right ventricular (RV) dysfunction, contributing to higher mortality [3,4]. The pathogenesis of PH in ARDS is multifactorial and includes hypoxic pulmonary vasoconstriction (HPV), hypercapnia and acidosis, hemolysis, endothelial injury, vascular remodeling, and microvascular thrombosis [5,6]. In addition, mechanical ventilation itself may exacerbate PH by causing alveolar overdistension and increased pulmonary vascular resistance (PVR) [7]. PH correlates with the severity of hypoxemia and is associated with worse clinical outcome throughout the course of ARDS [8,9]. This highlights the importance of monitoring pulmonary hemodynamics, particularly in patients with severe disease.

Veno-venous extracorporeal membrane oxygenation (V-V ECMO) is increasingly used as a rescue therapy in patients with severe ARDS unresponsive to conventional treatment [10]. By improving oxygenation and carbon dioxide clearance, V-V ECMO may attenuate hypoxic pulmonary vasoconstriction and facilitate the application of lung-protective ventilation strategies. Consequently, pulmonary artery pressure and right ventricular afterload may be significantly reduced [11]. However, despite these theoretical benefits, pulmonary hypertension and RV dysfunction can still develop during V-V ECMO and have been associated with worse outcomes, occasionally requiring conversion to veno-arterial (V-A) or veno-venoarterial (V-VA) ECMO for hemodynamic support [12,13]. The aim of this study was to characterize pulmonary hemodynamics in a large cohort of severe ARDS patients supported with V-V ECMO by analyzing daily pulmonary artery pressure throughout the ECMO course, identifying independent physiological determinants of mPAP, and assessing the prognostic relevance of early mPAP trajectory rather than a single baseline value.

Materials and methods

This was a retrospective observational study based on prospectively collected data. The prospective collection of clinical and physiological variables for all patients admitted to the ICU of Fondazione IRCCS San Gerardo dei Tintori, and their use for retrospective research, was approved by the local ethics committee (Comitato Etico Brianza) in July 2016 (Reference No. 714). No additional, study-specific approval was required, as retrospective epidemiological analyses using anonymized administrative or clinical data do not require further authorization under local regulations. Informed consent was waived due to the retrospective nature of the study and the exclusive use of anonymized patient identifiers.

Adult patients with ARDS who received V-V ECMO between January 2003 and September 2024 were included. For patients who underwent more than one ECMO run, only the first run was considered. Patients without a pulmonary artery catheter during ECMO were excluded.

Data were collected from ECMO initiation until decannulation or death. Baseline characteristics included sex, age, body mass index (BMI), comorbidities, ARDS etiology, and severity indices at ECMO initiation, specifically the PaO₂ to FiO₂ ratio, the respiratory system compliance, the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score and the Sequential Organ Failure Assessment (SOFA) score. Pre-ECMO interventions such as inhaled nitric oxide (iNO), prone positioning, vasopressor use, and the duration of non-invasive ventilation (NIV) and invasive mechanical ventilation (IMV) were also recorded. ECMO duration, ICU mortality, and hospital mortality were collected for all patients.

Daily data collection

For each patient, data were collected daily at a consistent timepoint during the morning and included:

- Blood gas analyses: arterial and mixed venous samples at 100% FiO₂ (which were used to compute pulmonary shunt), arterial samples at clinical FiO₂, and samples from the ECMO circuit inlet and outlet;
- Systemic and pulmonary hemodynamic: systolic, diastolic, and mean pulmonary artery pressures, pulmonary artery occlusion pressure, mean systemic arterial pressure, central venous pressure, cardiac output, and heart rate;
- Ventilator settings;
- Adjunctive therapies during V-V ECMO.

The intrapulmonary shunt fraction (Q_s/Q_t) was calculated from samples obtained at 100% FiO₂ using the classical oxygen-content formula:

$$\frac{Q_s}{Q_t} = \frac{C_{capO_2} - C_{artO_2}}{C_{capO_2} - C_{venO_2}}$$

where C_{capO_2} is the pulmonary capillary oxygen content, C_{artO_2} is the arterial oxygen content, and C_{venO_2} is the mixed venous oxygen content sampled from the pulmonary artery catheter.

In the subset of patients who had a pulmonary artery catheter (PAC) before ECMO, respiratory and hemodynamic parameters before the ECMO start were also collected.

Statistical Analysis

Continuous variables were reported as median [interquartile range], according to distribution, and categorical variables as absolute (relative) frequencies (after exclusion of missing data).

In patients with a PAC in place before ECMO initiation, respiratory and hemodynamic parameters were compared between the day before and the first day of ECMO using the Wilcoxon signed-rank test.

To identify independent determinants of mPAP during ECMO, we performed a longitudinal multivariable analysis using a linear mixed-effects model. The dependent variable was daily mPAP recording for each ECMO day. Fixed effects covariates included venous pH (pH_v), PvCO₂, PvO₂, SvO₂, shunt fraction (Q_s/Q_t), mean arterial pressure (MAP), cardiac output (CO), pulmonary artery occlusion pressure (PAOP), PEEP, respiratory system compliance, and ECMO day. These variables were selected because they represent physiologically established determinants of pulmonary artery pressure. Arterial blood gas variables were not included to avoid collinearity, as arterial oxygenation during ECMO is strongly influenced by venous oxygen content and intrapulmonary shunt, which were already incorporated in the model. ECMO settings were not included in the analysis because they do not directly influence pulmonary artery pressure, but rather act indirectly through their effects on oxygenation, carbon dioxide clearance, and acid–base balance, and would therefore be likely to introduce collinearity as well. Patient identifier was included as a random effect to account for inter-individual variability. Repeated measures were modeled using a first-order autoregressive structure (AR[1]) with ECMO day as the repeated factor. Model performance was evaluated by comparing observed mPAP values with both marginal (fixed-effects only) and conditional (fixed + random effects) predictions.

To explore the prognostic impact on hospital mortality, mean pulmonary artery pressure (mPAP) on day 1 and the mPAP trajectory over the first five ECMO days were first evaluated in univariable analyses. mPAP trajectory was quantified by calculating, for each patient, the slope of the least-squares regression line fitted to the mPAP values recorded during the first five ECMO days; this slope represents the average daily change in mPAP over that period. Only patients with available mPAP measurements for all five ECMO days were included in the trajectory analysis. Both variables were considered as exposure variables and then entered into a multivariable logistic regression model together with other clinically significant variables that may differently contribute to mortality during ECMO, as follows: demographics (age); past medical history and ventilatory load (RESP score); clinical illness severity (SOFA score); and lung injury severity (pre-ECMO respiratory system compliance). Hospital mortality was used as the dependent variable.

Results of the longitudinal mixed-effects model are presented as unstandardized β coefficients with 95% confidence intervals, whereas results of the logistic regression analysis are reported as odds ratios (ORs) with 95% confidence intervals. A two-tailed p-value <0.05 was considered statistically significant. All analyses were performed using JMP Pro 18 (SAS Institute, Cary, NC, USA).

Results

A total of 240 consecutive patients with ARDS supported with V-V ECMO were identified during the study period. We excluded 15 patients in whom the PAC was not inserted for clinical contraindications, resulting in a final study population of 225 patients.

Baseline demographic and clinical characteristics of the study cohort are summarized in Table 1.

	TOTAL (n=225)
SEX, F	75 (33%)
AGE, years	51 [43-59]
BMI, kg/m ²	27.3 [24.5-31.5]
SOFA score before ECMO	7 [5-10]
RESP score before ECMO	3 [1-5]
Crs before ECMO, ml/cmH ₂ O	30 [23-38]
PaO ₂ /FiO ₂ before ECMO, mmHg	72 [58-91]
Comorbidities	
Hypertension	63 (29%)
Asthma/COPD	20 (9%)
Vascular disease (peripheral or coronary)	15 (7%)
Chronic heart failure	4 (2%)
Immunodepression/Immunosuppressive therapy	34 (15%)
Causes of ARDS	
Pneumonia	199 (88%)
Type	
Viral	103 (52%)
Bacterial	76 (38%)
Fungal	3 (2%)
Aspiration	2 (1%)
Unknown	15 (8%)
Autoimmune disease	16 (7%)
Trauma	5 (2%)
Septic Shock	2 (1%)
Other causes	3 (1%)
Pre-ECMO interventions	
Days of NIV	1 [0-2]
Days of IMV	2 [1-6]
iNO	67 (30%)
Prone Position	141 (63%)
Vasopressors	135 (60%)
Patients receiving medications for PH during ECMO	49 (22%)
Outcomes	
Mortality during ECMO, n (%)	62 (28%)
Hospital mortality, n (%)	68 (30%)
ECMO duration, days	14 [9-26]
Hospital length of stay, days	35 [23-58]

Table 1. Baseline characteristics and outcomes of the study population.

Data are presented as absolute frequency (percentage) or median [interquartile range].

Abbreviations: BMI = body mass index; SOFA = Sequential Organ Failure Assessment; RESP = Respiratory ECMO Survival Prediction; Crs = respiratory system compliance; COPD = chronic obstructive pulmonary disease; NIV = non-invasive ventilation; IMV = invasive mechanical ventilation; iNO = inhaled nitric oxide; PH = pulmonary hypertension.

Most patients were males, and median age was 51 years. The most frequent etiology of ARDS was viral pneumonia, with almost half of cases due to Covid-19 (41 patients), followed by bacterial pneumonia. Less common causes include fungal pneumonia, autoimmune disease, aspiration, trauma, and sepsis.

Hemodynamic data were available for a total of 4,433 ECMO days. Of the 4,433 ECMO-days analyzed, mPAP values were available for 4,426 timepoints (>99%). Given this minimal amount of missing data, no imputation was performed, and analyses were conducted using only available data.

The median of mPAP values collected daily during all 4,433 days was 27 mmHg [23–32], with 91% of all measurements exceeding 20 mmHg (see mPAP distribution, Figure S1 – Supplementary Material). 221 out of 225 patients (98%) had a value of mPAP >20 mmHg during their ECMO course. Pulmonary vasodilator therapy was administered in 49/225 (22%) patients. At the time of treatment initiation, median mPAP was 34 [30–37] mmHg. Sildenafil was the most prescribed agent, used as monotherapy in 32 patients (65%) and in combination with other agents in 9 patients (18%). Additional information on pharmacologic management of pulmonary hypertension is provided in **Table S1**.

Median ECMO duration was 14 days [9–26], and median hospital length of stay was 35 days [23–58]. Hospital mortality was 30%.

To investigate variables independently associated with daily mPAP values collected during ECMO support, a multivariable longitudinal mixed-effects linear model was developed. The estimates derived from this model are reported in Table 2.

Variable	estimate	standard error	p value
ECMO duration (days)	0.03 [0.02 - 0.05]	0.0078	<0.0001
PvO ₂ (mmHg)	-0.03 [-0.04 - -0.02]	0.0055	<0.0001
SvO ₂ , %	-0.07 [-0.12 - -0.02]	0.0248	0.0044
PvCO ₂ , mmHg	0.01 [-0.01 - 0.04]	0.0132	0.3719
pHv	-18.48 [-21.99 - -14.97]	1.7923	<0.0001
Qs/Qt	2.36 [1.17 - 3.54]	0.6045	<0.0001
CO, l/min	0.32 [0.23 - 0.42]	0.0473	<0.0001
MAP, mmHg	0.06 [0.05 - 0.07]	0.0050	<0.0001
PAOP, mmHg	0.61 [0.57 - 0.65]	0.0201	<0.0001

PEEP, cmH ₂ O	0.27 [0.21 - 0.34]	0.0342	<0.0001
C _{RS} , ml/cmH ₂ O	-0.07 [-0.09 - -0.06]	0.0089	<0.0001

Table 2. Independent determinants of mean pulmonary artery pressure (mPAP) during V-V ECMO.

Results of the multivariable longitudinal mixed-effects analysis with daily mPAP as the dependent variable. Regression coefficients, standard errors, 95% confidence intervals, and p-values are reported for each covariate included in the model. Fixed-effects covariates represent physiological determinants of pulmonary vascular load during ECMO and include venous pH (pH_v), PvCO₂, PvO₂, SvO₂, shunt fraction (Q_s/Q_t), mean arterial pressure (MAP), cardiac output (CO), pulmonary artery occlusion pressure (PAOP), positive end-expiratory pressure (PEEP), and respiratory system compliance (CRS). Random intercepts account for inter-individual variability.

Longer ECMO duration, lower PvO₂ and SvO₂, lower venous pH, higher intrapulmonary shunt fraction (Q_s/Q_t), higher cardiac output, higher mean arterial pressure, higher pulmonary artery occlusion pressure (PAOP), higher PEEP, and lower respiratory system compliance were independently associated with increased mPAP. In contrast, PvCO₂ was not independently associated with mPAP.

The model demonstrated acceptable performance, with fixed effects explaining a marginal R² of 0.41, while the full model - including random effects - reached a conditional R² of 0.74 (both p < 0.001).

In 55 patients (24.4%), a PAC was in place before ECMO start, allowing comparison of systemic and pulmonary hemodynamic parameters between pre-ECMO support and the first day of ECMO. Mean pulmonary arterial pressure (mPAP) significantly decreased from 31 [27–34] mmHg before ECMO to 27 [23–32] mmHg on day 1 of ECMO (p < 0.001). Further details on hemodynamic and respiratory parameters before and after ECMO start are shown in **Table S2**.

Outcome analysis

To assess the prognostic impact of pulmonary pressures, we first evaluated day-1 mPAP and the mPAP trajectory over the first five ECMO days in univariable analyses. Day-1 mPAP was not significantly associated with hospital mortality (p = 0.87). In contrast, the mPAP trend displayed a significant univariable association with mortality (p = 0.006), with steeper early increases in mPAP corresponding to a higher probability of death.

A visual overview of mortality across strata of day-1 mPAP and across categories of early mPAP trajectory is provided in the Supplementary Material (Figures S2 – Panel A/B).

In the multivariable logistic regression model evaluating hospital mortality (see Forest Plot - Figure 1), the trajectory of mPAP over the first five ECMO days remained the strongest independent predictor of outcome. Each 1-mmHg/day increase in mPAP slope was associated with a 1.89-fold higher odds of hospital mortality

(CI 1.33–2.77). In contrast, mPAP on day 1 was not independently associated with mortality (OR 1.04, 95% CI 0.96–1.13).

Among the covariates, a higher RESP score was independently associated with improved survival (OR 0.76, 95% CI 0.64–0.90). Conversely, the SOFA score at ECMO initiation did not demonstrate a statistically significant association with mortality (OR 1.06, 95% CI 0.95–1.19). Higher pre-ECMO respiratory system compliance was independently associated with lower mortality (OR 0.60 per 10 mL/cmH₂O increase, 95% CI 0.38–0.92). Age showed no significant association (OR 1.27 per 10 years, 95% CI 0.85–1.94).

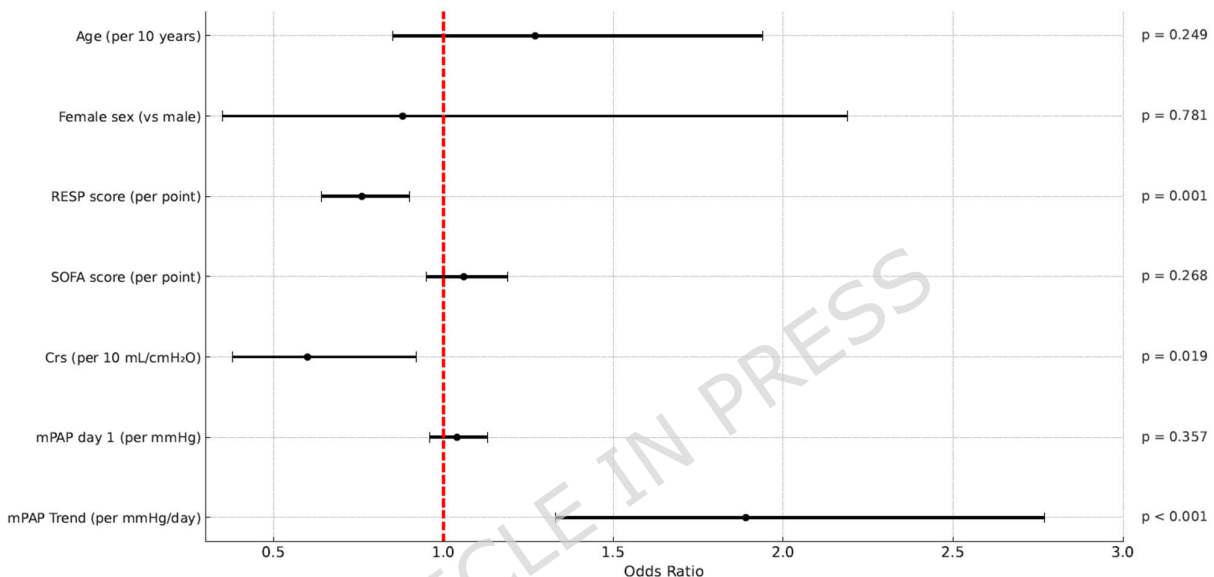


Figure 1. Forest plot of the multivariable logistic regression model evaluating predictors of hospital mortality in patients undergoing V-V ECMO. Odds ratios (ORs) and 95% confidence intervals (CIs) are shown for the following covariates: age (per year), RESP score (Respiratory ECMO Survival Prediction, per point), SOFA score (Sequential Organ Failure Assessment, per point), respiratory system compliance before ECMO (per 10 mL/cmH₂O), mean pulmonary artery pressure (mPAP) on day 1 (per mmHg), and mPAP trend during the first five ECMO days (per mmHg/day). The red dashed line indicates OR = 1 (no effect).

Discussion

In this large single-center cohort of 225 ARDS patients supported with V-V ECMO and monitored with a pulmonary artery catheter, daily pulmonary artery pressure measurements revealed that pulmonary hypertension was common, with median mPAP values consistently above the diagnostic threshold of 20 mmHg on most monitored days. Using a longitudinal mixed-effects model, we identified several physiologic variables that were independently associated with higher mPAP, including greater intrapulmonary shunt fraction, lower venous pH, higher pulmonary artery occlusion pressure, higher PEEP, higher cardiac output, higher mean arterial pressure, and reduced respiratory system compliance. In contrast, higher venous oxygen tension and higher mixed-venous oxygen saturation were associated with lower mPAP values.

Importantly, beyond the baseline assessment, early trajectory of mPAP during the first five ECMO days emerged as an independent predictor of hospital mortality. This finding suggests that early dynamic changes in pulmonary vascular load may convey more prognostic information than a single measurement obtained on day 1, likely reflecting evolving pathophysiological processes that are not captured by isolated values.

Taken together, these results indicate that serial monitoring of mPAP during the initial phase of V-V ECMO provides clinically relevant information, both for understanding the determinants of pulmonary hypertension and for identifying patients at higher risk of adverse outcomes. Early trends in pulmonary pressures may therefore support better population enrichment, risk stratification, and potentially more tailored management strategies for pulmonary hypertension in ECMO-supported ARDS patients.

Burden of pulmonary hypertension during V-V ECMO

In our population, 98% of patients had at least one mPAP value above 20 mmHg during their ECMO course. Reported prevalence of PH in ARDS patients undergoing V-V ECMO is variable, likely due to heterogeneity in the criteria used to define PH. Our findings are consistent with the 92% prevalence described by Beiderlinden et al. in 103 patients with severe ARDS [14]. Unlike previous studies, however, we applied the current ESC/ERS guideline threshold of 20 mmHg [1]—rather than the older cutoff of 25 mmHg used by Beiderlinden and colleagues—and we restricted our analysis to patients supported with V-V ECMO. In contrast, Namendys-Silva et al. reported a lower prevalence of PH of 46% [15]. This may be attributable to stricter PH definition criteria adopted by the authors, who deliberately excluded patients with pre-existing clinical conditions (e.g., cardiac or respiratory diseases) that could have predisposed them to PH prior to ARDS onset. Overall, our results confirm a high burden of pulmonary hypertension in this patient population.

Key determinants of mPAP

In the subgroup of patients with PAC monitoring at ECMO initiation (**Table S1**), a significant reduction in mPAP from 31 [27–34] to 27 [23–32] mmHg was observed, consistently with previous reports [11,16]. This decrease likely reflects improved gas exchange, attenuation of HPV, and the adoption of lung-protective ventilation strategies. However, despite these favourable effects, pulmonary pressures may remain elevated or even worsen during V-V ECMO. Therefore, our analysis aimed to investigate, in patients supported with V-V ECMO for ARDS, the relationship between mPAP trends and specific ARDS-related factors contributing to persistent pulmonary hypertension.

Higher intrapulmonary shunt was independently associated with increased mPAP. Large shunt fractions reflect extensive parenchymal consolidation and reduced functional lung size, consistent with the “baby

lung” concept [17], in which respiratory system compliance represents its clinical correlate. These structural changes may mechanically compress the pulmonary vascular bed, thereby increasing PVR and mPAP. In addition, intrapulmonary shunt contributes to hypoxemia, which activates hypoxic pulmonary vasoconstriction (HPV), a compensatory mechanism that limits shunt-related hypoxemia but inevitably increases pulmonary vascular resistance and mPAP[5,18]. Accordingly, the inverse association between mPAP and venous oxygenation (PvO₂ and SvO₂) observed in our study is physiologically coherent and consistent with previous evidence.[5,11,12,18].

V-V ECMO attenuates HPV by improving oxygen delivery and correcting acidosis[19]. In our cohort, however, venous oxygenation values on day 1 of ECMO were largely above the hypoxic threshold for HPV, suggesting that factors related to lung structural damage and reduced compliance, rather than persistent hypoxic vasoconstriction alone, contributed to sustained elevations in pulmonary artery pressure[20,21].

Venous pH was inversely associated with mPAP, reflecting the vasoconstrictive effects of acidosis on pulmonary circulation [22]. In contrast, PaCO₂ was not independently associated with mPAP, suggesting that the pulmonary vascular effects of hypercapnia may be largely mediated by pH rather than by CO₂ per se. This finding is in line with some previous reports,[23,24], although conflicting data exist [3,25], underscoring the ongoing uncertainty regarding the role of CO₂ in modulating pulmonary vascular tone.

Another determinant of elevated mPAP was higher PEEP. Although PEEP is essential for lung protection [26,27], excessive levels may cause overdistension, leading to mechanical compression of pulmonary capillaries, increased PVR, and higher pulmonary pressures [7,28–32]. In our cohort, median PEEP was 15 cmH₂O and remained comparable across the three subgroups. This value is higher than the median of 8 cmH₂O reported in two prospective studies [3,25] on acute *cor pulmonale* in ARDS patients managed with protective ventilation but not supported by ECMO. Notably, those studies did not identify an independent association between PEEP and pulmonary pressures, suggesting the potential for a dose-dependent effect. Moreover, a direct transmission of a fraction of the applied airway pressure to the pulmonary vasculature - particularly in West zone 1 regions where alveolar pressure exceeds both arterial and venous pressures - may further contribute to increased PAP.

Higher cardiac output was independently associated with elevated mPAP. In ARDS, hypoxic pulmonary vasoconstriction, endothelial injury, and inflammation impair the physiological buffer of the pulmonary capillary bed, so that increases in cardiac output further elevate pulmonary artery pressures [33]. This aligns with the findings from the physiological study by Spinelli and colleagues, who showed that increasing ECMO blood flow, by raising SvO₂, reduced PAP, cardiac output, and RV stroke work [19].

We also observed a positive association between PAOP and mPAP, possibly reflecting a post-capillary component of pulmonary hypertension secondary to left heart dysfunction [34,35], or the impact of right ventricular overload on left ventricular filling through ventricular interdependence [36].

In our analysis, the patient-level random effect accounted for a substantial share of the explained variability, resulting in a conditional R-squared of 74% compared with a marginal R-squared of 41%. A contribution of roughly 30% from random effects is expected in longitudinal mixed-effects models and reflects the considerable between-patient heterogeneity that such models are designed to capture. However, it also implies that, in an external validation setting - where individual random effects cannot be estimated - the model's performance would at most approximate the marginal R-squared.

Association of mPAP with outcome

In this cohort of 225 adults undergoing V-V ECMO for ARDS, overall mortality was 30%, slightly lower than 37% reported in the CESAR trial [37] and the 35% observed in the EOLIA trial [38].

Most available evidence on outcomes of patients with pulmonary vascular dysfunction during ARDS focuses on acute *cor pulmonale* rather than PH alone. In a large cohort of moderate-to-severe ARDS patients, acute *cor pulmonale* was associated with a ~40% hospital mortality [3], closely mirroring the 38% mortality we observed in patients with elevated mPAP. Since acute *cor pulmonale* represents the most severe consequence of PH, it is likely that some patients in our Increased-mPAP group had unrecognized right ventricular (RV) dysfunction, though this could not be confirmed due to the absence of systematic echocardiographic data.

By analyzing daily pulmonary pressure data in this large ECMO cohort, we were able to assess their prognostic relevance. The strong association between the mPAP trajectory during the first five ECMO days and hospital mortality observed in the univariable analysis remained robust after adjustment for baseline parameters, including age, sex, RESP score, SOFA score, pre-ECMO compliance, and mPAP at ECMO day 1. Among the confounders, only RESP score and respiratory system compliance remained independently associated with ARDS mortality. This aligns with a recent reanalysis of the LUNG SAFE dataset, which identified respiratory mechanics as a robust early marker of lung injury severity[39] with strong prognostic significance[40]. Notably, the multivariable analysis confirmed that early, dynamic changes in mPAP were much stronger predictors of outcome than static day-1 values, suggesting that a worsening pulmonary vascular load during the early ECMO course may reflect a pathophysiological deterioration that isolated measurements cannot capture. This holds both prognostic value and therapeutic relevance for the management of pulmonary hemodynamic.

Strengths and limitations

This study has several strengths, including a relatively large cohort of 225 patients supported with V-V ECMO and the availability of prospectively collected daily hemodynamic and respiratory gas exchange data. However, some limitations must be acknowledged. First, the retrospective design may have introduced bias, and not all relevant variables could be systematically captured. Second, the choice of day 5 as a time frame to assess mPAP trajectories was arbitrary. This may limit generalizability, although it allows to have a significant continuous data granularity over the first days of ECMO in most of the included patients. Third, despite the use of multivariable modeling, residual confounding cannot be excluded. Moreover, the limited number of outcome events in our cohort (68 in-hospital deaths) imposed methodological constraints on the complexity of the multivariable mortality model. Consistent with the commonly accepted rule of approximately 10 outcome events per variable, the model could reliably include no more than 6–7 covariates. Accordingly, even if we acknowledge that several physiological variables may have prognostic relevance in patients with ARDS undergoing V-V ECMO, we deliberately selected a limited set of clinically well-established predictors of mortality in ECMO-supported ARDS, to minimize the risk of overfitting and to preserve model interpretability and robustness. Finally, systematic echocardiographic data were not available as, in our cohort, echocardiographic examinations were performed at the discretion of the treating physicians and were not standardized in terms of timing, protocol, or reported variables. Information available in the medical charts was frequently qualitative rather than quantitative, preventing reliable integration into longitudinal analyses of pulmonary pressure trajectories. Moreover, interventions commonly used in ARDS - such as high PEEP levels and prone positioning - frequently impair image quality and feasibility, further limiting consistent quantitative echographic assessment. As a result, due to the absence of echographic data, it was not possible to determine the true incidence or severity of right ventricular dysfunction and failure in this population or to directly correlate these findings with pulmonary pressure trends. Nonetheless, while echocardiography remains a cornerstone of bedside right ventricular evaluation, pulmonary artery catheterization provided continuous and quantitative mPAP measurements, which were essential for the trajectory-based analyses central to this study.

Conclusions

Intrapulmonary shunt fraction, PEEP, respiratory system compliance, venous oxygenation, and pH emerged as independent determinants of pulmonary hypertension during ECMO. An early upward trend in mPAP was independently associated with a higher mortality. Serial monitoring of mPAP may therefore provide population enrichment, clinically relevant prognostic information and inform therapeutic management of pulmonary hemodynamics. Importantly, we do not advocate routine pulmonary artery catheterization in all patients receiving V-V ECMO. Rather, our findings suggest a potential role for invasive pulmonary

hemodynamic monitoring in selected patients at higher risk of right ventricular dysfunction or with early signs of RV failure, in whom continuous pulmonary pressure assessment may offer additional pathophysiological and prognostic insight. Further prospective studies are warranted to confirm these findings and to better define the role of pulmonary pressure monitoring in guiding the management of pulmonary hemodynamics in ARDS patients supported with ECMO.

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