Impact of Pulse Pressure on Acute Brain Injury in Venoarterial ECMO Patients with Cardiogenic Shock During the First 24 Hours of ECMO Cannulation: Analysis of the Extracorporeal Life Support Organization Registry

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Research Article

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Abstract

Background: Low pulse pressure (PP) in venoarterial-extracorporeal membrane oxygenation (VA-ECMO) is a marker of cardiac dysfunction and has been associated with acute brain injury (ABI) as continuous-flow centrifugal pump may lead to endothelial dysregulation.

Methods: We retrospectively analyzed adults (≥18 years) on "peripheral" VA-ECMO support for cardiogenic shock in the Extracorporeal Life Support Organization Registry (1/2018-7/2023). Cubic splines were used to establish a threshold (PP≤10 mmHg at 24 hours of ECMO support) for "early low" PP. ABI included central nervous system (CNS) ischemia, intracranial hemorrhage, brain death, and seizures. Multivariable logistic regressions were performed to examine whether PP≤10 mmHg was associated with ABI. Covariates included age, sex, body mass index, pre-ECMO variables (temporary mechanical support, vasopressors, cardiac arrest), on-ECMO variables (pH, PaO_2, $PaCO_2$), and on-ECMO complications (hemolysis, arrhythmia, renal replacement therapy).

Results: Of 9,807 peripheral VA-ECMO patients (median age=57.4 years, 67% male), 8,294 (85%) had PP>10 mmHg vs. 1,513 (15%) had PP≤10 mmHg. Patients with PP≤10 mmHg experienced ABI more frequently vs. PP>10 mmHg (15% vs. 11%, p<0.001). After adjustment, PP≤10 mmHg was independently associated with ABI (adjusted odds ratio [aOR]=1.25, 95% confidence interval [CI]=1.06-1.48, p=0.01). CNS ischemia and brain death were more common in patients with PP≤10 mmHg vs. PP>10 mmHg (8% vs. 6%, p=0.008; 3% vs. 1%, p<0.001). PP≤10 mmHg was associated with CNS ischemia (aOR=1.26, 95%CI=1.02-1.56, p=0.03) but not intracranial hemorrhage (aOR=1.14, 95%CI=0.85-1.54, p=0.38).

Conclusions: Early low PP (≤10 mmHg) at 24 hours of ECMO support was associated with ABI, particularly CNS ischemia, in peripheral VA-ECMO patients.

Introduction

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly used to treat patients with refractory cardiogenic shock (CS).[1–4] Acute brain injury (ABI), including intracranial hemorrhage (ICH), ischemic stroke, and hypoxic-ischemic brain injury (HIBI) occurs in up to 20% of adults on VA-ECMO support and is associated with increased mortality risk.[5] Blood pressure variables, such as pulse pressure (PP), defined as the difference between systolic (SBP) and diastolic (DBP) blood pressure, have been shown to be important surrogate markers of cardiovascular function in patients on mechanical circulatory support.[6 7, 8]

VA-ECMO operates with a continuous-flow centrifugal pump, which is associated with endothelial dysregulation/dysfunction[9, 10] Although the precise mechanism is not entirely understood, this ensuing endothelial cell dysregulation resulting from nonpulsatile flow predisposes patients to neurological injury such as ABI. Therefore, PP may be a good surrogate marker for predicting neurological outcomes in ECMO patients. A recent study demonstrated PP < 20 mmHg within 12 hours of ECMO cannulation was

associated with ABI in 123 VA-ECMO patients.[11] Still, this study was limited by small sample size, from single center, and including central VA-ECMO and post-cardiotomy shock patients who are at higher predisposition of ABI.[12] Furthermore, peripheral VA-ECMO patients have hemodynamics states that are associated with vascular and perfusion abnormalities[13] and are thus an important population to investigate the association between PP and ABI.

Using the largest registry of ECMO patients globally, the Extracorporeal Life Support Organization (ELSO) Registry, we sought to investigate the association between early PP and ABI in peripheral VA-ECMO patients. We hypothesized that low PP in the first 24 hours of ECMO support was independently associated with higher occurrence of ABI.

Methods

Study design and population

This study was approved by the Johns Hopkins Hospital Institutional Review Board with a waiver of informed consent since this was a retrospective observational study (IRB00216321). The ELSO Registry is an international multicenter registry from over 500 ECMO centers.[14] The Registry collects demographics, pre-ECMO comorbidities, pre-ECMO and on-ECMO hemodynamic and arterial blood gas (ABG) information, on-ECMO neurological and other systemic complications, and outcomes such as mortality.[15] Comorbidity information was recorded using the *International Classification of Diseases, 10th Revision (ICD-10)* codes.

We included patients who were 1) 18 years of age or older; and 2) supported with “peripheral” VA-ECMO and diagnosed with CS from 2018–2023. We excluded repeat ECMO runs within the same patient to avoid complexity and bias. We also excluded patients with missing blood pressure (systolic and diastolic at 24 hours of ECMO support) and cannulation information, central cannulation, on-ECMO percutaneous ventricular assist device or central venous access device support, coronary artery bypass graft or percutaneous coronary intervention, and post-cardiotomy shock. Patients with these conditions were excluded as they could impact the interpretation of PP readings and their association with ABI.

Data collection

The ELSO Registry collects ABG and hemodynamic information before and after ECMO cannulation (i.e., “pre-ECMO” and “on-ECMO”, respectively). Pre-ECMO ABGs were drawn at maximum 6 hours before ECMO cannulation, and pre-ECMO ventilator settings were recorded within 6 hours of ECMO cannulation. If multiple ABGs existed within a specific duration, the pre-ECMO ABG that was closest to the beginning of ECMO cannulation was selected. On-ECMO ABGs were drawn after ECMO cannulation started, no longer than 30 hours post-cannulation. If multiple ABGs were taken, the on-ECMO ABG nearest to 24 hours after the start of cannulation was chosen. On-ECMO hemodynamics were gathered closest to 24

hours after ECMO cannulation, though they could be collected at 18–30 hours after cannulation. Each variable was abstracted by a trained ELSO data manager/abstracter and was collected simultaneously.

Definitions

On-ECMO PP was calculated as “SBP at 24 hours” - “DBP at 24 hours”. Delta partial pressure of arterial carbon dioxide ($PaCO_2$) was calculated as “On-ECMO $PaCO_2$ at 24 hours” - “Pre-ECMO $PaCO_2$”. Pre-ECMO ventilator settings included conventional ventilation, high-frequency oscillatory ventilation, other high frequency ventilation (high frequency jet ventilation or percussive ventilation), other non-specified ventilations, and absence of ventilation. Pre-ECMO additional temporary mechanical circulatory support (tMCS) included intra-aortic balloon pump (IABP), Impella®, and left and right ventricular assist devices (though patients supported with on-ECMO tMCS were excluded from the analysis, as previously described). Pre-ECMO vasopressor infusions included dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin. Infusions were treated as a binary variable, meaning we treated them as the presence or absence of the infusions. Pre-ECMO vasopressor infusions were utilized for at least 6 hours within 24 hours of the start of ECMO cannulation. Pre-ECMO cardiac arrest was defined as an event that required the use of cardiopulmonary resuscitation in conjunction with the administration of external cardiac massage within 24 hours of ECMO cannulation. Central cannulation was defined as placement of the reinfusion cannula directly into the aorta. Peripheral cannulation was defined as placement of cannula in a site other than the aorta (peripheral vessels).

On-ECMO complications included cardiac arrhythmia, hemolysis, renal replacement therapy, gastrointestinal hemorrhage, and ECMO circuit failure. Definitions for each complication are in the **Supplemental Methods**.

ABI was defined as the presence of central nervous system (CNS) infarction (ischemic stroke), diffuse ischemia (hypoxic-ischemic brain injury, HIBI), intra/extra parenchymal hemorrhage, intraventricular hemorrhage, seizures determined by electroencephalograph or clinically, and neurosurgical intervention (examples include intracranial pressure monitor, external ventricular drain, and craniotomy) and brain death during ECMO support. CNS ischemia was defined as ischemic stroke (determined by ultrasound, computed tomography, CT, or magnetic resonance imaging, MRI) and HIBI (determined by CT or MRI). ICH included intra/extra parenchymal hemorrhage and intraventricular hemorrhage (both determined by CT or MRI).

Outcomes

The primary outcome was ABI during ECMO support between patients with PP $\leq$ 10 vs. PP > 10 mm Hg. The secondary outcomes were subtypes of ABI, CNS ischemia and ICH.

Statistical Analysis

Continuous variables were represented as median with interquartile range (IQR). Categorical variables were presented as frequency with percentages. The Wilcoxon rank-sum and Pearson’s chi-square tests were utilized to compare continuous and categorical variables, respectively. Differences in PP between

those with ABI vs. those without ABI were compared with Wilcoxon rank-sum. Statistical significance was set at a p-value < 0.05. Data missingness was handled with multiple imputation with five separately imputed datasets (Rubin's Rules)[16] to augment statistical power. Continuous, unordered categorical, and dichotomous missing variables were imputed using regression with predictive mean matching, polytomous logistic regression, and logistic regression. All missing variables are shown in **Supplemental Table 1**.

Cubic spline analysis was utilized to non-linearly model the impact of PP on ABI. Based on inflection points ("spline knots") in this model, combined with prior data and clinical knowledge, we determined an appropriate PP threshold (≤ 10 mmHg) for logistic regression analysis. Boxplots were used to descriptively portray the association between PP vs. ABI. We performed univariable and multivariable logistic regression for ABI, CNS ischemia, and ICH in peripherally cannulated patients to determine if PP ≤ 10 mmHg was a significant risk factor for each of these outcomes even after adjustment for clinically relevant covariates. We chose covariates selected *a priori* based on clinical judgement and prior data for each model.[5, 17] Adjusted covariates in the ABI model included age, sex, body mass index, pre-ECMO variables (additional tMCS, vasopressor infusions, cardiac arrest), on-ECMO variables (pH, arterial partial pressure of oxygen, PaO_2), delta $PaCO_2$, and on-ECMO complications (hemolysis, arrhythmia, renal replacement therapy). In the CNS ischemia (ischemic stroke or HIBI) model, age, sex, pre-ECMO variables ($PaCO_2$, PaO_2, pH, vasopressor infusions, cardiac arrest), delta $PaCO_2$, and on-ECMO complications (ECMO circuit failure, arrhythmia) were included in the adjustment. In the ICH model, age, sex, pre-ECMO variables (additional tMCS, vasopressor infusions, cardiac arrest), on-ECMO variables (PaO_2, pH), delta $PaCO_2$, and on-ECMO complications (ECMO circuit failure, gastrointestinal hemorrhage, hemolysis, renal replacement therapy) were included in the adjustment. In an exploratory analysis, we performed a multivariable logistic regression model for central VA-ECMO patients to determine if PP was associated with ABI. Adjusted odds ratios (aOR) were presented with 95% confidence intervals (CIs). All statistical analyses were performed using R Studio (R 4.1.2, www.r-project.org).

Results

Study population

Of 18,701 VA-ECMO patients with CS, we included 9,807 patients in our study after the inclusion and exclusion criteria (Fig. 1**)**. Cubic spline analysis of the ELSO Registry showed an inflection point at a PP of 10 mmHg when non-linearly modeling the impact of pulse pressure on ABI; therefore, we chose this value as our threshold in our analysis. Of 9,807 peripheral VA-ECMO patients (median age = 57.4 years, 67% male), 8,294 (85%) had a PP > 10 mmHg vs. 1,513 (15%) had a PP ≤ 10 mmHg (Table 1**)**. Age, sex, body mass index, and race/ethnicity were similar between both groups. The median duration of ECMO support was 4.9 days (IQR = 2.9-8.0).

A total of 1,096 (11.1%) patients experienced ABI. Patients with PP ≤ 10 mmHg experienced ABI more frequently than those with PP > 10 mmHg (n = 220, 15% vs. n = 876, 11%, p < 0.001, **Supplemental Table 2**). Overall, 608 (6.2%) patients experienced CNS ischemia (ischemic stroke or HIBI) and 311 (3.2%) patients experienced ICH. CNS ischemia and brain death were more common in patients with PP ≤ 10 mmHg vs. those with PP > 10 mmHg (n = 121, 8% vs. n = 487, 6%, p = 0.002; n = 43, 3% vs. n = 124, 1%, p < 0.001). Patients with PP ≤ 10 mmHg were more likely to die vs. those with PP > 10 mmHg (n = 1,021, 67% vs. n = 3,813, 46%, p < 0.001).

Acute brain injury

Baseline clinical characteristics and demographics were also compared between patients with ABI vs. without ABI (**Supplemental Table 2**). Patients with ABI had a lower on-ECMO PP vs. those without ABI [median (IQR), 27(14–42) vs. 30(17–44) mmHg, p < 0.001] (Fig. 2**).**

In a multivariable logistic regression after adjusting for pre-selected clinically relevant covariates, on-ECMO PP ≤ 10 mmHg was independently associated with ABI (aOR = 1.25, 95%CI = 1.06–1.48, p = 0.01, Table 2, Fig. 3**)**. Additional risk factors associated with ABI included a higher delta $PaCO_2$ (aOR = 1.10 per 10 mmHg increase, 95%CI = 1.05–1.15, p < 0.001), pre-ECMO cardiac arrest (aOR = 2.05, 95%CI = 1.78–2.36, p < 0.001), hemolysis (aOR = 1.81, 95%CI = 1.42–2.32, p < 0.001), arrhythmia (aOR = 1.41, 95%CI = 1.19–1.66, p < 0.001), and renal replacement therapy (aOR = 1.41, 95%CI = 1.23–1.61, p < 0.001). Higher on-ECMO PaO_2 (aOR = 0.99 per 10 mmHg increase, 95%CI = 0.986–0.996, p < 0.001) was protective against ABI.

Central nervous system ischemia (ischemic stroke and hypoxic-ischemic brain injury)

In a multivariable logistic regression, on-ECMO PP ≤ 10 mmHg was independently associated with CNS ischemia (aOR = 1.26, 95%CI = 1.02–1.56, p = 0.03, **Supplemental Table 3**, Fig. 4**).** On-ECMO PP ≤ 10 mmHg was also independently associated with ischemic stroke by itself (aOR = 1.34, 95%CI = 1.04–1.72, p = 0.02). Additional risk factors associated with CNS ischemia included delta $PaCO_2$ (aOR = 1.10 per 10 mmHg increase, 95%CI = 1.04–1.15, p < 0.001), arrhythmia (aOR = 1.55, 95%CI = 1.27–1.91, p < 0.001), and pre-ECMO cardiac arrest (aOR = 2.21, 95%CI = 1.85–2.65, p < 0.001). Pre-ECMO vasopressor infusions (aOR = 0.79, 95%CI = 0.66–0.94, p = 0.01) were protective against CNS ischemia.

Intracranial hemorrhage

In a multivariable logistic regression, on-ECMO PP ≤ 10 mmHg was not significantly associated with ICH (aOR = 1.14, 95%CI = 0.85–1.54, p = 0.38, **Supplemental Table 4**, Fig. 5). Risk factors associated with ICH included hemolysis (aOR = 1.80, 95%CI = 1.21–2.67, p < 0.001), renal replacement therapy (aOR = 1.73, 95%CI = 1.36–2.20, p < 0.001), ECMO circuit failure (aOR = 1.58, 95%CI = 1.15–2.17, p < 0.001),

gastrointestinal hemorrhage (aOR = 1.58, 95%CI = 1.07–2.33, p = 0.02), and pre-ECMO cardiac arrest (aOR = 1.41, 95%CI = 1.11–1.78, p = 0.01).

Exploratory analysis – central cannulation

In a univariable logistic regression analysis for ABI, on-ECMO PP ≤ 10 mmHg was also significantly associated with ABI in central VA-ECMO patients (OR = 1.40, 95%CI = 1.01–1.93, p = 0.04) and for ischemia (OR = 1.56, 95%CI = 1.08–2.25, p = 0.02). In a multivariable logistic regression, on-ECMO PP ≤ 10 mmHg was not associated with ABI (aOR = 1.17, 95%CI = 0.83–1.64, p = 0.38), CNS ischemia (aOR = 1.46, 95%CI = 0.99–2.13, p = 0.05,), or ICH (aOR = 1.35, 95%CI = 0.71–2.56, p = 0.36), in central VA-ECMO patients (**Supplemental Tables 5–7)**.

Discussion

In this ELSO Registry analysis of 9,807 peripheral VA-ECMO patients, we found that a low PP (≤ 10 mmHg) measured at 24-hours of ECMO support was independently associated with greater occurrence of ABI in peripheral VA-ECMO patients after adjusting for pre-selected clinically relevant covariates. Additionally, low PP was associated with CNS ischemia but not ICH. We also identified other risk factors for ABI in peripheral VA-ECMO patients: higher delta $PaCO_2$, pre-ECMO cardiac arrest, and on-ECMO hemolysis, cardiac arrhythmia, and renal replacement therapy.

There may be multiple mechanisms at play that can lead to PP influencing ABI in this cohort. One potential mechanism relates to the loss of pulsatility that occurs inherently with VA-ECMO and is enhanced by adjustment of pump speeds,[18–20] as nonpulsatile flow is associated with elevated vascular resistance, increased muscular sympathetic nervous system activity, coronary artery disease, limited oxygen consumption, and interruption of cerebral autoregulation.[21–23] These factors have been associated with increased incidence of ABI[24–29] in non-ECMO patients. Additionally, patients undergoing coronary artery bypass graft with IABP and cardiopulmonary bypass (i.e., nonpulsatile flow) have been shown to have less endothelial activation[30–33] and to observe a reduction in nitric oxide[34, 35] due to systemic inflammatory response syndrome.[9, 36, 37] Patients on the ECMO circuit frequently experience extreme changes in hemodynamic parameters such as PaO_2[17] and $PaCO_2$,[38–40] which were previously shown to be associated with ABI. These blood gas derangements, combined with already compromised endothelium function and nonpulsatile cerebral blood flow,[41] may lead to ABI. Additionally, as left ventricular (LV) venting may lower PP and further predispose VA-ECMO patients to ABI, future research is warranted to investigate the effects of tMCS such as IABP and Impella® on the association between PP and ABI.

Our results demonstrated that low PP was associated with CNS ischemia but not ICH in peripheral VA-ECMO. Induced by ECMO circuit, the absence of pulsatility is associated with reduced O_2 consumption and impaired cerebral autoregulation, potentially contributing to CNS ischemia.[21] Furthermore, low PP

can indicate inadequate cardiac contractility, and thus systemic hypoperfusion, which may increase the risk of CNS ischemia. Interestingly, in contrast to previous literature describing that a larger delta $PaCO_2$ was associated with ICH,[42] our study demonstrated that delta $PaCO_2$ was associated with CNS ischemia rather than ICH. These results did not persist in central VA-ECMO which may be due to different hemodynamic states between both cohorts.[13] Other additional key factors such as the use of systemic anticoagulation, duration of ECMO support, hemolysis, and platelet imbalance may also be involved in the pathophysiology of ICH.[43] Overall, these findings suggest that additional research is necessary to clarify how certain risk factors lead to either CNS ischemia or ICH in peripheral VA-ECMO patients.

Interestingly, unlike a previous study suggesting severe hyperoxia is associated with ABI,[17] an increase in PaO_2 was a protective factor for ABI in our analysis. One explanation is that aggressive oxygen therapy helps mitigate the effects of potential hypoxemia during ECMO support as hypoxemia in ECMO patients is well documented.[44, 45] Furthermore, a higher PaO_2 may help increase regional brain oxygen tension[46] and accordingly improve the cerebral metabolic rate of oxygen. We also note we did not “bin” PaO_2 values (continuous variable) by groups as this previous study did which may increase their risk of bias.[47] Overall, these results suggest that additional research with methodically rigorous study design is necessary to elucidate the mechanisms regarding how these physiological variables lead to ABI in continuous blood flow under the ECMO circuit.

Early assessment and recognition of myocardial function using low PP during the first 24 hours of ECMO support has important clinical implications. Recognizing low PP may allow providers to promptly develop appropriate management techniques, including fine-tuning ECMO settings and using inotropes/vasopressors,[48] LV venting,[49] or pulsatile ECMO flow[50] to improve hemodynamics. Notably, our analysis showed that the use of vasopressors before ECMO support was protective of ABI, supporting our speculation. Additionally, upon recognizing low PP, clinicians can consider more vigilant and standardized neuromonitoring strategies to ensure adequate cerebral perfusion and prevent occurrence/worsening of ABI, which is especially important in peripheral VA-ECMO due to the potential for differential oxygenation.[51]

Limitations

Our analysis was retrospective and observational, thus limiting our ability to determine causation effects. Additionally, the ELSO Registry lacks granular ABG data, only allowing us to extract one pre-ECMO and one on-ECMO data point for each patient in our analysis. Similarly, for PP we are limited to a single value at 24 hours, however, it is unclear if there is significant variance over the first 24 hours that would influence interpretation. This methodology has also been previously validated in an ELSO Registry analysis of PP and mortality in 2,400 VA-ECMO patients.[52] Furthermore, it is unclear how such variance would systematically bias our results as any variation should be at random and thus favor the null hypothesis. Additionally, low PP may represent a population with higher severity of illness which may explain the higher occurrence of ABI despite attempting to account for this with statistical modeling. The

ELSO Registry also does not contain specific anticoagulation data, which is a known risk factor for ABI. Nevertheless, we adjusted for many ECMO-specific and clinically relevant covariates in our analysis, and low PP was still independently associated with ABI. Additionally, our study represents the largest and most comprehensive analysis to-date investigating the association between PP and ABI in VA-ECMO patients. We also used methodically rigorous methods in our analysis including multiple imputation to handle missing data, thus minimizing bias and invigorating the validity of our analysis[53] and cubic spline analysis when identifying a PP threshold to abate the loss of information and poor predictions when using continuous variables.[54] We also excluded ECMO patients simultaneously on LV venting devices as LV venting can directly modulate the PP in ECMO and thus could potentially confounding our findings.[3] Finally, the optimum ECMO pump flow rate based on body surface area for each patient was not able to be determined in the ELSO Registry and should be noted.

Conclusions

In the largest analysis to-date of peripheral VA-ECMO patients with CS, a PP reading of 10 mmHg or less at the 24-hour time point of ECMO support was associated with increased occurrence of ABI. Low early PP was also uniquely associated with CNS ischemia but not ICH. Accordingly, PP during ECMO support may serve as a distinct marker for ABI in this high-risk population. Given these findings, prospective observational studies investigating the association between PP and ABI with granular data and standardized neurological diagnoses is warranted.

Abbreviations

ABG	arterial blood gas
ABI	acute brain injury
aOR	adjusted odds ratio
CI	confidence interval
CNS	central nervous system
CS	cardiogenic shock
DBP	diastolic blood pressure
ECMO	extracorporeal membrane oxygenation
ELSO	Extracorporeal Life Support Organization
IABP	intra-aortic balloon pump
ICH	intracranial hemorrhage
IQR	interquartile range
LV	left ventricular
LVAD	left ventricular assist device
PaO_2	partial pressure of oxygen
PP	pulse pressure
SD	standard deviation
SBP	systolic blood pressure
tMCS	temporary mechanical circulatory support

Declarations

IRB Approval: This study was approved by the Johns Hopkins Hospital Institutional Review Board (IRB00216321) on 10/22/2019. The study title is “Retrospective Analysis of Outcomes of Patients on Extracorporeal Membrane Oxygenation”. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975.

ISHLT Ethics Statement: This study is in compliance with the ISHLT Ethics statement.

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Conflict of Interest and Sources of Funding:

Dr. Brodie receives research support from and consults for LivaNova. He has been on the medical advisory boards for Abiomed, Xenios, Medtronic, Inspira and Cellenkos. He is the President-elect of the Extracorporeal Life Support Organization (ELSO) and the Chair of the Executive Committee of the International ECMO Network (ECMONet), and he writes for UpToDate. The authors do not have any additional conflicts of interest to declare. SMC is supported by NHLBI (1K23HL157610) and Hyperfine (SAFE MRI ECMO study).

Author Contributions

AK and SMC contributed to the study conception and design. Data analysis was

performed by AK. The first draft of the manuscript was written by AK, JK, and CW and all authors

commented on previous versions of the manuscript. All authors read and approved the final

manuscript.

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Tables

Table 1. Baseline characteristics and clinical variables of venoarterial extracorporeal membrane oxygenation patients with cardiogenic shock stratified by pulse pressure.

	Total (n=9,807)	Pulse Pressure > 10 mm Hg (n=8,294, 85%)	Pulse Pressure ≤ 10 mm Hg (n=1,513, 15%)	P-value
Demographics				
Age (years)	57.4 (45.9-65.7)	57.3 (45.7-65.7)	57.7 (46.5-65.4)	0.46
Male sex	6,661 (67%)	5,640 (68%)	1,021 (67%)	0.71
Body Mass Index, kg/m^2	28.3 (24.6-33.0)	28.3 (24.5-33.1)	28.3 (24.9-32.4)	0.65
Race/ethnicity				0.36
Asian	1,099 (11%)	949 (11%)	150 (10%)	
Black	1,286 (13%)	1,071 (13%)	215 (14%)	
Hispanic	640 (7%)	543 (7%)	97 (6%)	
White	5,448 (56%)	4,605 (56%)	843 (56%)	
Others	1,334 (14%)	1,126 (14%)	208 (14%)	
Year ECLS				0.15
2018	1,360 (14%)	1,149 (14%)	211 (14%)	
2019	1,807 (18%)	1,559 (19%)	248 (16%)	
2020	1,780 (18%)	1,492 (18%)	288 (19%)	
2021	1,919 (20%)	1,633 (20%)	286 (19%)	
2022	2,166 (22%)	1,803 (22%)	363 (24%)	
2023	775 (8%)	658 (8%)	117 (8%)	
Past medical history				
Diabetes	1,161 (12%)	985 (12%)	176 (12%)	0.82

Hypertension	1,759 (18%)	1,498 (18%)	261 (17%)	0.47
Atrial fibrillation	1,211 (12%)	1,049 (13%)	162 (11%)	***0.04***
Cardiomyopathy	995 (10%)	855 (10%)	140 (9%)	0.23
COPD	281 (3%)	244 (3%)	37 (2%)	***<0.001***
COVID-19 status	242 (2%)	185 (2%)	57 (4%)	***<0.001***
Pre-ECMO support				
Additional temporary mechanical circulatory support	3,977 (41%)	3,262 (39%)	715 (47%)	***<0.001***
Vasopressor infusions	6,967 (71%)	5,885 (71%)	1,082 (72%)	0.68
Inotrope infusions	3,752 (38%)	3,222 (39%)	530 (35%)	***0.005***
Pre-ECMO blood pressure variables				
Systolic blood pressure (mm Hg)	91 (77-108)	92 (78-109)	86 (72-102)	***<0.001***
Diastolic blood pressure (mm Hg)	57 (47-68)	57 (46.3-68)	59 (48-71)	***<0.001***
Mean blood pressure (mm Hg)	69 (59-79)	69 (59-79)	67 (56.7-79)	***0.02***
Pulse pressure (mm Hg)	33 (22-45)	34 (23-47)	26 (16-38)	***<0.001***
Mean arterial pressure (mm Hg)	13 (10-16)	13 (10-16)	13 (10-17)	0.49
Pre-ECMO ABG				
pH	7.28 (7.18-7.37)	7.29 (7.18-7.37)	7.3 (7.2-7.4)	***0.001***
HCO_3- (mEq/L)	19 (15-22.4)	19 (15.2-22.6)	18 (14-22)	***<0.001***
PaO_2 (mm Hg)	103 (71-188)	102 (71-187)	107 (71-192)	0.23
$PaCO_2$ (mm Hg)	40 (32-48.8)	40 (32.2-48.8)	39 (32-48.8)	0.13
Lactate (mmol/L)	6.3 (3.1-11)	6 (3-10.6)	7.8 (3.9-12)	***<0.001***

SpO_2 (%)	97 (92-100)	97 (92-100)	97 (91-100)	0.41
SaO_2 (%)	97 (92-99)	97 (92-99)	97 (92-99)	0.58
On-ECMO blood pressure variables				
Systolic blood pressure (mm Hg)	95 (83-108)	98 (88-111)	76 (69-83)	***<0.001***
Diastolic blood pressure (mm Hg)	64 (57-72)	63 (56-71)	70 (63-78)	***<0.001***
Mean blood pressure (mm Hg)	74 (67-81)	74 (68-82)	72 (65-80)	***<0.001***
Pulse pressure (mm Hg)	30 (17-44)	34 (23-47)	5 (3-8)	***<0.001***
Mean arterial pressure (mm Hg)	12 (10-14)	12 (10-14)	12 (10-15)	***<0.001***
On-ECMO ABG				
pH	7.42 (7.38-7.47)	7.43 (7.38-7.47)	7.41 (7.36-7.46)	***<0.001***
HCO_3- (mEq/L)	24.1 (21.8-27)	24.3 (22-27)	24 (21-27)	***<0.001***
PaO_2 (mm Hg)	132.8 (90-224)	125 (87.9-200)	202.5 (118-342.8)	***<0.001***
$PaCO_2$ (mm Hg)	37.5 (33-42)	37.1 (33-42)	38 (34-42.35)	***<0.001***
Lactate (mmol/L)	2.1 (1.3-3.8)	2 (1.3-3.4)	2.8 (1.5-5.4)	***<0.001***
SpO_2 (%)	99 (97-100)	99 (97-100)	99 (97-100)	***0.004***
SaO_2 (%)	98 (97-99)	98 (97-99)	99 (98-100)	***<0.001***
$\Delta PaCO_2$	-2 (-11.3-6)	-2.1 (-11.43-5.8)	-1 (-11-7.05)	***0.009***
Pump flow rate (4 hours, L/min)	3.8 (3.2-4.37)	3.8 (3.2-4.34)	3.9 (3.2-4.45)	***0.007***
Pump flow rate (24 hours, L/min)	3.92 (3.28-4.47)	3.9 (3.24-4.43)	4.01 (3.43-4.54)	***<0.001***
Days on ECMO support	4.9 (2.9-8)	4.88 (2.96-6.48)	5.04 (2.58-8.79)	0.78

Neurological complications on-ECMO				
Composite ABI	1,096 (11%)	876 (11%)	220 (15%)	***<0.001***
Composite Ischemia	608 (6%)	487 (6%)	121 (8%)	***0.002***
Ischemia	207 (2%)	168 (2%)	39 (3%)	0.20
Infarction	412 (4%)	329 (4%)	83 (5%)	***0.008***
Composite ICH	311 (3%)	252 (3%)	59 (4%)	0.09
Intra/extra parenchymal hemorrhage	193 (2%)	155 (2%)	38 (3%)	0.12
Intraventricular hemorrhage	71 (1%)	62 (1%)	9 (1%)	0.63
Brain death	167 (2%)	124 (1%)	43 (3%)	***<0.001***
Neurosurgical intervention	24 (1%)	22 (1%)	2 (1%)	0.57
Seizures confirmed by EEG	110 (1%)	88 (1%)	22 (1%)	0.85
Seizures clinically determined	105 (1%)	90 (1%)	15 (1%)	0.23
Other complications on-ECMO				
ECMO circuit mechanical failure	994 (10%)	852 (10%)	142 (9%)	0.65
Renal replacement theory	3,495 (36%)	2,862 (35%)	633 (42%)	***<0.001***
Hemolysis	463 (5%)	378 (5%)	85 (6%)	0.085
Cardiac arrhythmia	1,479 (15%)	1,196 (14%)	283 (19%)	***<0.001***
Gastrointestinal hemorrhage	527 (5%)	415 (5%)	112 (7%)	***<0.001***
Outcomes				
In-hospital mortality	4,834 (49%)	3,813 (46%)	1,021 (67%)	***<0.001***

Δ = delta

Table 2. Risk factors associated with *acute brain injury* in multivariable logistic regression analysis in peripheral VA-ECMO patients with cardiogenic shock.

	aOR	Lower 95% CI	Upper 95% CI	*P*-value
Age (by 10 years)	1.04	0.99	1.08	0.16
Female sex	0.92	0.80	1.05	0.22
Body mass index (by 10 kg/m^2)	1.15	0.52	2.53	0.72
Pre-ECMO variables	1.04	0.98	1.11	0.23
Additional temporary mechanical circulatory support	0.99	0.86	1.13	0.84
Vasopressor infusions	0.90	0.78	1.03	0.13
Cardiac arrest	2.05	1.78	2.36	**<0.001**
On-ECMO variables				
Pulse pressure ≤ 10 mm Hg	1.25	1.06	1.48	**0.01**
PaO_2 (by 10 mm Hg)	0.991	0.986	0.996	**<0.001**
pH (decreasing, per 0.1 units)	7.59	0.002	2.25E4	0.62
Delta $PaCO_2$ (by 10 mm Hg)	1.10	1.05	1.15	**<0.001**
On-ECMO Complications				
Hemolysis	1.81	1.42	2.32	**<0.001**
Arrhythmia	1.41	1.19	1.66	**<0.001**
Renal replacement therapy	1.41	1.23	1.61	**<0.001**

Missing values were handled with multiple imputations to increase statistical power. Pre-ECMO temporary mechanical circulatory support consisted of an intra-aortic balloon pump, Impella, and left ventricular assist devices. Pre-ECMO vasopressor infusions included dopamine, epinephrine,

norepinephrine, phenylephrine, and vasopressin. Hemolysis was defined as a peak plasma hemoglobin of at least 50 mg/dL occurring at least once during the ECMO run and sustained for at least 2 consecutive days. aOR: adjusted odds ratio CI: confidence interval. ECMO: extracorporeal membrane oxygenation. PaO_2: arterial partial pressure of oxygen. $PaCO_2$: arterial partial pressure of carbon dioxide.

Figures

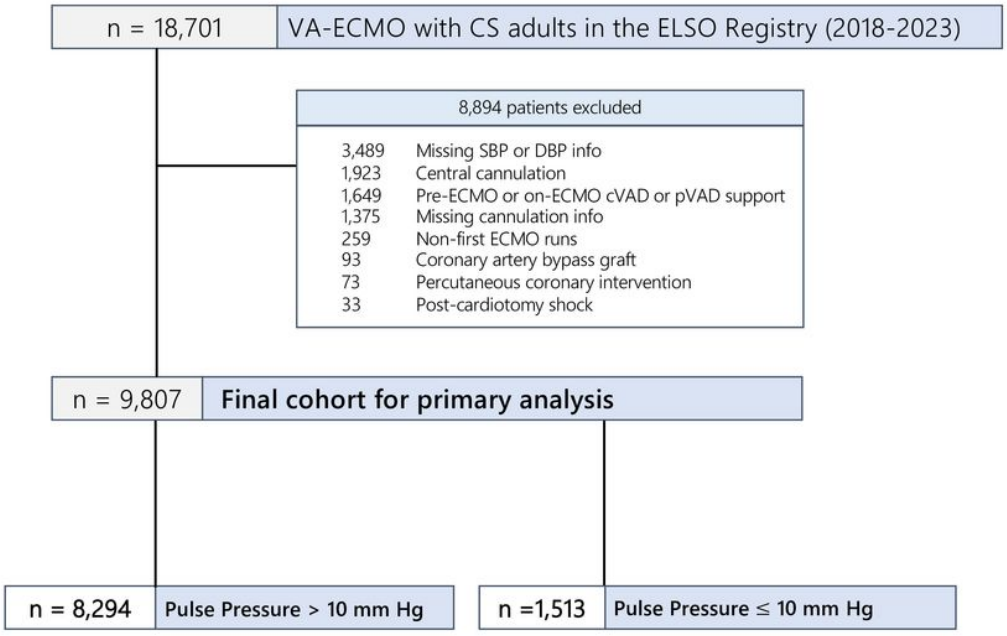

Figure 1

Flow diagram for the creation of our study cohort.

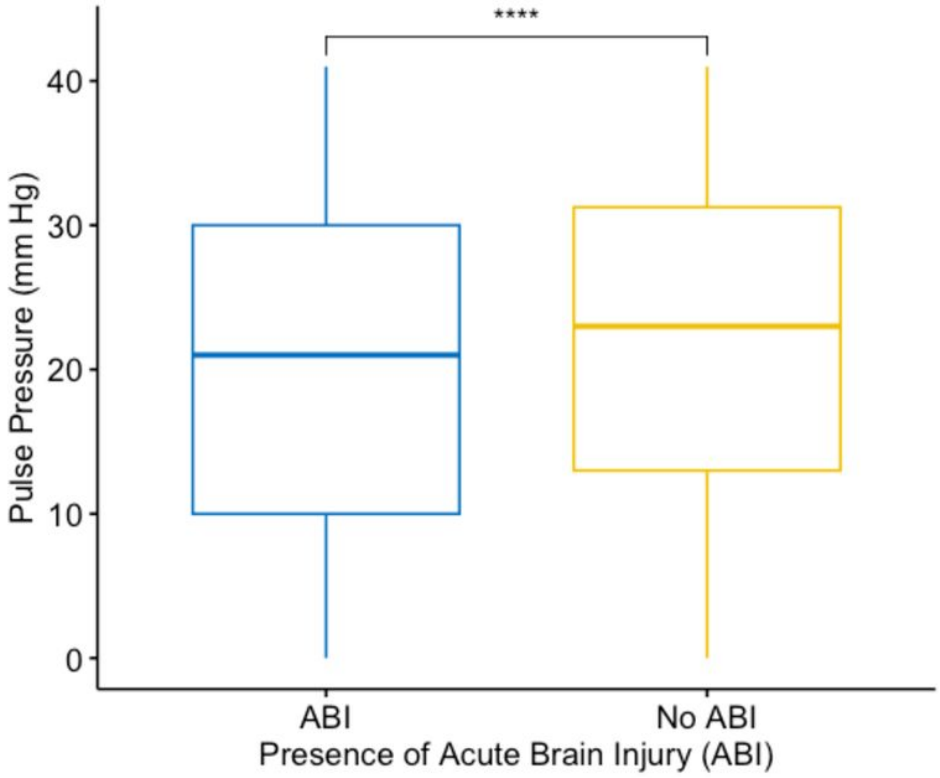

Figure 2

Boxplot of pulse pressure (y-axis) vs. peripheral venoarterial extracorporeal membrane oxygenation patients with acute brain injury and those without acute brain injury (x-axis).

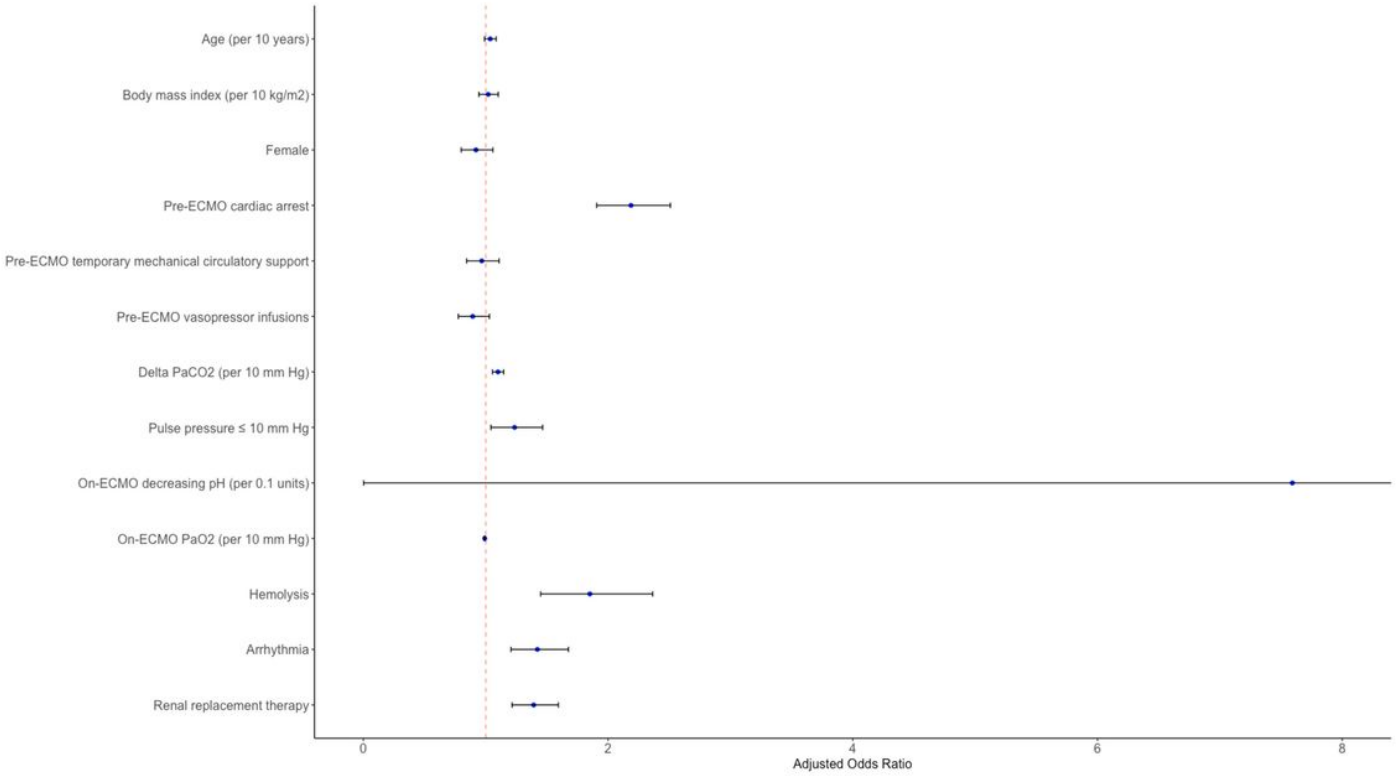

Figure 3

Forest plot of multivariable logistic regression model for occurrence of acute brain injury in peripheral venoarterial extracorporeal membrane oxygenation patients.

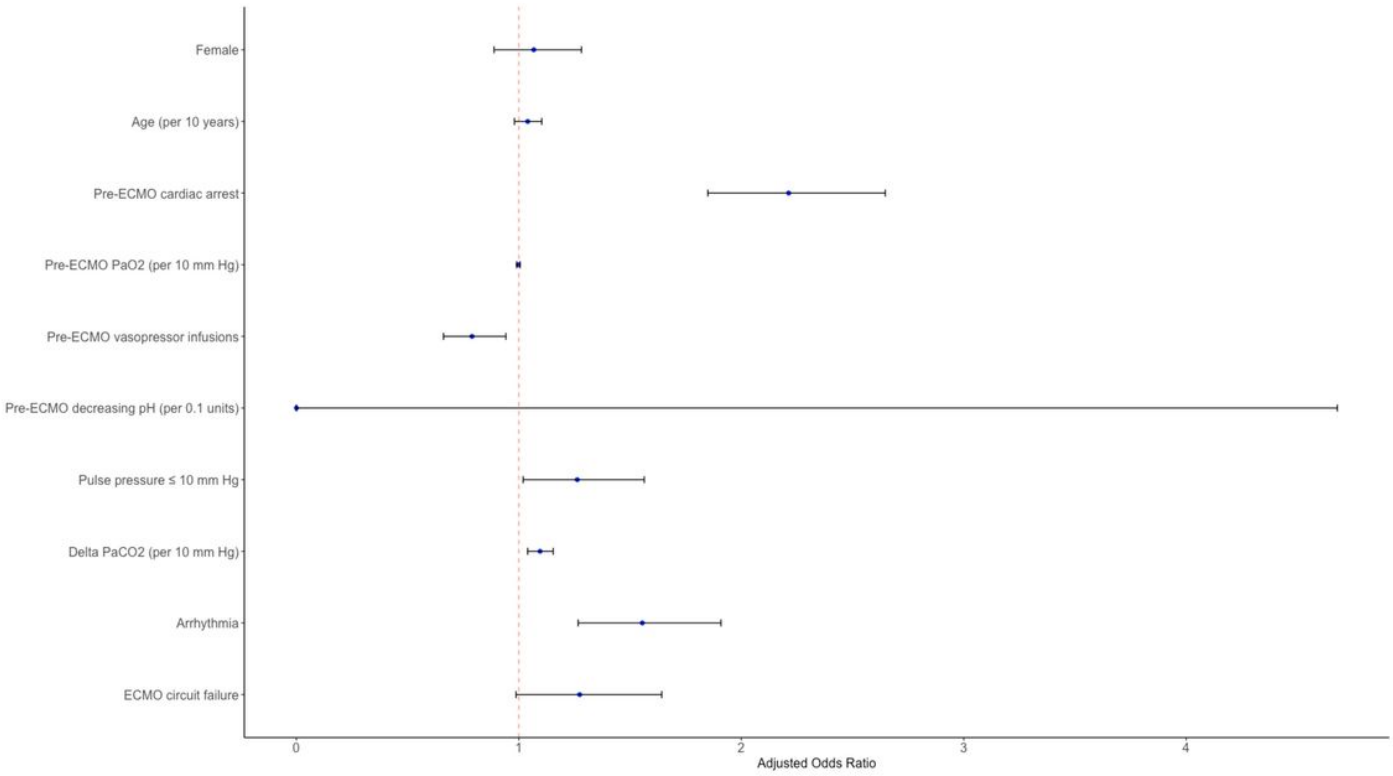

Figure 4

Forest plot of multivariable logistic regression model for occurrence of central nervous system ischemia in peripheral venoarterial extracorporeal membrane oxygenation patients.

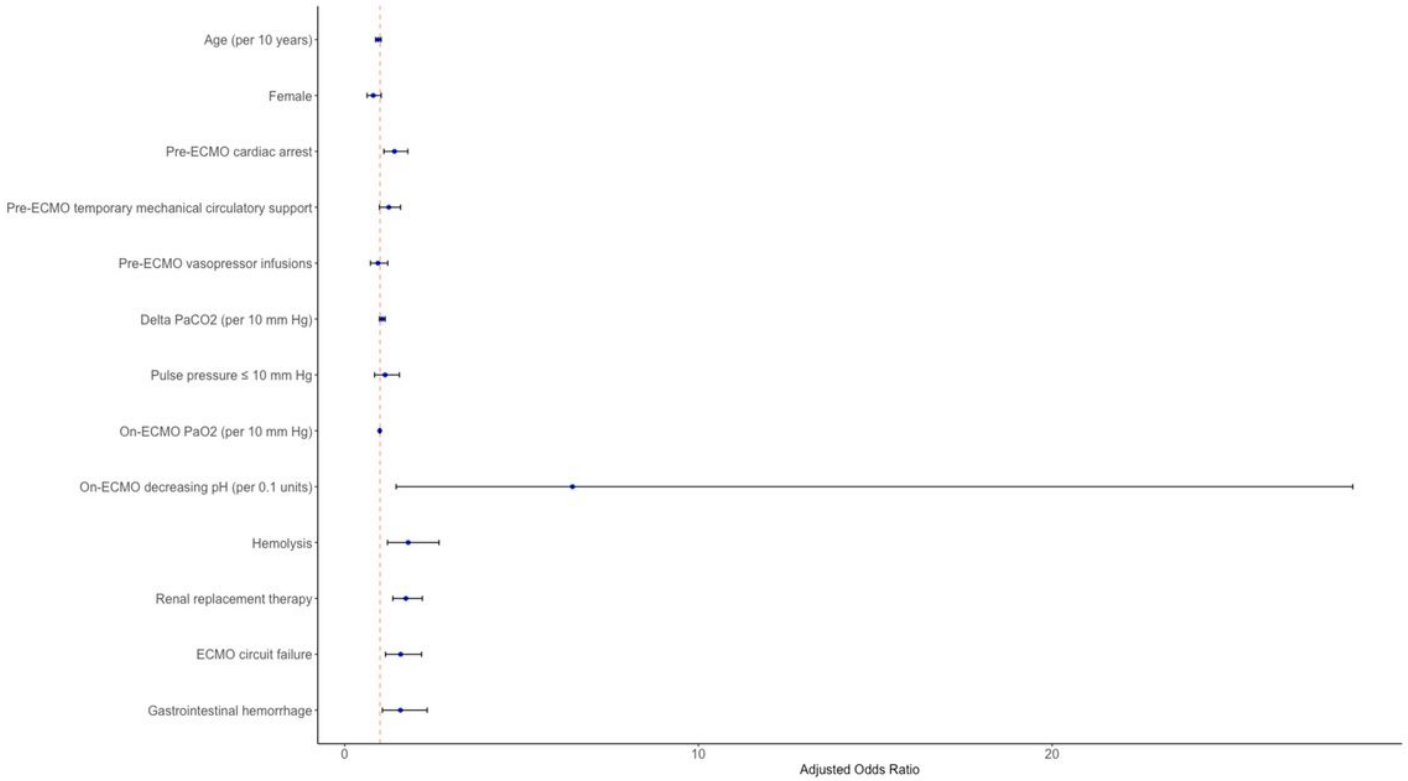

Figure 5

Forest plot of multivariable logistic regression model for occurrence of intracranial hemorrhage in peripheral venoarterial extracorporeal membrane oxygenation patients

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMethods.docx
- SupplementalTablesv5.docx