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Advances in extracorporeal life support in critically ill patients, volume II

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Advances in extracorporeal life support in critically ill patients, volume II

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Editorial: Advances in extracorporeal life support in critically ill patients, volume II

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Editorial on the Research Topic
Advances in extracorporeal life support in critically ill patients, volume II

Initially used as a salvage strategy for patients with refractory cardiac and/or respiratory failure, Extracorporeal Membrane Oxygenation (ECMO) has grown in popularity since its successful application outside the operating room in the 1970's, and this trend is particularly evident in the current years (1–4). In addition, the number of centers able to provide ECMO support has expanded drastically with evolving technology and simplifying procedures (3). Therefore, the Research Topic of indications, procedures, management, and even transport of ECMO patients will never be out of date.

In this Research Topic, we were able to collect volume II of advances in extracorporeal life support in critically ill patients (https://www.frontiersin.org/research-topics/33279/advances-in-extracorporeal-life-support-in-critically-ill-patients-volume-ii). The topic comprises 17 papers in this Research Topic, of which 12 are original researches and five are case reports, encompassing indications, procedure, management and complications of extracorporeal life support.

As a salvage therapy, ECMO can be life-saving in numerous clinical scenarios (5, 6). In this volume, Xu et al. reported a case of a 14-year-old adolescent male patient with an anomalous left coronary artery originating from the right coronary sinus rescued by VA-ECMO and Intra-Aortic Balloon Pump followed. In addition, ECMO are often used as a supportive technique to perform surgeries in all kinds of emergent conditions (7). Zhang et al. reported a case of a human immunodeficiency virus patient with severe lower tracheal obstruction underwent rigid bronchoscopy, airway tumor resection and Y-type silicone stent with ECMO supported. While Tian et al. (b) reported a case of ECMO allowing AngioJet thrombectomy in a patient with severe multiple trauma and acute massive pulmonary embolism. Nowadays, VA-ECMO is being increasingly performed by the percutaneous technique, usually under ultrasound guidance (8, 9). Correspondingly, percutaneous decannulation of VA-ECMO in these patients is thereby receiving growing concerns (9–11). In this volume, Tian et al. (a) reported a case of successfully decannulation of VA-ECMO with Perclose ProGlide device application and achieved total percutaneous post-closure of femoral arteriotomies. Except for ECMO, this volume also collected a case of hemophagocytic lymphohistiocytosis secondary to NK-type non-Hodgkin lymphoma and Epstein-Barr virus reactivation, which was presented with multiorgan

dysfunction and distributive shock as the main manifestation, and was successfully treated by cytokine hemoadsorption.

In recent years, prophylactic use of ECMO in the intraoperative period has been increasingly reported. Zhao Y. et al. conducted a single center, retrospective study to evaluate the clinical outcomes and complications in lung transplantation recipients receiving intraoperative ECMO support, and found that patients received prophylactic ECMO support exhibited better survival and acceptable complication rates. Bai et al. assessed the value of prophylactic use of VA-ECMO in high-risk percutaneous coronary intervention. The consequence indicated that in complex and high-risk coronary artery lesions, ECMO utilization helps to attain safe and feasible revascularization.

Currently, it is common to transport ECMO patients to large referral centers for further treatment. In this volume, Zhao Y. C. et al. brought a retrospective analysis of 126 ECMO patients transferred from regional hospitals to large medical centers, finding no deaths reported though few life-threatening complications occurred during transport, and implying that transferring ECMO patients is feasible as long as careful evaluation and adequate preparation has conducted.

The effectiveness of life support relies on well-timed interventions, which requires moment-by-moment access to key information relevant to the technique adopted. Teng et al. evaluated the concordance between one commercial point-of-care activated partial thromboplastin time (POC-APTT) instrument and the laboratory APTT test in adult patients underwent ECMO support while accepting anticoagulation with unfractionated heparin. Although the consistency was weak and the commercial instrument evaluation was not fungible with the laboratory APTT test, the idea of POC assessing APTT is worth encouraging. Shi et al. explored the value of a multimodal neuromonitoring (MNM) protocol that holds promise for timely detection of neurological injury in VA-ECMO-supported patients. It turned out that the protocol can help identify and treat latent neurological injury in a timely manner, and ultimately improve long-term neurological outcomes. Cousin et al. evaluated carboxyhemoglobin as a novel marker for the incidence of ECMO oxygenator dysfunction. As a surrogate for free hemoglobin, carboxyhemoglobin demonstrated a better response.

Some inherent concerns of ECMO support, such as recirculation for VV-ECMO and vascular complications for VA-ECMO, were all covered in this volume. Fisser, Palmér et al. revealed that femoro-jugular configuration causes less recirculation by comparing recirculation fraction between femoro-jugular and jugulo-femoral VV-ECMO configurations. Also, the team identified risk factors for higher recirculation fraction including excessively short distance between cannula tips, higher ECMO flow, and lower heart rate. Hu et al. retrospectively analyzed the data from 179 adult patients underwent VA-ECMO, and drew a conclusion that for limb ischemia prediction, diabetes, application concomitant Intra-Aortic Balloon Pump, and peak vasoactive-inotropic score are independent risk factors. Fisser, Armbrüster et al. investigated the prevalence data on arterial and venous vascular complications among patients requiring VA-ECMO, and concluded the high incidence of the conditions, implying that screening for vascular complications and accepting anticoagulation should be implemented in such patients.

Early identification of ECMO patients with unsatisfactory prognosis would prompt early intervention and thus might make a change to the outcome. Huang et al. reported that after ECMO initiation, there is a great correlation between the serum total bilirubin and survival, as the risk of 28-day mortality remarkably elevated if hyperbilirubinemia occurs. Thus, the team recommended serum total bilirubin as a predictor for both its effect and its convenience to measure. Jin et al. retrospectively analyzed data collected from 101 pediatric patients receiving VA-ECMO to identify the risk factors of in-hospital death, and to validate the reliability of the current scoring system, including the Pediatric Extracorporeal Membrane Oxygenation Prediction (PEP) model, Pre-cannulation Pediatric Survival After VA-ECMO (Pedi-SAVE) score, and Post-cannulation Pedi-SAVE score. They found that lactate level and infectious complications before and during the ECMO application respectively were in-hospital mortality risk factors. Also, The pre-ECMO PEP score and the post-cannulation Pedi-SAVE score performed a high predictive capacity for in-hospital mortality in children patients underwent post-cardiotomy VA-ECMO.

In summary, this Research Topic compiled a series of cases and research articles that are related to ECMO support. We appreciate the work of all authors, reviewers, and editors for this volume, and we do believe that this volume will provide readers with new insights and inspiration for future research.

Author contributions

G-wT drafted the manuscript. Y-SC, MH, ND, and ZL edited the manuscript, contributed to the Research Topic, and approved the publication of this editorial. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Use of Carboxyhemoglobin as an Early Sign of Oxygenator Dysfunction in Patients Supported by Extracorporeal Membrane Oxygenation

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Introduction: Plasma free hemoglobin is the gold standard for monitoring hemolysis in extracorporeal membrane oxygenation (ECMO) but its routine use has some limitations. Carboxyhemoglobin (HbCO) is also a marker of intravascular hemolysis. We aimed to investigate HbCO as a marker of both hemolysis and oxygenator dysfunction in patients supported by ECMO.

Methods: Retrospective analysis of patients on ECMO in an adult ICU in a tertiary hospital. HbCO was recorded every 6 h in the 48 h before and after oxygenator change in adult patients on ECMO support with an oxygenator dysfunction and replacement.

Results: The investigation of 27 oxygenators replacements in 19 patients demonstrated that HbCO values progressively increased over time and then significantly decreased after oxygenator change. Median oxygenator lifespan was 14 days [interquartile range (IQR) 8–21] and there was no correlation between HbCO and oxygenator lifespan [Spearman coefficient 0.23 (p = 0.23)]. HbCO values at oxygenator change [HbCO median 2.7 (IQR 2.5–3.5)] were significantly higher than the HbCO values 1 week before [HbCO median 2.07 (IQR 1.86–2.8)] (p value < 0.001).

Conclusion: Our data highlight the potential role of HbCO as a novel marker for ECMO oxygenator dysfunction.

Keywords: carboxyhemoglobin, ECMO, critical care, hemolysis, oxygenator clotting

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) support is associated with a risk of hemolysis (1). In the present setting, the hemolysis phenomenon could be a sign of oxygenator dysfunction associated with continuous disseminated intravascular coagulation (DIC). To detect and monitor hemolysis, plasma-free hemoglobin monitoring is recommended by the Extracorporeal Life Support Organization (2). However, the availability of free hemoglobin monitoring has limitations as it is not universally available, and the result may take several hours to be obtained. Under such conditions, carboxyhemoglobin (HbCO) levels seem to be an accessible and reliable marker of hemolysis (3, 4). During hemolysis, heme is degraded by heme oxygenase into biliverdin, free iron

and carbon monoxide (5). Then, carbon monoxide binds with hemoglobin to form HbCO. There are several case reports of elevated HbCO in cases of hemolysis and oxygenator dysfunction in the current literature (6–8). However, there are currently no studies looking at the use of HbCO values as an early additional marker of ECMO oxygenator dysfunction.

Therefore, the aim of our study was to evaluate the evolution of HbCO values over time before and after oxygenator replacement. HbCO monitoring could be used as a marker for oxygenator dysfunction in patients on ECMO as surrogate for free Hb, especially in hospitals that do not have a readily access to free Hb.

METHODS

The present study was conducted during a 20-month period (January 2020–August 2021) in the intensive care unit at Geneva University Hospital. The local ethics committee approved the study and waived the informed consent (BASEC number: 2020-00917). Patients with refractory cardiogenic shock supported by veno-arterial (VA)-ECMO or with refractory hypoxemia supported by veno-venous (VV)-ECMO were screened. HbCO measurement is currently performed in all patients in the unit by the blood gas analyzer.

The exclusion criteria were patients without HbCO available at least one week before ECMO implantation, patients with missing data on oxygenator dysfunction and the inability to collect HbCO before and/or after oxygenator change. ECMO use was based on ELSO recommendations for both VA and VV support (2). In the case of SARS-CoV 2 infection, our center follows an institutional algorithm validated by the Swiss Society of Intensive Care Medicine (9). ECMO management is summarized in the **Supplementary Material**. Oxygenator were replaced in cases low post-oxygenator PaO_2, increase of transmembrane pressure, visible oxygenator clot with diminished ECMO flow, consumptive coagulopathy or hemolysis. Such change was discussed between ECMO team members and carried out in the unit (2, 10).

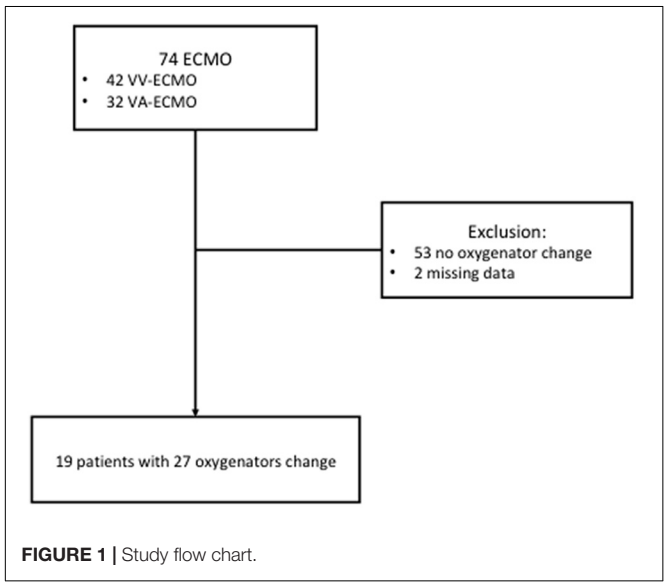

FIGURE 1 | Study flow chart.

Carboxyhemoglobin was recorded every 6 h in the 48 h before and after oxygenator change. Time at oxygenator change is labeled H0, as the first blood gazes in the hour after the oxygenator change. HbCO was measured using a blood gas analyzer [Radiometer ABL800 FLEX, Radiometer ABL90 FLEX PLUS or ABL90 FLEX (Radiometer RSCH GmbH, Thalwil, CH)]. We also recorded hemoglobin (Hb, g/L), lactate (mmol/L), pH, PaO_2 (kPa), and $PaCO_2$ (kPa) at each time point. We determined a baseline HbCO using the mean HbCO value seven days before the oxygenator change (range per patient 3–12), used as an internal control for baseline HbCO.

Continuous variables were described using medians with interquartile ranges (IQRs), and binomial variables were described using proportions. Values of HbCO were compared using the Wilcoxon signed-rank test between different time points. Spearman correlation was performed between oxygenator lifespan and HbCO. A p value ≤ 0.05 was considered significant. Statistical analyses were carried out using Stata Software (StataCorp, College Station, TX, United States).

RESULTS

During the study period, all patients receiving ECMO support were screened (**Figure 1**). The final population included 19 patients with 27 oxygenator replacements (range per patient 1–5). Patient characteristics are summarized in **Table 1**. **Figure 2A**

TABLE 1 | Population characteristics.

Age (years)	59 (IQR 55–65)
Sex (M)	13 (68%)
Diagnosis at time of ECMO cannulation	15 Covid-19 ARDS 3 Cardiogenic Shock (ischemic) 1 Massive Hemoptysis
ECMO support	16 Veno-venous (VV) 3 Veno-arterial (VA)
Length of stay in ICU (days)	38 (IQR 26–69)
Length of ECMO support (days)	28 (IQR 24–43)
Outcome (deceased)	11 (57%)
Oxygenator lifespan (days)	14 (IQR 8-21)
At oxygenator change	
HbCO (%)	2.7 (IQR 2.5–3.5)
Lactate (mmol/L)	1.1 (IQR 0.8–1.3)
Hemoglobin (g/L)	85 (IQR 77–91)
pH	7.45 (IQR 7.41–7.48)
paO2 (kPa)	8.9 (IQR 8.2–9.9)
paCO2 (kPa)	5.1 (IQR 4.5–5.4)

ARDS, acute respiratory distress syndrome; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; HbCO, carboxyhemoglobin.

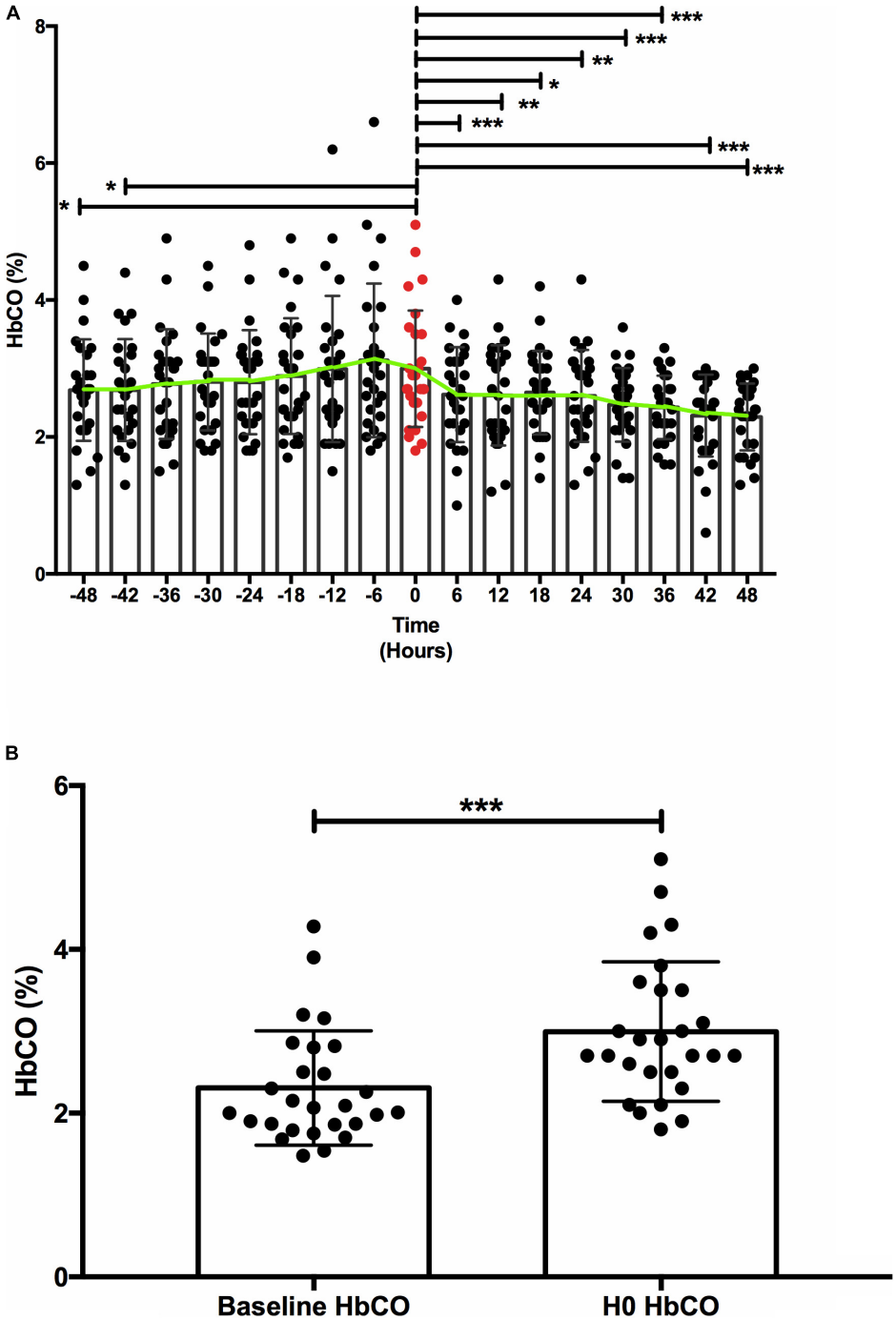

FIGURE 2 | Carboxyhemoglobin (HbCO) evolution. **(A)** HbCO evolution before/after oxygenator replacement. **(B)** Carboxyhemoblobin baseline compared to carboxyhemoglobin at oxygenator replacement. **(A)** Comparison of mean (±SD) HbCO before and after oxygenator replacement. Green line connects HbCO mean at each time point. The red value represents the HbCO value at the oxygenator change, at H0. Y axis: HbCO (%), X axis: time in hours. * < 0.05 ** < 0.01 *** < 0.001. **(B)** H0 HbCO was significantly higher [median 2.7 (IQR 2.5–3.5)] than baseline HbCO [median 2.07 (IQR 1.86–2.8)], with a *p* value < 0.001. Y axis: HbCO (%), X axis: time-point *** < 0.001.

shows the evolution of HbCO in the 48 h before and after the oxygenator change. Noticeably, after oxygenator change, all HbCO values were significantly lower than H0 HbCO. When compared to baseline HbCO, the H0 HbCO level was significantly higher, as shown in **Figure 2B**. Median oxygenator lifespan was 14 days (IQR 8–21). We did not find a correlation between HbCO and oxygenator lifespan, with a Spearman coefficient of 0.23 ($p = 0.23$). When compared, the lifespans of VV- and

VA-oxygenators were not significantly different: 16 days (IQR 9–21.5) for VV ECMO and 9 (IQR 4–11) for VA ECMO ($p = 0.08$). HbCO evolution between both groups (**Supplementary Figure 1**) shows that HbCO was higher in the case of VV ECMO.

DISCUSSION

In the present study, we showed in a representative group of patients a progressive increase and subsequent decrease in HbCO around the time of oxygenator replacement, suggesting a role for HbCO values as an early marker of oxygenator-induced hemolysis.

In the case of oxygenator dysfunction, microthrombi inside the ECMO membrane could produce hemolysis and then increase HbCO levels. HbCO monitoring could then be used in situation when plasma hemoglobin is inaccurate (e.g., significant hyperbilirubinemia or hyperlipidemia, extreme hemolysis with high plasma hemoglobin levels) or unavailable. In this regard, replacing the oxygenator restored HbCO levels. Such findings are similar to the report by Hoffman et al. (7), who described the evolution of HbCO before and after oxygenator replacement, and Kimura et al., who showed an HbCO increase on ECMO and a significant reduction after ECMO removal (11). Such an increased level of HbCO might be an indicator of impending oxygenator dysfunction, able to both induce thromboembolic events and increase mortality (6–8). Importantly, oxygenator lifespan was not associated with HbCO, suggesting that a functional oxygenator will not raise HbCO. Our data suggest a role for HbCO as a warning sign in cases of oxygenation difficulties or ECMO dysfunction. A progressive increase of HbCO level could be used as a warning sign of oxygenator dysfunction. Moreover, HbCO might also be used for the diagnosis of hemolysis with other associated markers, such as bilirubin or free hemoglobin.

The present study has some limitations. First, the design was retrospective with a limited number of patients. Second, it is important to note that other factors, such as systemic inflammation, cavitation or high RPM may impact HbCO (5). Due to laboratory limitation, we could not have made correlation between HbCO and other hemolysis marker such as free hemoglobin or haptoglobin. Finally, our design was based on the comparison of the trend of HbCO in the same patient with oxygenator dysfunction (own control), without comparing HbCO in patients with and with no oxygenator change.

In conclusion, the present study highlights the role of HbCO as a novel marker and monitoring of ECMO oxygenator dysfunction. Further studies are needed to investigate the use of HbCO in clinical settings and compare HbCO levels in patients with and without oxygenator change.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by BASEC number: 2020-00917. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

VC, RG, and KB: concept and design. VC and RG: data collection. VC and KB: data analysis and draft manuscript. VC, RG, BA, IS, and KB: critically revised and approved the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.893642/full#supplementary-material

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Veno-Arterial Extracorporeal Membrane Oxygenation in Elective High-Risk Percutaneous Coronary Interventions

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Background: The safety and feasibility of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) as mechanical circulatory support in high-risk percutaneous coronary intervention (HR-PCI) remain unclear.

Methods: This retrospective study included patients with complex and high-risk coronary artery disease who underwent elective PCI with VA-ECMO support pre-operatively during March 2019–December 2020. Rates of VA-ECMO-related complications, complications during PCI, death, myocardial infarction, and stroke during hospitalisation and 1-year post-operatively were analysed.

Results: Overall, 36 patients (average age: 63.6 ± 8.9 years) underwent PCI. The average duration of VA-ECMO support was 12.5 (range, 3.0–26.3) h. Intra-aortic balloon pump counterpulsation was used in 44.4% of patients. The SYNTAX score was 34.6 ± 8.4 pre-operatively and 10.8 ± 8.8 post-operatively ($P < 0.001$). Intraoperative complications included pericardial tamponade ($N = 2$, 5.6%), acute left-sided heart failure ($N = 1$, 2.8%), malignant arrhythmia requiring electrocardioversion ($N = 2$, 5.6%), and no deaths. Blood haemoglobin levels before PCI and 24 h after VA-ECMO withdrawal were 145.4 ± 20.2 g/L and 105.7 ± 21.7 g/L, respectively ($P < 0.001$). Outcomes during hospitalisation included death ($N = 1$, 2.8%), stroke ($N = 1$, 2.8%), lower limb ischaemia ($N = 2$, 5.6%), lower limb deep venous thrombosis ($N = 1$, 2.8%), cannulation site haematoma ($N = 2$, 5.6%), acute renal injury ($N = 2$, 5.6%), bacteraemia ($N = 2$, 5.6%), bleeding requiring blood transfusion ($N = 5$, 13.9%), and no recurrent myocardial infarctions. Within 1 year post-operatively, two patients (5.6%) were hospitalised for heart failure.

Conclusions: Veno-arterial extracorporeal membrane oxygenation mechanical circulation support during HR-PCI is a safe and feasible strategy for achieving revascularisation in complex and high-risk coronary artery lesions. VA-ECMO-related complications require special attention.

Keywords: veno-arterial extracorporeal membrane oxygenation, elective high-risk percutaneous coronary interventions, safe and feasible, complications, outcomes

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INTRODUCTION

Elective revascularisation procedures for coronary artery disease include percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). While guidelines recommend CABG as the procedure of choice in patients with complex and high-risk coronary artery disease, PCI usage as a revascularisation strategy is increasing in patients who are not suitable for CABG (1–4). While revascularisation (PCI or CABG) can improve the prognosis of patients with complex coronary artery lesions (5, 6), the rate of revascularisation in these patients is low (7, 8). Complex and high-risk coronary artery disease lesions can be revascularised using high-risk PCI (HR-PCI). However, HR-PCI is associated with various complications, such as no coronary artery reflow, coronary artery dissection, pericardial tamponade haemodynamic instability, and cardiac arrest (3). Therefore, HR-PCI represents challenge for interventional cardiologists. The current literature suggests that this type of revascularisation can be completed with mechanical circulation support (3, 4, 9). Mechanical circulation support devices used during HR-PCI include intra-aortic balloon pump (IABP) counterpulsation, extracorporeal membrane oxygenation (ECMO), Impella (Abiomed, Danvers, MA, United States), and TandemHeart (LivaNova Medical Technology Co., Ltd., Pittsburgh, PA, United States) devices (4, 10). Since haemodynamic instability or cardiac arrest can occur during HR-PCI, ECMO can provide strong circulatory support and significantly improve patient prognosis (11). However, veno-arterial (VA)-ECMO can increase the risk of complications, such as cardiac afterload, lower limb arterial ischaemia, blood cell destruction, and increased risk of infection (10). Since clinical data using VA-ECMO as mechanical circulation support in HR-PCI are currently lacking, no recommendations are included in the guidelines. This study aimed to analyse the results of the prophylactic use of VA-ECMO during HR-PCI.

MATERIALS AND METHODS

Study Population and Design

This single-centre retrospective observational study included 36 patients who underwent elective HR-PCI with VA-ECMO support between March 2019 and December 2020. Patients ranged in age from 18 to 85 years. Indications of VA-ECMO use in patients were: (1) left ventricular ejection fraction (LVEF) ≤35%; (2) LVEF >35%; simultaneous merging with the following criteria: (a) coronary artery calcification that requires rotary grinding, (b) unprotected left main coronary artery, and (c) coronary arteries with two chronic total occlusions (CTOs) and one severe stenosis. Indications in these patients included unstable angina pectoris, acute myocardial infarction, and old myocardial infarction. Patients with cardiogenic shock were not included. All patients underwent implantation of ECMO before PCI, and the VA-ECMO mode was chosen. The common femoral artery and vein were selected for ECMO approach in all the patients. An arterial cannulae at 15–19 French (F) and a venous cannulae at 19–21F were chosen as they are 1–2 mm smaller than the inner diameter of the blood vessel. Distal perfusion ipsilateral to the femoral artery cannulation was performed with a 6F catheter. All cannulations were performed under ultrasound guidance. Heparin (100 units/kg before ECMO insertion) was used as anticoagulation strategy. The activated clotting time was maintained for 180–200 s during ECMO insertion and for 250–350 s during PCI. All patients were given 300 mg aspirin and 180 mg ticagrelor or 300 mg clopidogrel orally before PCI and routinely after PCI. ECMO blood flow was initially set to 2.0 L/min and subsequently adjusted according to a patient's blood pressure.

Patients who had refused CABG were considered for elective HR-PCI after evaluation by the interventional team. Clinical and PCI data, collected by reviewing electronic medical records, included demographic information, comorbidities, characteristics of the coronary artery lesions, and major adverse cardiovascular and cerebrovascular events (MACCEs), such as all-cause mortality, recurrent myocardial infarction, stroke, and hospitalisation due to heart failure. The incidence of follow-up MACCEs after discharge was obtained via telephone interviews. Acute kidney injury (AKI) is defined as any of the following (12): (1) increase in serum creatine (SCr) by ≥0.3 mg/dl (≥26.5 μmol/L) within 48 h; (2) increase in SCr to ≥1.5 times of baseline value, which is known or presumed to have occurred within the prior week; and (3) urine volume <0.5 ml/kg/h for 6 h. According to the fourth edition of the global myocardial infarction, acute myocardial infarction refers to increase and/or decrease of serum cardiac troponin at least 1 time higher than the upper limit of the normal range with concurrent clinical evidence of acute myocardial ischaemia, including (13): (1) symptoms of acute myocardial ischaemia; (2) new ischaemic electrocardiogram changes; (3) new pathogenesis of Q wave; (4) imaging evidence of new viable myocardial loss or abnormal ventricular wall segmental movement; and (5) coronary artery thrombosis confirmation by coronary angiography or intracavitary imaging examination. Coronary artery disease was defined as any of the followings (14): (1) left main coronary artery stenosis ≥50%, (2) one or more main coronary arteries stenosis ≥70%, and (3) microvascular dysfunction and coronary artery spasm that result in exercise and stress-related chest symptoms. CTO refers to coronary artery obstruction with positive Thrombolysis in Myocardial Infarction (TIMI) blood flow level 0 and occlusion time ≥3 months, if there are ipsilateral bridging or ipsilateral collateral vessels, complete occlusion is still considered despite TIMI blood flow level >0 in distal occluded vessels (15). The SYNTAX and European System for Cardiac Operative Risk

Abbreviations: AKI, acute renal injury; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass grafting; CI, confidence interval; CRRT, continuous renal replacement therapy; CTO, chronic total occlusion; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; F, French; HR, hazard ratio; HR-PCI, high-risk percutaneous coronary intervention; EuroSCORE, European system for cardiac operative risk evaluation; IABP, intra-aortic balloon counterpulsation pump; J-CTO, CTO registry of Japan; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiovascular and cerebrovascular events; MT, medical therapy; NSTEMI, Non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; PVAD, percutaneous ventricular assist device; SCr, serum creatinine; TIMI, thrombolysis in myocardial infarction; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Evaluation (EuroSCORE) scores were calculated online (http://syntaxscore.org/calculator/start.htm and http://www.euroscore.org/calc.html, respectively). CTO Registry of Japan (J-CTO) scores were calculated for patients with CTO lesions (16). Bleeding events were defined according to the Bleeding Academic Research Consortium (BARC) criteria, and bleeding requiring transfusion was defined as BARC type 3a and 3b bleeding (17). The study protocol, which conformed to the ethical guidelines of the 1975 Declaration of Helsinki, was approved by the Ethics Committee of the First Hospital of Lanzhou University (Approval No. LDYYLL-2021-469). The requirement for informed consent was waived due to the retrospective nature of the study.

Clinical Outcomes

Clinical outcomes included MACCEs during hospitalisation and within 1 year after PCI. The safety endpoints included lower limb ischaemia, deep venous thrombosis, intubation-related haematoma, pseudoaneurysm, arteriovenous fistula, acute renal injury, bacteraemia, and bleeding requiring blood transfusion.

Statistical Analyses

All data analyses were performed using STATA V.17 (Stata Corporation, College Station, TX, United States). Metrological data by or approximate to a normal distribution were expressed as means ± standard deviations. If not normally distributed, metrological data were expressed as medians and quartile spacing [M (Q1–Q3)]. Count data were expressed as numbers and/or percentages [*N* (%)]. Normally distributed continuous variables were reported as means ± standard deviations. Continuous variables that were not normally distributed were expressed as M (Q1–Q3). Binary or categorical variables were reported as numbers and percentages [*N* (%)]. A paired *t*-test was used to compare the mean values of the related variables before and after ECMO support. A Kaplan–Meier analysis was performed to plot the survival curves. All tests were two-tailed. Statistical significance was set at $P < 0.05$.

TABLE 1 | Baseline characteristics of patients included in the study.

Parameter	ECMO (*N* = 36)
Age (years)	63.6 ± 8.9
Sex, male	34 (94.4%)
Current smoker	18 (50.0%)
Hypertension	16 (44.4%)
Diabetes mellitus	12 (33.3%)
Hyperlipidaemia	2 (5.6%)
Prior stroke	1 (2.8%)
Prior MI	7 (19.4%)
Prior CABG	2 (5.6%)
Prior PCI	2 (5.6%)
Early renal insufficiency	1 (2.8%)
Late renal insufficiency	2 (5.6%)
LVEF (%)	
≤35	9 (25.0%)
35–45	5 (13.9%)
≥45	22 (61.1%)
Systolic blood pressure (mmHg)	125.6 ± 24.1
Diastolic blood pressure (mmHg)	74.5 ± 11.5
Heart rate (beats/min)	75.6 ± 14.4
UA	21 (58.3%)
AMI	7 (19.4%)
OMI	8 (22.2%)
Refused surgery	36 (100%)
Length of stay (days)	
Cardiac care unit	4.5 (3.0–7.5)
Hospital	13.5 (9.0–16.0)

Data are presented as means ± standard deviations, N (%), or medians (Q1–Q3).
AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OMI, old myocardial infarction; PCI, percutaneous coronary intervention; UA, unstable angina.

RESULTS

Baseline Characteristics

In total, 36 patients (average age, 63.6 ± 8.9 years) were included in this study. Among the patients, 34 (94.4%) were men. Most patients had previous comorbidities. Overall, 61.1% of the patients had LVEF ≥45, 25.0% had LVEF ≤35, 13.9% had a LVEF of 35–45%. Pre-operatively, the haemodynamic parameters of all patients were stable, including those with unstable angina pectoris (58.3%), acute myocardial infarction (19.4%), and old myocardial infarction (22.2%). All patients declined the CABG procedure. The duration of hospital stay was 13.5 (9.0–16.0) days, and the duration of stay in the coronary care unit was 4.5 (3.0–7.5) days. Baseline characteristics are summarised in **Table 1**.

Angiographic and procedural data are summarised in **Table 2**. The average EuroSCORE I was 7.8 ± 2.3. The pre-PCI and post-PCI SYNTAX scores were 34.6 ± 8.4 and 10.8 ± 8.8, respectively ($P < 0.001$). The most common coronary artery lesions were three-vessel lesions (50.0%). CTO lesions, most of which involved one or two vessels, were present in 77.8% of patients. The average J-CTO score was 1.3 ± 0.9. Coronary artery disease was mainly of the left anterior descending artery (94.4%), followed by the left main coronary artery (41.7%). Additionally, 25.0% of the patients had coronary artery calcification. Revascularisation was performed in two branches in 57% of the patients with an average of 3.0 (2.0–4.0) stents implanted. All HR-PCI procedures were completed successfully. The average duration of ECMO support was 12.5 (3.0–26.3) h. Additional IABP counterpulsation was used in 44.4% of patients. Patients received IABP support mainly for the following reasons: acute left heart failure after the use of VA-ECMO, left ventricular blood stasis indicated by cardiac ultrasound, and contrast agent retention in the coronary sinus during PCI. IABP was also used in patients with poor cardiac function after the weaning from VA-ECMO. Intraoperative complications included pericardial tamponade ($N = 2$, 5.6%), acute left-sided heart failure ($N = 1$, 2.8%), and malignant arrhythmia requiring electrical cardioversion ($N = 2$, 5.6%).

TABLE 2 | Angiographic and procedural characteristics of patients included in this study.

Parameter	ECMO ($N = 36$)
EuroSCORE I	7.8 ± 2.3
Baseline SYNTAX score	
≤22	3 (8.3%)
23–32	9 (25.0%)
≥33	24 (66.7%)
SYNTAX score pre-PCI	34.6 ± 8.4
SYNTAX score post-PCI	10.8 ± 8.8
J-CTO score	1.3 ± 0.9
Number of diseased vessels	
One vessel	0 (0)
Two vessels	8 (22.2%)
Three vessels	18 (50.0%)
Four or more vessels	10 (27.8)
Number of vessels treated	
One vessel	8 (22.2%)
Two vessels	20 (55.6%)
Three vessels	6 (16.7%)
Four or more vessels	2 (5.6%)
Number of CTOs	
One vessel	15 (41.7%)
Two vessels	13 (36.1%)
Three vessels	0 (0)
Lesion location	
Left anterior descending	34 (94.4%)
Left circumflex	28 (77.7%)
Right coronary artery	28 (77.7%)
Ramus	4 (11.1%)
Left main	15 (41.7%)
Isolated	0 (0)
Plus one vessel	0 (0)
Plus two vessels	5 (13.9%)
Plus three or more vessels	10 (27.8%)
Coronary artery calcification	9 (25.0%)
Number of stents placed	3.0 (2.0–4.0)
Duration of device support (h)	12.5 (3.0–26.3)
Combined IABP counterpulsation	16 (44.4%)
Distal perfusion cannula	2 (5.6%)
Device malfunction	0 (0)
Blood pressure reduction during operation	9 (25.0%)
Lowest systolic blood pressure (mmHg)	65.0 ± 11.5
Lowest diastolic blood pressure (mmHg)	47.7 ± 10.7
Vasoactive-inotropic score	39.7 ± 21.2
Maximum ECMO blood flow (L/min)	3.2 ± 0.3
MACCE during operation	
Pericardial tamponade	2 (5.6%)
Acute Left ventricular failure	1 (2.8%)
Malignant arrhythmia	2 (5.6%)
Death	0 (0)

Data are presented as means ± standard deviations, N (%), or medians (Q1–Q3).
CTO, chronic total occlusion; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MACCE, major adverse cardiac and cerebrovascular event; PCI, percutaneous coronary intervention.

TABLE 3 | Comparison of laboratory and cardiac function parameters before and after PCI.

Parameter	Pre-PCI	Post-PCI	*P*-value
Hb (g/L)	145.5 ± 19.9	105.5 ± 21.4	<0.001
PLT ($\times 10^9$/L)	179.8 ± 52.9	162.1 ± 52.3	0.15
eGFR	85.5 ± 24.2	86.9 ± 30.3	0.39
LVEF (%)	46.8 ± 11.6	48.1 ± 9.0	0.06
LVEDV (ml)	152.2 ± 55.8	157.1 ± 61.1	0.50
CO (L/min)	4.8 ± 1.0	4.8 ± 1.0	0.74
CI (L/min/m^2)	2.7 ± 0.5	2.7 ± 0.5	0.76

CI, cardiac index; CO, cardiac output; eGFR, estimated glomerular filtration; Hb, haemoglobin; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PLT, platelets.

TABLE 4 | Clinical outcomes.

Parameters	ECMO ($N = 36$)
In-hospital mortality	1 (2.8%)
Re-infarction	0 (0)
Ischaemic stroke	1 (2.8%)
Limb ischaemia	2 (5.6%)
Deep venous thrombosis	1 (2.8%)
Arteriovenous fistula	0 (0)
Pseudoaneurysm	0 (0)
Cannulation site hematoma	4 (11.4%)
Acute kidney injury	2 (5.6%)
Bacteraemia	2 (5.6%)
Bleeding requiring transfusion	5 (13.9%)
Continuous renal replacement therapy	1 (2.8%)

Data are presented as N (%).
ECMO, extracorporeal membrane oxygenation.

None of the patients died during PCI. There were nine patients with significantly reduced intraoperative blood pressure, which was maintained by increasing ECMO blood flow and treating with vasopressor drugs. The lowest intraoperative systolic blood pressure and diastolic blood pressure of these patients were 65.0 ± 11.5 and 47.7 ± 10.7 mmHg. The vasoactive-inotropic score was 39.7 ± 21.2. The maximum intraoperative ECMO blood flow was 3.2 ± 0.3 L/min.

Changes in blood cell counts, renal function parameters, and cardiac ultrasound indices are summarised in **Table 3**. The average blood haemoglobin level was 145.5 ± 19.9 g/L before PCI and 105.5 ± 21.4 g/L after removal of ECMO ($P < 0.001$). Renal function parameters and cardiac ultrasound indices did not differ significantly between the period before PCI and the 24-h period after the removal of ECMO.

Clinical Outcomes

Table 4 summarises the outcomes during hospitalisation included death ($N = 1$, 2.8%) due to bacteraemia, stroke ($N = 1$, 2.8%). No myocardial infarctions occurred during hospitalisation. Other important events included lower limb

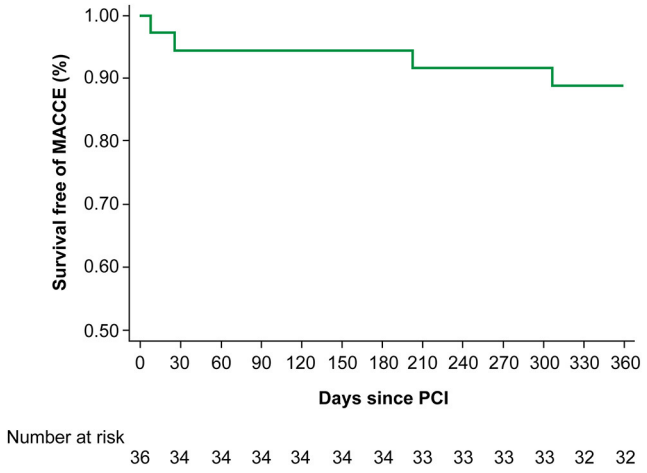

FIGURE 1 | The incidence of MACCE within 12 months of PCI. MACCE, major adverse cardiovascular and cerebrovascular event; PCI, percutaneous coronary intervention.

ischaemia ($N = 2$, 5.6%), lower limb deep venous thrombosis ($N = 1$, 2.8%), cannulation site haematoma ($N = 2$, 5.6%), bacteraemia ($N = 2$, 5.6%), and bleeding requiring blood transfusion ($N = 5$, 13.9%), and AKI ($N = 2$, 5.6%). One patient with AKI was treated with continuous renal replacement therapy (CRRT) due to oliguria and electrolyte disturbance, while the other patient showed no significant decrease in urine volume and was stable without CRRT.

Figure 1 illustrates the incidence of MACCEs within 12 months of PCI. One (2.8%) patient died and one (2.8%) patient had ischaemic stroke during hospitalisation, two (5.6%) patients were hospitalised for heart failure. There were no myocardial infarctions.

DISCUSSION

The results from 36 patients in this study suggest that using VA-ECMO during elective HR-PCI is safe and feasible, with low mortality and complication rates. For patients with complex and high-risk coronary artery disease, selective HR-PCI supported by VA-ECMO can be used as an alternative revascularisation strategy to CABG. These results are consistent with those of other single-centre studies (18–21).

Patients with complex and high-risk coronary artery disease present with the following three characteristics: first, severe coronary artery disease, such as multi-vessel disease or unprotected left trunk, chronic obstructive disease and calcification, and consequent complications; second, comorbidities including heart failure, diabetes, previous CABG, and advanced age; and third, haemodynamic changes, such as haemodynamic instability, shock, or severe left ventricular dysfunction (3, 4).

As an elective revascularisation strategy for complex and high-risk coronary artery disease, PCI revascularisation is the preferred choice for one or two coronary artery lesions with or without left anterior descending artery stenosis, whereas CABG is preferred for patients with left main coronary artery disease with a SYNTAX score ≥23, three-vessel disease without diabetes with a SYNTAX score ≥23, and three-vessel disease with diabetes (1). The results of the 10-year SYNTAX trial revealed no difference between PCI and CABG in all-cause mortality 10 years after revascularisation. In our subgroup analysis, the survival rate of patients with three-vessel coronary artery disease in the CABG group was higher than that in the PCI group. However, there was no difference between PCI and CABG in the survival rates of patients with left main coronary artery disease. Consequently, in patients with triple-vessel disease or left main artery disease, revascularisation strategy (PCI or CABG) is decided by the cardiac surgeons and interventional physicians (2). For complex high-risk coronary artery disease, overall revascularisation rates remain low irrespective of PCI or CABG. In one study, 4,414 patients with non-ST-elevation myocardial infarction (NSTEMI) were divided into low-risk, medium-risk, and high-risk groups according to the Global Registry of Acute Coronary Events score. While the rate of revascularisation in the high-risk group was significantly lower than that in the low-risk group, the overall rates of revascularisation (PCI or CABG) increased gradually with time (7). In another observational study focusing on revascularisation in patients with NSTEMI and multi-vessel coronary artery disease with diabetes complications ($N = 29{,}769$), only one-third of the patients underwent CABG within 6 years, and nearly half underwent PCI. While the overall revascularisation rate increased, 17.3% of patients did not receive revascularisation treatment. Additionally, while the proportion of patients who received PCI treatment increased gradually, the proportion of those who received CABG treatment remained unchanged.

It has been suggested that revascularisation (PCI or CABG) in patients with complex, high-risk coronary artery disease can improve their prognosis (5, 6). However, HR-PCI includes several challenges (3, 9): (1) There is a dearth of research data because of insufficient revascularisation rates and a lack of objective and accurate evidence supporting an optimal revascularisation strategy; (2) Interventional doctors may underestimate the benefits of revascularisation in such patients; (3) Revascularisation in coronary artery disease patients is difficult, intraoperative procedures and complications may also have serious adverse effects on haemodynamic parameters in these patients; (4) Operators are required to master techniques, such as fractional flow reserve, intravascular ultrasound, and optical coherence tomography. Therefore, a considerable number of interventional physicians may lack the required competence.

A growing body of clinical evidence suggests the usefulness of left heart assist devices as circulatory support in HR-PCI. The results of the IABP-SHOCK II trial suggested that IABP, an older circulatory assist device, was ineffective in patients with circulatory failure (22). Al-Khadra et al. evaluated non-emergency PCI with a percutaneous ventricular assist device (PVAD) and IABP support in patients with no cardiogenic shock and acute myocardial infarction, respectively. According to their findings, patients undergoing a PVAD-supported PCI exhibited significantly lower in-hospital mortality rates than

patients treated with an IABP (23). ECMO can be used for powerful haemodynamic mechanical circulation support during elective HR-PCI (10, 11). When VA-ECMO is used in HR-PCI, not only the cardiac functional status of the patient, but also the severity of coronary artery disease should be fully considered by the interventional physician. Because of the risk of potentially severe hemodynamic instability in severe coronary artery disease during PCI. Therefore, in this study, in addition to patients with LVEF $\leq$ 35%, we considered that patients with LVEF $>$ 35% who needed rotational atherectomy during PCI, unprotected left main disease, and two CTOs with one coronary artery severe stenosis also needed VA-ECMO support. The severity of coronary artery disease requires an indication for VA-ECMO support, and more research evidence is currently needed. Four single-centre, small-sample-size studies on VA-ECMO-supported HR-PCI reported that VA-ECMO is safe and effective as a mechanical circulation support strategy for HR-PCI. Additionally, elective HR-PCI supported by VA-ECMO is a feasible choice for patients who do not qualify for CABG—or are considered very high-risk—with good short-term and long-term prognoses (18–21). Currently, there are few clinical data on HR-PCI supported by VA-ECMO, and its benefits need to be further verified using randomised controlled trials. To implement this strategy, experienced ECMO and cardiac interventional physicians' teams are required. Compared with other percutaneous mechanical assist devices, ECMO is more difficult to operate. Additionally, its complications have affected its clinical development and patient prognosis (24). The ability to prevent and manage such complications mainly depends on the team's ability to diagnose, treat, and nurse patients on ECMO. Studies have demonstrated that an ECMO treatment of $>$20 critical patients per year can maintain the level of experience in ECMO treatment centres (25) and that the mortality rate in adult ECMO centres treating $>$30 cases per year is significantly lower than that in centres treating $<$6 cases per year (26).

The main complications of ECMO in this study included vascular puncture complications, lower limb ischaemia, deep venous thrombosis, bleeding, increased left ventricular afterload, acute renal injury, and infection.

This study evaluated all patients using ultrasound at the puncture site (including the femoral artery and femoral vein) before ECMO intubation. To avoid lower limb ischaemia and thrombosis, the vessel diameter should be at least 1–2 mm larger than that of the intubation cannula (27). The recommended solution for lower limb ischaemia is to place a short distal 6–8 F perfusion catheter in the ipsilateral superficial femoral or dorsalis pedis artery (24, 27). In this study, lower limb ischaemia improved after a distal perfusion catheter was placed in two (5.7%) patients. The trigger for distal reperfusion catheter placement is the 5P sign of acute limb ischaemia, characterised by persistent pain with pallor, pulselessness, paraesthesia, and paralysis. Moreover, ultrasound can be used to evaluate the blood flow in punctured blood vessels, the presence of atherosclerotic plaques, and calcification at the puncture site to avoid catheter placement in such areas. No arteriovenous fistula or pseudoaneurysm complications were observed in this study, which was related to ultrasound-guided percutaneous cannulation. Based on our experience, the placement of arterial and venous cannulae was ultrasound-guided rather than fluoroscopic. While adequate anticoagulation is required during ECMO, anticoagulation therapy carries a potential bleeding risk. Four (11.1%) patients in this study developed haematoma at the intubation site, and five (13.9%) patients received a blood transfusion due to decreased haemoglobin levels, primarily due to loss of blood in the tube, during weaning from ECMO.

In this study, IABP was used as the left ventricular decompression strategy in 44.4% of patients, while the remaining patients were supported by ECMO alone. With increases in blood flow, VA-ECMO tends to increase the left ventricular afterload. The most common devices used for left ventricular unloading during VA-ECMO are Impella (Abiomed) and IABPs, while other strategies include atrial septostomy, surgical left ventricular apical drainage, positive inotropic drugs, diuretics, or continuous renal replacement therapy (10, 11). Compared with no unloading, any unloading strategy can reduce the mortality of patients with VA-ECMO (28). In patients who undergo VA-ECMO for cardiogenic shock, there is no significant difference in haemodynamic parameters between IABP and Impella (Abiomed) in left ventricular afterload reduction. However, the use of IABP combined with ECMO may help reduce the mortality rate and improve the 180-day survival rate (29). IABP is the most commonly used left ventricular decompression device in VA-ECMO because it can be implanted percutaneously at the bedside within a short period and is easy to operate. IABP combined with VA-ECMO in patients with cardiogenic shock can significantly reduce the in-hospital and 28-day all-cause mortality rates and contribute to successful weaning from ECMO (30). For selective HR-PCI supported by VA-ECMO, the timing of IABP as a left ventricular unloading strategy requires further research.

Acute kidney injury is a prognostic complication of ECMO. Studies have reported that the rate of severe AKI requiring renal replacement therapy during ECMO is approximately 45% (31). While ECMO can improve renal function, it can simultaneously increase AKI risk. AKI in patients on ECMO support is often caused by multiple factors, such as ischaemia-reperfusion injury, inflammatory reactions, and ECMO damage to blood cells (32). A single-centre retrospective study of 2,660 patients with coronary heart disease who underwent PCI, including 1,128 patients with non-complex PCI and 1,532 patients with complex PCI, reported no difference in contrast-associated kidney injury between the two groups. This finding suggested that complex PCI does not increase the rate of contrast-induced renal injury (33). It is believed that HR-PCI does not increase contrast-associated AKI. In this study, two patients developed kidney injury post-operatively, which corresponds to a low AKI rate. This observation may be related to the short duration of ECMO and the small number of patients in this study.

The infection rate in patients on VA-ECMO registered with the Extracorporeal Life Support Organisation during 2014–2018 was 7.6% (24). The common complications of VA-ECMO infection are bacteraemia and sepsis. The infection rate increases gradually with the prolongation of ECMO support. More than 53% of patients with infection-related complications develop them within 2 weeks of ECMO initiation (26). The rate of ECMO-associated infections in patients in this study was 5.6%. The duration of ECMO support was 12.5 (3.0–26.3) h, and the

relatively shorter ECMO uptime contributed to the low rate of ECMO-related infections. However, infection rate seems high given the short duration of support in this study, we reviewed the clinical data of both patients with ECMO-associated infections and found that both patients received combined IABP and one patient received combined CRRT for AKI. Therefore, the increased mechanical support may increase the risk of infection in patients.

LIMITATIONS

This study was a single-centre retrospective study with a small sample size. Additionally, vascular complications might have been underestimated as women, whose smaller blood vessels may result in more cannulae-size-related complications, were underrepresented in this study. Based on our experience, we plan to perform a randomised controlled trial with VA-ECMO as circulating support during HR-PCI to further clarify the indications for and timing of VA-ECMO in HR-PCI (ChiCTR2100046630).

CONCLUSIONS

Prophylactic use of VA-ECMO as a circulatory support device during elective HR-PCI is safe and feasible. Complication and MACCE rates during the use of ECMO in HR-PCI and the rate of MACCE at 1-year post-operatively were low. The optimal timing of HR-PCI using VA-ECMO requires further validation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Hospital of Lanzhou University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MB, AL, CP, SH, WQ, JZ, and BZ performed the study. WQ and JZ performed the analyses. MB, AL, and CP drafted the manuscript. MB helped supervise the project. All authors contributed to the article and approved the submitted version.

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Outcomes of Transferred Adult Venovenous and Venoarterial Extracorporeal Membrane Oxygenation Patients: A Single Center Experience

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Objectives: Extracorporeal membrane oxygenation (ECMO) patients with or without transport both have high hospital mortality rate and there are few data on adult VA-ECMO transport patients. Hence, this study was designed to analyze factors that affect the outcomes of patients with ECMO transport.

Methods: This study retrospectively enrolled 126 ECMO patients transferred from regional hospital to the First Affiliated Hospital of Zhengzhou University by our ECMO team during June 2012 to Sept 2020. Data were calculated and analyzed.

Results: The median distance of transportation was 141 (76–228) km, the median transport time consuming was 3 (1.3–4) h, the percentage of complications during transport was 40.5% (except for bleeding on cannula site, and no one death during transport), and the survival rate in hospital was 38.9%. Compared with survivors, the non-survivors were older and showed higher SOFA score, longer time with ECMO assisted, longer time in ICU and in hospital. However, after divided into VA-ECMO and VV-ECMO groups, the older age showed no significant difference between survivors and non-survivors groups of VA-ECMO patients. Moreover, the Cox regression survival analysis showed that higher SOFA score and lactate level indicated higher ICU mortality of VA-ECMO patients while higher SOFA score, higher lactate level, older age and lower MAP after transportation (<70mmHg) indicated higher ICU mortality of VV-ECMO patients. However, there was no significant difference of comorbidities and complications in survivors and non-survivors groups of ECMO patients.

Conclusions: The transportation for ECMO patients can be feasible performed although life-threatening complications might occur. The SOFA score and the lactate level could be used to evaluate the risk of ICU mortality of transportation ECMO patients. Besides, lower MAP after transportation (<70mmHg) had potential predictive value for short-term outcome of VV-ECMO patients.

Keywords: transportation, extracorporeal membrane oxygenation, intensive care unit mortality, mean arterial pressure, complications

INTRODUCTION

For patients with severe reversible refractory respiratory or circulatory failure, extracorporeal membrane oxygenation (ECMO) is now recognized as a lifesaving procedure. The Extracorporeal Life Support Organization (ELSO), an authoritative organization, collects a large amount of ECMO-related data and provides therapy guidelines including ECMO transportation programs. The mortality of specialized high-volume centers was showed lower than that of regional hospitals and the ELSO recommends transported ECMO-supported individuals to centers at least 30 adult supported individuals per year (1). Other large-scale studies have also confirmed that interhospital ECMO transports to large-volume ECMO centers reduces mortality significantly (2–4).

The survival rate of ECMO supported patients was low. A referral center compared the outcomes of 51 transferred and 215 in-house venoarterial ECMO (VA-ECMO) supported patients and found there was no significant difference in the mortality rate (56.7 vs. 60.8%) (5). The mortality rate of ECMO-supported patients during transportation was reported as low as 0.15% (6–9). It seems that initiating ECMO at an outlying hospital and transferring patients to large referral center for continued care may result in similar survival outcomes. However, the transferred and in-house ECMO supported patients existed many differences. First of all, the composition of the two types of patients is different. There are fewer adults and VA models for transporting patients, and patients who are overly ill may not choose to be transported. Secondly, the medical conditions of the transfer vehicle are not as good as in the hospital, and it also involves the cooperation of the ECMO team, the occurrence of complications during the transfer, and the maintenance of various indicators during the transportation. Therefore, although the prognosis of the two types of patients is similar, we hypothesized that there may be different risk factors affecting the transportation ECMO patients' prognosis. In the present study, we enrolled 126 adult transferred ECMO patients. Among them, the proportion of VA-ECMO was larger than that of previous studies. We calculated their baseline characteristics and indicators at three different time points, and then analyzed the impact of different indicators on short-term prognosis.

The aim of this work is to seek factors that may affect and even could evaluate the survival rate of VA and venovenous (VV) ECMO supported transportation patients.

MATERIALS AND METHODS

Study Design and Patients

The present study fully complied with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China (no. 2020-KY-429).

Our study retrospectively enrolled adult patients treated with ECMO in regional hospitals by our mobile teams and transferred to the First Affiliated Hospital of Zhengzhou University immediately from June 2012 to Sept 2020. The exclusion criteria were as follows: 1) aged<18 years old; 2) the sequential organ failure assessment (SOFA) score >18; 3) low platelet count (<50 × 10^{12}/L), intracranial hemorrhage or other contraindications to heparin treatment; 4) no further indication after optimal treatment; and 4) secondary transports (the patients is already on ECMO before our team arrived) (**Figure 1**). Finally, 42 VA-ECMO supported patients and 84 VV-ECMO ones who had indications for ECMO transportation were enrolled and then divided into hospital survival group and non-survival group.

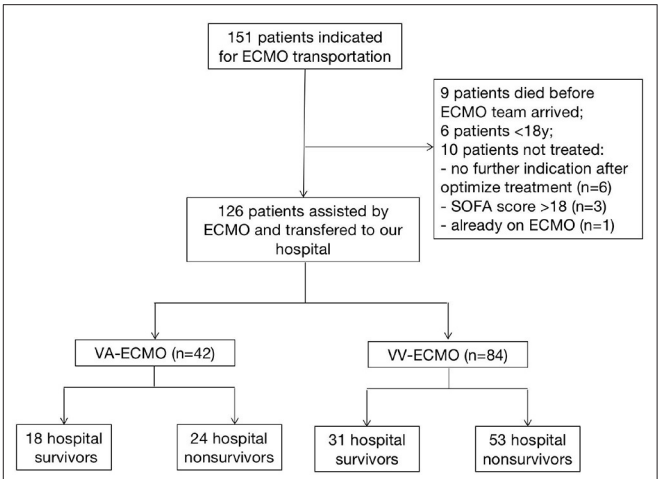

FIGURE 1 | The flow chart.

The clinical data, modes of support (venovenous or venoarterial), the time of ECMO assisted, mechanical ventilation, intensive care unit (ICU) stay and hospital stay were collected. The indications for ECMO, the distance, the time consuming and the complications of transportation were recorded. Complications of transported ECMO patients were divided into equipment complications and patients ones (2). Equipment complications were consisted by clotting of ECMO system, pump failure, ECMO system air embolism and oxygen deficit (9). Clotting of ECMO system was that a blood clot larger than 3.0 mm can be seen near the membrane. Pump failure was referred to the sudden stop of the centrifugal pump. ECMO system air embolism was defined as more than 30 ml of air entering the ECMO system, which cannot be discharged by itself, and needs to be manually exhausted. Oxygen deficit was the large amount of oxygen used by ventilators and ECMO machines in transferred patients and needs to be deployed urgently. The patient complications were containing hemorrhage (respiratory and/or gastrointestinal tract hemorrhage, intracranial hemorrhage and bleeding on cannula site), lower limb ischemia, emergency orotracheal intubation, cardiac arrest, scald and epilepsy. According to the ELSO definition of severe bleeding (10), hemorrhagic complication was defined as: clinically significant bleeding requiring the administration of 2 packed red blood cells or more within 24 h, or a drop in hemoglobin of at least 2 g/dL within 24 h excluding haemolysis and/or bleeding from specific sites such as the central nervous system and/or bleeding requiring specific interventions such as embolisation, surgery, etc. Lower

limb ischemia was referred to ischemia manifestations such as coldness, mottled, cyanosis, etc. on either side of the lower limbs. Emergency orotracheal intubation was a sharp drop in the oxygenation index which need to orotracheal intubation immediately during the transfer of ECMO patients. Cardiac arrest was defined as patient's heart stops beating during transit and CPR is required. Scald was the formation of skin blisters caused by the main pump of EMCO contacting the body of the patient and the main pump being heated for a long time. Seizures was epileptic symptoms such as convulsions during transport. The severity of the illness was assessed based on the SOFA score before ECMO initiation. Besides, heart rate (HR), respiratory rate (R), mean arterial pressure (MAP), the levels of lactate, the arterial partial pressure of oxygen (PaO_2) and the arterial partial pressure of carbon dioxide ($PaCO_2$) were obtained in three time points (before ECMO boarding, after ECMO boarding and patient's condition is relatively stable, transported to the hospital).

Mobile ECMO Team and Equipment

The composition of the mobile ECMO team currently has no clear guidelines but has recommendations. A mature ECMO team usually including physicians, transport specialists, nurses, perfusionists, and other ECMO specialists (9). According to the recommendations, our mobile ECMO team consists of ECMO physician, emergency physician or intensive care physician, and intensive care nurse. Firstly, the team will evaluate the patient and indication of ECMO. Once transportation is needed, ECMO physician should manage the cannulation. The mobile ECMO team was in charge of the ECMO circuit, the ventilator, medications, the application of heparin, and resolve complications of transferred critically ill patient. Besides, the cannulation is often performed through percutaneously by ECMO physician.

All transport-related coordination was handled by the ECMO physician. The ECMO team, equipment, and critically ill patients were ground transferred by emergency ambulance. ECMO system used were ROTAFLOW centrifugal pump (Maquet Cardiopulmonary, Rastatt, Germany), SCP/SCPC (Stöckert, Munchen, Germany) or Bio-Console 560 (Medtronic,Minneapolis, USA). The ECMO oxygenator was MEDOS HILITE 7000LT (Medos Medizintechnik, Stolberg, Germany) or D905 EOS ECMO(Sorin, Mirandola, ITALY). All cannulations were peripheral. There were two approaches of cannulation in the transferred patients as femoro-femoral cannulation approach used in VA-ECMO assisted patients while femoro-jugular in VV-ECMO ones. For VV/VA ECMO, the following single lumen cannulas were used: Bio-Medicus 15–21 French (Fr)/18 cm, 15–21 Fr/50 cm (Medtronic); BE-PAL 15–21 Fr/23 cm,BE-PVL 19–23 Fr/55 cm (Maquet); OPTI 16–22 Fr/24cm, VFEM 18–22 Fr/55 cm(Edwards); or BMA 16–26 Fr/38.3 cm,BMA 18–28 Fr/80.7 cm(Medos). During transport, an MAQUET SERVO-i ventilator was used for patient monitoring, while blood gases and activated clotting times were assessed by using an MD-125(Beijing, China), MINI-II(Beaumont, Texas, USA) or Bio Trend(Medtronic, Minneapolis, USA).

TABLE 1 | Baseline characteristics of transferred ECMO patients.

	Total (n = 126)	Non–survival Group (n = 77)	Survival Group (n = 49)	P–value
Male gender, (n%)	59 (46.8)	37 (48.1)	22 (44.9)	0.732
Age (y)	45 ± 14	49 ± 13	39 ± 13	**<0.001**
BMI (Kg/M2)	23.6 ± 3.4	23.6 ± 3.0	23.7 ± 4.0	0.898
SOFA score	10 (8–12)	11 (10–12)	8 (6.5–11)	**<0.001**
Comorbidities, (n%)				
Type 2 diabetes	27 (21.4)	15 (19.5)	12 (24.5)	0.215
Hypertension	35 (27.8)	20 (25.9)	15 (30.6)	0.382
COPD	23 (18.3)	13 (16.9)	10 (20.4)	0.522
Indications for ECMO, (n%)				0.369
Pneumonia	55 (43.7)	34 (44.2)	21 (42.9)	
Fulminant myocarditis	11 (8.7)	7 (9.1)	4 (8.2)	
Coronary heart disease	9 (7.1)	3 (3.9)	6 (12.2)	
Others	51 (40.5)	33 (42.9)	18 (36.7)	
Cannulation time consuming (min)	31.8 ± 10.8	31.0 ± 10.8	33.2 ± 10.7	0.266
Distance of transportation (km)	141 (76–228)	141 (77–228)	141 (39.5–228)	0.459
Transport time consuming (h)	3 (1.3–4)	3 (1.4–3.9)	3 (1.1–4.5)	0.779
Liquid per hours (ml/h)	76 (41–138)	80 (45–155)	67 (35–116)	0.319
Urine per hours (ml/h)	45 (25–83)	45 (20–82)	44 (29–99)	0.189
Remote shunt (n %)	10 (7.9)	3 (3.9)	7 (14.3)	0.064
IABP (n %)	26 (20.6)	14 (18.2)	12 (24.5)	0.593
CRRT (n %)	82 (65.1)	48 (62.3)	34 (69.4)	0.422
Ventilation time, (h)	298.8 ± 142.5	306.9 ± 136.0	284.2 ± 154.1	0.411
ECMO assisted time, (h)	196 (124.5–324.8)	256 (129–372.5)	176 (121–204.5)	**<0.001**
Time in ICU, (d)	16.4 ± 7.2	13.3 ± 5.9	21.4 ± 6.2	**<0.001**
Time in hospital, (d)	17 (12.8–21.2)	14.8 (10.1–17.5)	22 (17.8–32.3)	**<0.001**
VA/VV ECMO, (n%)	42 (33.3)	24 (31.2)	18 (36.7)	0.522

The data was shown as the mean ± SD, median (interquartile 25–75) or n (percentage). Bold values indicate statistical significance. BMI, body mass index; COPD, chronic obstructive pulmonary disease; SOFA, sepsis–related organ failure assessment; IABP, intra–aortic balloon pump; CRRT, continuous renal replacement therapy; ICU, intensive care unit; VA/VV ECMO, veno–arterial/veno–venous extracorporeal membrane oxygenation.

Statistical Analysis

All collected data were statistically analyzed using SPSS 21.0 (Armonk, NY: IBM Corp.). Measurement data are presented as mean (± SD) or median (IQR), and the two groups compared by analysis of variance. Count data were expressed by frequency (composition ratio), and comparison between groups was by $\chi 2$

TABLE 2 | Comparison of the characteristics of the survivors and non-survivors of VA-/VV-ECMO.

	VA–ECMO survivors (*n* = 18)	VA–ECMO Non–survivors (*n* = 24)	*P*– value	VV–ECMO survivors (*n* = 31)	VV–ECMO Non–survivors (*n* = 53)	*P*– value
Male, (*n*%)	7 (38.9)	13 (54.2)	0.327	15 (48.4)	24 (45.3)	0.783
Age (y)	36 ± 17	43 ± 14	0.132	39 ± 12	51 ± 13	**<0.001**
BMI (Kg/M^2)	23.2 ± 4.2	23.0 ± 2.3	0.846	24.0 ± 3.9	23.9 ± 3.3	0.923
Remote shunt, (*n*%)	7 (38.9)	3 (12.5)	0.105	/	/	/
IABP, (*n*%)	12 (66.7)	14 (58.3)	0.582	/	/	/
CRRT, (*n*%)	11 (61.1)	16 (66.7)	0.710	23 (74.2)	32 (60.4)	0.199
SOFA score	10 (8–11)	12 (10.25–12.75)	**0.003**	8 (6–11)	11 (9.5–12)	**<0.001**
ACT pre–ECMO	143.72 ± 23.15	141.58 ± 21.04	0.756	150.71 ± 23.00	142.32 ± 20.32	0.086
ACT after–ECMO	394.39 ± 198.07	367.96 ± 182.75	0.657	371.74 ± 177.10	339.19 ± 149.34	0.371
ACT after–transported	214.78 ± 152.28	212.29 ± 98.41	0.949	220.39 ± 98.36	229.34 ± 149.39	0.767
APTT pre–ECMO	40.17 ± 6.30	40.32 ± 6.30	0.942	39.8 ± 12.55	40.57 ± 10.11	0.760
APTT after–transported	68.98 ± 36.50	79.21 ± 38.96	0.392	83.10 ± 42.79	85.46 ± 39.11	0.797
Sedation and analgesia						
Dexmedetomidine	18 (100)	24 (100)	–	31 (100)	53 (100)	–
Midazolam Maleate	13 (72.2)	19 (79.2)	0.720	10 (32.3)	23 (43.4)	0.361
Sufentanil	9 (50)	8 (33.3)	0.348	2 (6.5)	9 (17)	0.201
Remifentanil	9 (50)	16 (66.7)	0.348	29 (93.5)	44 (83)	0.201
Vasoactive agents						
Norepinephrine	10 (55.6)	12 (50)	0.764	1 (3.2)	4 (7.5)	0.647
Epinephrine	2 (11.1)	2 (8.3)	0.762	2 (6.5)	5 (9.4)	0.946
Dopamine	8 (44.4)	12 (50)	0.721	5 (16.1)	8 (15.1)	0.867
Dobutamine	4 (22.2)	5 (20.8)	0.914	1 (3.2)	1 (1.9)	0.998

The data was shown as the mean ± SD, median (interquartile 25–75) or n (percentage). Bold values indicate statistical significance. BMI, body mass index; SOFA, sepsis–related organ failure assessment; IABP, intra–aortic balloon pump; CRRT, continuous renal replacement therapy; VA/VV ECMO, veno–arterial/veno–venous extracorporeal membrane oxygenation; ACT, activated clotting time; APTT, activated partial thromboplastin time.

TABLE 3 | Comparison of the complications of the survivors and non-survivors of VA-/VV-ECMO.

	VA–ECMO survivors (*n* = 18)	VA–ECMO Non–survivors (*n* = 24)	*P*– value	VV–ECMO survivors (*n* = 31)	VV–ECMO Non–survivors (*n* = 53)	*P*– value
Equipment complications, (*n*%) Clotting of ECMO system	1 (5.6)	1 (4.2)	0.973	2 (6.5)	3 (5.7)	0.846
Pump failure	0 (0)	1 (4.2)	0.755	0 (0)	0 (0)	–
ECMO system air embolism	0 (0)	0 (0)	–	1 (3.2)	1 (1.9)	0.998
Oxygen deficit	1 (5.6)	0 (0)	0.429	1 (3.2)	1 (1.9)	0.998
Patient complications, (*n*%)						
Respiratory and/or gastrointestinal tract hemorrhage	4 (22.2)	6 (25)	0.932	5 (16.1)	8 (15.1)	0.867
Intracranial hemorrhage	0 (0)	2 (8.3)	0.178	1 (3.2)	1 (1.9)	0.998
Bleeding on cannula site	13 (72.2)	14 (58.3)	0.517	8 (25.8)	24 (45.3)	0.104
Lower limb ischemia	1 (5.6)	2 (8.3)	0.676	/	/	/
Emergency orotracheal intubation	0 (0)	0 (0)	–	0 (0)	1 (1.9)	0.975
Cardiac arrest	0 (0)	1 (4.2)	0.755	0 (0)	0 (0)	–
Scald	1 (5.6)	0 (0)	0.429	0 (0)	0 (0)	–
Epilepsy	0 (0)	2 (8.3)	0.178	0 (0)	3 (5.7)	0.293

The data was shown as n (percentage). VA/VV ECMO, veno–arterial/veno–venous extracorporeal membrane oxygenation.

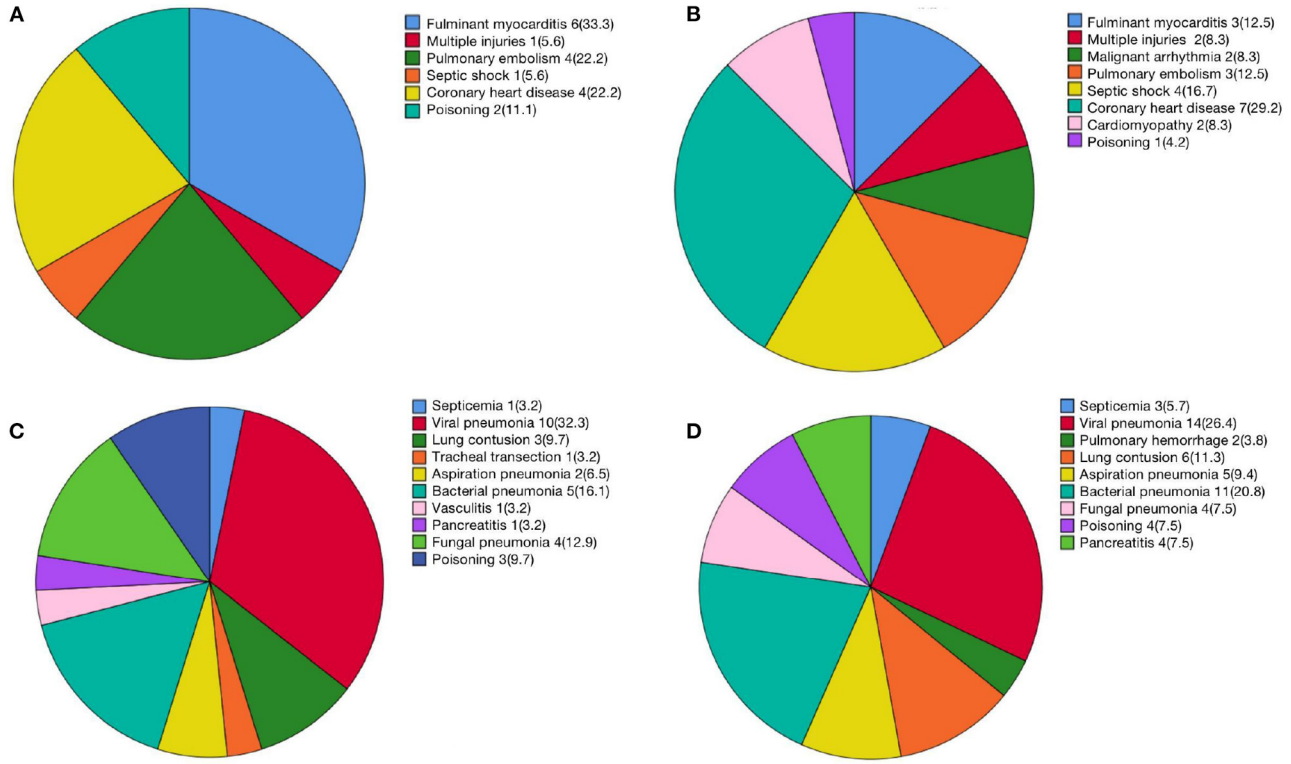

FIGURE 2 | Numbers and percentages of ECMO indications. **(A)** VA-ECMO survivors; **(B)** VA-ECMO non-survivors; **(C)** VV-ECMO survivors; **(D)** VV-ECMO non-survivors.

test or Fisher's exact test. $P < 0.05$ indicates that the difference is statistically significant. Survivor /non-survivor was selected for the dependent variable for the Cox regression analysis. Based on comparison of baseline information and relevant indicators, the independent variable for VA-ECMO patients was selected as age, SOFA score, post-transfer MAP and baseline lactate level, while for VV-ECMO patients as age, SOFA score, baseline lactate level, post-transfer heart rate, post-transfer respiratory rate and post-transfer MAP. The ROC curve was used to analyze the potential predictor for ICU mortality of ECMO patients and to find the cut-off value. The Cox regression survival analysis was performed to searching the risk factors of poor prognosis.

RESULTS

Characteristics of Transferred ECMO Patients

The characteristics of 126 enrolled patients are shown in **Tables 1**, **2**. The median distance of transportation was 141 (76–228) km, and the median transport time consuming was 3 (1.3–4) h (**Table 1**). As shown in **Table 1**, the transferred patients with 46.8% being male and the mean age was 45 ± 14 years old were divided into survival and non-survival group. Of the two groups, there was no significant difference in patients' gender, BMI, comorbidities, cannulation time consuming, distance of transportation, transport time consuming, ventilation time, remote shunt, the application of auxiliary equipment (intra-aortic balloon pump/IABP and continuous renal replacement therapy/CRRT), and the percentage of VA/VV ECMO ($p > 0.05$, **Table 1**). Compared with survivors, the non-survivors were older and showed higher SOFA score, longer time with ECMO assisted, longer time in ICU and in hospital (age: 49 ± 13 years vs.39 ± 13 years; median SOFA score: 11(10–12) vs. 8(6.5–11); median ECMO assisted time: 256(129–372.5) h vs. 176 (121– 204.5) h; time in ICU:13.3 ± 5.9 days vs. 21.4 ± 6.2days; time in hospital: 14.8 (10.1–17.5) days vs. 22 (17.8–32.3) days; all $P < 0.001$, respectively, **Table 1**). However, after divided into VA-ECMO and VV-ECMO groups, the older age showed no significant difference between survivors and non-survivors groups of VA-ECMO patients ($p = 0.132$) but remain significantly difference in VV-ECMO group (39 ± 12 years vs. 51 ± 13 years, $P < 0.001$, **Table 2**). Furthermore, the differences of SOFA score were still exist in survivors and non-survivors groups of VA and VV ECMO patients (VA-ECMO group: 10 (8–11) vs. 12 (10.25–12.75), $p = 0.003$; VV-ECMO group: 8 (6–11) vs. 11 (9.5-12), $P < 0.001$; respectively, **Table 3**).

Figure 2 described numbers and percentages of ECMO indications of different groups in detail. As shown in **Figure 2**; **Table 1**, the most common indication for VV-ECMO was pneumonia ($n = 55$, 43.7%), including viral pneumonia, bacterial pneumonia, fungal pneumonia, and aspiration pneumonia. Coronary heart disease ($n = 11$, 8.7%) and fulminant myocarditis

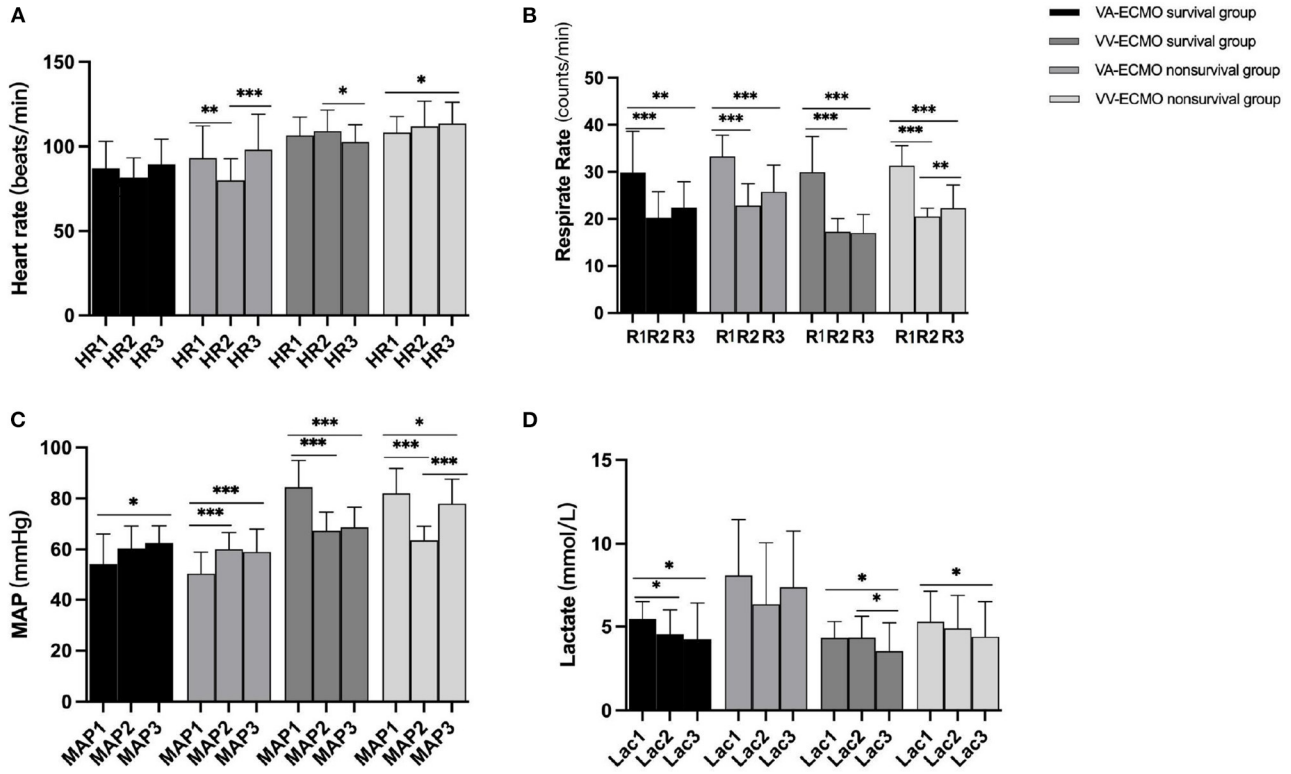

FIGURE 3 | (A–D) Intra-group comparison of three time point (1= before ECMO boarding; 2= after ECMO boarding and patient's condition is relatively stable; 3= transported to the hospital). * indicate $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$, respectively.

($n = 9$, 7.1%) were the important compositions of indications for VA-ECMO (**Figure 1**; **Table 2**).

Moreover, the levels of activated clotting time (ACT) and activated partial thromboplastin time (APTT) in the time of pre-transfer and post-tranfer, the percentage of sedation/analgesia and vasoactive agents had no significant difference between survivors and non-survivors groups of VA-ECMO and VV-ECMO patients (all $p > 0.05$, **Table 2**).

Description and Comparison of Complications During ECMO Transportation

Except for bleeding on cannula site, a total of 51 patients (40.5%) occurred complications during transportation, of which the percentage of patients' complications was 74.5% (**Table 3**). In detail, the VA-ECMO survivors were suffered 13 cases of bleeding on cannula site, 4 cases of respiratory and/or gastrointestinal tract hemorrhage, 1 case of lower limb ischemia, 1 case of scald, 1 case of clotting of ECMO system and 1 case of oxygen deficit during the transport. At the same time, the VA-ECMO non-survivors were appeared 13 cases of bleeding on cannula site, 6 cases of respiratory and/or gastrointestinal tract hemorrhage, 2 cases of intracranial hemorrhage, 2 cases of lower limb ischemia, 2 cases of epilepsy, 1 case of cardiac arrest, 1 case of clotting of ECMO system and 1 case of pump failure. Moreover, the transferred VV-ECMO survivors were suffered 8 cases of bleeding on cannula site, 5 cases of respiratory and/or gastrointestinal tract hemorrhage, 1 cases of intracranial hemorrhage, 2 cases of clotting of ECMO system, 1 case of ECMO system air embolism, and 1 case of oxygen deficit, while the VV-ECMO non-survivors were showed 24 cases of bleeding on cannula site, 8 cases of respiratory and/or gastrointestinal tract hemorrhage, 1 cases of intracranial hemorrhage, 3 cases of epilepsy, 1 case of emergency orotracheal intubation, 3 cases of clotting of ECMO system, 1 case of ECMO system air embolism, and 1 case of oxygen deficit (**Table 3**).

Among the patients who were occurred complications, the cases of hemorrhage was calculated to be the most common one (**Table 3**). As shown in **Table 3**, there was no significantly difference between the survivors and non-survivors of transferred VA and VV ECMO groups (all $p > 0.05$).

Comparison of the Monitoring Indicators Between the Survivors and Non-survivors of VA-/VV-ECMO in Different Time Points

The monitoring indicators including HR, R, MAP, the levels of lactate, PaO_2, and $PaCO_2$ were recorded and analyzed. All of the monitoring indicators were obtained in three time points (before ECMO boarding, after ECMO boarding and patient's condition is relatively stable,

TABLE 4 | Comparison of the indexes of the survivors and non-survivors of VA-/VV-ECMO.

	VA–ECMO survivors ($n = 18$)	VA–ECMO Non–survivors ($n = 24$)	*P*– value	VV–ECMO survivors ($n = 31$)	VV–ECMO Non–survivors ($n = 53$)	*P*– value
Heart rate (beats/min)						
Time point 1	87.00 ± 16.05	93.21 ± 19.02	0.259	106.55 ± 10.91	108.19 ± 9.65	0.491
Time point 2	81.50 ± 11.77	79.96 ± 12.90	0.689	109.06 ± 12.47	111.85 ± 14.94	0.362
Time point 3	89.44 ± 14.92	98.13 ± 20.89	0.124	102.65 ± 10.34	113.51 ± 12.70	**0.000**
Respiratory rate (counts/min)						
Time point 1	29.50 ± 8.75	33.33 ± 4.48	0.102	29.94 ± 7.58	31.30 ± 4.27	0.362
Time point 2	20.22 ± 5.59	22.83 ± 4.66	0.118	17.29 ± 2.76	20.51 ± 1.74	**0.000**
Time point 3	22.44 ± 5.51	25.75 ± 5.67	0.065	17.00 ± 3.94	22.26 ± 4.98	**0.000**
Mean arterial pressure (MAP) (mmHg)						
Time point 1	82 (78–90)	78 (72.5–88.25)	0.239	85 (78–90)	54 (46.5–69.5)	**0.018**
Time point 2	65.5 (63–75)	64 (60–66)	0.884	64 (61–67)	60 (56–64)	0.294
Time point 3	66.5 (62.25–75)	67.5 (64–74.25)	0.155	78 (72–86)	62 (56.2–70.5)	**0.000**
Lactate level (mmol/L)						
Time point 1	5.45 ± 1.05	8.11 ± 3.33	**0.000**	4.33 ± 0.98	5.29 ± 1.83	**0.002**
Time point 2	4.57 ± 1.43	6.34 ± 3.72	**0.041**	4.43 ± 1.28	4.89 ± 1.98	0.123
Time point 3	4.26 ± 2.16	7.36 ± 3.40	**0.000**	3.55 ± 1.68	4.40 ± 2.11	**0.046**
Arterial partial pressure of oxygen (PaO_2) (mmHg)						
Time point 1	60.22 ± 15.07	54.63 ± 11.84	0.202	49.25 ± 10.87	51.44 ± 5.44	0.300
Time point 2	144.33 ± 70.24	174.83 ± 96.30	0.242	79.44 ± 15.51	81.03 ± 13.67	0.637
Time point 3	157.78 ± 60.47	173.46 ± 64.95	0.426	83.26 ± 8.77	86.19 ± 11.79	0.198
Arterial partial pressure of carbon dioxide ($PaCO_2$) (mmHg)						
Time point 1	39.78 ± 10.07	34.25 ± 12.09	0.114	61.88 ± 18.65	57.55 ± 15.02	0.276
Time point 2	30.50 ± 7.91	33.21 ± 6.33	0.241	39.28 ± 9.74	35.88 ± 9.81	0.128
Time point 3	29.17 ± 3.63	30.25 ± 6.10	0.478	34.57 ± 11.01	30.30 ± 8.92	0.072

The data was shown as the mean ± SD or median (interquartile 25–75). Bold values indicate statistical significance. VA/VV ECMO, veno–arterial/veno–venous extracorporeal membrane oxygenation. Time point 1, before ECMO boarding; Time point 2, after ECMO boarding and patient's condition is relatively stable; Time point 3, transported to the hospital.

transported to the hospital). After ECMO performed, the respiratory rate and the levels of lactate of the transferred ECMO patients were reduced and improved significantly (**Figure 3**). Interestingly, when compared the MAP of three different time points, the MAP of VA-ECMO patients was elevated while that of VV-ECMO patients was decreased (**Figure 3**).

Moreover, there was no significant difference in HR, R, MAP, PaO_2, and $PaCO_2$ between VA-ECMO survivors and non-survivors excepted the levels of lactate in three time points (before ECMO boarding: 5.45 ± 1.05 mmol/L vs. 8.11 ± 3.33 mmol/L, $P < 0.001$; after ECMO boarding and patient's condition is relatively stable: 4.57 ± 1.43 mmol/L 6.34 ± 3.72 mmol/L, $p = 0.041$; transported to the hospital: 4.26 ± 2.16 mmol/L vs. 7.36 ± 3.40 mmol/L, $P < 0.001$; respectively, **Table 4**). However, the survivors and non-survivors of the VV-ECMO manifested significantly differences in the baseline levels of lactate (4.33 ± 0.98 mmol/L vs. 5.29 ± 1.83mmol/L, $p = 0.002$, **Table 4**) and the VV-ECMO survivors seemed have lower HR and R but higher MAP after transportation (HR: 102.65 ± 10.34 beats/min vs. 113.51 ± 12.70 beats/min, $P < 0.001$; R: 17.00 ± 3.94 counts/min vs. 22.26 ± 4.98 counts/min, $P < 0.001$; MAP: 78 (72–86) mmHg vs. 62 (56.2–70.5) mmHg, $P < 0.001$; respectively, **Table 4**).

Comparison of the Outcomes Between the Survivors and Non-survivors of VA-/VV-ECMO

Age, SOFA score, MAP after transportation, and the baseline levels of lactate were finally choose as variables for the Cox regression survival analysis of VA-ECMO and VV-ECMO transferred patients. As shown in **Table 5**, the high SOFA scores and the baseline lactate levels were indicated the poor prognosis of transferred VA-ECMO patients (SOFA score: 1.562 (1.135–2.151), $p = 0.006$; Lactate level: 1.135 (1.015–1.268), $p = 0.026$; respectively). Concerning to the outcomes of VV-ECMO transferred patients, older age and lower MAP after transportation were associated the high ICU mortality excepted the high SOFA scores and the baseline lactate levels (age: 1.022 (1.001–1.044), $p = 0.045$; MAP after transportation: 0.939 (0.914–0.965), $P < 0.001$; SOFA score: 1.200 (1.054–1.366), $p = 0.006$; Lactate level: 1.285 (1.084–1.522), $p = 0.004$; respectively, **Table 5**).

The AUC of lower MAP after transportation for the mortality of transferred VV-ECMO patients were 0.889 (95%CI:0.822–0.956, $P < 0.001$, **Figure 4**) and the cut-off value of MAP after transportation was 69.5 mmHg with a high sensitivity and specificity (sensitivity: 96.8%, specificity 75.5%, **Figure 4**). Then, the Cox regression survival analysis curve of VV-ECMO patients'

TABLE 5 | Cox regression survival analysis of VA–ECMO and VV–ECMO patients.

	VA–ECMO patients	*P*–value	VV–ECMO patients	*P*–value
Age	–	0.764	1.022(1.001–1.044)	**0.045**
SOFA score	1.562 (1.135–2.151)	**0.006**	1.200 (1.054–1.366)	**0.006**
MAP after transportation	–	0.488	0.939 (0.914–0.965)	**<0.001**
Lactate level	1.135 (1.015–1.268)	**0.026**	1.285 (1.084–1.522)	**0.004**

The data was shown as the Exp (B) and 95%CI. Bold values indicate statistical significance. VA/VV ECMO, veno–arterial/veno–venous extracorporeal membrane oxygenation; SOFA, sepsis–related organ failure assessment; MAP, mean arterial pressure.

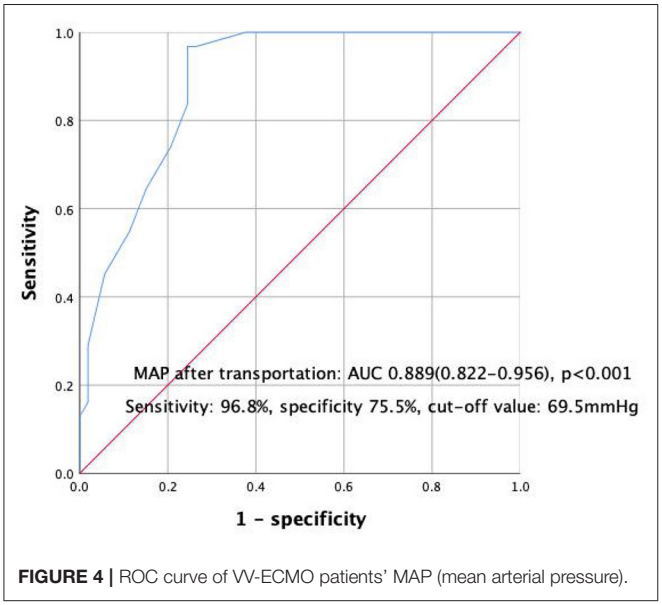

FIGURE 4 | ROC curve of VV-ECMO patients' MAP (mean arterial pressure).

MAP showed that the survival rate could improved when the MAP after transportation not < 70 mmHg (**Figure 5**).

DISCUSSION

The present study retrospectively analyzed 84 VV-ECMO and 42 VA-ECMO critically ill adults patients primary transferred by our mobile ECMO team and all of the cannulation is performed through percutaneously by ECMO physician. The ECMO transport is feasible as no death occurred in our study. The results of our study showed that the higher baseline lactate and SOFA score indicated poor prognosis of all ECMO transport patients, and lower MAP after transportation (<70 mmHg) had potential predictive value for short-term outcome of VV-ECMO patients.

In recent years, ECMO has played an increasingly important role in saving critically ill patients. However, the regional hospitals and the relatively small-volume centers are often inadequately equipped and inexperienced, which increases patient mortality. After the ELSO has collected a large number of ECMO patients and ECMO transport data, it is recommended that critical patients be transported to a large ECMO center for further treatment after evaluation, which may improve the survival rate of critically ill patients (1). To date, there have been many published studies on ECMO transport, most of which only included patients who were transported by VV-ECMO, and included some neonates and infants. In addition, there are no recognized guidelines for ECMO transfer, such as the composition of the ECMO transfer team, the indicators that need to be paid attention to during the transportation, and the occurrence and treatment of complications during the transfer. Therefore, the characteristics of this study are that all the included patients are adults, and the possible risk factors that affect the prognosis of VA-ECMO and VV-ECMO transport patients are separately discussed.

Our mobile ECMO team consists of ECMO physician, cardiac surgeon, and intensive care nurse, and they are experienced in prehospital emergency medicine, ECMO physiology, ECMO technology, and intensive care. The ECMO physician will handled all transport-related coordination and performed percutaneously vessels' cannulation. The mobile ECMO team was in charge of the ECMO circuit, the ventilator, medications, the application of heparin, and resolve complications of transferred critically ill patient. The feasibility of inter-hospital ECMO transfer is supported by most published data, and during transport, the mortality rate is reported low than 0.5% (11). In a recent literature review, authors analyzed 2,647 transferred patients reported in the years 2013 to 2019, and found that there were 4 deaths (mortality rate: 0.15%) were directly associated to medical transfers (6–9). Our ECMO team was experienced and no death occurred during the transportation for ECMO patients in our center till now.

However, life-threatening complications might occur during ECMO transport. The complications or adverse events during transport often be categorized into five major groups, including patient, equipment, vehicle, environment and personnel. In the Karolinska center papers published by Broman et al., the complications' percentage distribution of 322, 514, and 908 transfers were described in detail, and then reported that complications were predominantly patient-related (70, 65, and 62%, respectively) (8, 12, 13). In our center, the percentage of patients complications was 74.5% (**Table 3**), and hemorrhage was occupied the most common complication. The high incidence of hemorrhage is due to the application of anticoagulant drugs, blood vessel damage caused by intubation, and patient movement after intubation.

In 2019, Dalia et al. analyzed the data of 51 transferred and 215 in-house ECMO supported patients, and the survival rate of the two groups showed no significant difference (5). Lactate and SOFA scores are currently recognized predictors of the poor prognosis of ECMO supported patients. Recently, a observation in the Danish population revealed that the lower levels of lactate was associated to higher survival rate with a

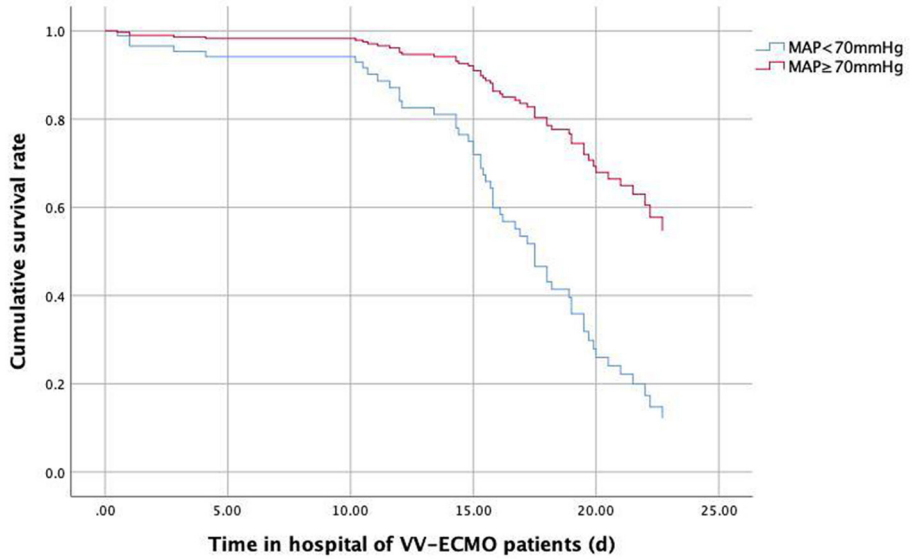

FIGURE 5 | Cox regression survival analysis curve of VV-ECMO patients' MAP.

good neurological outcome (14). A recent study included 106 patients revealed that the progressive hyperlactatemia after VA-ECMO initiation for adult patients with cardiogenic shock is a sensitive and specific predictor of hospital mortality (15). Another study with 72 patients with cardiac arrest demonstrated that the metabolic state, expressed as level of lactate just before VA-ECMO initiation seems more predictive of outcome than cardiopulmonary resuscitation duration or absence of return of spontaneous circulation (16). Results from a real-world clinical experience with the percutaneous extracorporeal life support system suggested that only serum lactate concentration at admission could be proven as independent predictor of patients' outcome, and patients with lactate concentrations above 10 mmol/L exhibited > 95% mortality (17). Wu et al. found that SOFA score calculated before ECMO showed the prognostic value in a cohort of 45 patients treated with ECMO for cardiac or respiratory failure (18). Lindskov et al. showed that the SOFA score calculated at day 1 after ECMO initiation was a predictive factor of low survival rate (19). Roch et al. demonstrated that SOFA was associated with mortality prior to ECMO in ARDS patients treated with VV-ECMO who have all been cannulated in distant hospitals (20). Our present study also believed that the baseline lactate and SOFA scores before ECMO preformed were related to the prognosis of transferred ECMO patients.

However, few published literature reported whether changes in monitoring indicators (MAP, HR, et al.) during patient transfer have an impact on the ECMO supported transport patients' prognosis. Sun et al. reported that average MAP <65 mmHg in the first 6 h of ECPR indicates a poor neurological prognosis for ECPR patients (21). Our study retrospectively enrolled 126 adult VA and VV ECMO patients transferred from regional hospital to the First Affiliated Hospital of Zhengzhou University by our ECMO team during June 2012 to Sept 2020, and found that lower MAP after transportation (<70 mmHg) had potential predictive value for short-term outcome of VV-ECMO patients, while the SOFA score and the lactate level could be used to evaluate the risk of ICU mortality of transportation ECMO patients.

This study is a single-center retrospective study with a small sample size, so the conclusion still needs a multi-center, large-sample, prospective randomized controlled study to further verify. Moreover, the present study only enrolled transferred ECMO patients, but it not included in-hospital ECMO patients. There might existed different mortality predictors between the transport and in-hospital ECMO patients. In addition, our study selected indicators at different time points to analyzing. Perhaps it is more meaningful to choose the average value of the special time periods for find the valuable outcome predictors of transferred VA and VV ECMO patients. Finally, the vehicle of transport need to be further improved, for example, long-distance transportation can use helicopters.

CONCLUSION

The transport of ECMO supported patients by our experienced mobile ECMO team is feasible although life-threatening complications might occurred during transportation. The baseline lactate and SOFA score are predictors of transportation ECMO patients' ICU mortality. Besides, lower MAP after transportation (<70 mmHg) had potential predictive value for poor prognosis of transferred VV-ECMO patients but not VA-ECMO ones.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (No. 2020-KY-429). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Y-CZ and XZ designed the study and wrote the first draft of the manuscript. JL, G-WF, and M-JH verified data extraction, data analysis, and reviewed the manuscript. HZ, X-XL, and Z-QW supervised the data acquisition, data analysis, and interpretation. All authors read and approved the final manuscript.

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A Standardized Multimodal Neurological Monitoring Protocol-Guided Cerebral Protection Therapy for Venoarterial Extracorporeal Membrane Oxygenation Supported Patients

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Background: The main objective of this study was to investigate the role of a multimodal neurological monitoring (MNM)-guided protocol in the precision identification of neural impairment and long-term neurological outcomes in venoarterial extracorporeal membrane oxygenation (VA-ECMO) supported patients.

Methods: We performed a cohort study that examined adult patients who underwent VA-ECMO support in our center between February 2010 and April 2021. These patients were retrospectively assigned to the "with MNM group" and the "without MNM group" based on the presence or absence of MNM-guided precision management. The differences in ECMO-related characteristics, evaluation indicators (precision, sensitivity, and specificity) of the MNM-guided protocol, and the long-term outcomes of the surviving patients were measured and compared between the two groups.

Results: A total of 63 patients with VA-ECMO support were retrospectively assigned to the without MNM group ($n = 35$) and the with MNM group ($n = 28$). The incidence of neural impairment in the without MNM group was significantly higher than that in the with MNM group (82.1 vs. 54.3%, $P = 0.020$). The MNM group exhibited older median ages [52.5 (39.5, 65.3) vs. 31 (26.5, 48.0), $P = 0.008$], a higher success rate of ECMO weaning (92.8 vs. 71.4%, $P = 0.047$), and a lower median duration of building ECMO [40.0 (35.0, 52.0) vs. 58.0 (48.0, 76.0), $P = 0.025$] and median ECMO duration days [5.0 (4.0, 6.2) vs. 7.0 (5.0, 10.5), $P = 0.018$] than the group without MNM. The MNM-guided protocol exhibited a higher precision rate (82.1 vs. 60.0%), sensitivity (95.7 vs. 78.9%), and specificity (83.3 vs. 37.5%) in identifying neural impairment in VA-ECMO support patients. There were significant differences in the long-term outcomes of survivors at 1, 3 and 6 months after discharge between the two groups ($P < 0.05$). However, the results showed no significant differences in ICU length of stay (LOS), hospital LOS, survival to discharge, or 28-day mortality between the two groups ($P > 0.05$).

Conclusion: The MNM-guided protocol is conducive to guiding intensivists in the improvement of cerebral protection therapy for ECMO-supported patients to detect and treat potential neurologic impairment promptly, and then improving long-term neurological outcomes after discharge.

Keywords: VA-ECMO, neurologic impairment, multimodal neurological monitoring, protocol, long-term outcomes

INTRODUCTION

Some critical patients receive prolonged extracorporeal membrane oxygenation (ECMO) support following the gradual increase in the application of ECMO technology, resulting in the increasing incidence of various complications, which will have a significant impact on the final outcome (1, 2). Central nervous system (CNS) injury is, undoubtedly, a major complication of ECMO, and the causes of such injury vary due to the complexity of ECMO and its invasive nature (3, 4).

According to the Extracorporeal Life Support Organization (ELSO), CNS complications can have a significant impact on long-term survival in ECMO-supported patients (3). In addition, ECMO support during cardiopulmonary resuscitation, named extracorporeal cardiopulmonary resuscitation (ECPR) (5), uses cardiopulmonary bypass to maintain circulatory exhaustion in cardiac arrest (CA) patients in whom traditional CPR is difficult to reverse and has also been increasingly popularized and recognized (6, 7). However, ECPR patients may develop secondary cerebral ischemia and hypoxia during CPR and may receive prolonged cardiopulmonary bypass, therefore, varying degrees of CNS impairment are more likely to occur, such as mild cognitive impairment, cerebral apoplexy, cerebral hemorrhage, ischemic hypoxic encephalopathy, and even brain death (8, 9).

Therefore, the timely identification of a CNS injury by neural monitoring technology during the ECMO support period will contribute to the early initiation of brain protection and intervention therapy, which is conducive to the recovery or alleviation of brain injury. In this case, in the intensive care unit (ICU), multiple neural monitoring modes, such as electrophysiological methods, intracranial pressure measurements, and cerebral oxygenation, are thought to contribute to the prediction and pathophysiological interpretation of brain injury after CA (10).

The operational management of ECMO is complex and challenging. Although most extracorporeal circulation support centers or ICUs have procedures in place to guide their management, CNS injuries that develop in the course of ECMO support are often overlooked. Therefore, the present study aims to guide intensivists with the improvement of cerebral protection therapy for ECMO-supported patients using the multimodal neurological monitoring (MNM) protocol to detect and treat potential neurologic impairment promptly and improve the outcomes of patients.

METHODS

Study Setting and Population

This study was a cohort study. All data were collected from in-hospital and out-of-hospital adult (>18 years old) patients who underwent venoarterial extracorporeal membrane oxygenation (VA-ECMO) support in Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, between February 2010 and April 2021. This research was reviewed by the Ethics Committee of Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, and the information of relevant patients was anonymously processed to protect privacy.

Patients admitted from August 2018 underwent daily neurological examinations (physiological and pathological reflexes), and Glasgow Coma Scale (GCS) scores were recorded by two researchers with neurological backgrounds. We established a bedside brain monitoring protocol based on quantitative electroencephalogram (qEEG), transcranial color Doppler ultrasonography (TCCD), and regional cerebral oxygenation (rScO2), named the multimodal neurological monitoring (MNM) protocol (**Figure 1**), to guide intensivists in the improvement of management practices for ECMO-supported patients and to detect and treat possible neurologic impairment as early as possible. These patients were enrolled in the "With MNM" group.

Patients admitted from February 2010 to August 2018 who underwent traditional and routine ECMO management according to the changes in cardiac function and perfusion indicators (urine volume, lactic acid, mean arterial pressure, etc.) were enrolled in the "Without MNM" group.

Our previous study identified neurological impairment (11): temporal or persistent mental and physical features such as coma, delirium, depression, epilepsy, hypoxic-ischemic encephalopathy, ischemic stroke, cerebral hemorrhage, and death; and a GCS score <15 (patients with endotracheal intubation <11) or cerebral performance category score (CPC) ≥2 after eliminating the disturbance of sedation and analgesia.

Exclusion criteria:

1. Primary CNS disease before admission or previous neuropsychic symptoms.
2. Incomplete and missing cases.
3. Duration of ECMO support <24 h.

General Management Protocol

The MNM-guided protocol included the following (**Figure 2**): (1) after ECMO, continuous qEEG monitoring and $rScO_2$ monitoring were performed. If there were no obvious physical

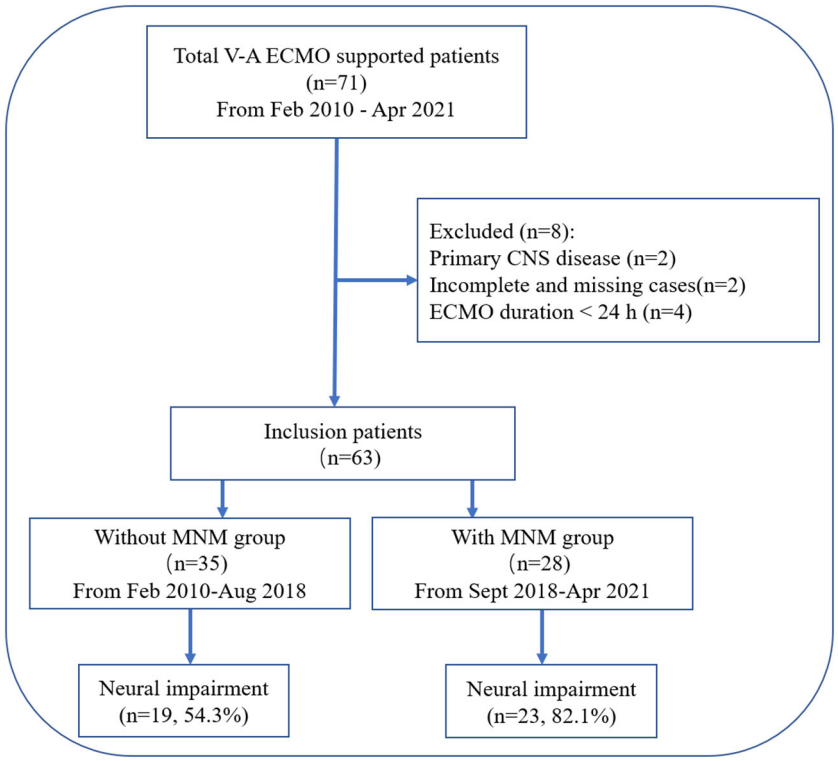

FIGURE 1 | Flow chart of the patient cohort. VA-ECMO, venoarterial extracorporeal membrane oxygenation; CNS, central nervous system; MNM, multimodal neurological monitoring.

features of neurologic damage within 72 h, the monitoring duration was changed to 30 minutes per day. (2) Bedside TCCD detection was performed twice a day. The blood flow rate and pulse index (PI) of the bilateral middle cerebral arteries (MCAs) were observed, and the bilateral optic nerve sheath diameter (ONSD) was measured to evaluate intracranial blood flow and pressure. (3) Daily neurological examination was performed. (4) Patients underwent ECPR and GCS <8, or after identifying the patients with neurologic impairment through the above procedures, clinicians adjusted the ECMO flow, MAP and circulation volume or administered analgesia, sedation and antiepileptic drugs to maintain the balance among cerebral perfusion, brain oxygen delivery and consumption. For patients with intracranial hematoma, cerebral edema, hypoxic-ischemic encephalopathy and ischemic stroke, clinicians transferred the patients to the imaging center to undergo CT scans to further confirm the diagnosis, and while ensuring patient safety, the next intervention was decided.

qEEG

qEEG was recorded using the international 10–20 system of electrode placement (NicoletOne Monitor EEG Software, NICVUE 2.9.1, Nicolet, United States) as soon as possible after ECMO support (12, 13). The qEEG was examined by using six electrodes in the left frontal (F3), right frontal (F4), left parietal (P3), and right parietal (P4) positions with ground in the frontal midline and reference in the central midline. The parameters of qEEG included 4 patterns. (1) Amplitude-integrated electroencephalogram (aEEG): aEEG patterns were classified into the following categories to assess cerebral cortex function: continuous normal voltage, discontinuous normal voltage, low voltage, flat, burst suppression, and status epilepticus. (2) Relative Band Power (RBP): RBP could reflect the degree of coma and sleep cycle by directly displaying the percentage of EEG frequencies (δ, θ, α and β) with four kinds of colors (red, yellow, green and blue). (3) Alpha variability: reflects the cerebral blood perfusion and cerebral oxygen metabolism of patients with the patterns of a bar chart. (4) Spectral entropy indicates the depth of sedation or coma. All clinical researchers received special instruction in use of the EEG monitoring operating system. EEG recordings and quantitative EEG trends were reviewed and interpreted by researchers with a professional background in neurology.

TCCD

According to a previous study (14, 15), bedside TCCD (Philips Ultrasound CX50, Bothell, United States) was performed to insonate the bilateral MCAs and brain parenchyma, and then cerebral flow velocities (CBFVs) and PI values were calculated to assess intracerebral pathology. The quality of the data obtained by TCCD is highly influenced by operator-dependent factors such as skill and experience. The ultrasound operators in the

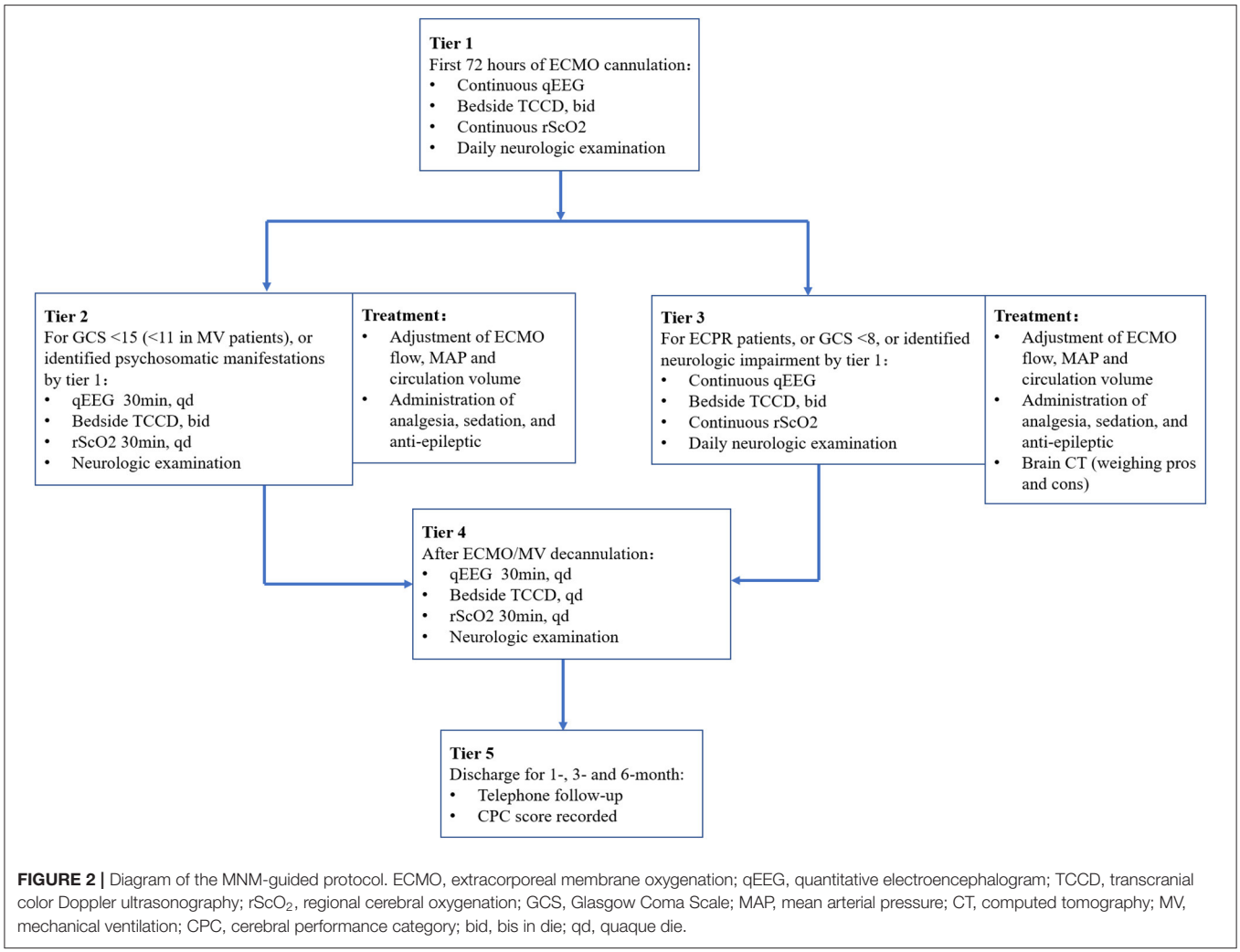

FIGURE 2 | Diagram of the MNM-guided protocol. ECMO, extracorporeal membrane oxygenation; qEEG, quantitative electroencephalogram; TCCD, transcranial color Doppler ultrasonography; $rScO_2$, regional cerebral oxygenation; GCS, Glasgow Coma Scale; MAP, mean arterial pressure; CT, computed tomography; MV, mechanical ventilation; CPC, cerebral performance category; bid, bis in die; qd, quaque die.

present study completed the training courses of the China Critical Ultrasound Research Group (CCUSG) and obtained qualification certificates.

In addition, the bilateral ONSD was measured by TCCD to reflect intracranial pressure (ICP) (16). The ONSD was measured 3 mm behind the retina and exhibited strong prediction of intracranial hypertension (ICP $\geq$ 20 mmHg) by a cutoff value of above 5 mm (17).

$rScO_2$

$rScO_2$ monitoring by near-infrared spectroscopy (NIRS) offers a validated noninvasive measure of global oxygen delivery and consumption (18, 19). Continuous $rScO_2$ monitoring was performed by two NIRS sensors (ECO-N17-C22 L, EnginMed, Suzhou, China) placed on the patients' forehead as soon as possible after ECMO support, and rSO2 values between 55 and 75% were taken as normal rSO2 according to the product manuals. We prefer to record trends of $rScO_2$ rather than the absolute values.

Data Acquisition Outcomes

Patients' baseline characteristics and ECMO-related characteristics were acquired. The primary study outcome was the incidence of neural impairment during ECMO or recovery from ECMO. Secondary outcomes included ICU length of stay (LOS), hospital LOS, 28-day mortality, and neurologic functioning assessed by a CPC score ($\geq$2) at the 1-, 3- and 6-month follow-ups after discharge. The evaluation indicators (precision, sensitivity, and specificity) of the MNM-guided protocol were calculated.

Statistical Analysis

All data were statistically processed by SPSS 25.0 statistical software. Categorical variables and continuous variables are represented as counts (percentages, %) and medians (interquartile range, IQR). The chi-square test or Fisher's exact test was used for categorical variables, and Student's *t* test or the Mann–Whitney *U* test was used for continuous variables. A $p < 0.05$ was considered statistically significant.

TABLE 1 | Comparison of baseline characteristics of patients.

	All patients	MNM protocol		
	***n* = 63**	**Without (*n* = 35)**	**With (*n* = 28)**	***P***
Age (years, median)	40.0 (29.5, 60.5)	31 (26.5, 48.0)	52.5 (39.5, 65.3)	0.008
Sex, *n* (%)				
Male	39 (61.9)	18 (51.4)	21 (75.0)	0.056
Female	24 (38.1)	17 (48.6)	7 (25.0)	
Underlying diseases, *n* (%)				
Hypertension	17 (27.0)	6 (17.1)	11 (39.3)	0.049
Diabetes	8 (12.7)	2 (5.7)	6 (21.4)	0.063
CHD	6 (9.5)	2 (5.7)	4 (14.3)	0.249
Initiate etiology, *n* (%)				
AMI	25 (39.7)	7 (20.0)	18 (64.3)	< 0.001
AFM	29 (46.0)	20(57.1)	9 (32.1)	0.048
MA	16 (25.4)	8(22.9)	8 (28.6)	0.605
Others	8 (12.7)	6 (17.1)	2 (7.1)	0.236
Pre-ECMO characteristics (median)				
MAP (mmHg)	81.3 (69.5, 94.5)	77.8 (69.3, 87.8)	81.3 (78.3, 109.7)	0.142
CVP (cmH_2O)	11.0 (8.3, 16.0)	11.0 (8.0, 15.0)	11.0 (9.5, 18.0)	0.197
PH	7.32 (7.22, 7.41)	7.35 (7.28, 7.41)	7.28 (7.17, 7.41)	0.057
PaO_2 (mmHg)	103.6 (71.6, 207.6)	112.0 (73.4, 192.3)	98.3 (71.1, 209.1)	0.349
$PaCO_2$ (mmHg)	37.7 (28.3, 46.9)	37.9 (27.8, 45.0)	37.1 (30.8, 49.3)	0.240
Other intervenes, *n* (%)				
Pre-ECMO PCI	8 (12.7)	7 (20.0)	1 (3.6)	0.052
Post-ECMO PCI	14 (22.2)	1 (2.9)	13 (46.4)	< 0.001
IABP	30 (47.6)	15 (42.9)	15 (53.6)	0.397
Pre-ECMO MV	53 (84.1)	27 (77.1)	26 (92.9)	0.090
CRRT	36 (57.1)	17 (48.6)	19 (67.9)	0.124
Pre-ECMO score (median)				
SOFA score	11 (8.0, 14.0)	11 (6.0, 14.5)	12 (9.8,13.0)	0.543
APACHE-II score	20 (14.0, 24.0)	18 (11.5, 22.5)	21 (16.0, 26.0)	0.110
Outcomes (%, median)				
Neural impairment (%)	42 (66.7)	19 (54.3)	23 (82.1)	0.020
ICU LOS (days)	13.0 (9.0, 21.0)	14.0 (10.0, 19.0)	12.5 (8.8, 22.0)	0.698
Hospital LOS (days)	19.0 (12.5, 26.5)	21.0 (15.0, 26.5)	15.5 (10.8, 25.5)	0.788
Survival to discharge (%)	45 (71.4)	24 (68.6)	21 (75.0)	0.575
28-day mortality (%)	22 (34.9)	13 (37.1)	9 (32.1)	0.679

MNM, multimodal neurological monitoring; CHD, coronary heart disease; AMI, acute myocardial infarction; AFM, acute fulminant myocarditis; MA, malignant arrhythmia; ECMO, extracorporeal membrane oxygenation; MAP, mean arterial pressure; CVP, central venous pressure; PH, Potential of Hydrogen; PaO_2, Arterial oxygen partial pressure; $PaCO_2$, Arterial carbon dioxide partial pressure; PCI, percutaneous coronary intervention; IABP, intra-aortic balloon pump; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; SOFA, sequential organ failure assessment; APACHE-II, acute physiology and chronic health evaluation II; LOS, length of stay.

RESULTS

Comparison of Baseline Characteristics

After excluding 8 patients, a total of 63 patients with VA-ECMO support were retrospectively assigned to the without MNM group ($n = 35$) and the with MNM group ($n = 28$) based on the presence or absence of the "MNM-guided protocol" (**Figure 1**).

As shown in **Table 1**, the incidence of neural impairment in the without MNM group was significantly higher than that in the with MNM group (82.1 vs. 54.3%, $P = 0.020$). However, the results showed no significant differences in ICU LOS, hospital LOS, survival to discharge, or 28-day mortality between the two groups ($P > 0.05$). The results suggested that the MNM-guided protocol could significantly increase the detection rate of neural impairment but did not affect the short-term outcome of patients.

Meanwhile, the MNM group had an older median age [52.5 (39.5, 65.3) vs. 31 (26.5, 48.0), $P = 0.008$], a higher proportion of patients with acute myocardial infarction (64.3 vs. 20.0%, $P < 0.001$), and a higher proportion of patients who underwent percutaneous coronary intervention (PCI) after ECMO support (13 vs. 1%, $P < 0.001$) (**Table 1**). However, there was no significant difference in some baseline characteristics, laboratory indexes, or critical scores between the two groups.

TABLE 2 | Neural impairment in patients with VA-ECMO support.

	Without MNM ($n = 35$)		With MNM ($n = 28$)	
	Initial	**Definite**	**Initial**	**Definite**
Coma, *n* (%)	8 (22.9)	1 (2.9)	5 (17.9)	2 (7.1)
Delirium, *n* (%)	5 (14.3)	2 (5.7)	6 (21.4)	4 (14.3)
Seizure, *n* (%)	0 (0.0)	1 (2.9)	3 (10.7)	3 (10.7)
HIE, *n* (%)	1 (2.9)	2 (5.7)	3 (10.7)	3 (10.7)
Intracranial hemorrhage, *n* (%)	0 (0.0)	1 (2.9)	2 (7.1)	2 (7.1)
Ischemic stroke, *n* (%)	0 (0.0)	1 (2.9)	1 (3.6)	2 (7.1)
Total, *n* (%)	14 (40.0)	8 (22.7)	20 (71.4)	16 (57.1)

MNM, multimodal neurological monitoring; HIE, hypoxic ischemic encephalopathy.

TABLE 3 | Evaluation indicators of MNM-guided protocol.

	Without MNM ($n = 35$)	With MNM ($n = 28$)
TP (*n*)	15	22
FP (*n*)	10	5
TN (*n*)	6	1
FN (*n*)	4	1
Precision (%)	60.0	82.1
Sensitivity (%)	78.9	95.7
Specificity (%)	37.5	83.3

MNM, multimodal neurological monitoring; TP, true positive; FP, false positive; TN, true negative; FN, false negative; Precision = TP/(TP + FP); Sensitivity = TP/(TP + FN); Specificity = TN/(FP + TN).

The MNM-Guided Protocol Increases the Precision of Identifying Neural Impairment

Of these 63 patients, 42 patients (66.7%) suffered neural impairment, including temporal coma, delirium, seizure, hypoxic-ischemic encephalopathy, intracranial hemorrhage, ischemic stroke, and death (**Table 2**). As shown in **Table 2**, in the without MNM group, 13 patients were still in combination with coma or delirium 24–48 h after withdrawal from sedative drugs and were regarded as having neural impairment by initial evaluation. After that, 10 patients without positive physical features were regarded as having delayed awaking resulting from sedative drug accumulation and were excluded after further definite evaluation. Meanwhile, one patient with seizure, one with HIE, one with intracranial hemorrhage and one with ischemic stroke were not identified in the initial assessment. For the patients in the MNM group, 27 patients were regarded as having neural impairment in the initial assessment, exhibited by GCS < 15, discontinuous normal voltage and increased δ frequency in aEEG, $rScO_2 < 55$, MCA-PI increased (>1.05) or decreased (<0.6). Five patients had sedative drug accumulation after further assessment, and one case of ischemic stroke was not identified in the initial assessment. In addition, the MNM-guided protocol exhibited a higher precision rate (82.1 vs. 60.0%), sensitivity (95.7 vs. 78.9%), and specificity (83.3 vs. 37.5%) in identifying neural impairment in VA-ECMO support patients (**Table 3**).

These results suggested that the MNM-guided protocol can significantly increase the accuracy of identifying neural impairment in patients supported by VA-ECMO.

The MNM-Guided Protocol Improves the Precision Management of VA-ECMO-Supported Patients

In the present study, 32 patients (50.8%) underwent ECPR, and there was a significant difference between the "with MNM" and the "without MNM" groups (71.4 vs. 34.3%, $P = 0.003$) (**Table 4**). In addition, the median duration of building ECMO [40.0 (35.0, 52.0) vs. 58.0 (48.0, 76.0), $P = 0.025$] and median ECMO duration [5.0 (4.0, 6.2) vs. 7.0 (5.0, 10.5), $P = 0.018$] in the with MNM group were significantly lower than those in the without MNM group, and the success rate of ECMO weaning in the with MNM group was significantly higher than that in the without MNM group (92.8 vs. 71.4%, $P = 0.047$) (**Table 4**).

As shown in **Figure 3**, under the guidance of the MNM protocol, we can accurately adjust the ECMO flow rate, maintain appropriate afterload (MAP) and preload (CVP), and accelerate the removal of lactic acid to achieve the oxygen delivery and consumption balance of patients more quickly and to maintain tissue and microcirculation perfusion.

These results suggested that the skill level and operational proficiency of our ECMO team members have advanced considerably in recent years, and the MNM-guided protocol is conducive to the precision management of VA-ECMO-supported patients, helping the early withdrawal of ECMO.

Long-Term Outcomes of Survivors After Discharge

The long-term adverse neurological outcomes mentioned in this study were identified as neurological complications assessed by a CPC score at the 1-, 3- and 6-month follow-up after discharge, including HIE, stroke, hypomnesia, atypical neuropathy (others), and death (**Table 5**). As shown in **Table 6**, 45 patients survived 1 month after discharge, and 3 (14.3%) patients in the MNM protocol group suffered neurological complications, which was significantly lower than that in the without MNM group (11, 45.8%). The MNM group exhibited fewer neurological complications than the without MNM group in surviving patients between 3 months (25.0 vs. 61.9%, $P = 0.017$) and 6 months (15.0 vs. 52.4%, $P = 0.012$) after discharge. These results suggested that the MNM-guided protocol during ECMO support could significantly improve long-term neurological outcomes.

DISCUSSION

Following the gradual increase in the clinical application of ECMO and because of recent advances in managing critical illness, advanced age is not considered a contraindication to temporary mechanical circulatory support (20). In our study, the oldest age of patients receiving ECMO support was 78, and an increasing number of very elderly (>80) patients have exhibited good outcomes after short-term mechanical circulatory support (MCS) (21). Mortality and poor functional

TABLE 4 | Comparison of VA-ECMO related characteristics.

	All patients	MNM protocol		
	***N* = 63**	**Without (*n* = 35)**	**With (*n* = 28)**	***P***
ECPR, *n* (%)	32 (50.8)	12 (34.3)	20 (71.4)	0.003
Locations of ECMO, *n* (%)				
OR	8 (12.7)	1 (2.8)	7 (25.0)	0.009
ICU	51 (80.9)	30 (85.7)	21 (75.0)	0.282
ED	4 (6.3)	2 (5.7)	2 (7.1)	0.817
Duration of building ECMO (mins)	51.0 (40, 63.5)	58.0 (48.0, 76.0)	40.0 (35.0, 52.0)	0.025
VIS, median				
Pre-ECMO	20.0 (0, 102.0)	20.0 (0, 55.0)	23.0 (0, 111.3)	0.269
24h post-ECMO	10.0 (0, 18.9)	12.0 (1.5, 20.2)	8.9 (0, 16.5)	0.918
Continuous NP > 12h, *n* (%)	21 (33.3)	14 (40.0)	7 (25.0)	0.209
ECMO duration (days, median)	6.0 (5.0, 8.0)	7.0 (5.0, 10.5)	5.0 (4.0, 6.2)	0.018
MV parameter at 24 h post-ECMO (%, median)				
FiO_2 (%)	100 (70, 100)	100 (60, 100)	90 (80, 100)	0.749
PIP (cmH_2O)	20.0 (16.0, 22.0)	20.0 (16.0, 22.0)	21.0 (17.5, 24.3)	0.476
PEEP (cmH_2O)	8.0 (7.5, 10.0)	8.0 (6.0, 8.5)	10.0 (8.0, 10.0)	0.036
Complication, *n* (%)				
Cannulation site bleeding	45 (71.4)	25 (71.4)	20 (71.4)	1.000
Limb ischemia	7 (11.1)	5 (14.3)	2 (7.1)	0.370
ECMO weaning successful, *n* (%)	51 (80.9)	25 (71.4)	26 (92.8)	0.047

MNM, multimodal neurological monitoring; ECPR, extracorporeal cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; OR, operation room; ED, emergency department; VIS, vasoactive inotropic score [= dose of dopamine + dose of dobutamine + 100 × dose of epinephrine + 10 × dose of milrinone + 10,000 × dose of vasopressin + 100 × dose of norepinephrine (unit: μg/kg/min)]; NP, non-pulsate perfusion; MV, RR, respiratory rate; FiO_2, fraction of inspiration oxygen; PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure.

outcomes are often induced by neurological injury that results from underlying diseases and from complications associated with ECMO support itself (2, 22). Meanwhile, with the advancement of our management experience and technology, we have gradually expanded the application field of ECMO. For high-risk patients with acute coronary events, we prefer to perform ECMO-assisted percutaneous transluminal coronary intervention. The application of extracorporeal cardiopulmonary resuscitation (ECPR) in cardiac arrest patients is also increasing.

The management of VA-ECMO involves the optimization of ECMO flow, circulation capacity, and MAP. The traditional viewpoint is to maintain myocardium intrinsic contractility and left ventricular ejection with minimal ECMO flow and conservative circulation volume, combined with positive inotropic drugs, while maintaining systemic circulation and end-organ perfusion (23, 24). We have long believed that an ECLS facility should achieve at least 20 cases per year to ensure good and adequate patient outcomes and as an indicator for evaluating an experienced ECLS facility (25). In our opinion, it is more important for the good outcome of patients to strengthen precision management during ECMO support, including the adjustment of anticoagulants, prevention of catheter-related bloodstream infection and lower limb ischemic necrosis, especially the early identification and prevention of CNS complications. Zotzmann et al. (26). found that 10% of ECPR patients suffered intracranial hemorrhage (ICH) by early CT scan, highlighting the importance of standardized neural monitoring, especially in the early stages of ECMO support when neurological examination is limited due to deep sedation (27). However, brain CT scans have poor sensitivity for detecting mental diseases and acute ischemic brain injury, and the transfer of patients with ECMO support between departments inevitably involves high-risk or immediate-threat-of-life situations (28).

In our previous study, 65% of VA-ECMO-supported patients suffered neurological complications, and the identification of neurological complications mainly relied on subjective assessment methods such as GCS, CPC score, confusion assessment method for the ICU (CAM-ICU), and neuroimaging examination (11). To more accurately identify the neurological damage in ECMO-supported patients, we established the MNM-guided protocol, which is based on bedside noninvasive techniques such as qEEG, NIRS, and TCCD, combined with GCS and neurological examination, guiding clinicians to optimize the management of VA-ECMO patients. Our MNM-guided protocol is safe and has no adverse reactions. We hope to promote this multimodal, noninvasive monitoring process in more ECLS facilities, so that it can be accepted as a standard management protocol for ECMO-supported patients.

Several published reports have recommended enhanced bedside noninvasive neural monitoring techniques in patients with extracorporeal circulation support and cardiopulmonary resuscitation (13, 14, 29, 30). However, there are few reports that combine multiple technologies for cross-analysis and then form protocol-based guiding

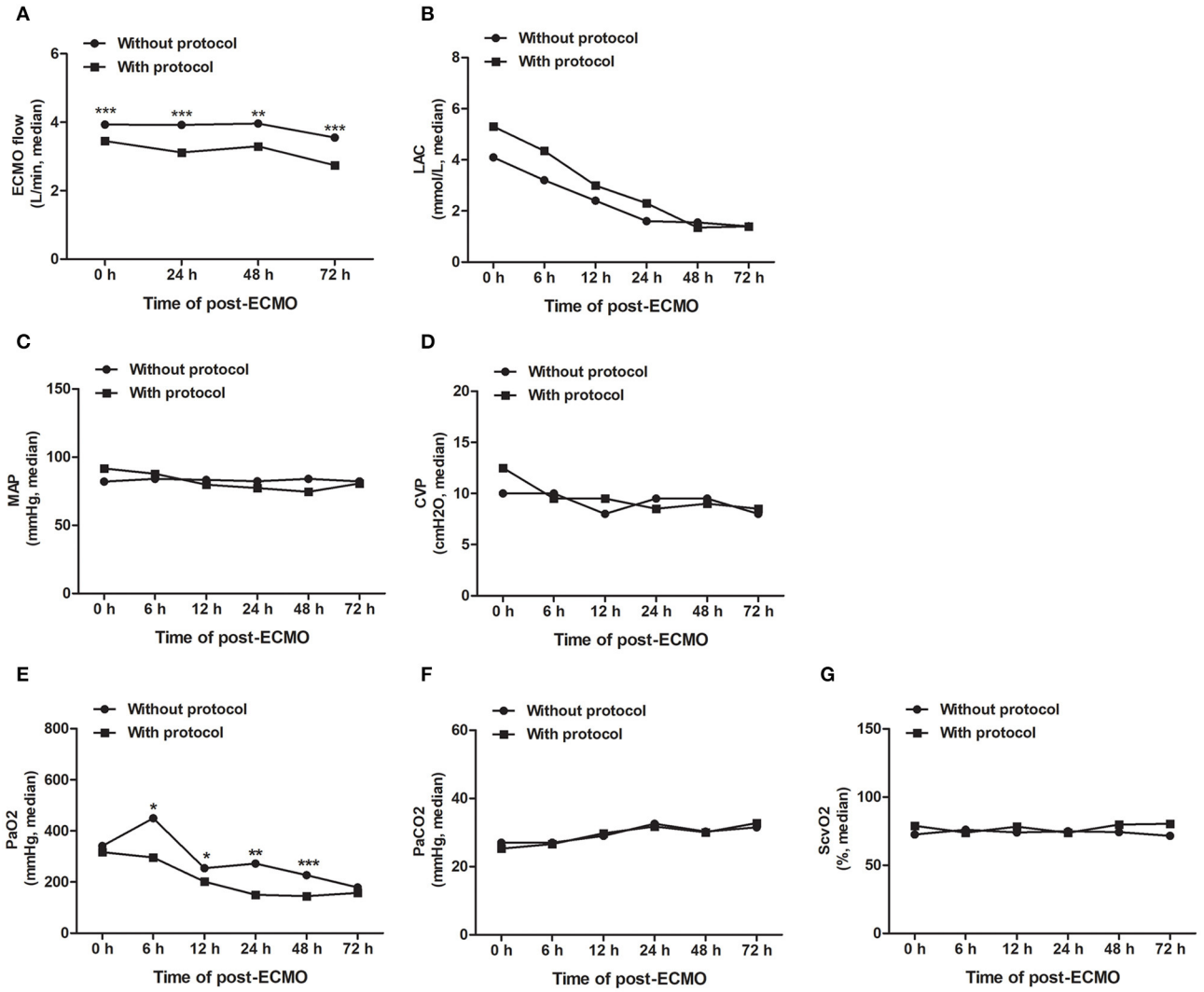

FIGURE 3 | The MNM-guided protocol improves the precision management of VA-ECMO-supported patients. Guided by the MNM protocol, we can accurately adjust the ECMO flow rate **(A)**, maintain appropriate afterload (MAP) and preload (CVP) **(B,C)**, and accelerate the removal of lactic acid **(D)** to achieve the oxygen delivery and consumption balance of patients **(E–G)**. ECMO, extracorporeal membrane oxygenation; MAP, mean arterial pressure; CVP, central venous pressure; $ScvO_2$, central venous oxygen saturation; LAC, lactic acid. All data are representative of the median, and the Mann–Whitney U test was used for the comparison. $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$.

strategies for ECMO management. In the present study, a simplified multiparameter quantitative EEG monitoring device was used, which is easy to operate and intuitive to understand and can be mastered by intensivists after 1–3 months of training.

NIRS measurements of $rScO_2$ have been applied to traumatic brain injury (TBI), cardiopulmonary resuscitation, stroke, cerebral hypoxia ischemia, acute coma, cardiac surgery, etc. (31–35). Compared with traditional cerebral oxygenation monitoring tools, it can quickly and effectively identify patients at risk of cerebral hypoxia under different pathophysiological conditions and can noninvasively, real-time and continuously monitor oxygen delivery and evaluate the severity of brain injury and predict outcomes.

However, crucially, the brain should have proper cerebral blood flow. We hope to conveniently monitor the resistance of cerebrovascular, cerebral blood flow velocity, and even whether there is cerebral vasospasm, cerebral edema, cerebral hemorrhage, brain midline shift, etc. We found that continuous non-pulsatile perfusion (NP) >12 h was an independent risk indicator for neurological complications in VA-ECMO-supported patients (11). TCCD is a noninvasive test that uses ultrasonography to estimate CBF. Understanding the changes in CBF is helpful to detect new vascular injury during ECMO support and to optimize cerebral perfusion. TCD and TCCD have been applied to stroke, TBI, hypoxic-ischemic encephalopathy, and neurological monitoring during ECMO support (36–39). Point-of-care ultrasound (PoCUS) visualization

TABLE 5 | Long-term neurological outcomes after discharge.

	1 month ($n = 45$)		3 months ($n = 41$)		6 months ($n = 41$)	
	MNM protocol		MNM protocol		MNM protocol	
	With (21)	Without (24)	With (20)	Without (21)	With (20)	Without (21)
CPC ≥ 2, *n* (%)	3 (14.3)	11 (45.8)	5 (25.0)	13 (61.9)	3 (15.0)	11 (52.4)
Neuropathy, *n* (%)						
HIE	2 (9.5)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stroke	1 (4.8)	3 (12.5)	1 (5.0)	2 (9.5)	1 (5.0)	2 (9.5)
Hypomnesia	0 (0.0)	5 (2.1)	2 (10.0)	5 (23.8)	1 (5.0)	5 (23.8)
Others	0 (0.0)	2 (8.3)	0 (0.0)	3 (14.3)	1 (5.0)	4 (19.0)
Death, *n* (%)	0 (0.0)	0 (0.0)	2 (10.0)	3 (14.3)	0 (0.0)	0 (0.0)

MNM, multimodal neurological monitoring; CPC, cerebral performance category; HIE, hypoxic ischemic encephalopathy; Others, atypical neuropathy.

TABLE 6 | Effect of MNM protocol on long-term neurological outcomes.

MNM protocol	Neural complications after discharge, *n* (%)		
	1 month ($n = 45$)	3 months ($n = 41$)	6 months ($n = 41$)
Without	11 (45.8)	13 (61.9)	11 (52.4)
With	3 (14.3)	5 (25.0)	3 (15.0)
P	0.023	0.017	0.012

MNM, multimodal neurological monitoring.

management of ECMO patients has played an important role in identifying indications, catheterization, flow adjustment, volume management, cardiac function evaluation, etc.

By integrating and cross-analyzing the data obtained from qEEG, $rScO_2$ and TCCD monitoring, we can promptly identify neurologic impairment in ECMO patients, and then guide clinicians to adjust the ECMO flow, circulation volume, vasoactive drug dose, target MAP, and mechanical ventilator parameters to maintain proper cerebral blood flow and cerebral perfusion, thereby improving cerebral protection therapy in a timely manner. This also helps clinicians determine whether it is necessary to take risks and transport patients to imaging centers for further radiological examination. Furthermore, published data have revealed persistent functional deficits associated with ECMO support, and neurologic complications following ECMO are associated with negative impacts on long-term quality of life (40, 41). Consistently, the present study also illustrated a positive association between the MNM-guided protocol and long-term neurological outcomes.

In recent years, clinical decisions driven by machine learning models combined with medical big data have attracted increasing attention. Layering patients offers the opportunity to achieve effective and precision medicine, a key task in personalized healthcare (42). In the field of critical care medicine, the application of big data can provide predictive and prognostic models (43, 44) and the discovery of subgroups or clusters of patients who share similar clinical and/or molecular characteristics (45, 46), physiological waveform analysis of bedside monitors and wearable devices (47, 48). Amorim et al. (49) compared the qEEG reactive machine learning method with expert assessment and indicated that machine learning models utilizing quantitative EEG reactivity data can predict long-term outcomes after cardiac arrest. However, the application of machine learning models based on multimodal big data in the treatment decision-making and prognosis analysis of ECMO patients has rarely been reported. Our team is working with software companies to develop a software platform and database that can integrate medical big data, such as multimodal monitoring and wearable devices, HIS databases, and electronic medical record databases, to assist clinicians in the decision-making process and to manage ECMO patients.

LIMITATIONS

This study has some limitations. First, as a single-center longitudinal observational retrospective study, the sample size was small and less convincing than RCT research. Second, in the process of data collection and analysis, there was a lack of stratified analysis of the effects of mechanical ventilation, intra-aortic balloon pump (IABP) and continuous renal replacement therapy (CRRT) on cerebral blood flow during the ECMO support process, especially the stratified analysis of the effects of pulsatile perfusion and MAP on cerebral perfusion, which may lead to biased results. Rigorous randomized clinical trials or alternative study designs are needed in the future.

CONCLUSION

We established a safe and adverse reaction-free MNM-guided protocol in the present study that provides complementarity among multimodal parameters, which is conducive to guiding intensivists in the improvement of cerebral protection therapy for ECMO-supported patients to detect and treat potential neurologic impairment promptly and then improving long-term neurological outcomes after discharge. We hope to promote this multimodal and noninvasive monitoring strategy in more ECLS facilities. In the future, machine learning models combined with multimodal AI big data may help intensivists make clinical

decisions, and implement real-time, precision management in ECMO-supported patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XS, QG, YL, MD, and XW: acquisition and analysis of data. XS: writing of the original manuscript and statistical analysis. XS and SX: revision and editing of the manuscript. MD and WH material, technical, and administrative support and supervision. WH, SX, XS, and QG contributed to study concept and design. All authors approved the final version of the manuscript and agree to be responsible for all aspects of the work.

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Serum Total Bilirubin With Hospital Survival in Adults During Extracorporeal Membrane Oxygenation

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Background: Extracorporeal membrane oxygenation (ECMO) is widely used for refractory cardiopulmonary failure treatment. The disadvantage of ECMO is its higher risk profile and clinical resource consumption. This observation examines the role of serum total bilirubin (TBIL) as a predictor of adult patient outcomes on ECMO support.

Methods: This retrospective observation reports a single-center experience with adults on ECMO support between 2018 and 2021. Data were collected regarding demographics, ECMO details, laboratory parameters, and outcomes. We examined the elevation of TBIL to predict survival and variables associated with hyperbilirubinemia.

Results: The patients who died within 28 days had a twofold higher peak level of TBIL than those who survived [73.10 (38.60, 98.64) vs. 34.50 (24.03, 54.85); $P = 0.003$]. Univariate logistic regression analyses demonstrated that high TBIL was remarkably associated with an elevated risk of 28-day mortality (OR: 7.25; 95% CI: 2.31–25.49; $P = 0.001$) and total mortality (OR: 5.71; 95% CI: 1.82–20.66; $P = 0.001$). The TBIL value was 65 μmol/L as the best cut-off value, and the observation group was divided into a high TBIL subgroup ($n = 21$) or a low TBIL subgroup ($n = 39$). The demographic and clinical features did not show a difference, whereas Sequential Organ Failure Assessment (SOFA) and APACHE II scores and ALT, AST, and LAC before ECMO initiation correlated with high or low TBIL ($P < 0.05$). For coagulation function at the time of TBIL peak, the levels of prothrombin time (PT), activated partial thromboplastin time (APTT), prothrombin time activity (PTA), and fibrinogen (FIB) were different between the two subgroups ($P < 0.05$). The SOFA score was potentially associated with hyperbilirubinemia after ECMO initiation, and the prediction accuracy was 0.800.

Conclusion: Serum total bilirubin elevation appears after ECMO initiation and correlates with survival, while other markers of liver injury do not. Serum total bilirubin is an easy-to-measure biomarker to be a predictor of survival after ECMO initiation.

Keywords: total bilirubin, hyperbilirubinemia, survival, extracorporeal membrane oxygenation, prognosis

BACKGROUND

Extracorporeal membrane oxygenation (ECMO) is increasingly used to treat refractory cardiopulmonary failure worldwide. Venovenous ECMO (VV-ECMO) is recommended for refractory hypoxia or hypoxic hypercapnia respiratory failure, whereas venoarterial ECMO (VA-ECMO) is recommended for refractory cardiac failure with/without respiratory failure (1, 2). ECMO should be used following the guidelines that have been demonstrated in ECMO centers to ensure its feasibility and safety (3). Understanding and knowledge of ECMO-related complications and predictors are part of the management protocols recommended by the Extracorporeal Life Support Organization (ELSO). A recent literature review (4) of 19 studies reported many predictors of ECMO-related complications, but the predictors were widely variable given the heterogeneity in patient severity, care, and training quality.

Bilirubin is a marker of liver dysfunction and has been included in a variety of scoring algorithms to assess critical patient prognosis (5, 6). Elevated serum bilirubin levels are not always induced by primary liver disease and may result from multiple conditions, such as hypoxia, toxins and drug injury, affecting liver function at different stages or simultaneously; therefore, elevated serum bilirubin is recognized as a marker of the generalized stress response (7, 8).

The relationship between liver function and survival has been investigated mainly in the context of VA-ECMO and postcardiac surgery (9), and few studies have reported on VV-ECMO (10), which may be related to systemic hypoperfusion. The Survival After Veno Arterial ECMO (SAVE) score defined liver injury before ECMO initiation. The serum bilirubin cut-off value was 33 μmol/L (1.93 mg/dl), and those of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were > 70 units/L (11). However, data on the fluctuation of these markers are not available, and cut-off values after the initiation of ECMO correlate with survival (12). In this study, we reported the association between elevated serum total bilirubin (TBIL) and adult patient outcomes during ECMO support, defined the cut-off value of TBIL and identified factors related to elevated TBIL. This information is a useful complement to ECMO management protocols and may help guide therapy when serum TBIL levels increase during ECMO support.

Abbreviations: ECMO, Extracorporeal membrane oxygenation; VV, Venovenous; VA, venoarterial; ELSO, Extracorporeal Life Support Organization; SAVE, Survival after venoarterial ECMO; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; DBIL, Direct bilirubin; CSELSO, Chinese Society of Extracorporeal Life Support Organization; LAC, lactate; ALB, albumin; ALP, alkaline phosphatase; HB, hemoglobin; PLTs, platelets; OR, odds ratio; ROC, receiver operating curve; AIC, Akaike information criterion; C-index, concordance index; BMI, Body mass index; IABP, Intra-aortic balloon pumping; ICU, Intensive care unit; MV, mechanical ventilation; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; INR, International normalized ratio; MELD-XI, Model for End-stage Liver Disease excluding INR; MELD, Model for End-Stage Liver Disease; PT, prothrombin time; APTT, activated partial thromboplastin time; PTA, prothrombin time activity; FIB, fibrinogen; MOF, multiple organ failure.

METHODS

This retrospective study was approved by the Anhui Medical University Medical Institutional Review Board. All 159 patients during the past 3 years (2018–2021) were included in the retrospective study to objectively assess TBIL fluctuation and the relationship between TBIL levels and related survival during adult patient ECMO support. Many cases were excluded, and the exclusion criteria are presented in **Figure 1**. All ECMO patients' uniform data, including demographic characteristics, details of ECMO, laboratory parameters, and outcomes, were reported through the Chinese Society of Extracorporeal Life Support Organization (CSELSO) registry and collected retrospectively.

The First Affiliated of Anhui Medical University, which offers all treatment modalities for acute and chronic cardiopulmonary failure, is a member of the CSELSO. All ECMO services were provided in the Critical Care Medicine Department, and the ECMO team was headed by the intensivists of our department. The systems used included Bio-Console 560 (Medtronic, Inc., Minneapolis, MN, United States) and Cardiohelp^{TM} (Maquet Inc., Rastatt, Germany). ECMO team members received CSELSO certification to minimize practice differences through standardized care and were well trained. Intensive care unit (ICU) nurses on the ECMO team also received training similar to that of ECMO specialists to monitor the ECMO circulation system. Cannulation, circuit and pump management and other

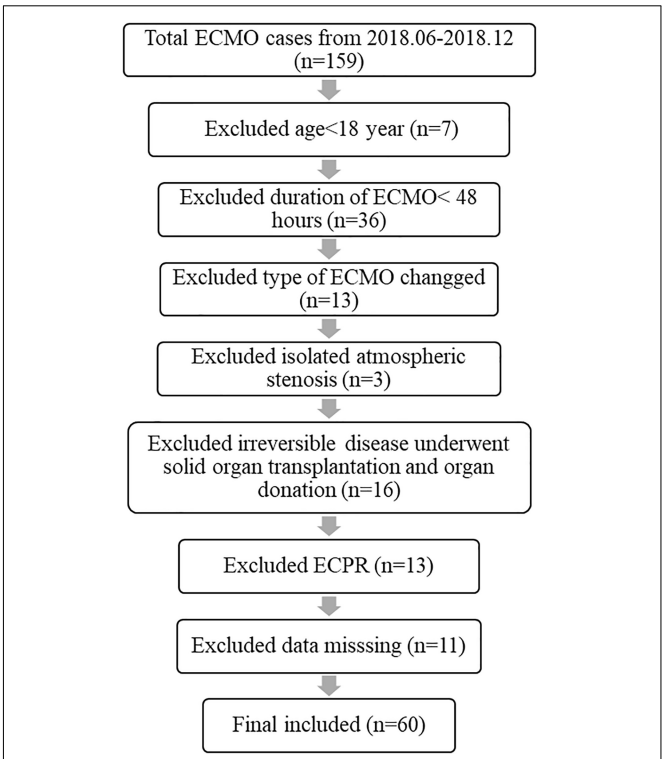

FIGURE 1 | Flow diagram of patient enrolment. ECPR, extracorporeal cardiopulmonary resuscitation.

procedures were performed by an intensivist-led team in our department. IV heparin (20 units/kg) was administered 5–10 min before cannula implantation if there was no active bleeding or contraindications to anticoagulation. Unfractionated heparin was used for anticoagulation. Compared with Activated Clotting Time (ACT) assays, the activated partial thromboplastin time (APTT) better correlates with heparin concentrations during ECMO support (13). Heparin anticoagulant was monitored by APTT. We maintained the APTT at 50–70 s, and the ACT range was 180–200 s as previously described (14).

Relevant data about liver function, including lactate (LAC), albumin (ALB), TBIL, AST, ALT, alkaline phosphatase (ALP), hemoglobin (HB) and platelets (PLTs), were also collected. Values for each variable were collected before cannulation, and the highest and lowest values observed throughout the ECMO support process were recorded. According to the SAVE score, TBIL greater than 33 μmol/L was considered elevated (11) and defined as hyperbilirubinemia.

STATISTICS

All statistical analyses were performed using RStudio (1.4.1717) and considered statistically significant when the *p*-value was less than 0.05. Categorized variables are described as numbers (percentages), and the chi-square test or Fisher's exact test was used for comparison. The variable distribution was explored and visualized by histogram. Based on the distribution, continuous variables were reported as the mean (standard deviation) or median (interquartile range) and compared with Student's *t*-test or Wilcoxon test between two independent groups. The correlation between two continuous variables is presented using dotted plots and calculated using the Spearman correlation coefficient. To obtain the odds ratio (OR), univariate and multivariate logistic regression analyses were performed. In multivariate analysis, continuous covariates were transformed into binary variables due to collinearity.

The optimal cut-off value for peak TBIL during ECMO was identified using 3 methods, i.e., receiver operating curve (ROC), Chi-square test, and logistic regression. For the ROC method, the optimal threshold should have the maximum sum of sensitivity and specificity. For the Chi-square test, the optimal threshold should have the greatest capacity to discriminate the two groups, i.e., the maximum value of the chi-square test statistic. For logistic regression, the optimal threshold should have the best univariate model fit, i.e., the lowest value of the Akaike information criterion (AIC) or the highest value of the concordance index (C-index).

TABLE 1 | Baseline characteristics of the included patients stratified by 28-day mortality.

Variable	Survival (*N* = 35)	Death (*N* = 25)	*P*-value	Total (*N* = 60)
Sex (female)	14 (40.0)	11 (44.0)	0.965	25 (41.7)
Age	50.00 (35.00, 58.50)	59.00 (53.00, 69.00)	0.007	53.00 (40.75, 65.25)
BMI	23.63 (2.86)	22.62 (3.39)	0.217	23.21 (3.11)
IABP (present)	3 (8.6)	5 (20.0)	0.369	8 (13.3)
Tobacco smoking (yes)	7 (20.0)	5 (20.0)	> 0.999	12 (20.0)
Alcohol drinking (yes)	6 (17.1)	4 (16.0)	> 0.999	10 (16.7)
ECMO type (VV)	22 (62.9)	12 (48.0)	0.378	34 (56.7)
Limb ischemia (present)	1 (2.9)	2 (8.0)	0.764	3 (5.0)
Sepsis (present)	17 (48.6)	7 (28.0)	0.181	24 (40.0)
MV time (day)	11.00 (8.00, 30.00)	7.00 (5.00, 12.00)	0.006	10.00 (7.00, 19.75)
ECMO time (hour)	159.00 (117.50, 240.50)	146.00 (106.00, 193.00)	0.315	155.50 (110.75, 234.75)
Total ICU stay (day)	25.00 (12.00, 39.50)	9.00 (5.00, 13.00)	< 0.001	13.00 (9.00, 28.00)
Total hospital stay (day)	29.00 (16.50, 47.00)	13.00 (7.00, 22.00)	< 0.001	22.00 (12.00, 35.25)
Parameters before ECMO				
SOFA score	10.94 (3.05)	13.96 (2.62)	< 0.001	12.20 (3.22)
APACHE II score	27.00 (21.00, 30.00)	33.00 (32.00, 35.00)	< 0.001	29.50 (24.75, 33.00)
AST (U/L)	58.00 (35.55, 524.50)	217.20 (66.00, 887.00)	0.121	79.50 (39.75, 735.00)
ALT (U/L)	47.00 (28.50, 285.50)	72.00 (36.00, 402.00)	0.205	50.50 (29.00, 316.75)
TBIL (μmol/L)	16.00 (11.40, 24.20)	17.67 (11.30, 37.90)	0.264	16.14 (11.28, 26.97)
DBIL (μmol/L)	6.69 (4.20, 9.20)	9.18 (5.74, 33.92)	0.221	6.69 (4.40, 10.30)
ALB (g/L)	33.39 (6.03)	33.56 (5.56)	0.915	33.46 (5.79)
LAC (mmol/L)	2.66 (1.88, 3.34)	4.60 (3.20, 10.58)	< 0.001	3.10 (2.29, 5.97)
HB (g/L)	116.80 (27.90)	113.08 (27.47)	0.61	115.25 (27.55)
PLT (10^9/L)	194.63 (102.57)	168.36 (77.92)	0.286	183.68 (93.29)

BMI, body mass index; IABP, intra-aortic balloon pumping; ECMO, Extracorporeal membrane oxygenation; ICU, intensive care unit; MV, mechanical ventilation; VV, Venovenous; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ALT, alanine transaminase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; ALB, albumin; LAC, lactate; HB, hemoglobin; PLT, platelet. Category variables were displayed with N (%); normally distributed variables were displayed with mean (standard deviation); skewed variables were displayed with median (P25, P75).

Given that this study considered many serological and score parameters as covariates and collinearity frequently existed across these indicators, conventional logistic regression was inappropriate to explore the potential determinants for a given outcome. As a result, the random forest algorithm was used to incorporate all the possible descriptors without data transformation or engineering. This technique is a decision tree-based method that has no assumption about the data distribution or inner correlation. Both categorized and continuous data on different scales can be addressed. An importance value is given to a variable to indicate its contribution to the outcome. Variables with importance values greater than zero were further included in the prediction model, and the performance was evaluated by 10-fold cross validation. This process was implemented using the R package "mlr3verse."

RESULTS

Patient Enrolment and Baseline Characteristics

Cardiac failures were noted in 26 cases (43.3%), including 12 (20%) with acute myocardial infarction, 8 (13.3%) with acute fulminant myocarditis, 4 (6.7%) with stress cardiomyopathy, and 2 (3.3%) with acute pulmonary embolism. Respiratory failure was noted in 34 cases (56.7%), including 19 (31.7%) with severe pneumonia (bacteria or virus), 4 (6.7%) with acute interstitial pneumonia, 4 (6.7%) with aspiration, 2 (3.3%) with asthma, 2 (3.3%) with diffuse alveolar hemorrhage, and 3 (5%) with severe trauma. The baseline characteristics before ECMO initiation are described in **Table 1**. The patients who died within 28 days had a twofold higher peak level of TBIL than those

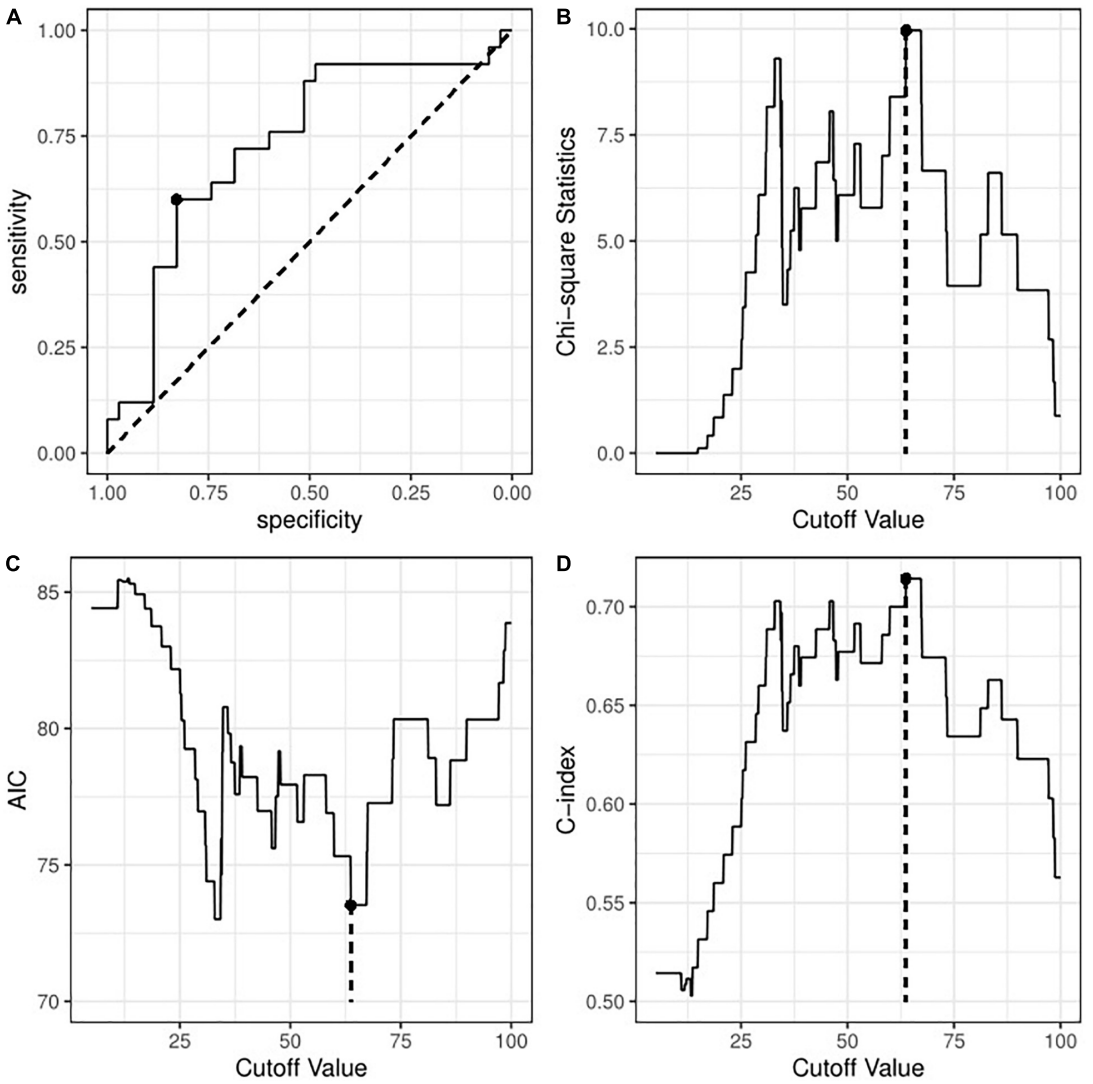

FIGURE 2 | Identification of optimal cut-off value for peak TBIL based on **(A)** the receiver operating curve method; **(B)** Chi-square test with maximum statistics; **(C)** logistic regression with minimum AIC; or **(D)** logistic regression with maximum C-index. TBIL, total bilirubin; AIC, Akaike information criterion; C-index, concordance index.

who survived [73.10 (38.60, 98.64) vs. 34.50 (24.03, 54.85); $P = 0.003$]. Similar results were observed between the patients who eventually survived [67.38 (36.83, 98.56) vs. 30.86 (21.37, 50.65); $P = 0.002$]. The causes of death in 25 patients (41.6%) in this study included multiple organ failure (MOF) in 14 patients, septic shock in 7 patients, refractory cardiac failure in 2 patients, and bleeding in 2 patients.

High Peak Total Bilirubin Levels Were Associated With the Risk of 28-Day and Total Mortality

We next transformed peak TBIL into a binary variable by determining the optimal cut-off value. **Figure 2A** shows that the threshold identified by the ROC method was 65.45 μmol/L with a sensitivity of 0.600 and a specificity of 0.829. **Figures 2B–D** consistently shows an optimal threshold ranging from 63.7 to 67.2 μmol/L. Taken together, we selected 65 μmol/L as the best cut-off value; thus, the patients were divided into a high TBIL subgroup (≥ 65 μmol/L; $N = 21$) or a low TBIL subgroup (< 65 μmol/L; $N = 39$). **Table 2** describes the characteristics of the two subgroups. The demographic and clinical features did not differ between the two groups, whereas some parameters before ECMO initiation, including Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation II (APACHE II), ALT, AST and LAC, correlated with high or low TBIL ($P < 0.05$).

Univariate logistic regression analyses demonstrated that high TBIL was remarkably associated with an elevated risk of 28-day mortality (OR: 7.25; 95% CI: 2.31–25.49; $P = 0.001$) and total mortality (OR: 5.71; 95% CI: 1.82–20.66; $P = 0.001$). **Figures 3A,B** also illustrates that the high TBIL subgroup had significantly more deceased cases ($P < 0.05$). After adjusting for age, ECMO type (VA vs. VV), sepsis (present vs. absent), LAC level before ECMO initiation (< 2 vs. ≥ 2) and APACHE II score before ECMO initiation (< 15 vs. ≥ 15), high TBIL was still correlated with the risk at 28 days (OR_{adj}: 7.23; 95% CI: 1.98–31.72; $P_{adj} = 0.004$) and total mortality (OR_{adj}: 4.79; 95% CI: 1.35–19.90; $P_{adj} = 0.020$).

The Association Between Peak Total Bilirubin Level and Secondary Outcomes

The patients successfully weaned from ECMO tended to have a lower peak level of TBIL [73.25 (37.62, 95.26) vs. 36.58 (24.00, 68.46)]; however, no statistical significance was observed ($P = 0.225$). Indeed, the high TBIL subgroup had a greater risk of failure weaning from ECMO according to univariate analysis (OR: 4.71; 95% CI: 1.55–15.36; $P = 0.008$; **Figure 3C**) and multivariate analysis (OR_{adj}: 4.33; 95% CI: 1.33–15.32; $P_{adj} = 0.018$). For other secondary outcomes (i.e., duration of hospital stay, duration of ICU stay, mechanical ventilation time, and ECMO duration), no statistically significant differences were observed between the high and low TBIL subgroups (**Figures 3D–G**). For coagulation function at the time of peak TBIL, the prothrombin time (PT), APTT, prothrombin time activity (PTA), and fibrinogen (FIB) levels differed between the two subgroups ($P < 0.05$, **Figures 3H–K**). In addition, peak TBIL was significantly correlated with these parameters (**Figure 4**).

TABLE 2 | Comparison of the characteristics between the patients with high and low TBIL during ECMO.

Variable	< 65 μ mol/L (*N* = 39)	≥ 65 μ mol/L (*N* = 21)	*P*-value	Total (*N* = 60)
Sex (female)	16 (41.0)	9 (42.9)	> 0.999	25 (41.7)
Age	51.00 (35.00, 63.50)	55.00 (51.00, 67.00)	0.127	53.00 (40.75, 65.25)
BMI	23.63 (2.80)	22.45 (3.56)	0.163	23.21 (3.11)
IABP (present)	4 (10.3)	4 (19.0)	0.577	8 (13.3)
Tobacco smoking (yes)	10 (25.6)	2 (9.5)	0.250	12 (20.0)
Alcohol drinking (yes)	8 (20.5)	2 (9.5)	0.468	10 (16.7)
ECMO type (VV)	23 (59.0)	11 (52.4)	0.827	34 (56.7)
Limb ischemia (present)	2 (5.1)	1 (4.8)	> 0.999	3 (5.0)
Sepsis (present)	16 (41.0)	8 (38.1)	> 0.999	24 (40.0)
Parameters before ECMO				
SOFA score	10.95 (2.90)	14.52 (2.44)	< 0.001	12.20 (3.22)
APACHE II score	28.00 (22.00, 32.00)	33.00 (31.00, 35.00)	0.001	29.50 (24.75, 33.00)
AST (U/L)	68.00 (35.55, 321.50)	308.00 (66.00, 1464.00)	0.019	79.50 (39.75, 735.00)
ALT (U/L)	46.00 (27.50, 82.00)	152.00 (38.00, 883.00)	0.025	50.50 (29.00, 316.75)
TBIL (μmol/L)	15.10 (11.25, 25.70)	21.50 (12.80, 29.80)	0.175	16.14 (11.28, 26.97)
DBIL (μmol/L)	6.00 (4.20, 9.20)	9.35 (7.32, 33.92)	0.051	6.69 (4.40, 10.30)
ALB (g/L)	34.47 (5.53)	31.58 (5.93)	0.065	33.46 (5.79)
LAC (mmol/L)	2.81 (2.15, 3.75)	4.60 (3.10, 9.92)	0.007	3.10 (2.29, 5.97)
HB (g/L)	119.82 (28.23)	106.76 (24.66)	0.080	115.25 (27.55)
PLT (10^9/L)	192.10 (86.86)	168.05 (104.61)	0.345	183.68 (93.29)

BMI, body mass index; IABP, intra-aortic balloon pumping; ECMO, Extracorporeal membrane oxygenation; VV, Venovenous; SOFA, Sequential Organ Failure Assessment; ALT, alanine transaminase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; ALB, albumin; LAC, lactate; HB, hemoglobin; PLT, platelet. Category variables were displayed with N (%); normally distributed variables were displayed with mean (standard deviation); skewed variables were displayed with median (P25, P75).

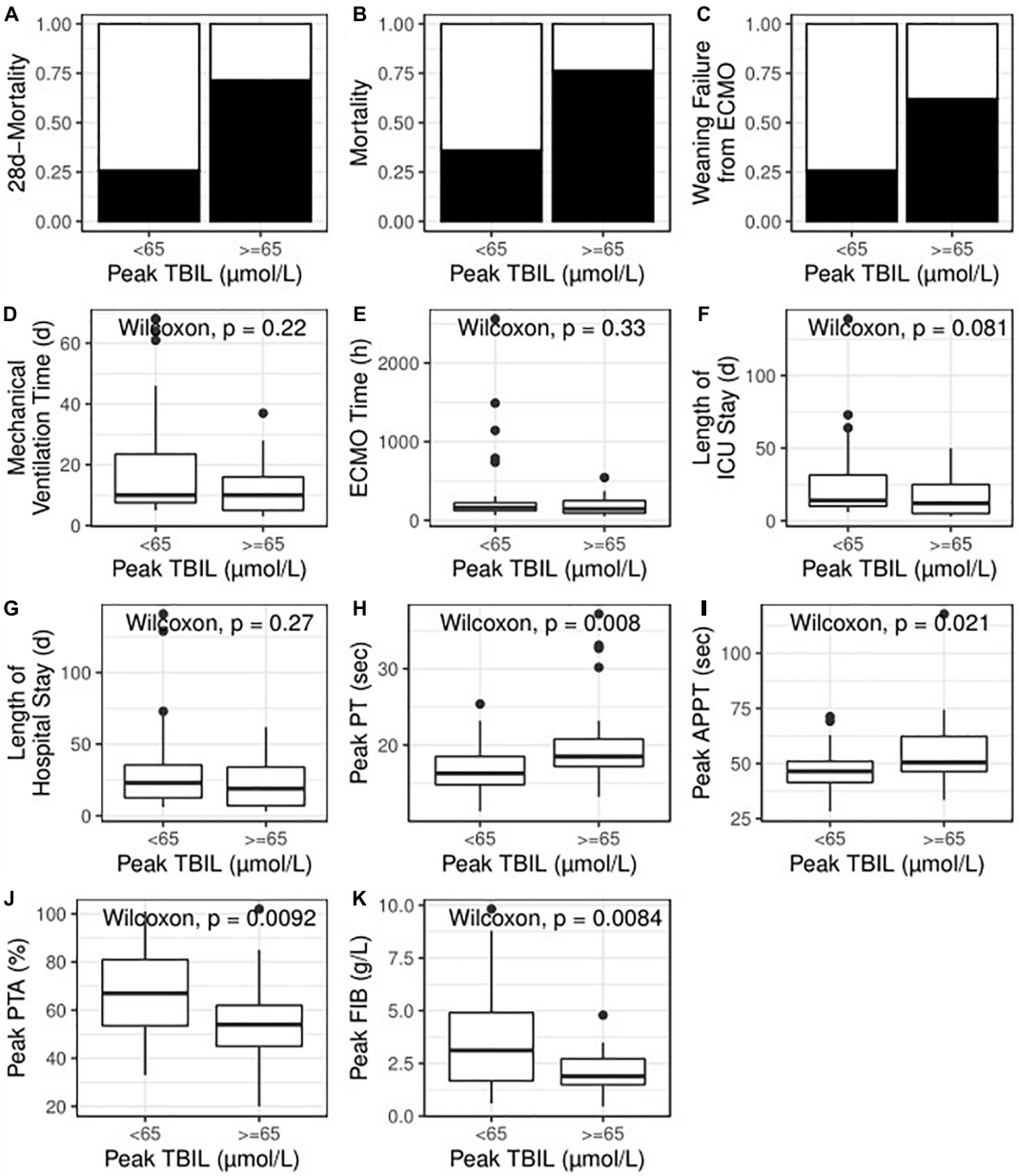

FIGURE 3 | High TBIL during ECMO indicated poor primary outcome **(A,B)**, poor secondary outcome **(C–G)** and abnormal coagulation function **(H–K)**. TBIL, total bilirubin; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; PT, prothrombin time, APTT, activated partial thromboplastin time; PTA, prothrombin time activity; FIB, fibrinogen.

Exploration of Potential Determinants That Could Predict the Occurrence of High Peak Total Bilirubin

Given that a high peak level of TBIL was apparently associated with worse outcome, we investigated possible predictors of its occurrence. We incorporated all the demographic features, clinical features, and parameters before ECMO into a random forest algorithm to predict the occurrence of TBIL peak levels greater than 65 μmol/L. **Figure 5** (left panel) demonstrates that 12 variables (red) were potentially associated with the outcome, of which the SOFA score before ECMO played the most important role. We next built a random forest prediction model with the 12 variables and obtained a prediction accuracy of 0.800 (**Figure 5** right panel).

DISCUSSION

To date, studies assessing how liver injury before ECMO initiation correlates with survival have mainly focused on patients supported by VA-ECMO. A small cohort reported that the Model

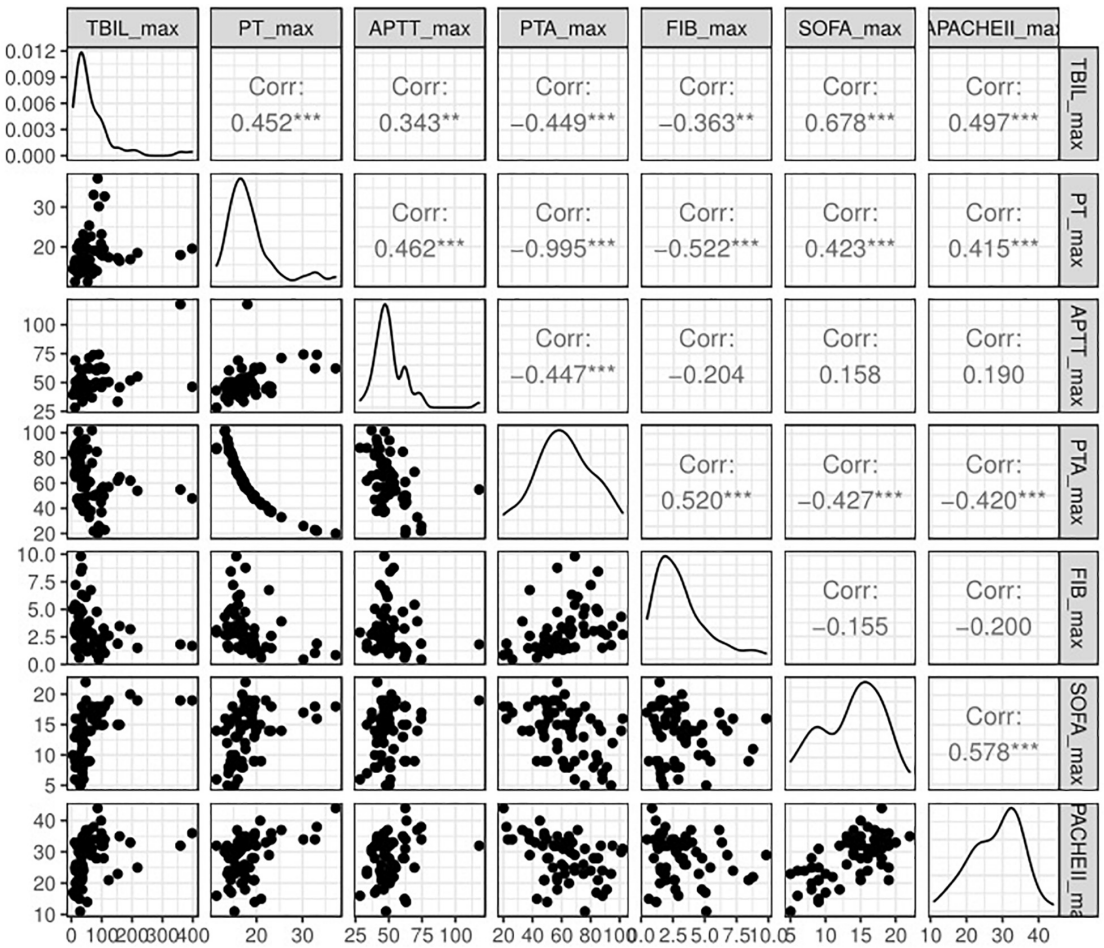

FIGURE 4 | Spearman correlation analysis of peak TBIL and other simultaneous clinical parameters. TBIL, total bilirubin; PT, prothrombin time, APTT, activated partial thromboplastin time; PTA, prothrombin time activity; FIB, fibrinogen; SOFA, Sequential Organ Failure Assessment.

for End-stage Liver Disease excluding INR (MELD-XI) score pre-calculation had a strong association with increased mortality (15), and similar findings were reported the Model for End-Stage Liver Disease (MELD) score in 49 patients who underwent heart transplantation (16). A cohort reported 240 patients with postcardiotomy cardiogenic shock and found that ALP and TBIL before ECMO initiation were the strongest predictors of 30-day mortality (17). Recently, findings regarding the definition of liver dysfunction remain unclear, and unifying trends and prognostic markers are not uniform among reports in the literature. Notably, liver function may be more difficult to objectively quantify before ECMO initiation (18, 19), and in many observations, liver function before ECMO initiation is often normal (20). These studies generally show that liver injury strongly affects prognosis, which may be due to acquired hemostasis, refractory peripheral vasodilation shock caused by nitric oxide metabolism disorder, and the absence of immune capacity caused by progressive liver injury (21).

A retrospective institutional database query found that the relevant parameters of liver function are usually normal before VA-ECMO initiation, but abnormalities in various markers develop after ECMO initiation. Finally, both bilirubin and lactate elevations correlated with increased mortality (22). Using a quantitative model, we definitively demonstrate that hyperbilirubinemia after ECMO initiation is a dominant factor in decreased survival and establish 65 μmol/L as the best cut-off value.

AST and ALT values are widely recognized as indicators of liver injury given their rapid increase to an early peak. However, in this study, the two variables are not prognostic factors of survival. This finding is consistent with prior results (20). A multivariable model showed that AST and ALT failed to achieve statistical significance. This finding might be attributed to the notion that elevated ALT and AST levels are only related to acute liver injury. Of note, the patients who died within 28 days had a twofold higher peak TBIL levels than those who survived, and similar results were observed between the patients who eventually survived and those who did not. However, some parameters (i.e., SOFA, APACHE II, ALT, AST, and LAC) also increased with high TBIL ($P < 0.05$).

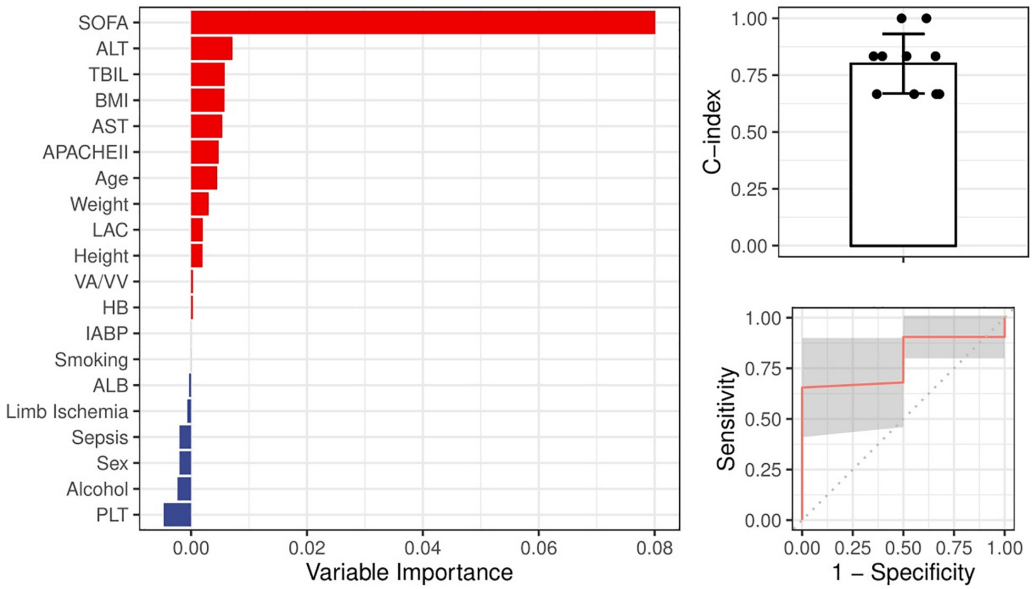

FIGURE 5 | Ranking of the potential indictors for the occurrence of high TBIL during ECMO based on the random forest algorithm. All variables were demographic features or parameters obtained before ECMO. A greater importance value suggested a closer relationship between the variable and the occurrence of high TBIL during ECMO.

The frequency and severity of liver dysfunction prior to ECMO initiation in this study were not significantly different between survivors and non-survivors, and most patients had normal liver function before cannulation. Given that a peak value of TBIL > 65 μmol/L was associated with worse outcome, we assessed possible predictors of elevated TBIL using the random forest algorithm and found that 12 variables, including age, BMI, and lactate, were potentially associated with the outcome. Specifically, the SOFA score before ECMO played the most important role, yielding a prediction accuracy of 0.800. Persistently elevated bilirubin levels may indicate that the liver has not recovered even after the elimination of the initial liver injury or that other new complications occur, leading to liver injury. We also found that coagulation function, including PT, APTT, PTA, and FIB, was significantly correlated with the peak TBIL value, which is interpreted as acquired hemostatic abnormalities secondary to liver dysfunction. Thus, the knowledge that serum TBIL elevation exceeds certain cut-off values indicates decreasing survival and is beneficial for further decision-making.

LIMITATIONS

The limitations of this study were that it was a single institution experience and a retrospective study. The primary diseases varied significantly, and we were unable to maintain homogeneity in therapeutic strategies, which may affect prognosis or add more residual confounders. The purpose of the study is to provide a reference for decision-making in patients on ECMO with hyperbilirubinemia, but the relatively low numbers of patients in this observation limited the statistical power.

Due to the relatively small sample size and heterogeneity of the participants, the confounders are unlikely to be fully addressed, especially for the undetected covariates. In real-world studies, instrument variables are able to balance the seen and unseen biases across the subgroups. Unfortunately, we failed to identify a possible instrumental variable from the available medical information, so we only adjusted the clinically and statistically important covariates that could be recognized. Therefore, the results could possibly extend current knowledge but should also be taken with caution due to the inherent limitations.

CONCLUSION

The main results of the study were as follows: (a) the patients who died within 28 days had twofold higher peak TBIL levels than those who survived; (b) the best threshold identified was 65 μmol/L; (c) hyperbilirubinemia was correlated with the risk of 28-day and total mortality; (d) 12 variables were potentially associated with hyperbilirubinemia, and the SOFA score before ECMO played the most important role. In conclusion, during ECMO support, elevated total serum bilirubin levels appear to be consistently associated with survival, whereas other markers of liver injury are not associated with survival. Serum total bilirubin is an easy-to-measure biomarker that serves as a predictor of survival after ECMO initiation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The First Affiliated Hospital of Anhui Medical University, the Committee on Medical Ethics. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RH and NL designed and drafted the manuscript. RH, XH, MF, MS, and NL were involved in the clinical care and management of the patients. CZ and MJ analyzed the data. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Commentary: Serum total bilirubin with hospital survival in adults during extracorporeal membrane oxygenation

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A Commentary on

Serum total bilirubin with hospital survival in adults during extracorporeal membrane oxygenation

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Introduction

Extracorporeal membrane oxygenation (ECMO) is increasingly being used as a life-saving therapy for patients with cardio-pulmonary dysfunction who have failed conventional treatment (1). ECMO support removes carbon dioxide from the patient's blood and returns oxygenated blood to the patient (2, 3). However, ECMO-associated complications—e.g., activation of complement and contact systems leading to cytokine release—pose significant risks to successful patient management. Moreover, complications such as acute kidney injury, pneumonia, sepsis, and bleeding are common during ECMO support (4). Recently, ECMO-associated liver injury or direct hyperbilirubinemia (DHB) has been receiving more attention in both adult and pediatric populations due to its association with high mortality (5–9). It is noteworthy that the incidence of DHB (defined as >3 mg/dL of serum bilirubin) was as much as 73% in patients undergoing venoarterial ECMO (VA-ECMO) (7). Monitoring of serum total bilirubin (TBIL) could therefore be useful for assessing prognosis in patients receiving ECMO.

Subsections relevant for the subject

Huang et al. (9) reported on the important role of serum TBIL in predicting survival in adults on ECMO support. Their work produced several key findings: First, the patients who died within 28 days had twice the peak level of TBIL as those who survived. Multivariate logistic regression analysis indicated that a high peak TBIL was correlated with mortality risk at 28 days and total mortality after adjusting for age, ECMO mode, sepsis, lactate level, and APACHE II score (a general measure of disease severity). Second, hyperbilirubinemia after ECMO initiation was a risk factor for worse prognosis. Third, TBIL, but not aspartate transaminase (AST) or alanine aminotransferase (ALT), was an important indicator of ECMO-associated liver injury, and therefore a significant predictor of prognosis, with the cutoff value of 65 μmol/L. Fourth, peak TBIL was associated with coagulation dysfunction, and was correlated with prothrombin time (PT), activated partial thromboplastin time (APTT), prothrombin time activity (PTA), and fibrinogen (FIB) levels. Fifth, there was a potential association between the sequential organ failure assessment (SOFA) score and hyperbilirubinemia after ECMO initiation. Taken together, these results demonstrate that TBIL is an optimal biomarker for assessing hospital survival in adults during ECMO.

Discussion

An increased bilirubin concentration during the first 48 h after admission was significantly associated with adverse long-term outcome in patients with moderate to severe acute respiratory distress syndrome (ARDS) (10). Patients with severe ARDS and increased bilirubin had high mortality rates at 24, 48, and 72 h after venovenous ECMO (VV-ECMO) initiation. However, increased bilirubin values before ECMO initiation was not associated with increased in-ICU mortality (6). ECMO-associated DHB was also associated with high mortality in children receiving ECMO support (8), as reported by Huang et al. (9). Round-the-clock monitoring of serum bilirubin would therefore be beneficial for the precision management of patients receiving ECMO.

Bilirubin is formed in hepatic Kupffer cells, in the monocytic macrophages of the spleen, and in bone marrow. In a normal adult, ∼250–300 mg of bilirubin is formed every 24 h, at a production rate of 3.8 mg/kg (11). DHB during VA-ECMO could be caused by the lack of pulsatile flow to end organs or by medication-induced liver injury. Moreover, circuit-induced hemolysis or a massive pathological intravascular hemolysis can contribute to the development of high mixed DHB in VA-ECMO patients. Besides DHB, ECMO-induced hemolysis leads to the most severe form of pump head thrombosis (12), and the rate of hemolysis is decreased with centrifugal pumps compared to roller pumps (13). More importantly, the causes of DHB in patients under ECMO support should be analyzed case-by-case.

Compared with non-survivors, bilirubin levels in survivors trended down on the day of ECMO initiation (14), suggesting that the timely and effective removal of bilirubin is necessary for improving outcomes. The hemolysis index (HI) assay on Abbott's Alinity CI system allows accurate determination of plasma free hemoglobin concentrations, enabling the assessment of ECMO-associated hemolysis and thereby helping to prevent and manage hemolysis-induced DHB (15, 16). Advanced strategies for the management of liver failure, including artificial liver support systems, plasma exchange, and bilirubin adsorption, are gradually seeing increased usage in critically ill patients. Huang et al. (9) showed that the SOFA score was potentially associated with hyperbilirubinemia occurrence after ECMO initiation, with a prediction accuracy of 0.800.

Currently, predicting the occurrence of ECMO-associated DHB still poses a challenge for intensivists. Integrating artificial liver support systems into the ECMO circuit might be useful for improving hospital survival of patients under ECMO support, but few data are available and these issues need further study.

Author contributions

CW and YZ drafted and edited the manuscript. Both authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Extracorporeal Membrane Oxygenation Followed by Intra-Aortic Balloon Counterpulsation Successfully Treated Cardiac Arrest Caused by Anomalous Origin of a Left Coronary Artery From the Right Coronary Sinus

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Background: Anomalous origin of a coronary artery (AOCA) is defined as the failure of the coronary artery to originate from the normal coronary sinus. The anomalous origin of the left coronary artery arising from the right coronary sinus is rare, dangerous and at risk of malignant arrhythmia, sudden death, and high mortality.

Case Presentation: In this study, we present a 14-year-old adolescent male who went to a hospital with transient unconsciousness after exercise, who subsequently developed cardio arrest due to malignant arrhythmia. He was admitted to the intensive care unit, and who subsequently received successful veno-arterial extracorporeal membrane oxygenation (VA ECMO) assisted circulation followed by intra-aortic balloon counterpulsation (IABP). Echocardiography and cardiac CTA were also performed, further confirming that the abnormal left coronary artery originated from the right coronary sinus. The patient subsequently underwent heart surgery.

Conclusion: The successful treatment of the patient in this report was attributed to the immediately VA ECMO, supplemented by IABP. Establishing clear diagnosis is a process of multidisciplinary joint diagnosis, which provides a reference for clinicians when encountering similar cases.

Keywords: ECMO, IABP, cardiac arrest, AOCA, case report

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INTRODUCTION

Anomalous origin of a coronary artery (AOCA) is generally caused by abnormal or incomplete development of coronary artery during the embryonic period. The overall detection rate of AOCA is approximately 0.6–1.3% (1, 2). Abnormal origin of left coronary artery from the right sinus is significantly rare (3), but it is frequently associated with early cardiac death, especially during vigorous exercise.

In this study, the patient was admitted to a hospital with transient unconsciousness during exercise, subsequently developed cardio arrest due to malignant arrhythmia, and was admitted to the intensive care unit (ICU). Veno-arterial extracorporeal membrane oxygenation (VA ECMO) followed by intra-aortic balloon counterpulsation (IABP) successfully saved the patient's life. He was finally diagnosed with AOCA, and later underwent follow-up treatment. ECMO, sequential IABP successfully rescued the cardiac arrest and cardiogenic shock caused by abnormal coronary origin (the left coronary artery originates from the right coronary sinus with an initial interarterial course) was rarely reported.

CASE PRESENTATION

A 14-year-old adolescent male was admitted to the intensive care unit (ICU) of our hospital due to sudden "transient unconsciousness while running 2 h ago." At that time, the patient was pale and sweating profusely, which resolved spontaneously after 2 min. After waking, he complained of chest tightness and cold limbs, and went to the emergency room. At that time, his blood pressure was 95/60 mmHg, heart rate 160/min, with ventricular tachycardia, respiratory rate 34/min. The emergency doctor gave amiodarone for anti-arrhythmic. Approximately half an hour later, the patient suddenly experienced ventricular fibrillation, loss of consciousness with a Glasgow Coma Score of 4 (GCS: E1, M1, V2). Immediately chest compressions, defibrillation, graded intravenous push of epinephrine, and tracheal intubation were performed. After cardiopulmonary resuscitation (CPR), the patient's blood pressure was 83/53 mmHg with a norepinephrine infusion of 2 ug/min.kg pump and lidocaine for antiarrhythmic. He had experienced syncope during exercise two times and both were relieved after rest without medical attention when he was 12 years old. There was no family history of sudden death. Emergency laboratory results were as follows: hemoglobin, 126 g/L, white blood cells, 11.55×10^9/L, platelet, 208×10^9/L, total bilirubin, 18.4 umol/L, alanine transaminase, 702 u/L, aspartate transaminase, 1197 u/L, creatinine, 143 umol/L, glucose, 17.5 mmol/L, lactate, 10.9 mmol/L, bicarbonate, 14.6 mmol/L, troponin I, 29.5 ng/ML, myoglobin, 18680 ng/ML, creatine kinase-MB, 501 u/L, N-terminal pro-BNP, 1430 pg/ML. An electrocardiogram showed a wide QRS complex tachycardia (**Figure 1A**). Emergency point-of-care ultrasound prompted: extremely weak heart contraction. Considering that the patient would suffer cardiac arrest again at any time, he was immediately admitted to the ICU.

When the ventilator with PEEP 16 cmH20, the patient still had a large amount of pink foamy sputum gushing out of the tracheal tube, and extensive blister sounds could be heard by stethoscope in both lungs. Simultaneously, he was anuria. High-dose vasopressor drugs (maximum norepinephrine, 3 ug/kg.min combinated epinephrine, 0.1 ug/kg.min [intravenously pumped]) were administered to maintain circulation. Fast echocardiography revealed diffusely weakened full ventricular wall motion and left ventricular ejection fraction (LVEF) of 20%. The patient was a student in the third year of junior high school, preparing for the high school entrance examination and was in a state of fatigue. He had no high-risk factors for myocardial infarction such as diabetes and coronary heart disease. Although he had no signs and symptoms of recent viral upper respiratory infection or enteroviral infection, he was diagnosed with acute fulminant myocarditis (FM), cardiogenic shock, malignant arrhythmias, cardiac arrest and post-CPR, multiple organ dysfunction syndrome, acute pulmonary edema, acute renal injury, acute hepatic dysfunction, and metabolism acidosis.

Considering his rapid clinical deterioration, bedside veno-arterial extracorporeal membrane oxygenation (VA ECMO) was implanted (right internal jugular vein-right femoral artery), and initial ECMO centrifugal pump speed was 3300 rpm which supported flow rate 3.0 L/min. The heat exchanger was setted 35.5°C to keep the patient's blood temperature was less than 36°C for brain resuscitation. The distal perfusion catheter was placed which directed a proportion of the returned oxygenated blood flow from the ECMO circuit to the distal of the right femoral artery to prevent limb ischemia. Considering the patient was volume overload, anuria, severe metabolic acidosis with acute renal injury, continuous renal replacement therapy (CRRT) was connected to the ECMO to provided solute depuration, fluid removal, and control of electrolyte and acid-base balance. The bleeding end of CRRT was connected behind the membrane of ECMO, and returned to the front of the ECMO membrane. Continuous venovenous hemofiltration (CVVH) with predominantly convective solute clearance was used. The formulation of CRRT was adjusted according to the blood gas results. He was administered high-dose methylprednisolone, concomitant antiviral therapy with acyclovir, and systemic anticoagulation with argatroban.

With the help of ECMO, the doses of vasopressor drugs were gradually reduced. After 20 h of ECMO, the patient became conscious and urinated with a urine output of 50 ml/h. We used remifentanil for pain relief and propofol for sedation, and we deactivated CRRT on hospital day (HD)3. By HD5, the patient's cardiac systolic function was progressively enhanced, and daily bedside echocardiography showed that LVEF gradually increased to 47% under the condition of ECMO flow rate of 2 L/min with 0.1 ug/min.kg of norepinephrine intravenously pumped. Therefore, we reduced the flow rate of ECMO to 1 L/min. There was no significant change in the patient's vasopressors for about 1 h, and ECMO was weaned. There was no significant change in the vasopressor drugs and LVEF after weaned from ECMO. Ventilator condition was pressure support ventilation (PSV) with the PEEP 6 cmH2O on HD6, so we removed the tracheal intubation. On the night of HD6, the patient complained of chest

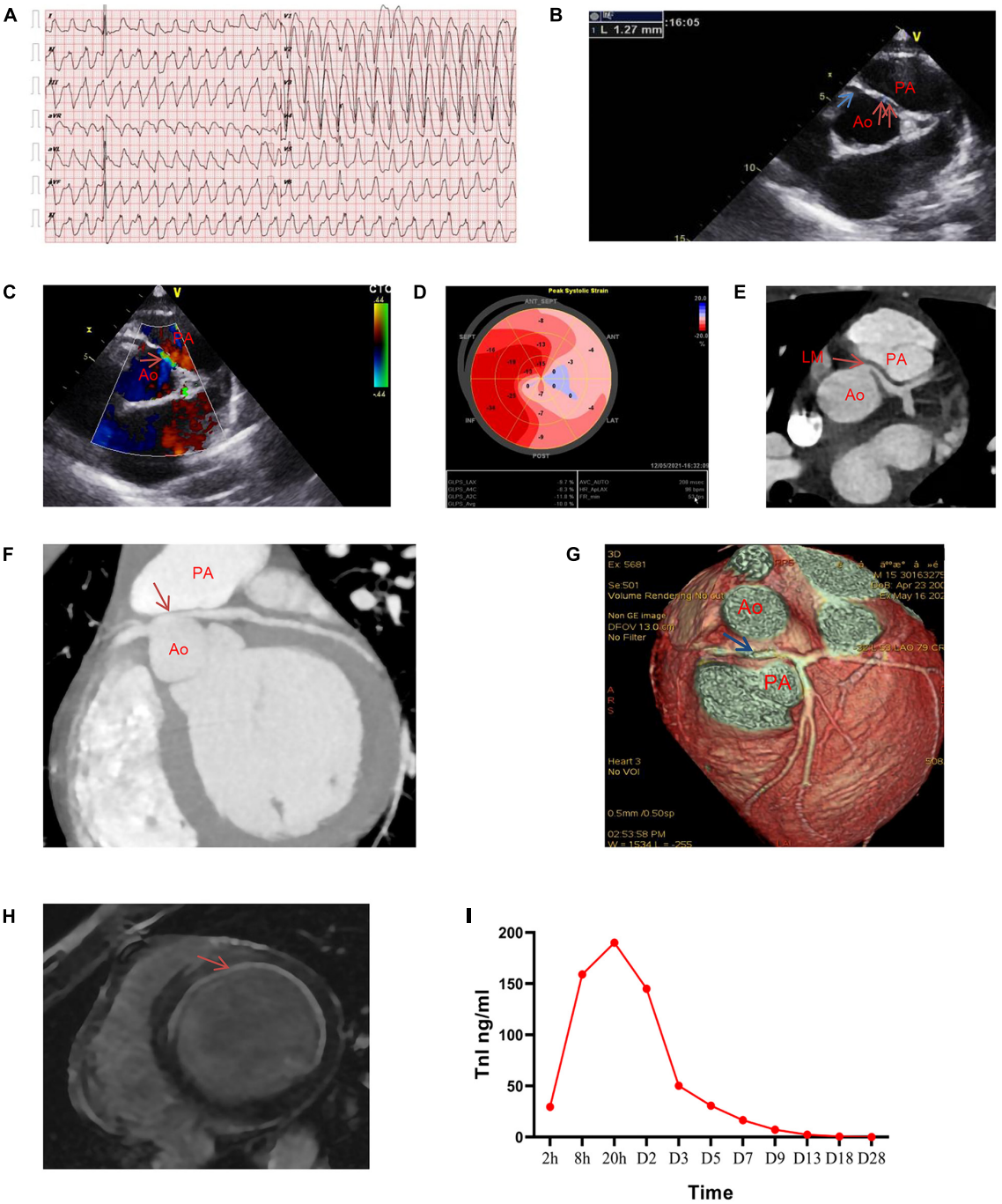

FIGURE 1 | Clinical images before surgery. **(A)** Emergency electrocardiogram revealing wide QRS complex tachycardia. **(B–D)** Images of transthoracic echocardiography on HD20 showing staged wall motion hypokinesia (extensive anterior wall, left ventricular lateral wall and apex), LVEF, 45%. **(B)** Parasternal short-axis view of echocardiography shows that the right coronary artery (blue single arrow) opens in the right coronary sinus, with an inner diameter of approximately 3.3 mm, and the left coronary artery (red double arrow) opens in the right coronary sinus and between the aorta and the pulmonary artery. The inner diameter of the opening is approximately 1.27 mm. **(C)** Acceleration of blood flow can be observed in the interarterial left main (LM) coronary artery (red arrow). **(D)** Ultrasound speckle tracking image shows the longitudinal strain of the anterior septum, left ventricular anterior wall, apex, anterior lateral wall, and posterior wall (left coronary artery area) decreases during systoling, whereas the posterior septum and left ventricular inferior wall (right coronary artery area) is normal. Left ventricular global longitudinal strain (GLS), –10%. **(E–G)** Images of coronary computed tomography angiography (CTA). Cross-sectional view of cardiac **(E)**, Maximum intensity projection (MIP) image **(F)**, and Volume-rendered (VR) image of the cardiac **(G)** revealing the left coronary artery originating from the right coronary sinus and coursing in an inter-arterial manner, with evident stenosis after being squeezed by the aorta and pulmonary artery. **(H)** Contrast-enhanced cardiovascular magnetic resonance image (MRI) reveals abnormal enhancement of left ventricular septum, anterior wall, lateral wall, considering the changes in subendocardial myocardial infarction. **(I)** Dynamic evolution of troponin I during hospitalization in the patient. LVEF, left ventricular ejection fraction; Ao, aorta; PA, pulmonary artery.

tightness and experienced cardiogenic shock again, while his blood pressure decreased, as low as 55/32 mmHg (0.3 ug/min.kg of norepinephrine combinated epinephrine 0.1 ug/min.kg). Bedside echocardiography revealed left ventricular filling, and his cardiac systolic function (LVEF, 38%) was worse than before (LVEF, 46% by HD6 before extubation). Thus, we placed IABP to support circulation. After the use of IABP, the patient's circulation improved again, the dose of vasopressor drugs was reduced. Repeat bedside echocardiography revealed that his cardiac function (LVEF, 46%) had improved. Therefore, we gradually reduced the IABP counterpulsation ratio from 1:1 to 1:3. At HD12, the IABP counterpulsation was stopped for 1 h. The patient had no chest tightness, normal urine output, no drop in blood pressure (0.05 ug/min.kg of norepinephrine), blood gas suggested no metabolic acidosis and IABP was removed.

The patient's vital signs were stable and there was no vasopressors on HD20. But his activity tolerance remained poor, and bedside echocardiography: left ventricular systolic function was still weak, and other cardiac functions were normal. Therefore, we decided to take the patient out of the ICU to further search for his underlying cause. Considering that he was a juvenile patient and suffered cardiac arrest after exercising, we began to pay attention to the coronary origin. Echocardiography on HD20 (**Figures 1B–D**) revealed LVEF, 45%. The left main (LM) coronary artery originated from the right coronary sinus with an initial interarterial course between the aorta and pulmonary artery, which was obviously compressed by the aorta especially during systole. The opening of the LM was narrowed with a diameter of 1.27 mm, and the blood flow of interarterial course was accelerated. Myocardial systolic longitudinal strain in the area of the left coronary artery was decreased (left ventricular global longitudinal strain [GLS], −10%). Coronary computed tomography angiography (CTA) (**Figures 1E–G**) revealed the varied origin of the left coronary artery, running between the aorta and pulmonary artery, and evident stenosis after being squeezed by the aorta and pulmonary artery. Contrast-enhanced cardiovascular magnetic resonance image (MRI) (**Figure 1H**) revealed abnormal enhancement of the left ventricular endocardium, suggesting subendocardial myocardial infarction. The patient's troponin I was up to 190 ng/ml (at 20 hours of onset), and then gradually decreased to normal level. **Figure 1I** showed dynamic evolution of troponin I during the patient's hospitalization.

The patient was diagnosed with congenital left coronary artery anomalies originating from the right coronary sinus with an interarterial course between the aorta and pulmonary artery, acute left ventricular subendocardial infarction, cardiogenic shock, malignant arrhythmias, cardiac arrest and post-CPR, multiple organ dysfunction syndrome, acute pulmonary edema, acute renal failure, acute hepatic dysfunction, and metabolism acidosis.

The patient had cardiac insufficiency, and New York Heart Association (NYHA) Class II. Therefore, long-term, restorative strategies for neuroendocrine inhibition with sacubitril/valsartan, metoprolol, and aspirin for platelet aggregation were administered therapeutically. On HD35, the patient was discharged, and follow-up treatment focused on improving myocardial remodeling and restoring cardiac function. Six months later, he underwent successful unroofing of the intramural portion in another hospital to relocate the left coronary artery in the appropriate sinus. Echocardiography 1 month post-operatively (**Figures 2A–C**) revealed LVEF, 40%, the opening diameter of the LM was 3.94 mm, and blood flow velocity was normal. Moreover, the GLS of the left ventricle was 6.1%. At follow-up, the patient came to our hospital for reexamination about once a month. He was in good physical and psychological condition. He had been taking oral sacubitril/valsartan, metoprolol, and aspirin. He was asymptomatic at rest, and his physical activity was mildly restricted (NYHA Class II cardiac function). The patient is currently suspended from school for recuperation, and at the same time studies moderately for 2 h a day, and is ready to return to school in the second half of the year. The progress and decision-making of the case above are reflected in the timeline (**Figure 3**).

DISCUSSION

Veno-arterial extracorporeal membrane oxygenation is a rescue therapy that can stabilize patients with hemodynamic compromise, with or without respiratory failure, for days or weeks (4). It is not uncommon to use ECMO, IABP, or a combination of both to rescue patients from cardiac arrest. But most of the studies were based on patients with cardiac arrest caused by acute coronary syndrome or acute fulminant myocarditis (5). We reported a case of ECMO followed by IABP successfully treated cardiac arrest and cardiogenic shock caused by AOCA.

The 14-year-old patient had cardiac arrest in the emergency room, and was in extremely critical state. In cardiology, the main indications for ECMO include cardiac arrest, cardiogenic shock, post-cardiotomy shock, refractory ventricular tachycardia, and acute management of complications of invasive procedures (4). Therefore, he had an absolute indication of ECMO. Considering the patient was volume overload, anuria, severe metabolic acidosis with acute renal injury, CRRT was connected to the ECMO. Among patients with cardiac arrest and ECMO support, those receiving CRRT tended to be more critically ill and had reduced survival (6). However, this patient had a good survival outcome, and it can provide the clinician with the treatment experience of ECMO combined with CRRT. On the night of the extubation, the patient experienced cardiogenic shock again. The reason could be without PEEP after extubation, the patient's blood volume returned to the heart was increased more than before. IABP can reduce afterload, increase cardiac output, optimize coronary flow and decrease oxygen consumption. It has been used to improve hemodynamic parameters in patients with cardiogenic shock for more than four decades (7). So the placement of IABP supported the patient's circulation.

The most common cause of cardiac arrest and cardiogenic shock was acute myocardial infarction, and a small part of the cause was acute FM, especially in young people (8). Fulminant myocarditis (FM) is an uncommon syndrome characterized

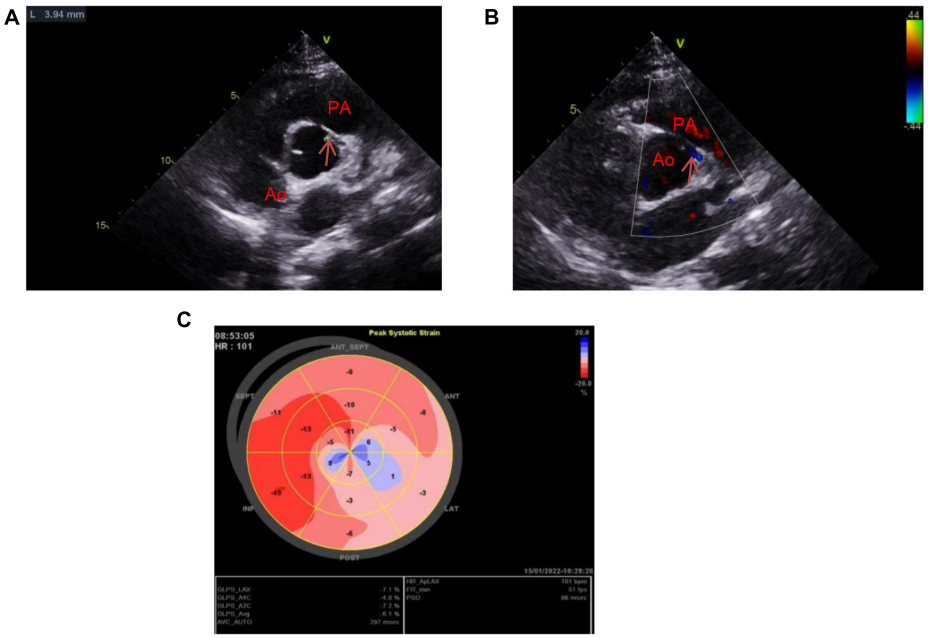

FIGURE 2 | Images of transthoracic echocardiography 1 month post-operatively illustrating staged ventricular wall motion hypokinesia (extensive anterior wall, left ventricular lateral wall, and apex) and LVEF, 40%. **(A)** After unroofing of the intramural portion, the diameter of the left coronary ostium is approximately 3.94 mm. **(B)** The LM blood flow is in normal velocity. **(C)** Ultrasound speckle tracking image shows GLS of the left ventricle, –6.1%.

by sudden and severe diffuse cardiac inflammation often leading to death resulting from cardiogenic shock, ventricular arrhythmias, or multiorgan system failure (9). In the real-world practice the diagnosis of FM has undoubtedly shifted from being mainly biopsy-based to cardiac magnetic resonance imaging-based (CMRI-based) for characterizing myocardial tissue changes and the measurement of high-sensitive troponin levels for identifying myocardial injury in most of clinical scenarios (10). But CMRI is not the initial diagnostic technique in patients in critical conditions (10). This patient was a 14-year-old teenager with no previous high-risk factors for myocardial infarction such as diabetes and coronary heart disease. In the pre-morbidity, he was tired due to preparing for the senior high school entrance examination. He was running at the time of onset. After resuscitation, arrhythmia was manifested as unsustainable circulation, severe cardiogenic shock, and elevated troponin level. The electrocardiogram showed wide QRS tachycardia, and there was no clear coronary location. The initial clinical diagnosis was considered to be acute FM, but not acute myocardial infarction. Therefore, we did not urgently perform coronary angiography with the support of ECMO.

The patient's vital signs in the later stage of hospitalization were relatively stable, but his cardiac function remained diminished. And then, it was very important to went out of the ICU to further improved the inspections (e.g., coronary ultrasound, coronary CTA, and cardiac MRI). The congenital abnormal origin of the left coronary artery was detected using transthoracic echocardiography, and confirmed with cardiac CTA. Enhanced cardiac MRI showed the acute subendocardial myocardial infarction of the left ventricle, confirming the etiological diagnosis.

The anomalous origin of the left coronary artery arising from the right coronary sinus is rare, approximately 0.01–0.04% (2). The abnormal coronary artery originating from the contralateral coronary sinus and running between the aorta and pulmonary artery with intramural deviation, is related to sudden death (grade III) (11). The patient had a history of syncope during exercise and accompanied by a significant increase in troponin I (up to 190 ng/ml). The pathogenesis of the patient may be that the compensatory cardiac systolic function was enhanced during vigorous activity, and the gap between the dilated aorta and the pulmonary artery became smaller, resulting in a exacerbated clamping effect, squeezing the LM, also known as "coronary artery sandwich anomaly" (12). This can lead to complete occlusion of the LM, causing acute subendocardial myocardial infarction and fatal malignant arrhythmias.

The presence of a AOCA can be suspected in the case of a young individual with ischemia-like symptoms (13). Coronary CTA is currently considered the gold standard, and cardiac MRI is becoming an alternative. Because of coronary angiography's invasiveness, relatively low spatial resolution, and lack of 3-dimensional images, it has been progressively replaced by coronary CTA (13). Transthoracic echocardiography is considered a key examination in the diagnostic workup of AOCAs in children, in whom optimal acoustic windows commonly allow the visualization of coronary ostia without radiation exposure (13). Although coronary angiography is not the gold standard for diagnosing AOCA, lack of early coronary angiography in this case is still a limitation of this case. Coronary

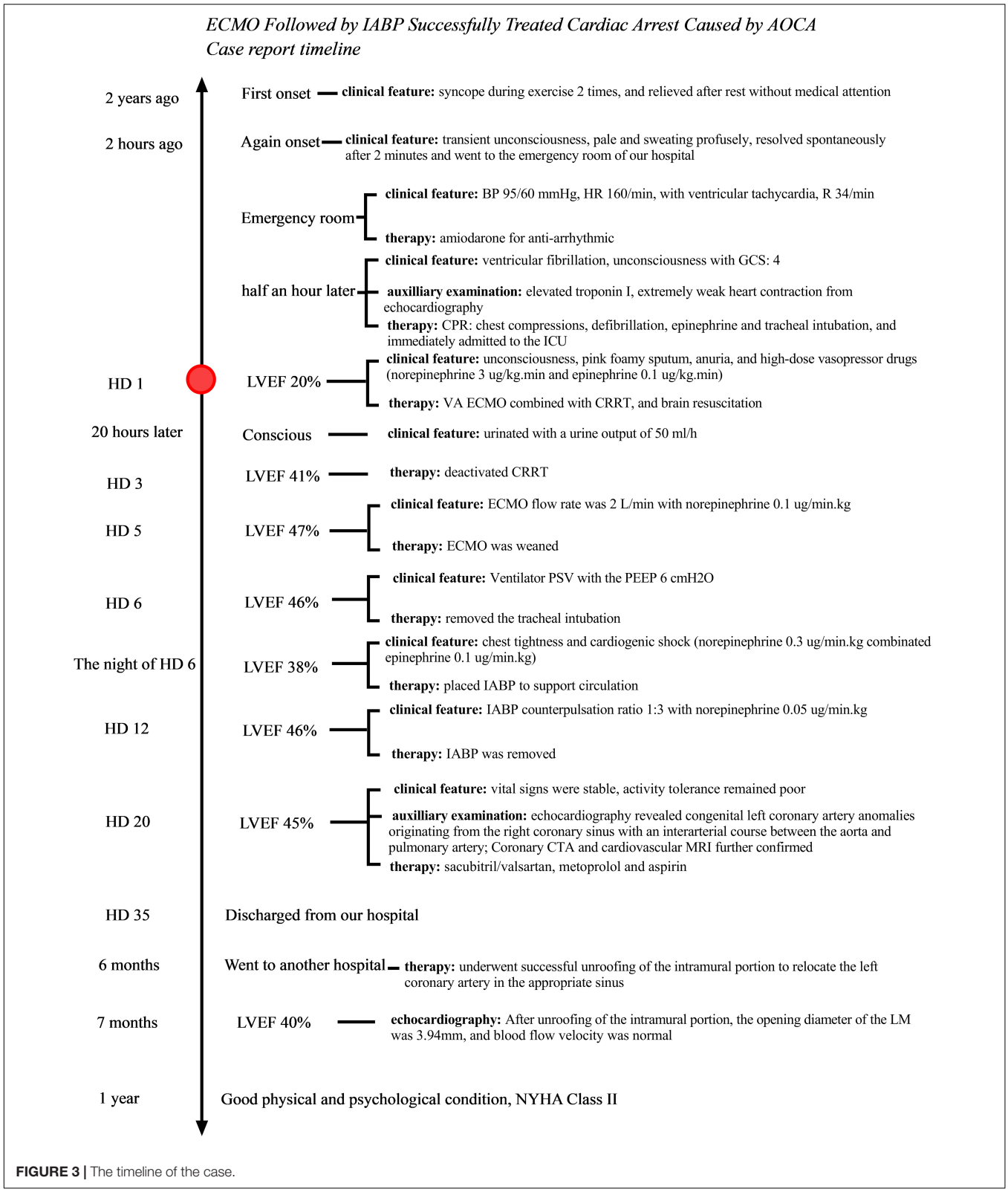

FIGURE 3 | The timeline of the case.

angiography remains critical in the diagnosis and differential diagnosis of patients with cardiogenic shock. Echocardiography in children with cardiogenic shock, attention should be paid to the origin of coronary arteries. ECMO and IABP can support the circulation of patients, so that patients can survive the period of malignant arrhythmia and severe shock, and the definitive

diagnosis can be identified and treated later. This suggests that it is important to investigate the causes of the critically ill patients' condition, but saving lives remains the first priority. For adolescent patients, sudden cardiorespiratory arrest, especially when related to increased activity, should be carefully ruled out to exclude congenital coronary artery origin and abnormal course, to reduce the occurrence of subsequent malignant events.

CONCLUSION

The successful treatment of this patient was attributed to the rapid ECMO assisted circulation, supplemented by IABP. Establishing clear diagnosis is a process of multidisciplinary joint diagnosis, which provides a reference for clinicians when encountering similar cases.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

XX, PX, and RZ drafted the manuscript and contributed to the case collection. XW, YC, and XH provided figures and formalized the manuscript. HL and JY reviewed the drafts and approved the final manuscript as submitted. All authors approved the submitted version.

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ORIGINAL RESEARCH
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An Agreement Study Between Point-of-Care and Laboratory Activated Partial Thromboplastin Time for Anticoagulation Monitoring During Extracorporeal Membrane Oxygenation

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Background: Laboratory activated partial thromboplastin time (LAB-aPTT) is a widely used laboratory assay for monitoring unfractionated heparin (UFH) therapy during extracorporeal membrane oxygenation (ECMO). But LAB-aPTT is confined to a central laboratory, and the procedure is time-consuming. In comparison, point-of-care aPTT (POC-aPTT) is a convenient and quick assay, which might be a promising method for anticoagulation monitoring in ECMO. This study was aimed to evaluate the agreement between POC-aPTT (hemochron Jr. Signature instruments) and LAB-aPTT for anticoagulation monitoring in adult ECMO patients.

Methods: Data of ECMO-supported adult patients anticoagulated with UFH in our institute from January 2017 to December 2020 was retrospectively reviewed. POC-aPTT and LAB-aPTT results measured simultaneously were paired and included in the analysis. The correlation between POC-aPTT and LAB-aPTT was assessed using Spearman's correlation coefficient. Bias between POC-aPTT and LAB-aPTT were described with the Bland-Altman method. Influence factors for bias were identified using multinomial logistic regression analysis.

Results: A total 286 pairs of aPTT results from 63 patients were included in the analysis. POC-aPTT and LAB-aPTT correlated weakly (r = 0.385, P < 0.001). The overall bias between POC-aPTT and LAB-aPTT was 7.78 [95%CI (−32.49, 48.05)] s. The overall bias between POC-aPTT and LAB-aPTT ratio (to normal value) was 0.54 [95%CI (−0.68, 1.76)]. A higher plasma fibrinogen level [OR 1.353 (1.057, 1.733), P = 0.017] was associated with a higher chance of POC-aPTT underestimating LAB-aPTT. While a lower plasma fibrinogen level [OR 0.809 (0.679, 0.963), P = 0.017] and lower UFH rate [OR

0.928 (0.868, 0.992), $P = 0.029$] were associated with a higher chance of POC-aPTT overestimating LAB-aPTT.

Conclusion: The present study showed poor agreement between POC-aPTT and LAB-aPTT. POC-aPTT was not suitable for anticoagulation monitoring in adult ECMO patients.

Keywords: activated partial thromboplastin time, point of care, extracorporeal membrane oxygenation, anticoagulation, unfractionated heparin

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) provides effective respiratory and circulatory support for patients with refractory respiratory failure or cardiogenic shock, improving the survival of these critically ill patients (1–3). In recent years, with the advancement of management and technology, ECMO has been increasingly utilized worldwide. Exposure of blood to non-biological surfaces and the shear stresses of the ECMO circuit activate the coagulation system. Initial fibrinogen deposition and subsequent activation of coagulation factors and complement allow platelets and leucocytes to adhere to the circuit surfaces and enhance thrombin generation (4, 5). Anticoagulation is required to prevent clot formation in this setting. Unfractionated heparin (UFH) is the most commonly used anticoagulant.

Point-of-care (POC) activated clotting time (ACT) is the most convenient and commonly used method for anticoagulation monitoring in ECMO. However, the correlation between ACT and heparin concentration is poor (6, 7). Laboratory activated partial thromboplastin time (LAB-aPTT) is a plasma-based assay and is considered superior to the point-of-care ACT as it shows a better correlation with UFH concentration (8). However, LAB-aPTT is confined to the central laboratory, and the procedure is time-consuming.

Several commercial point-of-care aPTT (POC-aPTT) instruments, including Hemochron Jr. Signature (Accriva Diagnostics, Inc., United States), could offer bedside POC-aPTT results within 3 min, making it a promising method for anticoagulation monitoring during ECMO. Hemochron Jr. Signature aPTT is a whole blood test, and the plasma aPTT is converted and displayed based on the whole blood result (9). The 2021 ELSO anticoagulation guideline mentioned that POC-aPTT test was available but with very limited studies on ECMO (10).

This study was aimed to evaluate the agreement between Hemochron Jr. Signature POC-aPTT and LAB-aPTT test.

MATERIALS AND METHODS

Patients

This was a single-center retrospective study. The study was approved by the institutional ethics board of Fuwai Hospital (NO.2021-1496). The requirement for written informed consent was waived.

This study retrospectively reviewed the clinical data of consecutive adult veno-arterial ECMO (VA-ECMO) patients at Fuwai Hospital from January 2017 to December 2020. Patients who had POC-aPTT and LAB-aPTT measured simultaneously were included in the study. Exclusion criteria were as follows: age < 18 years old, ECMO running time < 48 h, inter-hospital transfer on ECMO, using other anticoagulants (argatroban or bivalirudin).

Extracorporeal Membrane Oxygenation Management

The indication for VA-ECMO was refractory cardiogenic shock or acute heart failure despite maximum vasoactive agents (VIS > 40) and adequate volume therapy, with at least one of the following indexes: cardiac index < 1.8 L/min/m^2; left atrial pressure or pulmonary capillary wedge pressure > 20 mmHg; systolic arterial blood pressure < 90 mmHg or mean arterial pressure < 60 mmHg; urine output < 0.5 mL/kg/h, and uncorrectable/continuous metabolic acidosis. The contraindications were (1) severe irreversible neurological injury; (2) irreversible cardiac failure if transplantation or long-term VAD was not considered; (3) contraindication to anticoagulation; (4) uncontrolled surgical massive bleeding. The decision to initiate ECMO was made by a multidisciplinary ECMO team consisting of cardiologists, cardiac surgeons, intensivists, and perfusionists. Femoral-femoral cannulation was preferred in our institute. Central cannulation was chosen when femoral access was difficult or when the patient was complicated with respiratory failure.

MAQUET BE PLS 2050 circuit was used. ECMO flow was initially set at 50∼70 ml/(kg·min) and then adjusted to maintain hemodynamic stability and sufficient oxygen supply. UFH was the standard anticoagulant. For non-cardiotomy patients, 50–100 units/kg UFH was given to achieve a goal of ACT 180–200 s before cannulation. For post-cardiotomy patients, UFH was not given until bleeding was controlled with ACT or aPTT below target ranges.

ACT and POC-aPTT were monitored during ECMO every 3 h, while LAB-aPTT was monitored two to four times a day. UFH was titrated according to the above tests and the hemostatic status of the patients. Generally, aPTT goal was 50–80 s. UFH infusion rate was increased or

Abbreviations: VA-ECMO, veno-arterial extracorporeal membrane oxygenation; LAB-aPTT, laboratory activated partial thromboplastin time; POC-aPTT, point of care activated partial thromboplastin time; UFH, unfractionated heparin; ACT, activated clotting time; VIS, maximum vasoactive agents; ICU, intensive care unit; PPV, positive predictive value; NPV, negative predictive value.

decreased by 1–2 units/kg/h when aPTT was below 50 s or above 80 s, respectively. In situations of bleeding, the goal was 50–60 s. When clots were observed in the oxygenator and the risk of bleeding was low, the goal was 70–80 s or even higher.

Red blood cells (RBC) were transfused when hemoglobin was below 80 g/L. Platelet transfusion trigger was $50 \times 10^{9}/L$. Fibrinogen was given when the fibrinogen level was below 150 mg/dL. Fresh frozen plasma (FFP) was indicated when antithrombin III level was below 50% or INR was below 1.5.

Point of Care Activated Partial Thromboplastin Time Test

POC-aPTT was performed immediately after the blood sample was drawn from the patient using Hemochron Jr. Signature instrument (Accriva Diagnostics, Inc., United States). 50 μl of whole blood was disposed in the well of a specific 37°Cprewarmed size-use cartridge. The equipment automatically drew 15 μl of whole blood into the test tube. After mixing with the reagents, the sample was then exposed to optical detectors. The formation of a clot was indicated to the detectors by a slowing of the flow in the chamber. An internal chronometer linked to the detectors measured the time required to form the clot. POC-aPTT test cuvette was a self-contained disposable test chamber preloaded with a dried preparation of kaolin, phospholipid, stabilizers and buffers. The instrument reported plasma equivalent values mathematically converted from whole blood test results. The normal range of POC-aPTT was 23.2–38.7 s.

Laboratory Activated Partial Thromboplastin Time Test

LAB-aPTT was measured within 4 h after the blood sample was drawn from the patient. Before the test, the blood sample was stored at room temperature. LAB-aPTT was performed using Stago STA-R Evolution coagulation analyzer and original reagents (STA®PTTA, Stago, France). Reagents contained cephalin prepared from rabbit cerebral tissues and a particulate activator (silica) in a buffered medium, lyophilized. The time of fibrin formation was measured in the absence of cellular components by adding activators (silica), calcium and phospholipids to plasma samples. In addition, laboratory staff regularly carried out quality control of LAB-aPTT testing instruments and reagents (STA®—System Control N + P). The normal range was 28.5–43.5 s.

Data Collection and Categories

Data of the patients were retrospectively collected from the electronic medical record system, including demographics, indications, ECMO information, coagulation parameters and outcomes. LAB-aPTT and POC-aPTT tests of samples drawn at the same time were paired and included in the analysis. Laboratory test results of samples drawn at the same time and UFH dose were also collected.

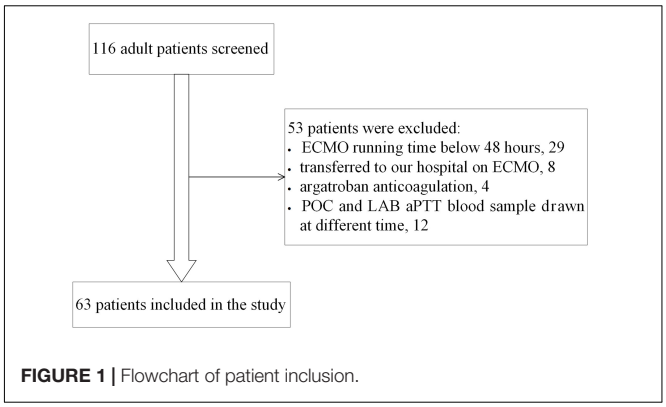

FIGURE 1 | Flowchart of patient inclusion.

Pairs of LAB-aPTT and POC-aPTT tests were classified into three bias categories depending on bias between POC aPTT and LAB aPTT value: (1) underestimate category: bias < -10 s; (2) accurate category: bias $-10 \sim 10$ s; (3) overestimate category: bias > 10 s.

Statistical Analysis

Continuous variables with normal distribution were presented as mean ± standard deviation and compared using the one-way ANOVA test. Continuous variables with abnormal distribution were presented as median (interquartile range) and compared using the Kruskal-Wallis test.

The agreement between POC-aPTT and LAB-aPTT for anticoagulation monitoring was assessed step by steply.

Firstly, correlations among LAB-aPTT, POC-aPTT and UFH doses were evaluated using the Spearman correlation coefficient.

Secondly, the Bland and Altman plots method was performed to describe biases between LAB-aPTT and POC-aPTT. The limits of agreement between LAB-aPTT and POC-aPTT were presented as bias (1.96 SD). aPTT values and aPTT ratios of the values to normal control were analyzed separately.

The Kruskal-Wallis test and multinomial logistic regression analysis were employed to analyze the association between biases (classified into three bias categories as mentioned above) and a set of variables including blood hemoglobin level, blood platelet count, plasma fibrinogen level, plasma D-dimer level, plasma antithrombin activity (AT), plasma prothrombin time (PT), and UFH dose. The variables were chosen because they were related to the coagulation system, and they were measured from the same blood sample with LAB aPTT. Only statistically significant variables in Kruskal-Wallis tests were used as covariates in multinomial logistic regression analysis. The reference category for the outcome variable was "accurate," and each of the other two categories was compared to this reference group.

Thirdly, the predictive performance of POC-aPTT for guiding UFH dose titration was evaluated, taking LAB-aPTT as the gold-standard method. The goals of aPTT varied across centers. aPTT could be maintained within the range of 50–80 s or 1.5–2.5 times normal, according to expert recommendations (10–12). Positive

TABLE 1 | Patient characteristics (n = 63).

Variables	All patients (n = 63)
Demographic data	
Age (year)	47.49 ± 13.12
Male, *n* (%)	36 (57.1%)
Height (cm)	166.6 ± 8.79
Weight (kg)	65.45 ± 12.75
Indication	
Postcardiotomy, *n* (%)	46 (73%)
Non-postcardiotomy, *n* (%)	17 (27%)
Laboratory values at 6 h after ECMO initiation	
Hemoglobin (g/L)	94 (81.5, 109.3)
Platelets (10^9/L)	88.5 (56.3, 149.3)
Creatinemia (μmol/L)	135.5 (116.1, 163.1)
Prothrombin time (s)	18.75 (16.28, 23.63)
Total bilirubin (μmol/L)	37.09 (22.88, 54.35)
Lactate (mmol/L)	6.75 (3.78, 11.10)
Outcome	
30-day Mortality, *n* (%)	25 (39.7%)
Duration of ECMO (hours)	153 (96, 192)
Mechanical ventilation time (days)	9 (6, 16)
Duration in the ICU (days)	18 (10, 27)
Length of stay (days)	33 (21, 45)
CRRT, *n* (%)	27 (42.9%)
Red blood cells transfusion during ECMO (u)	10 (4, 14)
Fresh frozen plasma transfusion during ECMO (ml)	800 (400, 1,800)
Platelet transfusion during ECMO (u)	1 (0, 3)

ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; ICU, intensive care unit.

predictive value (PPV) and negative predictive value (NPV) for diagnosing an aPTT <50 s (or < 1.5 times normal), 50–80 s (or 1.5–2.5 times normal) and >80 s (or >2.5 times normal) were calculated, respectively.

Statistical analysis was performed using SPSS 25.0 (IBM Corp., Chicago, IL, United States). For all analyses, 2-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Sixty-three eligible patients were included in the study (**Figure 1**), with 286 pairs of aPTT tests included in the agreement analysis. Forty-six patients (73%) were in the post-cardiotomy group. 30-day survival rate before discharge was 60.3%. Data of the patients are shown in **Table 1**.

Correlations Among Laboratory Activated Partial Thromboplastin Time, Point of Care Activated Partial Thromboplastin Time, and Unfractionated Heparin Doses

POC-aPTT and LAB-aPTT correlated weakly (r = 0.385, $P < 0.001$). UFH dose and LAB-aPTT correlated weakly (r = 0.31, $P < 0.001$). There was no correlation between UFH dose and POC-aPTT (r = 0.006, P = 0.917). Scatterplots of these data were depicted in **Figure 2**.

Bias Between Point of Care Activated Partial Thromboplastin Time and Laboratory Activated Partial Thromboplastin Time

Bland- Altman analysis for 286 pairs of aPTT tests showed that the overall bias between POC-aPTT and LAB-aPTT was 7.78 [95%CI (−32.49, 48.05)] s (**Figure 3A**). The overall bias between POC-aPTT and LAB-aPTT ratio (to normal value) was 0.54 [95%CI (−0.68, 1.76)] (**Figure 3B**).

Bland-Altman analyses were performed in postcardiotomy and non-postcardiotomy groups, respectively, to evaluate the influence of cardiac surgery on the consistency of the two methods. The biases of aPTT value in the postcardiotomy group and the non-postcardiotomy group were 5.06 [95%CI−28.82, 38.94)] s and 13.08 [95%CI (−34.84, 60.99)] s, respectively. The biases of aPTT ratio in postcardiotomy group and non-postcardiotomy group were 0.45 [95%CI (−0.55, 1.45)] and 0.70 [95%CI (−0.75, 2.15)], respectively (**Supplementary Figure 1**).

Influence Factors for Biases

Blood hemoglobin level, blood platelet count, plasma fibrinogen level, plasma D-dimer level, AT activity, PT, UFH dose, and LAB-aPTT were compared among the three bias categories (**Table 2**). Three statistically significant covariates (plasma fibrinogen level, AT activity, UFH dose) were put into the multinomial logistic regression analysis. A higher plasma fibrinogen level [OR 1.353 (1.057, 1.733), P = 0.017] was associated with a higher chance of POC-aPTT underestimating LAB-aPTT. While a lower plasma fibrinogen level [OR 0.809 (0.679, 0.963), P = 0.017] and a smaller UFH dose [OR 0.928 (0.868, 0.992), P = 0.029] were associated with a higher chance of POC-aPTT overestimating LAB-aPTT (**Table 3**).

Predictive Performance of Point of Care Activated Partial Thromboplastin Time on Unfractionated Heparin Doses Titration

Supplementary Tables 1, **2** showed distributions of aPTT results according to target ranges. Taking LAB-aPTT as a gold method, the predictive performance of POC-aPTT to accurately guide UFH dose titration was very poor. The diagnostic PPV and NPV of POC-aPTT to diagnose an aPTT <50 s (or < 1.5 times normal), 50–80 s (or 1.5–2.5 times normal) and > 80 s (or > 2.5 times normal) were listed in **Table 4**.

DISCUSSION

The present study was aimed to explore the agreement between POC-aPTT and LAB-aPTT for anticoagulation monitoring during ECMO. The results showed discordance between the two assays. Firstly, POC-aPTT and LAB-aPTT correlated weakly

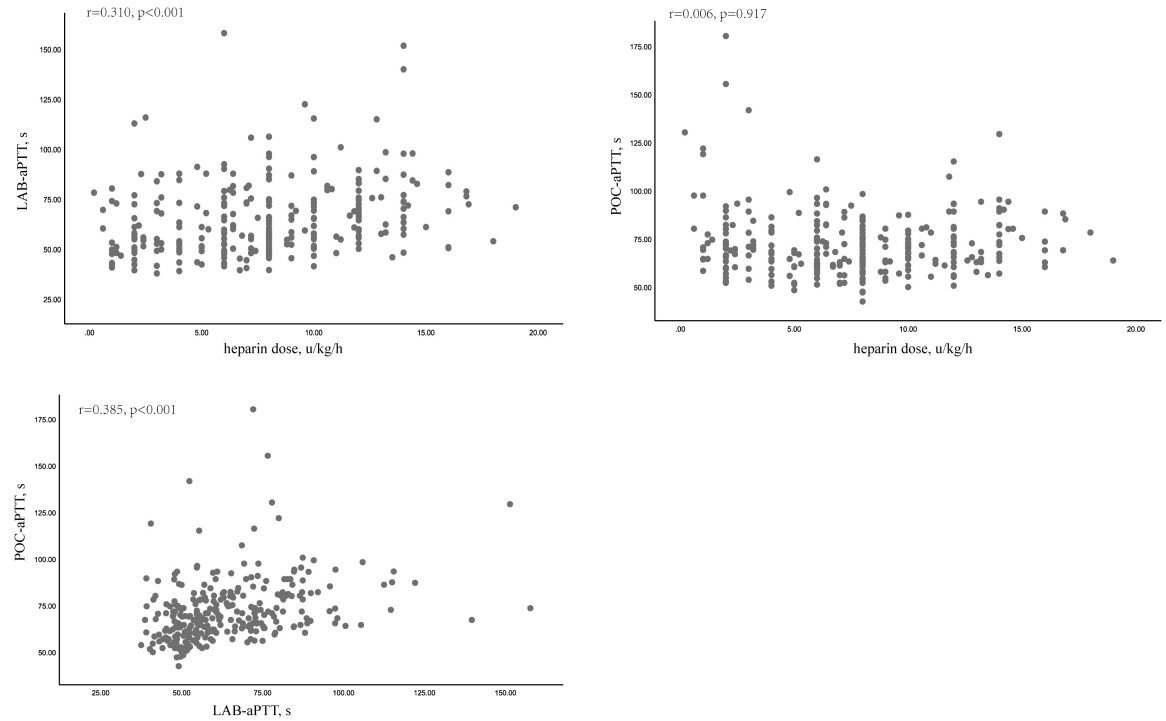

FIGURE 2 | Correlations among LAB-aPTT, POC-aPTT and UFH doses.

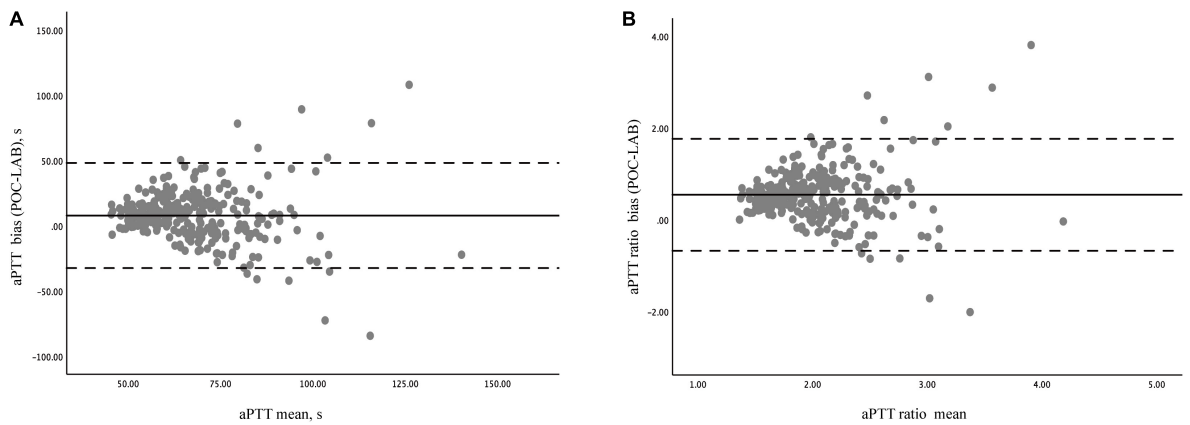

FIGURE 3 | Bland –Altman diagram of the difference and agreement between POC-aPTT and LAB-aPTT. **(A)** The total bias between POC-aPTT and LAB-aPTT value. POC-LAB: POC-aPTT value—LAB-aPTT value, aPTT mean: 1/2 × (POC-aPTT value + LAB-aPTT value). **(B)** The total bias between POC-aPTT and LAB-aPTT ratio. POC-LAB ratio: POC-aPTT ratio to the normal value—LAB-aPTT ratio to the normal value, aPTT ratio mean: 1/2 × (POC-aPTT ratio to the normal value + LAB-aPTT ratio to the normal value). The bias representatives the systematic error between the two judgments (bold line), the mean difference ± 1.96 standard deviations represents the limit of agreement or the 95% confidence interval (dotted line).

(r = 0.385, P < 0.001). No correlation was found between POC-aPTT and UFH dose. Secondly, the bias between POC-aPTT and LAB-aPTT was large (7.78 [95%CI (−32.49, 48.05)]). Thirdly, the agreement for guiding UFH titration between the two methods was poor.

The result of our study was similar to Ferring's study, which reported a large bias (17 ± 33.1 s) between POC-aPTT (CoaguCheck® Pro, Boehringer Mannheim Diagnostics, United States, Roche Diagnostics, Switzerland) and LAB-aPTT in surgical intensive care patients following cardiovascular or major abdominal surgery (13). Gauss et al. reported the bias between POC-aPTT (Hemochron Jr. Signature instruments) and LAB-aPTT ratio was 1.13 in patients with acute hemorrhage. 89% of the POC-aPTT values exceeded the predefined limits of agreement (9).

Methodological differences account for poor agreement between POC-aPTT and LAB-aPTT, with different reagents

TABLE 2 | Univariate analysis for bias categories.

Variables	Total	Underestimate bias <-10 (n = 36)	Accurate -10 ≤ bias ≤ 10 (n = 120)	Overestimate bias>10 (n = 130)	P-value
Hemoglobin (g/L)	92 (87,102)	93.5 (88,100)	91 (86,96.5)	91.5 (86,107)	0.187
Platelets (10^9/L)	64.5 (47,91)	72 (50.5,102)	60 (47.5,81.5)	58.5 (43,87)	0.270
Fibrinogen (g/L)	4.09 (2.94,5.39)	5.335 (4.40,6.30)	4.43 (3.55,5.70)	3.875 (2.82,4.54)	**0.000**
D-dimer	4.32 (2.23,7.59)	4.585 (3.09,7.37)	3.5 (1.97,6.64)	5.03 (2.43,9.27)	0.130
AT (%)	64 (46.25,78)	73 (61,87)	65 (54.5,79)	61.5 (43,80)	**0.001**
PT (s)	15.8 (14.6,18.6)	15.9 (14.9,17.6)	15.6 (14.4,17.7)	15.75 (14.5,18.8)	0.176
INR	1.26 (1.14,1.57)	1.265 (1.16,1.45)	1.24 (1.12,1.48)	1.26 (1.14,1.59)	0.126
UFH dose (u/kg/h)	8 (4.6,10)	8 (7,11.3)	8 (5.65,10.8)	6.55 (2,10)	**0.000**

AT, antithrombin; PT, prothrombin time; INR, international normalized ratio; UFH, unfractionated heparin; LAB-aPTT, laboratory activated partial thromboplastin time. Bold values indicate P values with statistically significant.

TABLE 3 | Multinomial logistic regression analysis for bias categories.

Covariates	Underestimate vs. accurate					Overestimate vs. accurate				
	Estimate (SE)	OR	95% Wald CL for OR		P-value	Estimate (SE)	OR	95% Wald CL for OR		P-value
			Lower	Upper				Lower	Upper	
Fibrinogen (g/L)	0.302 (0.126)	1.353	1.057	1.733	**0.017**	−0.212 (0.089)	0.809	0.679	0.963	**0.017**
AT (%)	0.013 (0.011)	1.014	0.992	1.035	0.218	−0.008 (0.007)	0.992	0.979	1.005	0.241
UFH dose (u/kg/h)	0.027 (1.033)	1.027	0.924	1.142	0.615	−0.075 (0.034)	0.928	0.868	0.992	**0.029**

SE, standard error; OR, odds ratio; AT, antithrombin; LAB-aPTT, laboratory activated partial thromboplastin time; POC-aPTT, point of care activated partial thromboplastin time. Bold values indicate P values with statistically significant.

and equipment. POC-aPTT test reagents are phospholipids and kaolin, while LAB-aPTT uses silicon dioxide, ellagic acid, calcium and phospholipid. The differences in reagents also account for the discordance between point-of-care viscoelastic coagulation tests in ECMO. Giani et al. (14) compared rotational thromboelastometry (ROTEM) INTEM assay, kaolin thromboelastography (TEG) and LAB-aPTT for ECMO anticoagulation monitoring and found that correlation with LAB-aPTT was higher for INTEM clotting time (R^2 = 0.34, P < 0.001) compared with Kaolin TEG R time (R^2 = 0.08, P = 0.014). A potential explanation was that compared to kaolin TEG, the reagent of INTEM was more similar to LAB-aPTT. The activator in Kaolin TEG assay is kaolin, while INTEM (ROTEM) activators are phospholipid and ellagic acid. The pre-analysis variables such as collection tube citrate concentration might incur variations between the two techniques (15).

Secondly, the results of the POC-aPTT test are not actually derived from plasma, which instead are obtained *via* whole blood tests and converted to plasma aPTT levels with an algorithm. The results of POC-aPTT are theoretically calibrated based on normal hematocrit and platelet count (16). Hemodilution, high shear force, hemolysis, UFH anticoagulation, and surgical bleeding during ECMO can decrease hemoglobin and platelet counts (17, 18). A study showed that the changes in hematocrit and platelet levels of blood samples might affect POC aPTT results (16), although the current study did not find the association of hematocrit and platelet with aPTT bias. Furthermore, the manufacturer's specification also recommends that blood samples with HCT < 20% should not be used for POC-aPTT measurement because the optical density of the sample is beyond the detection range of the instrument. In our study group, only 10% of the blood sample had blood hemoglobin levels below 8 g/dl.

TABLE 4 | Positive predictive value (PPV) and negative predictive value (NPV) of POC-aPTT taking LAB-aPTT as the gold standard method.

	PPV	NPV
POC-aPTT value		
<50 s	80.0%	77.9%
50–80 s	63.0%	50.0%
>80 s	36.9%	88.7%
POC-aPTT ratio to normal control		
<1.5	100%	66.3%
1.5–2.5	54.2%	28.2%
>2.5	11.9%	95.5%

Thirdly, the activation of blood components and coagulation pathway factors during ECMO might also affect the agreement of the two methods. In our study, we found that fibrinogen affected the bias between POC-aPTT and LAB-aPTT. A recent study also found that increased fibrinogen, FVIII, FXI, and FXII levels in ICU patients attenuated the association between POC-aPTT and LAB-aPTT (19). Toulon found the agreement between POC-aPTT (CoaguChek^{TM} Pro DM) and LAB-aPTT was unacceptable in patients undergoing bleeding surgery (20), and the bias of POC and LAB -aPTT increased with the increasing severity of coagulopathy. Considering cardiac surgery may lead to coagulopathy (21, 22), we performed subgroup Bland-Altman analyses in cardiotomy and non-cardiotomy groups and poor agreement was found in both populations.

In addition, our study found that a smaller UFH dose was associated with a higher chance of POC-aPTT overestimating LAB-aPTT. Therefore, when the UFH infusion rate was low,

using POC-aPTT for anticoagulation monitoring would increase the risk of thrombosis.

Although the agreement with LAB-aPTT is poor, POC-aPTT is still of some value during ECMO, especially when timely anticoagulation monitoring is required or during ECMO transport when LAB-aPTT is not available. The turnaround time of POC-aPTT is much shorter than LAB-aPTT. Lardinois reported that the turnaround time of LAB-aPTT was 92.0 min (IQR, 69.3–121.2), much longer than that of POC-aPTT ($P < 0.0001$) (19). A shorter turnaround time could help reduce thrombotic and hemorrhagic complications by avoiding insufficient or excessive anticoagulation, especially in the early stage of the ECMO run. PPV for diagnosing an aPTT value below 50 s was 80% in our study. Another study found a good correlation between LAB-aPTT and POC-aPTT when the results were < 60 s (23). Therefore, POC-aPTT could help identify insufficient anticoagulation quickly and prevent thrombosis in the ECMO circuit, which is essential in ECMO transport and during massive blood transfusions.

This study had some limitations. First of all, it was a retrospective study. Some essential variables were not available for analysis, including anti-Xa and coagulation factors. In our institute, coagulation factors were not routinely measured. Anti-Xa was not used for anticoagulation monitoring in ECMO patients until recently. Second, measurement failure could not be excluded. Third, only VA-ECMO patients were included in the study as our institute was a specialized cardiac center. Moreover, in the predictive performance analysis, aPTT goal was not determined according to the anti-Xa test locally. Finally, we did not compare POC-aPTT and LAB-aPTT on bleeding and thrombosis events as it was tough to retrospectively determine clinical hemostasis and bleeding status within 1–3 h before aPTT were tested.

CONCLUSION

The present study showed poor agreement between POC-aPTT and LAB-aPTT. POC-aPTT was not suitable for anticoagulation monitoring in adult ECMO patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study was approved by the Institutional Ethics Board of Fuwai Hospital (No.2021-1496), and the individual consent for this retrospective analysis was waived. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YT and SY designed the study, extracted the data, and drafted the manuscript. SY and GL performed data analysis. YZ wrote the sections of the manuscript. SL and BJ revised the manuscript for the final version. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.931863/full#supplementary-material

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Extracorporeal membrane oxygenation support for lung transplantation: Initial experience in a single center in China and a literature review

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Background: Extracorporeal membrane oxygenation (ECMO) is a versatile tool associated with favorable outcomes in the field of lung transplantation (LTx). Here, the clinical outcomes and complications of patients who underwent LTx with ECMO support, mainly prophylactically both intraoperatively and post-operatively, in a single center in China are reviewed.

Methods: The study cohort included all consecutive patients who underwent LTx between January 2020 and January 2022. Demographics and LTx data were retrospectively reviewed. Perioperative results, including complications and survival outcomes, were assessed.

Results: Of 86 patients included in the study, 32 received ECMO support, including 21 who received prophylactic intraoperative use of ECMO with or without prolonged post-operative use (pro-ECMO group), while the remaining 54 (62.8%) received no external support (non-ECMO group). There were no significant differences in the incidence of grade 3 primary graft dysfunction (PGD), short-term survival, or perioperative outcomes and complications between the non-ECMO and pro-ECMO groups. However, the estimated 1- and 2-year survival were superior in the pro-ECMO group, although this difference was not statistically significant (64.1% vs. 82.4%, log-rank $P = 0.152$; 46.5% vs. 72.1%, log-rank $P = 0.182$, respectively). After regrouping based on the reason for ECMO support, 30-day survival was satisfactory, while 90-day survival was poor in patients who received ECMO as a bridge to transplantation. However, prophylactic intraoperative use of ECMO and post-operative ECMO prolongation demonstrated promising survival and acceptable complication rates. In particular, patients who initially received venovenous (VV) ECMO intraoperatively with the same configuration post-operatively achieved excellent outcomes. The use of ECMO to salvage a graft affected by severe PGD also achieved acceptable survival in the rescue group.

Conclusions: Prophylactic intraoperative ECMO support and post-operative ECMO prolongation demonstrated promising survival outcomes and acceptable complications in LTx patients. Particularly, VV ECMO provided safe and effective support intraoperatively and prophylactic prolongation reduced the incidence of PGD in selected patients. However, since this study was conducted in a relatively low-volume transplant center, further studies are needed to validate the results.

KEYWORDS

lung transplantation, extracorporeal membrane oxygenation, prophylactic intraoperative ECMO support, post-operative ECMO prolongation, complications

Introduction

Lung transplantation (LTx) is the final therapeutic option for patients with end-stage pulmonary disease unresponsive to medical treatment (1). Pre-operative management, intraoperative manipulation, and post-operative management and recovery impact the success of LTx (2–4). Hence, suboptimal management during this complex surgery can jeopardize long-term survival of LTx recipients.

Extracorporeal membrane oxygenation (ECMO) is used with increasing frequency in LTx to provide prolonged cardiac and respiratory support (5–8). After careful patient selection and the involvement of a multidisciplinary team, several single- and multi-center studies have reported successful use of ECMO as a bridge to transplantation (BTT) (9–12) as well as a post-operative rescue strategy for primary graft dysfunction (PGD) (13), which has prompted intraoperative use of ECMO during LTx (7). Encouraging outcomes of ECMO for both short- and long-term intraoperative support have been reported (14–16). Moreover, prophylactic intraoperative use of ECMO and during the post-operative period in selected patients has been shown to improve perioperative and long-term outcomes of LTx recipients (15, 17, 18).

The increased frequency of perioperative ECMO support in recent years has improved the success of LTx as evidenced by improved survival and functional outcomes. Hence, the aim of the present study was to review the clinical outcomes and complications of LTx recipients who received ECMO support both intra- and post-operatively in a single center in China.

Methods

Patient population

The cohort of this single-center, retrospective study included 86 patients who underwent LTx at Shanghai Pulmonary Hospital affiliated with Tongji University (Shanghai, China) between January 2020 and January 2022. Of these patients, 54 received no external support (non-ECMO group) and 32 required ECMO support (ECMO group). Among the patients in the ECMO group, five received ECMO as a BTT (bridging ECMO group), 21 received prophylactic intraoperative use of ECMO with or without prolonged post-operative use (pro-ECMO group), and six received ECMO for rescue of PGD (rescue ECMO group) (Figure 1). The demographics of the donors and recipients as well as LTx information are summarized in Table 1. The study protocol was approved by the Institutional Research Ethics Board of Shanghai Pulmonary Hospital affiliated with Tongji University (approval no. K22-217) and conducted in accordance with the ethical principles for medical research involving human subjects described in the Declaration of Helsinki.

ECMO management

The decision to perform ECMO was made by an experienced multidisciplinary team based on current center guidelines. The main indication for ECMO as a BTT was persistent hypercapnia and/or hypoxic respiratory failure, defined as PCO_2 >80 mmHg and partial arterial oxygen pressure (PaO_2) to the fraction of inspired oxygen (P/F ratio) <70 mmHg. Following assessment of cardiac function, all five patients in the ECMO group received femoral–jugular venovenous (VV) ECMO as a BTT. The circuits were coated with heparin and composed of Quadrox PLS oxygenators (Bioline®; Maquet Cardiopulmonary AG, Hirrlingen, Germany), a centrifugal pump, and an integrated heat exchanger. A 15–17 French (Fr) cannula was used for the jugular vein and a 21 Fr cannula for the femoral vein (Maquet Cardiopulmonary AG). All cannulas were inserted percutaneously using the Seldinger technique. The same ECMO system was maintained for intraoperative and prolonged post-operative support.

Intraoperatively, the surgical technique and handling of ECMO were consistent throughout the study period and among all transplant surgeons. Central cannulation was performed for most of the patients. After opening the chest, the

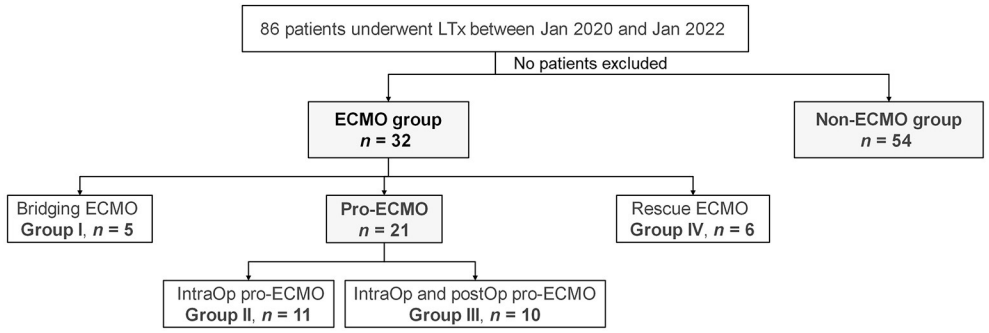

FIGURE 1
Flow chart of the study cohort.

patients received 2,000–3,000 IU of unfractionated heparin intravenously. The heparin dose was not repeated during surgery. Activated clotting time was routinely monitored. A 17 Fr arterial cannula was used for the ascending aorta and a 32 Fr curved-tip cannula for the right atrium. The ECMO flow was set to 50% of the predicted cardiac output and adapted according to hemodynamic and gas exchange demands.

Prolonged post-operative ECMO was conducted in accordance with the Vienna protocol (15). Briefly, the function of the implanted graft was evaluated 10 min after decannulation and immediately after chest closure. If pulmonary function tests failed to meet the pre-defined criteria (i.e., oxygen tension/inspired oxygen fraction >100, mean pulmonary arterial pressure/mean systemic arterial pressure <2/3, and normal size-equivalent tidal volume) or if there was clear worsening of either measurement, the same ECMO system was reinserted in the femoral–femoral venoarterial (VA) configuration and the patient was transferred to the intensive care unit (ICU) with the use of a running system. For prolonged ECMO, the patient received a therapeutic dose of heparin and activated clotting time was monitored at 180–220 s. In the PGD subgroup, femoral–jugular VV ECMO was employed in the ICU as a rescue strategy after LTx.

PGD definition

PGD occurs usually within 72 h after LTx as demonstrated by hypoxemia and non-cardiogenic pulmonary infiltrates on chest radiographs. The severity of PGD was graded at four time points starting from reperfusion of the second lung (T0) to 24 h (T24), 48 h (T48), and 72 h (T72) after LTx, in accordance with the latest consensus conference criteria of the International Society for Heart and Lung Transplantation (19). PGD grade 0 was defined as the absence of infiltrate on chest X-rays. In the presence of pulmonary infiltrates, PGD grades 1–3 were determined based on the P/F ratio as follows: PGD grade 1, P/F ratio >300 mmHg; PGD grade 2, P/F ratio of 200–300 mmHg; and PGD grade 3, P/F ratio <200 mmHg. Patients receiving prolonged post-operative ECMO with chest X-rays showing pulmonary infiltrations were classified as PGD grade 3.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation or median [range or interquartile range (IQR)]. Independent continuous variables between two groups were compared with the non-parametric Mann–Whitney test, while categorical variables were compared using the chi-squared test. A probability (P) value of ≤ 0.05 was considered statistically significant. The 1- and 2-year survival rates were estimated using the Kaplan–Meier method. Differences between groups were quantified using the log-rank test. Overall survival was defined as the period from LTx to death due to any cause and patients were censored at the last date of follow-up. Baseline covariates were balanced by the method of propensity score matching. The following parameters were included: age, sex, body mass index, primary diagnosis and type of transplant. Matched groups were compared using the Mann–Whitney test or the chi-squared test. The difference in survival between the matched groups was compared by a stratified log-rank test. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corporation, Armonk, NY, USA).

Results

Recipient characteristics

A total of 75 LTx recipients were included in non-ECMO and pro-ECMO groups. The characteristics of the LTx recipients are summarized in Table 1. There were no significant differences in age, sex, indications for LTx, waiting

TABLE 1 Patient characteristics.

	Total ($n = 75$)	Non-ECMO ($n = 54$)	Pro-ECMO ($n = 21$)	*P*-value
Donor				
Age, years (range)	43 (33–50)	45 (33–50)	37 (35–49)	0.520
Sex, *n* (male/female)	61/14	43/11	18/3	0.745
BMI, kg/m^2	22.6 ± 2.5	22.8 ± 2.6	22.3 ± 2.1	0.579
Last PaO_2 at $FiO_2 = 1.0$, mmHg (range)	415 (399–479)	419 (406–479)	413 (382–465)	0.330
Last $PaCO_2$ at $FiO_2 = 1.0$, mmHg (range)	37 (34–40)	37 (33–40)	37 (36–41)	0.655
First lung CIT, min	406 ± 79	401 ± 88	419 ± 47	0.307
Second lung CIT, min	518 ± 73	495 ± 69	543 ± 72	0.097
Air transportation, *n* (%)	60 (80.0)	43 (79.6)	17 (81)	1.000
Recipient				
Age, years (range)	64 (61–67)	64 (61–68)	63 (51–64)	0.083
Sex, *n* (male/female)	65/10	48/6	17/4	0.452
BMI, kg/m^2	21.0 ± 3.3	21.4 ± 3.1	19.8 ± 3.4	0.027
Diagnosis, *n* (%)				
IPF	38 (50.7)	29 (53.7)	9 (42.9)	0.123
COPD	18 (24.0)	14 (25.9)	4 (19.0)	
Bronchiectasis	7 (9.3)	6 (11.1)	1 (4.8)	
Re-transplant	4 (5.3)	2 (3.7)	2 (9.5)	
Pneumosilicosis	6 (8.0)	3 (5.6)	3 (14.3)	
IPAH or PVOD	2 (2.7)	0 (0)	2 (9.5)	
Waiting time, days (range)	43 (18–70)	36 (19–67)	48 (16–112)	0.624
Lung allocation score, points (range)	67 (51–83)	65 (51–81)	71 (58–87)	0.166
Left ventricular ejection fraction, % (range)	64 ± 5	64 ± 4	65 ± 6	0.359
Pulmonary artery systolic pressure, mmHg (range)	37 (29–51)	37 (28–47)	38 (33–54)	0.326
Type of LTx, *n* (%)				
Single-LTx	45 (60.0)	39 (72.2)	6 (28.6)	0.001
Bilateral-LTx	30 (40.0)	15 (27.8)	15 (71.4)	
Surgical duration, min (range)	280 (203–370)	248 (185–350)	345 (305–475)	0.001
Blood loss, ml (range)	1,000 (500–2,000)	800 (400–1,500)	2,000 (1,400–4,000)	<0.001
Intraoperative transfusion, U (range)	4 (0–10)	2 (0–7)	10 (6–14)	<0.001
Fresh frozen plasma, U (range)	10 (0–20)	0 (0–10)	20 (20)	<0.001
Follow-up duration, months (range)	9.1 (3.6–17.1)	9.4 (5.4–14.9)	7.7 (3.5–19.3)	0.967

BMI, body mass index; CIT, cold ischemia time; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; LTx, lung transplantation; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PVOD, peripheral vascular occlusive disease.

The values are presented as frequency/percentage and were compared with the chi-square test. Continuous variables with normal distributions are presented as the mean ± standard deviation, while variables with non-normal distributions are presented as the median and IQR. Variables with non-normal distributions were compared with the Mann–Whitney test. Significance was set at $P < 0.05$.

time, lung allocation score, left ventricular ejection fraction, pulmonary artery systolic pressure, and follow-up duration between the two groups. However, body mass index (BMI) was significantly lower in the pro-ECMO group than the non-ECMO group ($P = 0.027$) and bilateral LTx was more common in the pro-ECMO group ($P = 0.001$). Accordingly, the median surgical duration was longer (345 vs. 248 min, $P < 0.001$), blood loss was greater (2,000 vs. 800 ml, $P < 0.001$), and need for intraoperative transfusions of blood and fresh frozen plasma was greater (10 vs. 2 U, $P < 0.001$; 20 vs. 0 U, $P < 0.001$) in the pro-ECMO group as compared to the non-ECMO group.

Donor characteristics

The characteristics of the lung donors are detailed in Table 1. All lungs were retrieved from brain-dead donors. There were no differences in age, sex, and BMI between the two groups or in the partial pressure of oxygen (PaO_2) and partial pressure of carbon

TABLE 2 Perioperative outcomes.

	Total ($n = 75$)	Non-ECMO ($n = 54$)	Pro-ECMO ($n = 21$)	*P*-value
Length of mechanical ventilation, days (range)	3 (1–6)	2 (1–5)	4 (2–7)	0.967
Time in ICU, days (range)	18 (12–29)	17 (12–29)	20 (15–29)	0.165
Length of hospital stay, days (range)	44 (29–57)	41 (28–57)	45 (35–60)	0.409
Comorbidities, *n* (%)				
PGD 3 at 48 or 72 h	10 (13.3)	8 (14.8)	2 (9.5)	0.716
Post-operative hemodialysis	1 (1.3)	1 (1.9)	0 (0)	1.000
Revision surgery	4 (5.3)	1 (1.9)	3 (14.3)	0.064
VTE	13 (17.3)	8 (14.8)	5 (23.8)	0.497
Airway complications	15 (20.0)	12 (22.2)	3 (14.3)	0.535
Fungus infection	16 (21.3)	13 (24.1)	3 (14.3)	0.532
Pulmonary infection	18 (24.0)	12 (22.2)	6 (28.6)	0.561
Acute rejection	11 (14.7)	7 (13.0)	4 (19.0)	0.489
Chronic lung allograft dysfunction	9 (12.0)	5 (9.3)	4 (19.0)	0.256
30-day survival, *n* (%)	70 (93.3)	50 (92.6)	20 (95.2)	1.000
90-day survival, *n* (%)	64 (85.3)	44 (81.5)	20 (95.2)	0.251

ICU, intensive care unit; PGD, primary graft dysfunction; VTE, venous thromboembolism.

dioxide ($PaCO_2$) in pure oxygen at the time of retrieval. Cold ischemic time (CIT) between the first transplanted lung was comparable between the pro-ECMO and non-ECMO groups (419 ± 47 vs. 401 ± 88 min, $P = 0.655$), while CIT for the second transplanted lung was slightly longer in the pro-ECMO group, although this difference was not statistically significant ($P = 0.097$).

Perioperative outcome

As listed in Table 2, the median mechanical ventilation time, median ICU stay, and length of hospital stay were comparable between the non-ECMO and pro-ECMO groups (2 vs. 4 days, $P = 0.967$; 17 vs. 20 days, $P = 0.165$; 41 vs. 45 days, $P = 0.409$; respectively). In terms of post-operative complications, patients in the pro-ECMO group were more likely to require revision surgery (14.3% vs. 1.9%, $P = 0.064$). However, there was no significant difference in the 30- and 90-day survival rate between the two groups (92.6% vs. 95.2%, $P = 1.000$; 81.5% vs. 95.2%, $P = 0.251$, respectively) or in the incidence of other post-operative complications, including post-operative hemodialysis, PGD 3 at 48 or 72 h, venous thromboembolism (VTE), airway complications, fungal infection, pulmonary infection, acute rejection, and chronic lung allograft dysfunction.

Mid-term outcome

Although the estimated 1-year survival rate was higher in the pro-ECMO group than the non-ECMO group, this difference was not significantly significant (82.4% vs. 64.1%, log-rank $P = 0.152$, Figure 2). Similarly, the estimated 2-year survival rate was higher in the pro-ECMO group than the non-ECMO group, which was also not statistically significant (72.1% vs. 46.5%, log-rank $P = 0.182$, Figure 2).

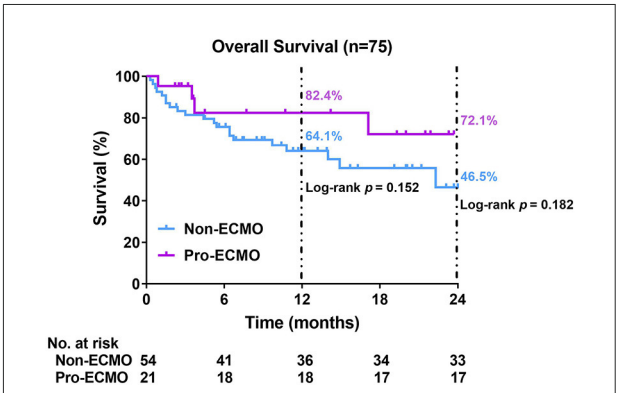

FIGURE 2
Kaplan–Meier curves for overall survival. Differences between the two curves were identified using the log-rank test. ECMO, extracorporeal membrane oxygenation.

Propensity score matching (PSM)

A PSM was performed to balance baseline covariates between the non-ECMO group and the pro-ECMO group. The matching parameters included: age, sex, BMI, primary diagnosis and type of transplant. As demonstrated in Table 3, PSM resulted

TABLE 3 Group characteristics of propensity-matched cohorts.

	Total ($n = 28$)	Non-ECMO ($n = 14$)	Pro-ECMO ($n = 14$)	*P*-value
Age, year	63 (58–65)	62 (56–64)	64 (62–67)	0.210
Gender, male/female	22/6	11/3	11/3	1.000
BMI (kg/m^2)	20.7±2.9	20.2±2.7	21.1±3.1	0.635
Diagnosis, *n* (%)				
IPF	13 (46.4)	6 (42.9)	7 (50.0)	0.120
COPD	6 (21.4)	3 (21.4)	3 (21.4)	
Bronchiectasis	3 (10.7)	3 (21.4)	0 (0)	
Re-transplant	2 (7.1)	0 (0)	2 (14.3)	
Pneumosilicosis	3 (10.7)	2 (14.3)	1 (7.1)	
IPAH or PVOD	1 (3.6)	0 (0)	1 (7.1)	
Type of LTx, *n* (%)				
Single-LTx	11 (39.3)	6 (42.9)	5 (35.7)	0.699
Bilateral-LTx	17 (60.7)	8 (57.1)	9 (64.3)	
30-day survival, *n* (%)	26 (92.9)	13 (92.9)	13 (92.9)	1.000
90-day survival, *n* (%)	25 (89.3)	12 (85.7)	13 (92.9)	1.000

BMI, body mass index; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension; PVOD, peripheral vascular occlusive disease; LTx, lung transplantation.

in 14 patients in each group. The matching process eliminated a greater proportion of the differences in baseline characteristics between the non-ECMO group and the pro-ECMO group, including BMI and type of transplant. There were no significant difference between matched groups in terms of the 30- and 90-day survival rate (92.9% vs. 92.9%, $P = 1.000$; 85.7% vs. 92.9%, $P = 1.000$, respectively).

ECMO subgroups

Having demonstrated the value of pro-ECMO for the prognosis of LTx recipients, all patients who received ECMO support were regrouped into the following four subgroups based on the stage of ECMO support: group I, bridging ECMO ($n = 5$); group II, prophylactic intraoperative ECMO (intraOp pro-ECMO, $n = 11$); group III, prophylactic intraoperative and post-operative ECMO (intra/postOp pro-ECMO, $n = 10$), and group IV, rescue ECMO ($n = 6$) (Table 4). As expected, the duration of ECMO support was shortest in group II with a median duration of 3 (IQR, 2–5) h and longest in group III with a median duration of 82 (IQR, 47–95) h ($P < 0.001$). All patients in group I received VV ECMO as a bridge to LTx. All patients in group II received VA ECMO. Half of the patients in group III received VA ECMO, which was extended into the post-operative period. Similarly, half of the patients in group IV were rescued with VV ECMO and half with VA ECMO. Idiopathic pulmonary fibrosis (IPF) was the major indication among the 4 groups. Pneumosilicosis and idiopathic pulmonary arterial hypertension (IPAH) or peripheral vascular occlusive disease (PVOD) only occurred in groups II and III, respectively. The 90-day survival rate was better in groups II and III than groups I and IV (100% and 90% vs. 40% and 67%, log-rank $P = 0.018$). There were no significant differences in the other variables among the 4 groups, which included duration of mechanical ventilation, ICU and hospital stays, ECMO weaning rate (survived ECMO), survived to hospital discharge (survived to DC), and 30-day survival.

ECMO-related complications

Hemorrhage and thrombosis were the most common complications of ECMO support. As demonstrated in Table 4, both VTE and circuit-related thrombosis were identified in 10 (31.25%) patients who received ECMO support. Arterial thromboembolic events were observed in 2 (6.25%) patients, while bleeding events that required reoperation were experienced by 4 (12.5%) patients. All patients who developed arterial thromboembolic events and bleeding belonged to the prolonged ECMO group. The incidence of VTE associated with ECMO was comparable among the four groups ($P = 0.561$). However, the incidence of circuit-related thrombosis varied with the highest incidence in the prolonged ECMO and rescue ECMO groups ($P = 0.013$).

Discussion

Extracorporeal membrane oxygenation is an extremely versatile tool in the field of LTx as it can serve as a BTT before transplantation, as a support modality during

TABLE 4 Patient characteristics with different modes of ECMO support.

	Bridging ECMO (group I, $n = 5$)	IntraOp pro-ECMO (group II, $n = 11$)	Intra/postOp pro-ECMO (group III, $n = 10$)	Rescue ECMO (group IV, $n = 6$)	*P*-value
ECMO duration, h (range)	57 (55–99)	3 (2-5)	82 (47–95)	68 (40–93)	<0.001
Initial ECMO mode, *n* (%)					
VV-ECMO	5 (100)	0 (0)	5 (50)	3 (50)	0.001
VA-ECMO	0 (0)	11 (100)	5 (50)	3 (50)	
Diagnosis, *n* (%)					
IPF	4 (80)	4 (36)	5 (50)	2 (33)	0.089
COPD	0 (0)	1 (9)	3 (30)	2 (33)	
Bronchiectasis	0 (0)	1 (9)	0 (0)	0 (0)	
Re-transplant	0 (0)	2 (18)	0 (0)	1 (17)	
Pneumosilicosis	0 (0)	3 (27)	0 (0)	0 (0)	
IPAH or PVOD	0 (0)	0 (0)	2 (20)	0 (0)	
Others	1 (20)	0 (0)	0 (0)	1 (17)	
ECMO-related complications, *n* (%)					
Bleeding requiring any form of surgical intervention	0 (0)	0 (0)	4 (40)	0 (0)	0.014
Intracranial bleeding	0 (0)	0 (0)	0 (0)	0 (0)	NA
Uncontrollable bleeding leading to death	0 (0)	0 (0)	0 (0)	0 (0)	NA
Arterial thromboembolic events	0 (0)	0 (0)	2 (20)	0 (0)	0.175
VTE	2 (40)	2 (18)	3 (30)	3 (50)	0.561
Circuit-related thrombosis	2 (40)	0 (0)	5 (50)	3 (50)	0.013
Length of mechanical ventilation, days (range)	7 (5-8)	3 (2-7)	6 (4–10)	7 (5–8)	0.267
Time in ICU, days (range)	20 (17–36)	20 (17–29)	21 (14-31)	22 (14–28)	0.817
Length of hospital stay, days (range)	36 (28–40)	40 (29–49)	49 (36–63)	61 (28–83)	0.474
Survived ECMO, *n* (%)	5 (100)	11 (100)	9 (90)	4 (67)	0.123
Survived to DC, *n* (%)	3 (60)	11 (100)	9 (90)	4 (67)	0.076
30-day survival, *n* (%)	4 (80)	11 (100)	9 (90)	5 (84)	0.392
90-day survival, *n* (%)	2 (40)	11 (100)	9 (90)	4 (67)	0.018

COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; PVOD, peripheral vascular occlusive disease; Survived ECMO, weaned from ECMO; Survived to DC, survived to hospital discharge; VA ECMO, venoarterial extracorporeal membrane oxygenation; VTE, venous thromboembolism; VV ECMO, venovenous extracorporeal membrane oxygenation.

transplantation, and as a rescue strategy after transplantation (3, 6–8). The data presented here confirmed the essential role of ECMO in LTx, especially the prominent contribution in the intra- and post-operative periods. These data demonstrate promising primary graft function and survival rates with prophylactic intraoperative and post-operative prolongation of ECMO support. Furthermore, the incidences of ECMO-related complications were acceptable in the patient cohort.

By optimizing gas exchange, pre-operative VV ECMO offers pulmonary support as a BTT. In this study, VV ECMO was used to successfully bridge LTx in five patients. Notably, 30-day survival was achieved in 4 (80%) patients, which is consistent with short-term survival (81.6%) in low-volume centers (20). However, 90-day survival was achieved only in 2 (40%) patients, which is lower than the 90-day survival rate in previous report (12). There are several possible reasons why early initial experience with ECMO as a BTT in our center was discouraging. First, the low-volume of transplantation in our center may partially explain the inferior survival rate since ECMO is a complex procedure and use in LTx favors a volume-outcome association (20, 21). Second, post-transplantation survival is lower for IPF than other indications (22). In this series, ECMO support was used in 4 IPF patients whose conditions deteriorated rapidly despite maximal medical therapy. It is difficult to successfully rehabilitate critically ill patients, which was detrimental to transplantation outcomes. In addition, ECMO as a BTT has evolved over the last two decades from an acute rescue therapy to a semi-elective procedure in an experienced high-volume transplant center (23). However, our center is still in the stage of acute rescue therapy.

Aside from pre-operative VV ECMO support as a BTT, VA ECMO is preferred intraoperatively for both hemodynamic

and respiratory support. The study conducted by the Hannover Group had a larger cohort of patients, but there were no differences in long-term outcomes and complications between patients who survived hospital discharge with intraoperative VA ECMO support and those without ECMO support, although ECMO recipients endured more complicated perioperative and early post-operative courses (14). Similarly, intraoperative VA ECMO resulted in lower PGD rates and superior 1-, 2-, 3-, and 5-year survival rates as compared to transplantation with no extracorporeal support based on two large cohorts of patients from the Vienna Group (15, 16). Furthermore, intraoperative VA ECMO support for LTx recipients with severe IPAH, a very difficult patient population, provides excellent outcomes as compared to the use of cardiopulmonary bypass (17). Due to the satisfying survival rates of patients who received intraoperative ECMO, recent studies have proposed routine or prophylactic use of intraoperative ECMO in LTx. In previous studies, routine use of ECMO during LTx improved early outcomes and post-operative lung function without increasing the incidence of extracorporeal-related complications (15, 16, 24, 25).

Intraoperative ECMO can be extended into the early post-operative period if graft function failed to meet established quality criteria or even to maintain ECMO "prophylactically" for high-risk recipients, such as those with pulmonary hypertension (7, 26–28). The Vienna Group extensively investigated the concept of prophylactic post-operative ECMO prolongation, particularly in patients with pulmonary hypertension and questionable graft function at the end of LTx, and found that prolongation of ECMO support resulted in excellent primary graft function and survival rates, thereby demonstrating a survival benefit in patients both with and without pulmonary hypertension (15, 16). Another independent study conducted by the same group (18) reported similar excellent survival data in a population with severe IPAH. Several other groups (17, 29) have also reported superior outcomes.

In line with these reports, 21 of 86 (47.2%) LTx recipients in the present study received pro-ECMO support, which included 16 (76.2%) who were adopted with the VA configuration, including 11 in the intraOp pro-ECMO group and five in the intra/postOp pro-ECMO group. The remaining 5 (23.8%) patients were initiated with VV ECMO and the same configuration was maintained post-operatively (Table 4). The incidence of PGD grade 3 at 48 or 72 h and short-term survival were comparable between patients who survived hospital discharge with pro-ECMO support and those without ECMO support (95.2% vs. 92.6%, respectively). However, the estimated 1- and 2-year survival rates were superior in the pro-ECMO group as compared to the non-ECMO group, although this difference was not statistically significant, possibly due to the relatively small cohort and limited follow-up period. Furthermore, the significantly lower BMI in the pro-ECMO group was predictive of improved graft survival, as previously reported (14).

Although VV ECMO is typically the preferred configuration as a BTT, relatively few studies have evaluated the use of VV ECMO support during LTx (6). A 2018 study by Hashimoto et al. (30) of intraoperative extracorporeal support during LTx in patients bridged with VV ECMO reported that VV ECMO was maintained in 59% of bridged patients, whereas 32% were converted to central VA ECMO due to compromised hemodynamics. Post-operatively, 41.2% were extended with VV ECMO. Notably, there were no significant differences in 90-day mortality and 5-year survival between these two groups, indicating the feasibility of intraoperative and post-operative prolongation of VV ECMO.

In our center, after splitting the intra/postOp pro-ECMO subgroup from the pro-ECMO group, 5 of 10 (50%) of patients were initiated with VV ECMO intraoperatively and remained on the same configuration post-operatively. All patients who received VV ECMO support were successfully weaned off and discharged from the hospital and achieved excellent 30- and 90-day survival rates. In contrast, one patient who received VA ECMO support died of severe IPAH while on ECMO, which resulted in a lower survival rate in this group. The predominant baseline disease was chronic obstructive pulmonary disease in the VV ECMO group and IPF and IPAH in the VA ECMO group. In this study, patients with IPAH underwent LTx with the VA ECMO strategy, which was directly extended into the post-operative period, as described in previous reports (15, 16, 18). However, in patients with baseline disease that only affects oxygenation, VV ECMO is sufficient to provide safe and effective support intraoperatively and to reduce the incidence of PGD post-operatively in a relatively low-volume transplant center. However, further studies are needed to validate these results.

Both VV ECMO and VA ECMO can be used post-operatively as a rescue therapy for hemodynamic instability or inadequate graft function, such as PGD. In the present study, 6.98% (6/86) of the cohort were rescued with ECMO for PGD post-operatively, which is within the reported range of 5.1% to 12.8% (31–33). Among these six patients, half required VA ECMO and half received VV ECMO. The 30-day survival was 84% in the rescue group, which is consistent with a previous report (34). The 90-day survival in this study was 67%, lower than in the intraOp pro-ECMO group and intra/postOp pro-ECMO group, but similar to several studies reporting 1-year survival rates after post-operative rescue ECMO of 59% to 78% (13, 33, 34).

Bleeding and thrombosis are major complications in patients supported with ECMO. In the current study, 14.3% (3/21) of patients in the pro-ECMO group developed bleeding events that required reoperations, which was comparable with the incidence in the non-ECMO group. No bleeding was observed in the intraOp pro-ECMO group, as all patients (4/10, 40%) who had bleeding events were in the intra/postOp pro-ECMO group, which was a higher incidence than in the prolonged ECMO group reported by Hoetzenecker et al. (15).

Thromboembolic events, such as arterial thromboembolism, were observed in 20% of patients in the intra/postOp pro-ECMO group, and the incidences of both VTE and circuit-related thrombosis were higher in each ECMO subgroup with the exception of the intraOp pro-ECMO group. However, there was no difference in the incidence of VTE between the pro-ECMO and non-ECMO groups.

The main limitations to this study were the single-center retrospective nature, relatively small sample size, and limited experience with ECMO as demonstrated by the slightly higher prevalence of related complications. Nonetheless, the estimated 1- and 2-year survival rates were relatively superior in the pro-ECMO group.

Conclusion

Taken together, these findings indicate that bridging strategies for LTx are sufficient as an acute rescue therapy, thus appropriate patient selection, such as those on a waiting list for LTx and well-rehabilitated patients, is important to achieve optimal results. Intraoperatively, prophylactic use of ECMO and prophylactic post-operative ECMO prolongation, particularly in patients with pulmonary hypertension and questionable graft function at the end of implantation, achieved satisfactory survival and acceptable complication rates. In addition, the VV ECMO strategy provided safe and effective support intraoperatively and reduced the incidence of post-operative PGD in selected patients in this relatively low-volume transplant center. Post-operatively, the use of ECMO as a rescue therapy to salvage a graft affected by severe PGD also provided acceptable survival.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Research Ethics Board of Shanghai Pulmonary Hospital affiliated with Tongji University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZha, CC, YZhu, GJ, and YL: conception, design and administrative support, data analysis, and interpretation. YS, RD, JS, XL, LS, JD, PZ, and MB: provision of study materials or patients. YS, RD, JS, and XL: data collection and assembly. All authors contributed to manuscript composition and approval of the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Limb Ischemia Complications of Veno-Arterial Extracorporeal Membrane Oxygenation

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Background: This study aimed to summarize and analyse the risk factors, clinical features, as well as prevention and treatment of limb ischemia complications in patients on veno-arterial extracorporeal membrane oxygenation (V-A ECMO).

Methods: We retrospectively analyzed 179 adult patients who had undergone V-A ECMO support in the Cardiac Care Unit of the First Hospital of Lanzhou University between March 2019 and December 2021. Patients were divided into the limb ischemia group (LI group) and the non-limb ischemia group (nLI group) according to whether limb ischemia occurred on the ipsilateral side of femoral artery cannulation. In the LI group, patients were salvaged with a distal perfusion cannula (DPC) according to each patient's clinical conditions. The baseline data and ECMO data were compared between the two groups, and risk factors for limb ischemia complications were screened using multiple logistic regression analysis.

Results: Overall, 19 patients (10.6%) had limb ischemia complications, of which 5 (2.8%) were improved after medication adjustment, 12 (8.4%) were salvaged with a DPC, and 2 had undergone surgical intervention. There were significant differences in terms of Extracorporeal Cardiopulmonary Resuscitation (ECPR), Intra-aortic balloon pump (IABP), peak vasoactive-inotropic score (VIS) within 24 h after ECMO (VIS-max), Left ventricular ejection fraction (LVEF), weaning from ECMO, and discharge rate between the two groups. ECPR, IABP, and VIS-max in the LI group were significantly higher than those in the nLI group, whereas weaning from ECMO, discharge rate, and LVEF were significantly lower in the LI group compared to those in the nLI group. Furthermore, multiple logistic regression analysis revealed that diabetes [odds ratio (OR) = 4.338, 95% confidence interval (CI): 1.193–15.772, $P = 0.026$], IABP (OR = 1.526, 95% CI: 1.038–22.026, $P = 0.049$) and VIS-max (OR = 1.054, 95% CI: 1.024–1.085, $P < 0.001$) were independent risk factors for limb ischemia complications in patients who underwent V-A ECMO.

Conclusion: Diabetes, prevalence of IABP and VIS-max value in analyzed groups were independent risk factors for predicting limb ischemia complications in patients who

underwent V-A ECMO. The cannulation strategy should be optimized during the establishment of V-A ECMO, and limb ischemia should be systematically evaluated after ECMO establishment. A DPC can be used as a salvage intervention for the complications of critical limb ischemia.

Keywords: V-A ECMO, limb ischemia, risk factors, distal perfusion, salvage intervention

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a mechanical cardio-respiratory support for heart and lung failure in which conventional treatment is ineffective and is increasingly becoming a bridge to permanent solution such as recovery, transplantation, more durable device, or decision. Over the past decade, the indications for ECMO have expanded, and the use of ECMO has increased exponentially (1–3). Establishing veno-arterial (V-A) ECMO by percutaneous femoral artery and venous cannulation is easy to perform, minimally invasive, and widely used in clinically. However, femoral artery cannulation may result in acute limb ischemia (ALI) of the ipsilateral limb. Severe limb ischemia can render the arterial blood supply of the lower extremities unable to meet the basic physiological and metabolic needs at rest (4–8), which may require secondary surgical intervention, or amputation and even be life-threatening (9–11). In a systematic meta-analysis by Cheng et al., the cumulative incidence of limb ischemia in ECMO-assisted patients was 16.9% (12). Therefore, detection, prevention, and management of ECMO-related ALI are critical (12–14). Many prevention strategies have been proposed to avoid limb ischemia including the selection of small arterial return cannula and cannulation side selection, cannulation technique, and placement of a smaller cannula for anterograde or retrograde (ankle) distal perfusion (15). Recently, a new bidirectional femoral arterial cannula has been proposed and tested during cardiopulmonary bypass (16). With peripheral femoral cannulation, distal perfusion ipsilateral to the femoral artery cannulation is recommended by the ELSO Red Book and guidelines (1). Currently, the placement of the distal perfusion cannula (DPC) is the most common method for preventing and treating limb ischemia complications (17, 18). However, the timing of DPC application is not clearly defined. There is a lack of clear evidence-based medical recommendations as to whether the distal perfusion catheter should be placed prophylactically or only if acute limb ischemia develops (1, 18–21).

Abbreviations: V-A ECMO, veno-arterial extracorporeal membrane oxygenation; LI, limb ischemia; nLI, non-limb ischemia; ALI, acute Limb ischemia; CCU, cardiac care unit; DPC, distal perfusion cannula; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; CRD, chronic respiratory disease; AMI, acute myocardial infarction; AFM, acute fulminant myocarditis; ECPR, extracorporeal cardiopulmonary resuscitation; HR-PCI, high-risk percutaneous coronary intervention; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BNU, blood urea nitrogen; HB, hemoglobin; APTT, activated partial thromboplastin time; GLU, glucose; LAC, lactic acid; IABP, intra-aortic balloon pump; CRRT, continuous renal replacement therapy; IMV, invasive mechanical ventilation; ED, emergency department; AC, arterial cannula; VIS, vasoactive inotropic score; LVEF, left ventricular ejection fraction; LOS, length of stay; NIRS, near-infrared spectroscopy; OR, odds ratios; CI, confidence intervals.

We reviewed the data of adult V-A ECMO-assisted patients at our hospital, as well as discussed the risk factors, clinical features, and summarized the prevention and treatment of limb ischemia complications in order to improve the prognosis of these patients.

MATERIALS AND METHODS

Study Population

We collected the clinical data of all adult patients who required V-A ECMO support between March 2019 and December 2012 in the Department of Cardiology of the First Hospital of Lanzhou University.

The inclusion criteria

(1) Patients with cardiogenic shock due to various etiologies requiring V-A ECMO assistance.
(2) Patients undergone High-risk Percutaneous Coronary Interventions (HR-PCI) who need V-A ECMO intraoperative assistance.
(3) Extracorporeal Cardiopulmonary Resuscitation (ECPR).
(4) Age between 18–80 years old.

The exclusion criteria

(1) Poor vascular access conditions, including lower extremity arterial occlusion, vascular dissection, etc.
(2) Death or weaning from ECMO due to irreversible reasons within 24 h.
(3) Patients with assistance duration < 4 h.
(4) Other types of shock.
(5) Incomplete baseline data.

Limb Ischemia

The severity of limb ischemia was graded according to the Rutherford classification (22). The amount of vasopressor should be considered and eventually reduced or discontinued after the establishment of V-A ECMO. At the same time, vasodilators are used to increase perfusion. Moreover, in the absence of bleeding, high levels of anticoagulation were maintained. DPC is placed salvagely in patients who cannot be improved by medication adjustment and in patients with Rutherford class IIb.

Near-Infrared Spectroscopy (NIRS) Oximetry

NIRS has been used to assess limb ischemia since May 2021. The Cerebral/Somatic Oximeter (Covidien lic.,5,100 C, IRELAND) was used in all patients. The Oximeter pads for all patients were placed longitudinally on the medial aspect of the inner calf on both the cannulated and non-cannulated legs. Covidien has designated in their literature for the Cerebral/Somatic Oximeter

that saturations below 40% require intervention and saturations from 40 to 50% is cautionary values for cerebral oximetry.

V-A ECMO Management

ECMO consists of a centrifugal pump, membrane oxygenator and heparinization tube (Maquet, PLS7050/2050, Germany or LivaNava, D905, Italy), femoral arteriovenous cannula (Medtronic, Bio-Medicus, United States), and air-oxygen mixer. V-A ECMO was established by percutaneous puncture of the femoral artery (Medtronic, Bio-Medicus, 15–19 Fr cannulation) and femoral vein (19–21 Fr) under the guidance of ultrasound. Femoral arterial and venous conditions were assessed by ultrasound before ECMO cannulation. The diameter of arterial cannulation was < 80% of the diameter of blood vessels.

Anticoagulant Management

Unfractionated heparin (80–100 U/kg) was given before cannulation, and cannulation was started after activated clotting time (ACT) of whole blood > 200 s. During the period of ECMO assistance, activated partial thromboplastin time (APTT) and D-dimer were used to monitor. APTT was monitored every 4–6 h and maintained at 40–60 S, and D-dimer was maintained without an obvious increasing trend.

ECMO Weaning

If the flow was reduced to < 20% of the ideal cardiac output, hemodynamic stability can be maintained with low dose or without positive inotropic drugs, blood oxygen saturation≥ 95%, and echocardiography indicated that the parameters of the left ventricle and right ventricle were up to the standard and LVEF ≥ 25%, these were the criteria for considering weaning in our study.

Distal Perfusion Cannula

For the distal perfusion cannulation, under ultrasound guidance, the superficial femoral artery was punctured in the opposite direction to the femoral artery cannulation, and an Avanti 6 F femoral sheath (Cordi, 504–606 X, Mexico) was routinely inserted and connected to the arterial end of ECMO.

We recommend the use of the "4S" scheme for the prevention and treatment of limb ischemia complications in patients on V-A ECMO.

Best Site Selection

The common femoral artery below the inguinal ligament and above the bifurcation is selected as the arterial puncture point.

Match Arterial Cannula Size

The selection of type and size of the arterial cannula should be based on a balance between the targeted flow rate and anatomical considerations, arterial cannula diameter was < 80% of the diameter of blood vessels, while choosing a cannula as smaller as possible based on cardiac function.

Systematic Evaluation

Limb ischemia should be evaluated promptly after ECMO is established, including clinical symptoms, signs and NIRS.

Salvage Intervention

All patients with critical limb ischemic complications should be salvaged with a DPC placement rather than a routine placement.

Data Collection

Baseline Characteristics

Age; sex; body mass index (BMI); body surface area (BSA); left ventricular ejection fraction (LVEF); relevant comorbidities, including hypertension, diabetes mellitus, coronary artery disease (CAD), and chronic respiratory disease (CRD); ECMO assistance reason, including acute myocardial infarction (AMI), acute fulminant myocarditis (AFM), extracorporeal cardiopulmonary resuscitation (ECPR), high-risk percutaneous coronary intervention (HR-PCI), and other causes. Other interventions, including intra-aortic balloon pump (IABP), continuous renal replacement therapy (CRRT), and invasive mechanical ventilation (IMV).

ECMO-Related Characteristics

The size of arterial cannulation; peak vasoactive-inotropic score within 24 h after ECMO established (VIS-max); ECMO duration; location of ECMO; ECMO weaning rate.

Outcome Indicators

Cardic Care Unit (CCU) length of stay (LOS); Hospital LOS; Successful weaning from ECMO; Discharge rate.

For calculating the vasoactive-inotropic score, all vasoactive drugs were integrated with coefficients and assigned corresponding weights, and the integrated value was used as the vasoactive drug score (vasoactive-inotropic, VIS). The calculation was as follows: VIS = dopamine + dobutamine+ 10 × milrinone + 100 × epinephrine + 100 × norepinephrine + 10,000 × vasopressin [(U / (kg ·min))].

Statistical Analysis

All data were processed using SPSS version 24.0. Categorical and continuous variables were represented as counts (%) and medians (interquartile range). A Chi-square or Fisher's exact test was used for categorical variables, and a Student's *t*-test or Mann–Whitney U test was used for continuous variables. A multiple logistic regression analysis was used to analyze statistically significant variables to identify independent risk indicators related to neurological complications, which were summarized as odds ratios (OR) and 95% confidence intervals (95% CI). Statistical significance was set at $p < 0.05$.

RESULTS

Comparison of Baseline Data

After excluding 15 patients, a total of 179 patients with V-A ECMO assistance were included. Patients were divided into the limb ischemia group (LI group) and a non-limb ischemia group (nLI group) based on the occurrence of limb ischemia complications (**Figure 1**). Among them, 146 cases were men (81.6%), 33 were women (18.4%), the average age was 59 (51, 67) years, ECMO duration was 82 (27, 120) h. 19 patients (10.6%) had limb ischemia complications, of which 5 (2.8%) improved after drug treatment, and 12 (8.4%) had salvage DPC placement.

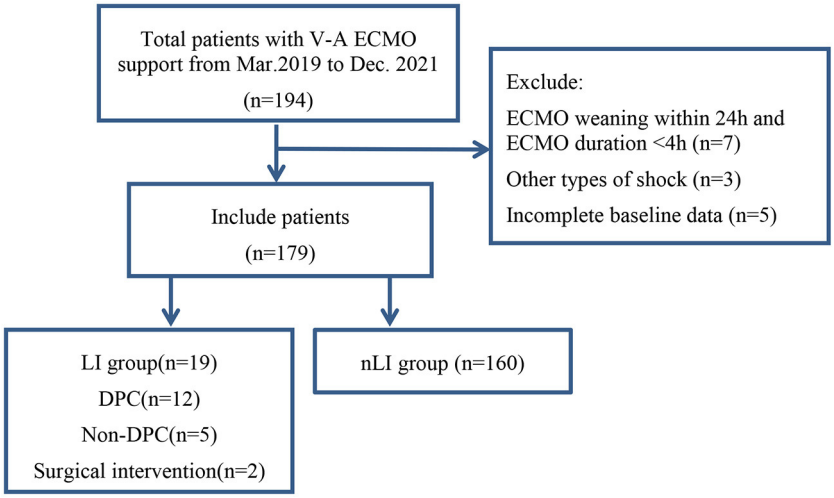

FIGURE 1 | Flow chart of patient cohorts. V-A ECMO, veno-arterial extracorporeal membrane oxygenation; DPC, distal perfusion cannula; LI, limb ischemia complications group; nLI, non-limb ischemia complications group.

There were no statistically significant differences between the LI group and the nLI group in terms of age, sex, BMI, BSA and other basic conditions and laboratory tests. Patients were considered to be more likely to develop limb ischemia complications when the relevant comorbidities were diabetes (38.9 vs. 23.0%, $P = 0.055$), and when their etiologies for ECMO support were ECPR (27.8 vs. 11.3%, $P < 0.046$). Median LVEF values were lower in the LI group compared with the nLI group [26 (18, 23) vs. 38 (25.5, 46), $P = 0.014$]. Meanwhile, the results showed the proportion of IABP (77.8 vs. 55.6%, $P = 0.03$) was higher in the LI group (**Table 1**). The primary outcome indicators were CCU LOS, hospital LOS, ECMO weaning rate and discharge rate. The results showed no significant differences in CCU LOS and hospital LOS between the LI and nLI groups. However, we found that the ECMO weaning rate (50 vs. 79.5%, $P = 0.005$) and the and discharge rate (38.9 vs. 70.8%, $P = 0.006$) of the LI group were significantly lower than those of the nLI group (**Table 1**).

Comparison of V-A ECMO-Related Data

The locations of ECMO surgery included the cath lab ($n = 66$, 36.9%), emergency department ($n = 51$, 28.4%), and CCU ($n = 58$, 32.4%), and the median ECMO duration [106 (53, 130.9) vs. 75 (25.3, 120) days, $P = 0.102$]; the location of ECMO surgery and the ECMO duration were not significantly related to the development of limb ischemia complications. However, we found significant differences between the LI and nLI groups with respect to the median VIS-max [44 (23, 62.8) vs. 16 (10, 24), $P = 0.014$] within 24 h after ECMO established (**Table 2**).

Clinical Features of Limb Ischemia Complication

Among the 19 patients, 7 were treated with 15 Fr cannulation, 11 with 17 Fr cannulation, and 1 with 19 Fr cannulation; 5 cases improved after drug treatment, 12 cases were salvaged with a DPC, including 11 with a 6 F sheath and 1 was single lumen central venous catheter. One developed superficial femoral artery thrombosis and underwent interventional arterial thrombectomy and stent implantation. Femoral artery thrombosis occurred in one patient after weaning, and thrombectomy was performed. After the intervention, the lower limb ischemia gradually improved, the clinical symptoms were relieved, and there were no lower limb ulcers, gangrene, amputation, or osteofascial compartment syndrome (**Table 3**).

Multivariate Analysis of Limb Ischemia Complications in Patients Underwent V-A ECMO

Result of the univariate analysis are shown in **Tables 1**, **2**. Baseline variables that were considered clinically relevant or that showed a univariate relationship with outcome were entered into a multiple logistic regression model. Candidate variables with a P value < 0.1 in univariate analysis were included in the multivariable model. The association were checked in the multivariable model, and after adjustment for ECPR, AMI, IMV, LVEF, and arterial cannula size, multivariate analysis revealed that Diabetes (OR, 4.338; 95% CI, 1.193–15.772; $P = 0.026$), IABP (OR, 1.526, 95% CI, 1.038–22.026; $P = 0.049$) and VIS-max (OR, 1.054, 95% CI, 1.024–1.085; $P < 0.00$) were independent risk factors for limb ischemia complications in patients on V-A ECMO (**Table 4**).

DISCUSSION

As a powerful life-support device, V-A ECMO is being increasingly used in clinical practice. This technique is an invasive procedure and may lead to related complications. Limb ischemia complications are often an important factor affecting the effect of ECMO. Previous studies reported that the incidence of distal limb ischemia on the ipsilateral femoral artery cannulation in patients with peripheral V-A ECMO ranges

TABLE 1 | Comparison of baseline characteristics of patients.

	All patients ($n = 179$)	Limb ischemia		*P*
		Yes ($n = 19$)	No ($n = 160$)	
Baseline characteristics				
Age (years)	59 (51,67)	60 (54.8,65)	59 (50.5,68)	0.176
Male, *n* (%)	146 (81.6)	14 (77.8)	132 (82.0)	0.66
BMI	21.8 (21.8,22.3)	26.2 (26.2,26.2)	21.8 (21.8,22.3)	0.55
BSA	1.74 (1.64,1.84)	1.65 (1.61,1.84)	1.75 (1.65,1.85)	0.39
Relevant comorbidities, *n* (%)				
Hypertension	72 (40.2)	9 (50)	63 (39.1)	0.372
Diabetes	44 (24.6)	7 (38.9)	37 (23.0)	0.055
CAD	150 (83.7)	16 (88.9)	134 (83.2)	0.537
CRD	10 (5.5)	2 (11.1)	8 (4.9)	0.282
ECMO assistance reason, *n* (%)				
AMI	116 (64.8)	15 (83.3)	101 (63.1)	0.083
AFM	21 (11.7)	1 (5.6)	20 (12.5)	0.358
ECPR	23 (12.8)	5 (27.8)	18 (11.3)	0.046*
HR-PCI	48 (26.8)	3 (16.7)	44 (27.5)	0.305
Other	7 (3.9)	1 (5.6)	6 (3.8)	0.743
Laboratory test				
AST (U/L)	38 (32, 46)	45 (36, 64)	34 (29, 51)	0.719
ALT (U/L)	33 (27, 56)	49 (31, 74)	42 (33, 58)	0.668
BUN(mmol/L)	5.54 (4.28, 7.31)	6.13 (4.79, 8.55)	5.76 (3.76, 8.21)	0.962
Hb (g/L)	95 (71, 124)	91 (69, 112.5)	98 (81, 117)	0.763
APTT (s)	86.5 (55.4, 160.2)	94.8 (62, 9, 174.6)	83.1 (54.6, 166.7)	0.882
GLU(mmol/L)	9.4 (6.5, 11.2)	9.9 (6.2, 10.8)	8.5 (7.4, 11.9)	0.365
LAC	7.3 (2.7, 8.7)	8 (4.5, 11)	6.7 (2.4, 7.7)	0.061
LVEF (%)	37 (25, 46)	26 (18, 38)	38 (25.5, 46)	0.019*
Other intervenes, *n* (%)				
IABP	103 (60.0)	14 (77.8)	89 (55.6)	0.030*
CRRT	51 (28.4)	7 (38.9)	44 (27.5)	0.303
IMV	58 (32.4)	9 (50)	49 (30.6)	0.093
Outcome				
Discharge, *n* (%)	67.5	38.9	70.8	0.006*
CCU LOS (days)	8 (5, 13)	8 (3, 14)	8 (6, 8)	0.704
Hospital LOS (days)	12 (8, 16)	10 (3, 19)	12 (13, 16)	0.596

*BMI, Body mass index; BSA, Body surface aera; CAD, Coronary artery disease; CRD, Chronic respiratory disease; AMI, Acute myocardial infarction; AFM, Acute fulminant myocarditis; ECPR, Extracorporeal cardiopulmonary resuscitation; HR-PCI, High risk percutaneous coronary intervention; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; BUN, blood urea nitrogen; Hb, hemoglobin; APTT, activated partial thromboplastin time; GLU, glucose; LAC, lactic acid; LVEF, Left ventricular ejection fraction; IABP, Intra-aortic balloon pump; CRRT, Continuous renal replacement therapy; IMV, Invasive mechanical ventilation; CCU, Cardiac Care Unit; LOS, length of stay; *, $P < 0.05$, the difference was statistically significant.*

from 10 to 50% (25, 26). This may be related to differences in ECMO indications, disease distribution, baseline characteristics, implantation techniques, definition of limb ischemia, detection tools, and timing of DPC insertion. In a study of Rastan et al. (24), 5.4% of patients with femoral artery cannulation experienced limb ischemia, and the use of DPC reduced limb ischemia and fasciotomy to < 40%. In a cohort study of 75 patients, the overall rate of limb ischemia was 14.7%, and the rate of limb ischemia remained 4.6% in patients treated with conventional DPC (21). Limb ischemia complications have been reported to be associated with unsuccessful ECMO weaning and have been shown to be independent predictors of in-hospital mortality (27, 28). We reviewed the incidence of limb ischemia complications, clinical features, and effectiveness of salvage DPC placement in adult patients assisted by V-A ECMO, as well as compared the effect of limb ischemia on ECMO weaning rate, discharge rate, and length of hospital stay. Our study found that the ECMO weaning and discharge rates in the LI group were significantly lower than those in the nLI group, which is consistent with previous reports in the literature. There was no significant difference in length of hospital stay between the two groups, which may be related to a higher rate of recovery and fewer serious complications. Our center is an adult heart center, with most patients with cardiogenic shock. The total incidence of limb ischemia was 10.3%, and the incidence of severe limb ischemia requiring salvage with a DPC placement was 6.5%. The incidence was relatively low, which may be related to disease distribution and treatment strategies.

TABLE 2 | Comparison of V-A ECMO related characteristics.

	All patients ($n = 179$)	Limb ischemia		*P*
		Yes ($n = 19$)	No ($n = 160$)	
Locations of ECMO				
Cath lab	66 (36.9)	9 (47.4)	57 (35.6)	0.316
ED	51 (28.4)	0	6 (3.8)	1
CCU	58 (32.4)	10 (52.6)	97 (60.6)	0.502
AC(F)	17 (15,17)	17 (16.5,17)	17 (15,17)	0.094
VISmax	17 (10,29)	44 (23,62.8)	16 (10,25)	0.014*
ECMO Duration (h)	82 (27,120)	106 (53,130.9)	75.1 (25.3,120)	0.102
Successful weaning from ECMO, *n* (%)	76.5	50	79.5	0.005*

*ECMO, Extracorporeal membrane oxygenation; ED, Emergency department; CCU, Cardiac Care Unit; AC, Arterial cannula; VIS, Vasoactive inotropic score; *, $P < 0.05$, the difference was statistically significant.*

TABLE 3 | Limb ischemia patients clinical features.

Features	Number	Treatment
ALI	5	Medication adjustment
	12	Medication adjustment + DPC
superficial femoral artery thrombus	1	embolectomy
common femoral artery thrombus	1	Incision and thrombectomy

ALI, Acute limb ischemia; DPC, Distal perfusion cannula.

ALI associated with V-A ECMO results from relative or absolute insufficiency of arterial blood flow to distal tissues, which is related to multiple factors. Larger size arterial cannulations may result in reduced lumen area and even vascular damage, resulting in limb ischemia (29). However, this relationship is not correlated, and ECMO cannula size depends on body surface area and ECMO mode, and is based on a match between target flow and vessel diameter (30). There was no significant difference in the size of arterial cannulation between the two groups in this study. Because of the lack of collateral circulation and the smaller diameter of the femoral artery, women and younger patients are prone to limb ischemia. The peripheral atherosclerotic disease also increases the risk of plaque displacement and injury during intubation and cannulation (7, 13). Diabetes and chronic respiratory disease are independent risk factors for limb ischemia during V-A ECMO (5, 31), which may be associated with chronic endothelial injury (32). In this study, the proportion of diabetes in the limb ischemia group was higher than that in the non-limb ischemia group, and multivariate analysis indicated that limb ischemia was independently associated with diabetes. Danial et al. (32) found that limb ischemia was independently associated with the Sequential Organ Failure Score (SOFA score). This also suggests that the patient's ability to compensate for hypoperfusion may affect vascular function. In addition, before the establishment of V-A ECMO, most patients are in a state of shock, requiring large doses of vasoactive drugs to maintain, especially in the ECPR state that causes vasoconstriction and acidic metabolites, which may affect distal perfusion. Our study also found that the LVEF in the ischemia group was significantly lower, the cardiac function was worse, the proportion of ECPR was higher than that in the non-ischemic group, and the VIS-max was significantly higher than that in the non-limb ischemia group. Therefore, after the establishment of ECMO, limb ischemia can be improved by drug adjustment (including reducing vasopressors, increasing vasodilators, and adequate anticoagulation) in some patients (9). For LV venting, patients with V-A ECMO-assisted cardiogenic shock often require a combined IABP, which may improve patient outcomes (33), but bilateral femoral arterial cannulation may lead to an increased risk of ALI (34). Multivariate regression analysis in this study also found that use of IABP in V-A ECMO patients was an independent risk factor for limb ischemia, and the application of dual distal perfusion catheters may be a strategy for the treatment of such patients (35).

TABLE 4 | Multivariate analysis of limb ischemia complications in V-A ECMO patients.

	OR	95%CI	*P*
Diabetes	4.338	1.193–15.772	0.026*
ECPR	1.437	0.253–8.587	0.667
AMI	1.828	0.377–8.878	0.454
IABP	1.526	1.038–22.026	0.049*
IMV	0.565	0.121–2.631	0.467
LVEF	0.467	0.944–1.041	0.730
AC	1.586	0.862–2.918	0.138
VIS-max	1.054	1.024–1.085	<0.001*

*ECPR, Extracorporeal cardiopulmonary resuscitation; AMI, Acute myocardial infarction; IABP, Intra-aortic balloon pump; IMV, Invasive mechanical ventilation; LVEF, Left ventricular ejection fraction; AC, Arterial cannula; VIS, Vasoactive inotropic score; *, $P < 0.05$, the difference was statistically significant.*

Considering the hazards caused by limb ischemia complications, all the patient on peripheral V-A ECMO should be closely monitored, especially unconscious patients. Clinical symptoms and signs are widely used in clinical practice as the primary assessment method. The classical description of patients with limb ischemia is grouped into a mnemonic device known as the 6 Ps, including: pain, pallor, paralysis, pulseless, paraesthesia, and paralysis (36). However, these signs may be deceptive for various reasons. The continuous flow of ECMO may render patients less pulsatile and make distal pulses less detectable. In patients with cardiogenic shock, the extremities often become colder due to a high dose of inotropes and pressors despite adequate perfusion. In addition, patients with endotracheal intubation and sedation and analgesia are unable to make immediate judgments. In these cases, a more sensitive tool to detect early distal-limb ischemia is warranted. Near-infrared reflectance spectroscopy (NIRS) technology can reflect local oxygen saturation (RSO2), and tissue oxygen saturation below 50% for a duration of more than 4 min is strongly associated with hypoperfusion (37, 38). Our center is mainly for awake and non-tracheal cannula ECMO patients, and the early clinical situation is easier to monitor. However,

in special populations, the combined use of NIRS to measure bilateral tissue oxygen saturation (SmO2) is helpful for early identification. The technical aspects of the various NIRS systems are not consistent. We have been using near-infrared reflectance spectroscopy as an auxiliary assessment tool for limb hypoperfusion since January 2021 but more samples are still needed to further validate its clinical relevance. Patients were also monitored to detect NIRS tissue saturation (StO2) differentials of 15% or more between the cannulated limb and the contralateral limb for the diagnosis of cannula-related obstruction to flow. The literature search for this paper found no references for intervention or cautionary values specific to distal limb saturations.

Prevention and treatment of limb ischemia should be individualized. Choosing a smaller size cannulation provides considerable clinical support and reduces complications, which is feasible in clinical practice (9, 23, 29, 39). In addition, evaluation of vascular access and selection of cannulation sites play an important role in preventing limb ischemia (1, 40–42). Proper anticoagulation, drug optimization and adequate perfusion of distal limb are necessary for patients who have occurred limb ischemia complications (9). At present, DPC is still the most commonly used invasive technique for the prevention and treatment of limb ischemia. In a meta-analysis of 1,850 patients, prophylactic DPC placement was found to reduce the incidence of limb ischemia (43). Rastan et al. (24) found that the use of DPC can reduce the risk of lower extremity ischemia and surgical intervention to $< 40\%$, so it is recommended to routinely place DPC in patients with peripheral V-A ECMO. However, there are corresponding risks associated with catheter placement, which may lead to lower extremity-related complications. In a retrospective study of 84 adult patients with V-A ECMO, Tanaka et al. found that even with prophylactic DPC placement, limb ischemic complications occurred in 12% of patients (13). Some studies suggested that DPC should be used as a salvage measure for limb ischemia after clinical assessment (21). In addition, the types of DPC used by different centers also vary greatly. The size of DPC ranges from 5 to 14 Fr and the most commonly used types are central venous catheters and vascular guide sheaths (usually 6–8 Fr) (44). In our study, we adopted the regimen of drug adjustment combined with DPC. For patients who cannot be improved by medication treatment or severe limb ischemia, DPC was placed as a salvage intervention. The limb ischemia in the whole group was improved, and no adverse events occurred, indicating DPC as a salvage intervention is feasible. Therefore, in order to prevent and treat V-A ECMO-related limb ischemia, we summarize it as a "4S" scheme (Best Site selection, Match arterial cannula Size, Systematic evaluation, Salvage intervention). During the establishment of V-A ECMO, a reasonable cannulation strategy can reduce the occurrence of limb ischemia complications to a certain extent. After ECMO was established, adequate timely evaluation and placement of DPC as a salvage intervention according to clinical conditions.

LIMITATION

This retrospective case-control study yielded some meaningful results for clinical guidance. However, there are still some limitations. First, this was a single-center retrospective study, and the distribution of disease are relatively single, which may cause selection bias. Second, no more objective indicators have been recorded and NIRS was not used in all patients to assess limb ischemia. In addition, there is a lack of short-and long term follow up on prognosis. Therefore, it is necessary to conduct a randomized controlled study to confirm the effectiveness of the placement of DPC as a salvage intervention.

CONCLUSION

In this study, limb ischemia complications were uncommon in patients receiving V-A ECMO assistance, but their occurrence may affect the ECMO weaning rate and survival rate. Diabetes, IABP, and VIS-max were independent risk factors for predicting limb ischemia complications in patients with V-A ECMO. It should be adequately evaluated during and after the establishment of V-A ECMO. DPC can be used as a measure of salvage for critical limb ischemic complications.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Affiliated the First Hospital of Lanzhou University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SH, AL, and MB: contributed to study concept and design. YW and WQ: acquisition and analysis of data. SH and AL: writing of the original manuscript and statistical analysis. MB and AL: revision and editing of the manuscript. BZ and CP: material, administrative support, and supervision. All authors approved the final version of the manuscript and agree to be responsible for all aspects of the work.

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Arterial and venous vascular complications in patients requiring peripheral venoarterial extracorporeal membrane oxygenation

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Introduction: The aim of this study was to investigate the prevalence of arterial and venous complications in patients requiring peripheral venoarterial extracorporeal membrane oxygenation (VA ECMO) and its risk factors at the time of cannulation and during extracorporeal membrane oxygenation (ECMO) support and to assess vascular complications in association with decannulation.

Material and methods: Between January 2010 to January 2020, out of 1,030 eligible patients requiring VA-ECMO, 427 with analyzable vascular screening were included. Duplex sonography and/or CT scan after decannulation were used to screen for thrombosis and pulmonary embolism as well as arterial complications. Near-infrared spectrometry (NIRS) was established at the time of cannulation and was continuously monitored during the ECMO therapy.

Results: The prevalence of venous complications was 27%. Thrombosis and pulmonary embolism were observed in 21 and 7% of patients, respectively. Pulmonary embolism was more frequently diagnosed in patients with thrombosis (22 vs. 3%, $p < 0.001$). In multivariate analysis, cannulation in the jugular vein was determined as a risk factor for venous thrombosis in contrast to the extent of anticoagulation. The prevalence of arterial complications was 37%, mainly ischemia followed by bleeding, dissection, and compartment syndrome. Vascular surgery was necessary for 19% of the patients, of whome 1% required major amputations. A distal perfusion cannula (DPC) was implanted at cannulation in 24% of patients and secondarily in 16% of patients after cannulation as required

during ECMO support. In the multivariate analysis, risk factors for leg ischemia at the time of cannulation were elevated D-dimers, lower NIRS on the cannulated leg, and lack of a DPC. The best discriminative parameter was the difference in NIRS between the non-cannulated leg and the cannulated leg. In contrast, during ECMO support, only the lack of a DPC was associated with leg ischemia. A similar rate of complications associated with decannulation, mainly arterial thrombosis, ischemia, or bleeding, was seen with percutaneous and surgical approaches (18 vs. 17%, $p = 0.295$).

Conclusion: Patients requiring VA ECMO should be routinely screened for vascular complications. The decision to insert a DPC should be evaluated individually. However, NIRS monitoring of the cannulated leg and the non-cannulated leg is essential to identify the legs at risk for critical ischemia. As complications associated with decannulation were equally distributed between percutaneous and surgical approaches, the applied method may be chosen according to local experience.

KEYWORDS

ECMO, vascular complication, ischemia, thrombosis, decannulation, bleeding, NIRS, risk factor

Introduction

Despite technological improvements and increasing clinical experience with venoarterial extracorporeal membrane oxygenation (VA ECMO), significant complications arise during VA-ECMO therapy either due to the therapy itself or due to the complexity of the critically ill patient.

A frequent complication in venovenous (VV) ECMO is thromboembolism, affecting more than 50% of patients to various extents (1). In contrast to the extensive knowledge available on VV ECMO, remarkably little is known about venous complications such as thrombosis and pulmonary embolism in patients requiring VA ECMO. This lack of knowledge is even more surprising considering the fact that patients requiring VA ECMO are more severely ill than patients requiring VV ECMO (2). For instance, patients requiring VA ECMO more frequently present with liver failure, which may affect coagulation, and often need different anticoagulation strategies than patients with VV ECMO support (3).

A distinct feature of peripheral VA ECMO in comparison to VV ECMO is the cannulation of a major artery, which is frequently accompanied by arterial vascular complications such as critical limb ischemia (4). It is known that critical limb ischemia during VA ECMO is associated with increased demands on medical resources, lower quality of life, and poor outcomes (5). Further, arterial vascular complications, such as bleeding, dissection, compartment syndrome, or initially failed puncture, and complications in association with decannulation are seldomly reported and need to be more emphasized.

Therefore, the aim of this study was to investigate the prevalence of arterial and venous vascular complications in patients requiring peripheral venoarterial extracorporeal membrane oxygenation (VA ECMO) and its risk factors at the time of cannulation and during ECMO support and to assess the complications in association with decannulation.

Abbreviations: CAD, coronary artery disease; CPC, cerebral performance category; CVD, cerebrovascular disease; DPC, distal perfusion cannula; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; IU, international units; PAD, peripheral artery disease; ROC, receiver operating curve; SOFA, sequential organ failure assessment; VA, veno-arterial; VV, veno-venous.

Materials and methods

Study subjects

All consecutive adult patients supported with VA ECMO at the University Hospital Regensburg between January 2010 and January 2020 were eligible for this analysis. Patients who had received central VA ECMO cannulation or had died during the ECMO therapy were excluded because screening for vascular complications after decannulation was not conducted in these patients.

Indications for VA ECMO were the cardiogenic shock of different etiologies and extracorporeal cardiopulmonary resuscitation (eCPR).

The study was conducted according to the Declaration of Helsinki on Good Clinical Practice. The requirement of individual patient consent and the necessity of approval for the data report were waived by the local ethics committee (20-1710-104) because of the retrospective, anonymized study design and of the analysis of data exclusively collected during routine care.

Patient data such as demographics, biochemistry, hemodynamic parameters, resuscitation status, sequential organ failure assessment (SOFA), and computed tomography images were extracted from the electronic patient data management system. The preexisting vascular risk status was defined according to the diagnosis of cerebrovascular disease (CVD), peripheral artery disease (PAD), or coronary artery disease (CAD). Disseminated intravascular coagulopathy was defined as that stated in a previous study (1), with good neurologic outcome as a cerebral performance score (CPC) of 1 (good cerebral performance) or 2 (moderate disability) and poor neurologic outcome as a CPC of 3–5 (6). Survival was assessed at discharge from the hospital.

Cannulation and decannulation technique and anticoagulation

In general, drainage cannulae were placed into the femoral vein and return cannulae into the femoral artery either on the same side (mainly during eCPR) or bilaterally. Adaptions were allowed according to the anatomy or the treating physician. The drainage and the return cannulae were implanted percutaneously *via* Seldinger's technique by an experienced intensivist or in the operation room by a surgeon. A vascular ultrasound scan was carried out prior to cannulation when possible. The size of the arterial and venous cannulae was chosen as previously published according to ultrasound findings, the desired ECMO flow rate, and the patients' physical dimensions (4). The position of the cannulae was checked with ultrasound and x-ray or CT scan. Patients without any previous therapeutic anticoagulation received a bolus of up to 5,000 IU unfractionated heparin for cannulation. The circuit design and components of cannulation are depicted in **Supplementary Figure 1**.

During ECMO support, we aimed for an activated partial thromboplastin time of 60 ± 5 s in accordance with current recommendations (3). Further details on anticoagulation have been previously published (1, 4) and are presented in **Supplementary Table 1**.

A distal wire-reinforced perfusion cannula (DPC, CruraSave femoral-Perfusion Set 7 Fr, Free life medical GmbH, Aachen, Germany) into the superficial femoral artery was not routinely inserted (**Supplementary Figure 2**). The placement of a DPC was usually made in the ICU in the case of clinical signs of reduced leg perfusion at the time of cannulation or during the ECMO therapy. The flow rate of the DPC was checked routinely every 8–24 h and more frequently in case of a decline in near-infrared spectrometry (NIRS) (4).

Decannulation was performed either percutaneously with manual compression at the bedside or by surgeons in the operating theater after discontinuation of anticoagulation for at least 4 h. After control of bleeding by manual compression and skin suture, an inflatable balloon tape system (SafeGuard; MeritEMEA, Limburg, The Netherlands) was attached for at least 24 h. The balloon device was stepwise deflated every 2–4 h until complete removal. Alternatively, a compression bandage was applied.

Venous complications

Screening for venous thrombosis was conducted with duplex sonography within 3 days after decannulation. The diagnosis was made by specially trained physicians in the case of incompressible veins and absent or reduced blood flow as indicated in a previously study (1, 7). Obstruction of the venous lumen diameter of >50% was classified as major thrombosis (1, 7). Additionally, all available CT scans made for various clinical indications after decannulation during the hospital stay were analyzed for new events of pulmonary embolism and thrombosis (1). Additionally, we assessed other complications such as bleeding at the site of cannulation, atrial/ventricular perforation, and compartment syndrome that might occur in parallel to thromboembolic complications.

Arterial complications

Risk factors for limb ischemia were collected from the initiation until the end of ECMO support. Regional oxygen saturation in both legs was continuously measured by NIRS (INVOS^{TM} 5100C, Medtronic, Minneapolis, United States). For the analysis of the entire ECMO support, NIRS was documented only one time a day, i.e., in the morning. Acute desaturation in NIRS as a sign of deterioration of perfusion/ischemia immediately resulted in further diagnostic workup and intervention to prevent limb ischemia (e.g., placement of a DPC). In addition, clinical signs of arterial complications of the leg (pallor, hypothermia, or pulselessness) or bleeding were checked routinely every 2 h. Doppler ultrasonography of the dorsalis pedis artery and the posterior tibial artery was routinely performed every 8 h and more frequently in the case of suspected ischemia. If possible, preventive measures to reduce the risk of limb ischemia such as improvement of leg perfusion were applied by means of reduction of vasopressors, infusion of vasodilators, or use of

inotropes. In the case of incipient limb ischemia of a cannulated leg without a primarily implanted DPC, a DPC was inserted with the guidance of ultrasound.

Based on previous publications, critical limb ischemia was defined as a decrease in NIRS by 25% compared to the contralateral leg, a decrease in absolute NIRS values below 40%, showing clinical signs of ischemia, or showing sonographic evidence of missing perfusion (4). Additionally, we assessed other complications such as arterial thrombosis, bleeding at the site of cannulation, arterial dissection, compartment syndrome, and vascular surgery. Moreover, physicians' documentation (including surgical protocols) and nurses' shift reports were screened for vascular complications.

Miscellaneous complications and complications associated with decannulation

Complications that could not be assigned to either the venous or arterial vascular system with certainty were considered miscellaneous complications, which included bleeding at the site of cannulation, arteriovenous fistula, and initially failed puncture during cannulation. We also assessed complications in association with decannulation such as ischemia, compartment syndrome, pseudoaneurysm, and bleeding.

Statistics

All quantitative data are expressed as median (interquartile range) and were compared with the Mann–Whitney-*U* test. Differences between the study groups were assessed with the Chi-squared test of independence for nominal variables or the Fisher's exact test as needed. Univariate logistic regression models were conducted to identify risk factors for venous thrombosis or limb ischemia. For limb ischemia, one model included parameters at the time of cannulation and the other model included parameters assessed during the ECMO therapy. The multivariat logistic regression model was adjusted for alle factors with a p values of less than 0.1 in the univariate

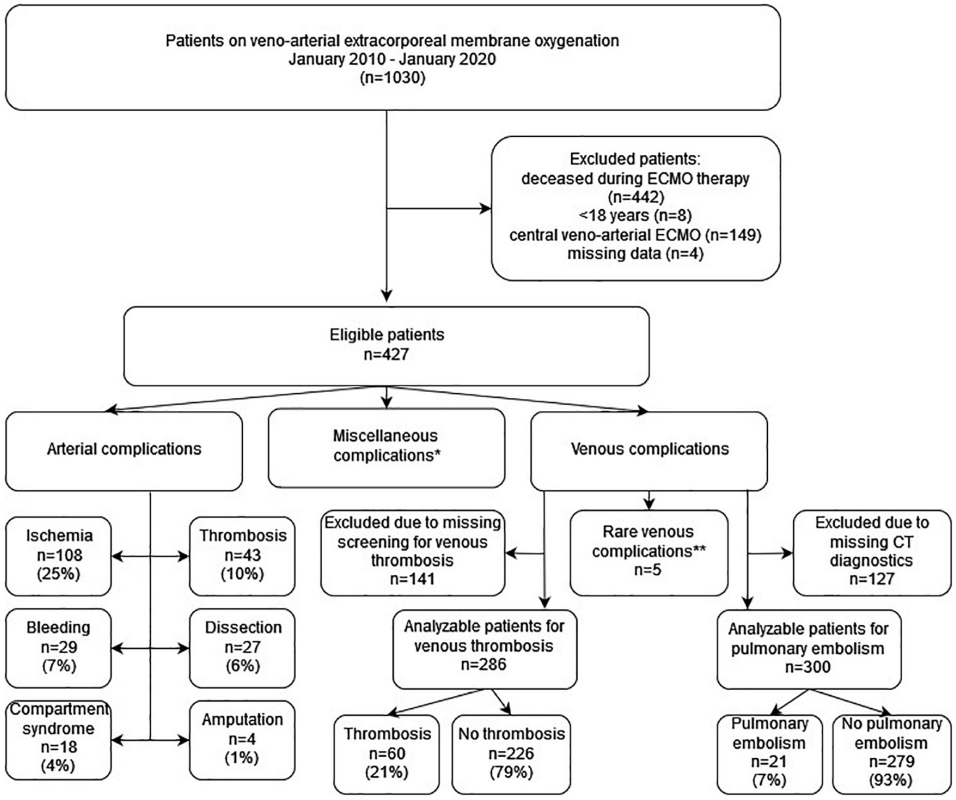

FIGURE 1
Flowchart of the observational study evaluating arterial and venous complications in survivors of venoarterial extracorporeal membrane oxygenation of the extracorporeal life support registry at Regensburg; ECMO, extracorporeal membrane oxygenation; CT, computer tomography; *miscellaneous complications included initially failed puncture (n = 24), bleeding (n = 20), and arteriovenous fistula (n = 1); **rare venous complications included bleeding (n = 2), right atrial/ventricular wall perforation (n = 2), and compartment syndrome of the leg with venous cannulation (n = 1).

analysis. In addition, a multivariate model for biochemistries according to limb ischemia was calculated. The cutoff points for NIRS were identified by receiver operating characteristic (ROC) analysis using the Youden index. All reported *p*-values were two-sided, and a *p*-value of ≤ 0.05 was considered statistically significant. Data entry and calculation were done using Microsoft EXCEL365 ProPlus (Microsoft, Redmond, WA, United States) and IBM SPSS Statistic software version 25.0 (SPSS Inc., Chicago, IL, United States).

Results

Study population

From January 2010 to January 2020, 1,030 patients required VA ECMO at the University Hospital Regensburg, Germany, of whom 427 were eligible for the evaluation of venous and arterial complications (Figure 1). Patients had a median age of 59 [50; 68] years, a body mass index of 26.5 [24.2; 29.4] kg/m^2, and were mainly men (73%); 64% of patients had arteriosclerosis and 22% had diabetes mellitus. Of the 427 patients, 161 (38%) of them received cannulation during eCPR (Supplementary Table 2). The SOFA score was 14 [12; 17], and 161 (38%) of the patients required renal replacement therapy. A DPC was implanted at cannulation in 101 (24%) patients and secondarily in 66 (16%) patients after cannulation as required during ECMO support. Baseline characteristics are summarized in Supplementary Table 3.

Venous complications

Screening for venous thrombosis was conducted in 67% (286/427) of patients. Venous thrombosis was prevalent in 21% (60/286) of patients and occlusion of the lumen diameter of > 50% was observed in 10% (29/286) of patients (Figure 2). After decannulation, thoracic CT scans with contrast dye were performed in 70% (300/427) of patients, of whom 7% (21/300) had pulmonary embolism. Pulmonary embolism was more frequently observed in those with thrombosis than those without thrombosis (22% [11/51]

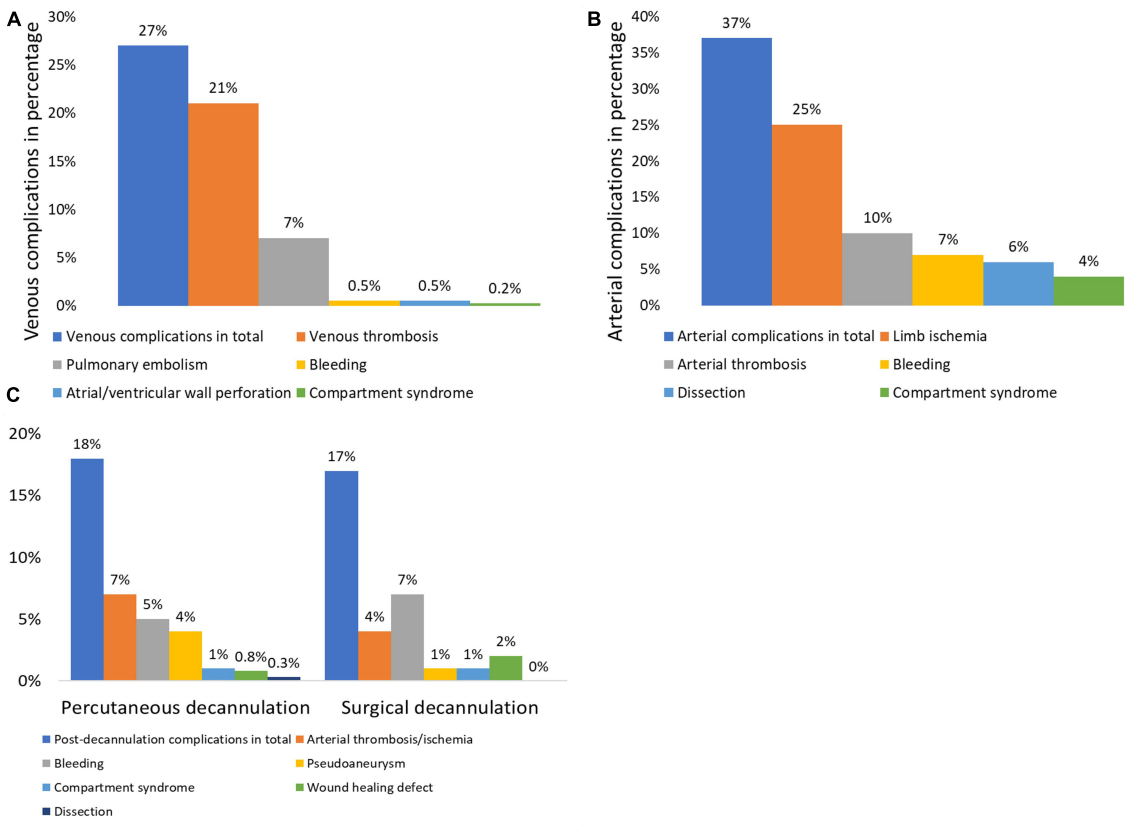

FIGURE 2
Prevalences of venous **(A)** and arterial **(B)** complications and **(C)** post-decannulation complications according to the type of decannulation in patients requiring venoarterial extracorporeal membrane oxygenation. Data are presented in percentages. All *p*-values comparing percutaneous vs. surgical decannulation are >0.05.

vs. 3% [5/168], $p < 0.001$). Overall, venous complications in patients undergoing screening for both pulmonary embolism and thrombosis were seen in 27% (60/219) of patients, including thromboembolic events in 26% (56/219) of them and other venous complications, such as bleeding at cannulation site ($n = 2$), right atrial/ventricular wall perforation ($n = 2$), and compartment syndrome of a leg with bilateral cannulation as a consequence of venous congestion ($n = 1$). Patients may have developed more than one complication.

Risk factors for venous thrombosis

Risk factors for venous thrombosis were cannulation in the jugular vein in comparison to the femoral vein and the use of a small-sized cannula for venous drainage, but the latter did not occur after correcting for body surface area (Table 1 and Supplementary Table 4). Venous thrombosis was associated neither with unilateral arterial and venous cannulations nor with biochemistries (Table 2).

Arterial complications

Complications associated with arterial cannulation were seen in 37% (158/427) of patients during ECMO support. Patients may have developed more than one complication; thus, limb ischemia was diagnosed in 25% (108/427) of patients, arterial thrombosis in 10% (43/427), bleeding in 7% (29/427), arterial dissection in 6% (27/427), and compartment syndrome in 4% (18/427). As a consequence, vascular surgery was performed in 19% (82/427) of patients, of whom 1% (4/427) required major amputation.

Risk factors for limb ischemia at time of cannulation

Patients with limb ischemia were more frequently resuscitated, less frequently received a DPC, had lower NIRS at the cannulated and higher absolute differences in NIRS between the cannulated leg and the non-cannulated leg at the time of cannulation, and had slightly higher ECMO flow

TABLE 1 Patient characteristics at cannulation with regard to venous thrombosis.

	N	Venous thrombosis *N* = 60	*N*	No venous thrombosis *N* = 226	*P*-value
Age, years	60	57 [48; 68]	226	59 [50; 68]	0.455
Sex, men	60	40 (67%)	226	161 (71%)	0.491
BMI, kg/m^2	60	26.2 [23.6; 29.4]	226	26.8 [24.2; 29.4]	0.734
Diabetes mellitus	60	12 (20%)	226	49 (22%)	0.777
Disseminated intravascular coagulation	52	4 (8%)	185	24 (13%)	0.297
History of malignancy	60	5 (8%)	223	29 (13%)	0.323
Immunosuppression	60	2 (3%)	226	15 (7%)	0.539
Resuscitation pre ECMO	60	41 (68%)	226	150 (66%)	0.774
SOFA	48	15 [13; 17]	180	14 [12; 17]	0.259
Days on ECMO	60	4 [3; 7]	226	4 [3; 6]	0.572
Renal replacement therapy	60	29 (48%)	226	81 (36%)	0.077
Size of arterial cannula, French	60	15 [15; 17]	226	15 [15; 17]	0.276
Size of venous drainage cannula, French	60	21 [21; 21]	226	21 [21; 23]	**0.036**
Site of venous drainage cannula	60		226		**0.003**
Jugular		6 (10%)		3 (1%)	
Femoral		54 (90%)		223 (99%)	
Arterial and venous cannula ipsilateral	57	24 (42%)	219	100 (46%)	0.631
APTT, s	59	56 (38; 103)	215	51 (37; 115)	0.417
D-dimer, mg/L	53	12 (3; 24)	188	9 (3; 25)	0.412
INR	50	1.4 (1.2; 2.0)	195	1.4 (1.1; 1.8)	0.374
Fibrinogen, mg/dL	53	260 (192; 513)	191	252 (159; 378)	0.101
Antithrombin III, %	52	57 (46; 67)	186	56 (42; 67)	0.504
Plasma free hemoglobin, mg/dL	46	195 (65; 434)	174	146 (59; 362)	0.480
Platelets, /nL	59	174 (136; 235)	218	188 (127; 259)	0.705

Data are presented as median [25th; 75th percentile] or frequencies, *n* (%). Significant *p*-values ($p < 0.05$) are marked in bold. $N = 286$. BMI, body mass index; ECMO, extracorporeal membrane oxygenation; SOFA, sequential organ failure assessment; APTT, activated partial thromboplastin time.

TABLE 2 Univariate and multivariate binary logistic regression models for venous thrombosis in survivors of venoarterial extracorporeal membrane oxygenation.

Variables	Unadjusted		Adjusted	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age, years	0.990 (0.970; 1.011)	0.357		
Sex, men	1.238 (0.673; 2.277)	0.491		
BMI, kg/m^2	1.008 (0.964; 1.054)	0.717		
Diabetes mellitus	1.107 (0.546; 2.246)	0.778		
Disseminated intravascular coagulopathy	1.789 (0.592; 5.409)	0.303		
History of malignancy	1.644 (0.608; 4.448)	0.327		
Immunosuppression	2.062 (0.458; 9.274)	0.346		
Resuscitation before ECMO	0.915 (0.497; 1.683	0.915		
SOFA	1.059 (0.964; 1.163)	0.234		
Days on ECMO	1.028 (0.974; 1.086)	0.317		
Renal replacement therapy	1.675 (0.943; 2.975)	0.079	1.421 (0.777; 2.597)	0.254
Size of arterial cannula, French	0.862 (0.690; 1.077)	0.190		
Size of arterial cannula per body surface area, French/m^2	0.906 (0.666; 1.233)	0.530		
Size of venous cannula, French	0.714 (0.526; 0.970)	**0.031**[a]		
Size of venous cannula per body surface area, French/m^2	0.896 (0.701; 1.144)	0.379		
Site of venous cannula, jugular	8.259 (2.002; 34.082)	**0.004**	7.187 (1.701; 30.370)	**0.007**
Arterial and venous cannula ipsilateral	1.155 (0.641; 2.083)	0.631		
APTT, seconds	0.995 (0.970; 1.020)	0.683		
D-dimer, mg/L	1.010 (0.985; 1.035)	0.450		
Fibrinogen, mg/dL	1.000 (0.998; 1.002)	0.687		
Antithrombin III, %	1.008 (0.990; 1.028)	0.381		
Plasma free hemoglobin, mg/dL	1.001 (0.998; 1.005)	0.379		
Platelets, /nL	0.995 (0.989; 1.001)	0.085	1.000 (0.997; 1.003)	0.825
International normalized ratio	0.612 (0.147; 2.553)	0.500		

All parameters including biochemistries were assessed at the time of cannulation. Significant *p*-values ($p < 0.05$) are marked in bold. OR, odds ratio; CI, confidence interval; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; SOFA, sequential organ failure assessment; APTT, activated partial thromboplastin time.
[a]Not included in the model because it is not significant after correction for BMI.

rate. No differences between the groups with and without limb ischemia were seen according to unilateral compared to bilateral cannulation, cannula size, or vasopressor therapy (Table 3). At the time of cannulation, the statistically best predictive NIRS value for limb ischemia was 18% (sensitivity 93%, specificity 18%) on the cannulated leg (Supplementary Figure 3). When comparing the difference between the non-cannulated leg and the cannulated leg with regard to limb ischemia, an absolute NIRS difference of 17% resulted in a sensitivity of 82% and a specificity of 60% (Supplementary Figure 4). In multivariate analysis, lack of a DPC, lower NIRS in the cannulated leg, and elevated D-dimers were associated with limb ischemia (Table 4).

Risk factors for limb ischemia during extracorporeal membrane oxygenation support

During the entire ECMO support, patients with limb ischemia had lower median activated partial thromboplastin time (aPTT) and median NIRS values in the non-cannulated leg. Additional biochemistries, NIRS values, and vasopressors during ECMO support are provided in Supplementary Table 6. NIRS of the non-cannulated leg was associated with limb ischemia in the univariate analysis, but not in the multivariate analysis. The only factor that was associated with limb ischemia in the multivariate analysis was the lack of a DPC (Table 5).

Miscellaneous complications and complications associated with decannulation

Patients requiring a DPC at any time of ECMO treatment were more often diagnosed with limb ischemia, arterial thrombosis, and dissection and were in need of more packed red blood cells per day on ECMO support (Supplementary Table 7).

Initially failed puncture was seen in 6% (24/427), bleeding in 5% (20/427), and arteriovenous fistula in 0.2% (1/427). Complications in association with decannulation were observed

TABLE 3 Patient characteristics at the time of cannulation with regard to ischemia.

	N	Ischemia *N* = 108	*N*	No ischemia *N* = 319	*P*-value
Age, years	108	57 (49; 65)	319	60 (50; 69)	0.100
Sex, men	108	77 (71%)	319	233 (73%)	0.725
BMI, kg/m^2	108	26.3 (23.5; 30.5)	319	26.5 (24.2; 29.4)	0.983
Diabetes mellitus	108	22 (20%)	319	71 (22%)	0.681
Vascular risk (PAD, CAD, CVD)	108	74 (69%)	319	199 (62%)	0.251
Resuscitation pre ECMO	108	82 (76%)	319	208 (65%)	**0.039**
SOFA	90	14 (12; 18)	241	14 (12; 17)	0.338
Renal replacement therapy	108	42 (39%)	319	122 (38%)	0.905
Cannula specifics					
Percutaneous cannulation	108	103 (95%)	318	301 (95%)	0.771
Initially failed puncture	108	13 (12%)	319	11 (3%)	**<0.001**
Size of arterial cannula, French[a]	108	16 (15; 17)	319	15 (15; 17)	0.221
Size of venous cannula, French	108	21 (21; 21)	319	21 (21; 23)	0.078
Drainage and return cannulae ipsilateral	100	47 (47%)	287	118 (41%)	0.305
Distal perfusion cannula *a priori*	103	13 (13%)	296	88 (30%)	**<0.001**
NIRS cannulated leg, %	33	35 (28; 51)	59	49 (35; 61)	**0.035**
NIRS non-cannulated leg, %	21	63 (55; 65)	33	65 (53; 72)	0.310
NIRS difference between non-cannulated and cannulated leg, %[b]	21	25 (20; 37)	33	9 (0; 23)	**0.015**
ECMO blood flow, L/min	99	3.0 (2.5; 3.6)	306	2.9 (2.3; 3.3)	**0.044**
Mean arterial pressure, mmHg	101	55 (40; 65)	308	55 (41; 65)	0.745
Norepinephrine, µg/kg/min	106	0.36 (0.18; 0.74)	314	0.30 (0.14; 0.65)	0.218
Epinephrine, µg/kg/min	106	0.14 (0.00; 0.32)	314	0.10 (0.00; 0.24)	0.409
Chemistries					
APTT, s	102	50 (37; 89)	310	54 (37; 105)	0.797
D-dimer, mg/L	84	13 (4; 32)	255	7 (2; 19)	**0.006**
International normalized ratio	77	1.40 (1.20; 1.90)	250	1.40 (1.20; 1.80)	0.676
Fibrinogen, mg/dL	81	247 (149; 381)	257	266 (189; 394)	0.299
Antithrombin III, %	78	51 (46; 60)	248	57 (43; 67)	0.181
Plasma free hemoglobin, mg/dL	70	216 (72; 460)	221	134 (57; 345)	**0.043**
Platelets, /nL	103	182 (125; 284)	311	180 (136; 243)	0.928

Data are presented as median [25th; 75th percentile] or frequencies, *n* (%). Significant *p*-values ($p < 0.05$) are marked in bold. $N = 427$.
[a]Further details are presented in Supplementary Table 5.
[b]Only in patients with elective cannulation.
BMI, body mass index; PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; ECMO, extracorporeal membrane oxygenation; SOFA, sequential organ failure assessment; NIRS, continuous near-infrared spectrometry; APTT, activated partial thromboplastin time.

in 17% (72/427) of patients. The most common decannulation complications were arterial thrombosis or ischemia, bleeding, and pseudoaneurysm, which were similarly distributed between percutaneous and surgical decannulation approaches (Table 6).

Outcome

After decannulation, 71% (302/427) of patients were discharged from the hospital with good neurological outcome in 76% (229/302) of them. Survival and good neurologic outcome were lower in those with limb ischemia than in those without limb ischemia (60% [65/108] vs. 74% [237/319], $p = 0.005$; 67% [42/63] vs. 80% [187/233], $p = 0.022$; missing data of CPC in $n = 6$).

Discussion

This study provides novel insights into arterial and venous vascular complications in patients requiring and surviving VA ECMO. First, the prevalence of venous thrombosis was 21% and that of pulmonary embolism was 7%. The risk factor for venous thrombosis was venous jugular cannulation. Second, arterial complications were observed in 37% of patients. Risk factors for ischemia at the time of cannulation were lower NIRS of the cannulated leg and lack of a DPC. A difference of an absolute 17% in NIRS values between the non-cannulated leg and the cannulated leg showed the best predictive value for limb ischemia. Vascular complications associated with decannulation were observed in 17% of patients

and were similarly distributed between percutaneous or surgical decannulation approaches.

Prevalence and risk factors for venous thromboembolism in survivors of venoarterial extracorporeal membrane oxygenation

Data on venous complications in patients requiring VA ECMO are scarce (8, 9). In an autopsy study in postcardiotomy patients by Rastan et al. (9) ($n = 78$), a slightly higher prevalence of venous thrombosis (32%) and pulmonary embolism (15%) was reported in comparison to 21 and 7% in the current study. Compared to previous data from our VV ECMO cohort, the prevalence of venous thrombosis in the current study with VA ECMO was considerably lower (1). Reasons for these lower rates might result from the different patient populations with less time on ECMO support, the single venous ECMO cannula access, and the higher aPTT target levels. Nevertheless, it is important to emphasize that pulmonary embolism was observed more than seven times more frequently in those with thrombosis than in those without thrombosis. These findings support the need for systematic post-decannulation ultrasound screening in patients requiring VA ECMO.

In line with the aforementioned studies (1, 9), venous thrombosis was more prevalent in the jugular cannulated than in

TABLE 4 Univariate and multivariate binary logistic regression models for limb ischemia at the time of cannulation in survivors of veno-arterial extracorporeal membrane oxygenation.

Variables	Unadjusted		Model I		Model II	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age, years	0.989 (0.973; 1.006)	0.203				
Sex, men	0.917 (0.565; 1.489)	0.725				
Body mass index, kg/m^2	1.000 (0.965; 1.037)	0.986				
Diabetes mellitus	1.119 (0.654; 1.916)	0.681				
Vascular risk	0.762 (0.479; 1.213)	0.252				
Resuscitation pre ECMO	1.683 (1.023; 2.768)	**0.040**	2.013 (0.693; 5.849)	0.199		
SOFA	1.052 (0.981; 1.127)	0.157				
RRT						
Cannula specifics						
Initially failed puncture	3.832 (1.662; 8.833)	**0.002**	0.733 (0.087; 6.185)	0.775		
Size of arterial cannula, French	1.053 (0.914; 1.214)	0.472				
Size of venous cannula, French	1.165 (0.947; 1.434)	0.149				
Drainage and return cannulae ipsilateral	0.787 (0.498; 1.244)	0.305				
No distal perfusion cannula *a priori*	0.341 (0.181; 0.643)	**0.001**	0.182 (0.053; 0.623)	**0.007**		
NIRS cannulated leg, %	0.974 (0.949; 1.000)	**0.049**	0.958 (0.926; 0.992)	**0.015**		
NIRS non-cannulated leg, %	0.989 (0.952; 1.027)	0.561				
NIRS difference between non-cannulated and cannulated leg[a], %	1.035 (1.000; 1.071)	0.053				
ECMO blood flow, L/min	1.427 (1.044; 1.949)	**0.026**	0.578 (0.248; 1.349)	0.205		
Lactate, mg/dL	1.003 (0.999; 1.008)	0.125				
Mean arterial pressure, mmHg	0.998 (0.984; 1.013)	0.824				
Norepinephrine, µg/kg/min	1.022 (0.829; 1.258)	0.841				
Epinephrine, µg/kg/min	1.444 (0.878; 2.372)	0.148				
Chemistries						
APTT, s	0.999 (0.992; 1.005)	0.639				
D-dimer, s	1.026 (1.007; 1.046)	**0.008**			1.023 (1.001; 1.046)	**0.038**
International normalized ratio	0.880 (0.659; 1.175)	0.386				
Fibrinogen, mg/dL	0.999 (0.998; 1.001)	0.398				
Antithrombin III, %	0.989 (0.976; 1.003)	0.114				
Plasma free hemoglobin, mg/dL	1.001 (1.000; 1.001)	**0.046**			1.001 (1.000; 1.001)	0.146
Platelets, /nL	1.000 (0.998; 1.002)	0.819				

All parameters including biochemistries were assessed at the time of cannulation. Significant *p*-values ($p < 0.05$) are marked in bold. OR, odds ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; NIRS, continuous near-infrared spectrometry; APTT, activated partial thromboplastin time.

[a]Not included in the multivariate analysis due to over-adjustment with the NIRS cannulated leg.

TABLE 5 Univariate and multivariate binary logistic regression models for limb ischemia over the entire duration of ECMO support in survivors of venoarterial extracorporeal membrane oxygenation.

Variables	Unadjusted		Model I	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Days on ECMO	0.988 (0.964; 1.033)	0.918		
APTT, s	0.988 (0.969; 1.007)	0.201		
D-dimer, mg/L	1.011 (0.991; 1.031)	0.294		
International normalized ratio	1.395 (0.572; 3.402)	0.465		
Fibrinogen, mg/dL	0.999 (0.997; 1.001)	0.222		
Antithrombin III, %	0.994 (0.980; 1.010)	0.466		
Plasma free hemoglobin, mg/dL	1.000 (0.998; 1.003)	0.698		
Platelets, /nL	0.999 (0.995; 1.004)	0.807		
NIRS cannulated leg, %[a]	0.999 (0.968; 1.031)	0.960		
NIRS non-cannulated leg, %[a]	0.964 (0.932; 0.996)	**0.027**	0.970 (0.925; 1.016)	0.199
Norepinephrine, μg/kg/min	4.023 (0.345; 46.978)	0.267		
Epinephrine, μg/kg/min	1.221 (0.021; 71.658)	0.924		
Subsequent implantation of distal perfusion cannula[b]	48.558 (21.695; 108.682)	<**0.001**	59.540 (19.756; 179.446)	<**0.001**

All parameters but distal perfusion cannula are depicted as median values during the ECMO therapy.
[a]NIRS was measured continuously but recorded for the study one time daily.
[b]Distal perfusion cannula (DPC) were not prophylactically used in each ECMO cannulation, but these patients received a DPC after cannulation in the course of ECMO support. Significant *p*-values ($p < 0.05$) are marked in bold.
OR, odds ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; APTT, activated partial thromboplastin time; NIRS, continuous near-infrared spectrometry.

the femoral cannulated veins. Interestingly, no difference in the rate of thrombosis was seen in bilateral compared to unilateral cannulation. Unexpectedly, the use of a small-sized venous cannula was associated with venous thrombosis. However, after correcting for body surface, the use of a small-sized venous cannula positively correlated with the diameter of the peripheral veins (10), and no association was observed anymore.

Prevalence and risk factors for arterial limb ischemia in patients requiring venoarterial extracorporeal membrane oxygenation

Frequencies of arterial complications, mainly limb ischemia, range from 2 to 52% due to different cannulation techniques and definitions of limb ischemia (11). In the current study, limb ischemia occurred in 25% of the patients and (12) was associated with mortality, as indicated in other studies. Therefore, to improve outcomes in patients on peripheral femoral VA ECMO, it is essential to detect patients at risk for limb ischemia at the time of cannulation and during the entire ECMO support. We identified lower NIRS values at the time of cannulation as an independent risk factor for the development of limb ischemia. However, the difference in NIRS values between the non-cannulated leg and the cannulated leg for limb ischemia at the time of cannulation was the best predictive value, eventually embedding the general hemodynamic status and the local perfusion of the arterially cannulated leg. Moreover, lack of a DPC, as reported by Tanaka et al. (13), and elevated D-dimers were associated with limb ischemia in contrast to unilateral compared to bilateral cannulation.

Over the entire ECMO support, only the lack of a DPC was associated with limb ischemia but not NIRS. The latter result seems to be in contrast to some smaller studies (each $n < 65$) (14–16); however, it can be explained by the usage of median values over the entire ECMO run without the inclusion of event-driven drops in NIRS values in case of acute ischemia. Thus, we believe NIRS monitoring to be essential to detect limb ischemia early to take immediate action to avoid severe complications.

Miscellaneous complications and complications associated with decannulation

Notably, only 24% of patients required a DPC during cannulation and 16% of them after cannulation, which is in contrast to other studies with substantially higher (>90%) DPC placement rates at the beginning of ECMO support (17). Despite that, our rate of major amputations was lower compared to other studies (17–19). In addition, it has to be taken into account that DPC might be accompanied by vascular complications itself and more bleeding due to multiple unsuccessful sticks, dislodgement, or kinking. Therefore, the decision for DPC placement should be made on an individual basis.

TABLE 6 Complications associated with decannulation in survivors of venoarterial extracorporeal membrane oxygenation.

	Total $N = 427^{*}$	Percutaneous decannulation $N = 264$	Surgical decannulation $N = 148$	*P*-value
Cumulative complication rate	72 (17%)	47 (18%)	25 (17%)	0.295
Arterial thrombosis/ischemia[a]	24 (6%)	18 (7%)	6 (4%)	0.220
Bleeding	22 (5%)	12 (5%)	10 (7%)	0.205
Pseudoaneurysm[b]	13 (3%)	11 (4%)	2 (1%)	0.196
Compartment syndrome	5 (1%)	3 (1%)	2 (1%)	1.000
Dissection	1 (0.2%)	1 (0.3%)	0 (0%)	1.000
Wound healing defect	5 (1%)	2 (0.8%)	3 (2%)	0.334

Data are presented as frequencies, *n* (%). Patients may develop more than one complication.
*Missing information on type of decannulation in $N = 15$.
[a]Includes occlusion of the superficial femoral and common femoral artery and more distal arterial thrombosis.
[b]Includes one ateriovenous fistula.

Complications other than limb ischemia are seldomly reported or grouped together (17, 19, 20). In particular, initially failed puncture at the site of cannulation has never been reported as a risk factor for limb ischemia. This complication is of interest because it may be avoidable by accurate identification of the vessels by applying ultrasound during cannulation. However, this association was not robust in the multivariate analysis.

Data on vascular complications in association with decannulation are lacking besides a case series comparing a percutaneous closure device with surgical decannulation reporting higher complication rates after the surgical approach (21, 22). The best method for decannulation either surgically or percutaneously is still unclear (23). In this analysis, decannulation was conducted percutaneously in more than 60% of patients with similar complication rates than with surgical decannulation. However, it is noteworthy that, irrespective of the decannulation method, limb ischemia, bleeding, and pseudoaneurysm were observed in 6, 5, and 3%, respectively. In consequence, all patients should routinely be screened after decannulation for potential complications (23).

Strength and limitations

The strength of the current study is the systematic screening for both arterial *and* venous complications and the inclusion of rare complications as well as of complications associated with decannulation. The exact timing of complications was limited by the applied screening strategy. The classification of risk factors for limb ischemia into those risks at the time of cannulation and risks during the entire ECMO support may help clinicians to identify patients with a high risk of limb ischemia at cannulation and during the ECMO therapy.

Due to the retrospective design, underreporting of complications may have occurred. The multivariate analysis was only carried out for the most frequent events. For the analysis over the entire ECMO support, NIRS was documented only one time per day. Patients with central VA ECMO and those with the application of a percutaneous closure device for decannulation were not included in this analysis.

Conclusion

Patients with VA-ECMO should be routinely screened for vascular complications, and necessary anticoagulation should be provided as arterial and venous complications under peripheral VA ECMO are frequently seen. A drainage cannula in the jugular vein was a risk factor for venous thrombosis and should be avoided, if possible. The placement of a DPC was necessary in 40% of patients and the decision to insert a DPC should be evaluated individually. NIRS monitoring of the cannulated and the non-cannulated leg at the time of cannulation and during ECMO is essential to identify limbs at risk for critical ischemia to allow immediate action to avoid severe complications. As complications associated with either percutaneous or surgical decannulation were equally distributed, the applied method may be chosen according to local experience and patient-specific factors.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by University of Regensburg, Germany,

20-1710-104. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CF and ML were responsible for the conception, hypotheses delineation, and the design of the study, for the acquisition of data, the analysis and interpretation of this information, and for writing the article and its revision prior to submission. CF, ML, and CA were responsible for drafting the manuscript and were involved in the acquisition of data, the analysis and interpretation of this information, and the critical revision of the article prior to submission. CW, RS, MF, AP, DL, KP, CS, and TM were involved in the acquisition of data, the analysis and interpretation of results, and the critical revision of the article prior to submission. All authors contributed to the article and approved the submitted version.

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Conflict of interest

ML was received lecture honoraria form Fresenius Medical Care.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.960716/full#supplementary-material

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Mortality prediction in pediatric postcardiotomy veno-arterial extracorporeal membrane oxygenation: A comparison of scoring systems

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Background: Pediatric postcardiotomy veno-arterial extracorporeal membrane oxygenation (VA-ECMO) patients have high mortality and morbidity. There are currently three scoring systems available to predict mortality: the Pediatric Extracorporeal Membrane Oxygenation Prediction (PEP) model, Precannulation Pediatric Survival After VA-ECMO (Pedi-SAVE) score, and Postcannulation Pedi-SAVE score. These methods provide risk stratification scores for pediatric patients requiring ECMO for cardiac support. However, comparative validation of these scoring systems remains scarce. We aim to assess the ability of these models to predict outcomes in a cohort of pediatric patients undergoing VA-ECMO after cardiac surgery, and identify predictors of in-hospital mortality.

Methods: A retrospective analysis of 101 children admitted to Fuwai Hospital who received VA-ECMO from January 1, 2010 to December 31, 2020 was performed. Patients were divided into two groups, survivors ($n = 49$) and non-survivors ($n = 52$) according to in-hospital mortality. PEP model and Pedi-SAVE scores were calculated. The primary outcomes were the risk factors of in-hospital mortality, and the ability of the PEP model, Precannulation Pedi-SAVE and Postcannulation Pedi-SAVE scores to predict in-hospital mortality.

Results: Postcannulation Pedi-SAVE score accessing the entire ECMO process had the greatest area under receiver operator curve (AUROC), 0.816 [95% confidence interval (CI): 0.733–0.899]. Pre-ECMO PEP model could predict in-hospital mortality [AUROC = 0.691 (95% CI: 0.565–0.817)], and Precannulation Pedi-SAVE score had the poorest prediction [AUROC = 0.582(95% CI: 0.471–0.694)]. Lactate value at ECMO implantation [OR = 1.199 (1.064–1.351), $P = 0.003$] and infectious complications [OR = 5.169 (1.652–16.172), $P = 0.005$] were independent risk factors for in-hospital mortality.

Conclusion: Pediatric cardiac ECMO scoring systems, including multiple risk factors before and during ECMO, were found to be useful in this cohort. Both the pre-ECMO PEP model and the Postcannulation Pedi-SAVE score were found to have high predictive value for in-hospital mortality in pediatric postcardiotomy VA-ECMO.

KEYWORDS

veno-arterial extracorporeal membrane oxygenation, pediatric, risk prediction, in-hospital mortality, postcardiotomy

Introduction

Postcardiotomy veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is performed ∼6% of neonates and children who undergo congenital heart disease (CHD) surgery as a rescue for intractable cardiopulmonary failure (1). Despite advances in technology and experience, pediatric ECMO mortality and costs remain high (2, 3). According to the 2022 Extracorporeal Life Support Organization (ELSO) international registry, in-hospital mortality in patients with cardiac ECMO support is 56% in neonates and 46% in children (4). Diverse risk factors before and during ECMO, including patient-related variables and clinical management, are linked with significant adverse effects on clinical outcomes (2). However, the lack of well-documented prognostic prediction models and randomized controlled trials complicate the prediction of successful surgical outcomes and mortality when pediatric postcardiotomy VA-ECMO is used (5).

Development, study, and application of prediction models for ECMO has been ongoing, and prediction scores for adult respiratory ECMO (6–8), adult cardiac ECMO (9–11), pediatric respiratory and neonatal respiratory ECMO (12–15) have been well-established and validated by multiple centers. Effective predictive models play an essential role in assessing risk and predicting prognosis. Unfortunately, children with CHD have highly heterogeneous anatomies and pathophysiologies, making it challenging to develop risk prediction models for pediatric VA-ECMO patients after CHD surgery. Scoring systems for pediatric cardiac ECMO are few and have only recently appeared.

The first available prognostic model for pediatric patients who receive extracorporeal cardiopulmonary resuscitation (ECPR) or require cardiac ECMO, the Pediatric Extracorporeal Membrane Oxygenation Prediction (PEP) model (5), was published in 2018. Only recently, in 2022, were the Precannulation Pediatric Survival After VA-ECMO (Pedi-SAVE) and Postcannulation Pedi-SAVE scoring methods developed, based solely on variables stored in the ELSO registry (16). The PEP model was developed using prospectively collected data in the Bleeding and Thrombosis on ECMO (BATE), a study of eight Collaborative Pediatric Critical Care Research Network (CPCCRN) sites (5, 17). It is a pre-ECMO evaluation model which includes eight predictor variables (indication for ECMO, age, congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS), baseline pH in arterial blood, partial thromboplastin time, international normalized ratio (INR), and documented blood stream infection (D-BSI) prior to ECMO), and is calculated as described in: https://www.cpccrn.org/calculators/ecmoprediction/. This prognostic model was developed using the 514 ECMO runs, and externally validated by 4,342 ELSO patients (18). Mortality prediction ranges from 0 to 100 percent, with a lower score predicting better survival. The two Pedi-SAVE scoring methods were developed and validated from the data of 10,091 pediatric cardiac patients in the ELSO registry who had been supported with initial VA-ECMO. The Precannulation Pedi-SAVE score ranges from 0 to 81 points, in 5 risk categories, with a higher score predicting better survival. Eight precannulation variables (clinical group, age, race, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) mortality category, pre-ECMO blood gas pH, precannulation acid buffer, total number of cardiac procedures, and indication for failure to wean from CPB) provide an effective tool for benchmarking pediatric VA-ECMO populations before ECMO initiation. Five pre-ECMO variables (clinical group, age, race, maximum STAT mortality category, pre-ECMO blood gas pH), as well as pump flow at 24 h and complications, constitute the Postcannulation Pedi-SAVE score. It has the best performance when used to evaluate the ELSO registry data, with a C-statistics probability of 0.70, compared to 0.64 in the PEP model, and 0.62 in the Precannulation Pedi-SAVE score. The Postcannulation Pedi-SAVE score is divided into 5 risk groups, with scores varying from 0 to 159. A higher mortality is predicted by a lower score. The details of these three prediction scores are shown in Table 1.

Pediatric postcardiotomy VA-ECMO outcomes are investigated to identify factors associated with in-hospital mortality, and the utility of the three prediction models for children who received VA-ECMO support after CHD surgery are compared.

Materials and methods

Study population and groups

Data from 105 consecutive pediatric patients (aged younger than 18 years) who received postcardiotomy VA-ECMO from January 2010 to December 2020 at Fuwai Hospital were collected. Four patients were excluded due to ECMO running time <24 h. The remaining 101 patients were divided into two groups based on in-hospital mortality: survivors ($n = 49$), and non-survivors ($n = 52$). Demographics, pre-ECMO variables, complications, and clinical outcomes were collected. The institutional ethics board of Fuwai Hospital approved the study (NO: 2020-1346). Being a retrospective analysis, individual consent was waived.

Outcomes and definitions

Primary outcomes were the risk factors associated with in-hospital mortality, and the value of PEP, Precannulation Pedi-SAVE, and Postcannulation Pedi-SAVE scores in predicting in-hospital mortality. Secondary outcomes included the association between the three prediction scores and clinical outcomes, and the predictive value of the PEP model and Precannulation Pedi-SAVE score for complications.

ELSO defined complications (16). Cardiovascular complications included the usage of inotropes on ECMO, cardiopulmonary resuscitation (CPR), myocardial stun, arrhythmia, hypertension requiring vasodilators, and tamponade. Hemorrhagic complications included gastrointestinal (GI) hemorrhage, cannulation or surgical site bleeding, hemolysis [plasma-free hemoglobin (pFHb) > 50 mg/dl], and disseminated intravascular coagulation (DIC). Infection was detected by blood, sputum, or urine cultures, and viral nucleic acid detection. Mechanical complications were defined as circuit changes due to circuit component clots, and oxygenator, or pump failure. Renal complications were classified as creatinine levels above 1.5 times baseline, or the need for renal replacement therapy. Neurological complications were defined as clinical symptoms (such as seizures) or neurological abnormalities revealed by imaging, such as hemorrhage, stroke, or ischemia. Pulmonary complications included pneumothorax requiring treatment, and pulmonary hemorrhage. Successful weaning from ECMO was defined as survival >48 h after weaning.

ECMO system

Patients in our center received VA-ECMO support for the following indications: (a) Cardiac support: failure to wean from cardiopulmonary bypass (CPB); low cardiac output syndrome (LCOS); (b) ECPR; and (c) Respiratory support (19).

Patients received a right atrium-ascending aorta cannula through the original surgical incision if they were <30 kg; otherwise, a femoral vein-femoral artery cannula was performed. The ECMO system was composed of an oxygenator (Hilite 800/2400 LTTM, Medos Medizintechnik AG, Stolberg, Germany; Quadrox PLS® MAQUET Cardiovascular, Hirrlingen, Germany; Sorin, Italy), a centrifugal pump (Jostra; Maquet Inc., Rastatt, Germany), and polyvinyl chloride (PVC) tubing. Priming the system was done with Plasma-Lyte A (PLA, Baxter Healthcare, Deerfield, IL, USA). Additionally, when needed, 20% human albumin, 500–1,000 units of unfractionated heparin (UFH), sodium bicarbonate, packed red blood cells (RBC), or fresh frozen plasma (FFP) were added.

ECMO management

After ECMO initiation, pump flow was maintained at 40–220 ml/kg/min, and vasoactive drugs were gradually reduced to obtain a mean arterial pressure (MAP) of 40–70 mmHg, arterial blood oxygen saturation (SO_2) no <95%, and venous blood SO_2 above 70%. Ventilator parameters were set according to the lung protective principle, with positive end-expiratory pressure of 4–10 cmH_2O, peak inspiratory pressure of <20 cmH_2O, and a ventilation rate of 8–20 breaths/min, and fraction-inspired oxygen level of 0.3–0.6. Fentanyl and imidazole were administrated for anesthesia and sedation. An UFH dose was infused for systemic anticoagulation, and was adjusted according to activated partial thromboplastin time (APTT), activated clotting time (ACT), and chest-tube drainage. The target APTT was 50–80s, and ACT was 140–200s. Antibiotics were used prophylactically to avoid infection. The ECMO system was checked every hour for mechanical complications. Negative fluid balance was maintained with the assistance of diuretics, peritoneal dialysis, or continuous renal replacement therapy (CRRT). Routine bedside transthoracic echocardiography and chest X-rays were performed daily, while computed tomography (CT), and magnetic resonance imaging (MRI) were employed according to patient condition and the doctor's judgment. Other detailed approaches to managing pediatric postcardiotomy VA-ECMO have been previously described in literature (19).

Statistical analyses

Continuous variables were represented by median (interquartile range; IQR), and analyzed by Mann–Whitney *U*-test. Categorical variables were expressed as a percentage of *n* (%), and analyzed by Fisher's exact test or chi-square test. Logistic stepwise regression analyses were undertaken to

TABLE 1 Details of the pediatric ECMO prediction scores.

Variables		PEP model	Precannulation Pedi-SAVE score	Postcannulation Pedi-SAVE score
Data set		CPCCRN-BATE study	ELSO registry	
Cases		514 (<19 years)	Model development ($n = 6,727$); Validation ($n = 3,364$) (0 days−18 years)	
Study year		December 2012 to September 2014	January 2001 to December 2015	
Pre-ECMO variables	Demographics	Age	Age, Race	
	ECMO modes	VV-ECMO, VA-ECMO	VA-ECMO	
	Diagnosis	CDH, MAS, others	SVCHD, BVCHD, Primary CM, Secondary CM, pulmonary hypertension	
	Cardiac surgery	——	Maximum STAT mortality category, Total number of cardiac procedures <2, Failure to wean from CPB	Maximum STAT mortality category
	Laboratory parameters	pH, APTT, INR	pH	pH
	Special issues	Pre-ECMO documented blood infection	Precannulation acid buffer	——
Mid-ECMO variables	Pump flow (mL/kg/min)	——	——	Post-ECMO pump flow at 24 h
	Complications	——	——	Cardiovascular, Hemorrhagic, Infectious, Mechanical, Neurologic, Pulmonary, Renal
Risk groups		Ten	Five	Five
Application		Pre-ECMO evaluation	Pre-ECMO evaluation	Overall ECMO evaluation

ECMO, Extracorporeal Membrane Oxygenation; PEP, Pediatric Extracorporeal Membrane Oxygenation Prediction; Pedi-SAVE, Pediatric Survival After Veno-arterial ECMO; CPCCRN, Collaborative Pediatric Critical Care Research Network; BATE, Bleeding and Thrombosis on ECMO, ELSO, Extracorporeal Life Support Organization; VV, venovenous; VA, venoarterial; CDH, congenital diaphragmatic hernia; MAS, meconium aspiration syndrome; SVCHD, single ventricle congenital heart disease; BVCHD, biventricular congenital heart disease; CM, cardiomyopathy; STAT, Society of Thoracic Surgeons-European Association of Cardiothoracic Surgery; CPB, cardiopulmonary bypass; APTT, activated partial thromboplastin time, INR international normalized ratio.

assess predictors of in-hospital mortality. All variables were evaluated for correlation with survival to discharge through univariate analysis. Univariable analysis factors with $P < 0.10$ were entered into the models, followed by forward stepwise multiple logistic regression analysis to identify predictors of in-hospital mortality. PEP model, Precannulation Pedi-save, and Postcannulation Pedi-SAVE scores were calculated for all patients. Area under the receiver operating characteristic curve (AUROC) and Hosmer-Lemeshow (HL) goodness-of-fit test were used to assess the performance of the three prediction scores. Spearman rank correlation was used to test for correlation among ECMO duration, hospital length of stay, ICU length of stay, ventilation time, and prediction scores. The receiver operating characteristic (ROC) curve was analyzed to explore the predictive value of the PEP model and Precannulation Pedi-SAVE score for complications. The data was analyzed and visualized with SPSS 22.0 (SPSS, Inc., Chicago, IL, USA), and GraphPad Prism 8.0 (GraphPad Software, Inc., San Diego, CA, USA), respectively.

Results

Demographics and pre-ECMO variables

The median age of patients at ECMO implantation in the cohort was 12.7 (6.0, 39.3) months, and the median weight was 8.5 (5.9, 12.8) kilograms. Minimum age was 3 days, and minimum weight was 2.6 kilograms. More than half (63.4%) of the ECMOs were performed for cardiac support, including 51 patients who were unable to wean off CPB, and 13 patients who had LCOS. About a quarter (24.8%) of the patients received ECPR, and ECMO for respiratory support accounted for 12 cases. Of the patients in this cohort which were diagnosed with heterogeneous CHD, transposition of the great arteries (TGA; 19.8%) was the most common diagnosis (Supplementary Table 1), while arterial switch operations (ASO; 24.8%) were the most common surgical procedure (Supplementary Table 2).

TABLE 2 Patient characteristics of survivors and non-survivors.

Variables	Total ($n = 101$)	Survivors ($n = 49$)	Non-survivors ($n = 52$)	*P*-value
Demographics, pre-ECMO, and mid-ECMO variables				
Male sex	63 (62.4)	30 (61.2)	33 (63.5)	0.840
Weight (kg)	8.5 (5.9, 12.8)	9.4 (5.9, 13.9)	8.3 (5.9, 12.3)	0.311
Age (m)	12.7 (6.0, 39.3)	13.9 (6.4, 42.4)	10.1 (5.4, 37.3)	0.425
RACHS-1 class	3.0 (2.0, 4.0)	3.0 (2.5, 4.0)	3.0 (2.0, 4.0)	0.529
Redo-cardiac surgery	27 (26.7)	14 (28.6)	13 (25.0)	0.822
STAT mortality category	4.0 (2.0, 4.0)	3.0 (2.0, 4.0)	4.0 (2.0, 4.0)	0.120
CPB time (min)	259.0 (156.5, 366.5)	269.0 (161.0, 379.0)	246.0 (145.3, 342.0)	0.550
Clamp time (min)	119.0 (74.5, 153.5)	117.0 (76.5, 158.0)	125.0 (73.3, 151.0)	0.921
Indications				
ECPR	25 (24.8)	8 (16.3)	17 (32.7)	0.068
Cardiac	64 (63.4)	37 (75.5)	27 (51.9)	0.022
Respiratory	12 (11.9)	4 (8.2)	8 (15.4)	0.360
Preoperative infection	9 (8.9)	4 (8.2)	5 (9.6)	1.000
PH at ECMO implantation	7.4 (7.3, 7.5)	7.4 (7.4, 7.5)	7.4 (7.3, 7.5)	0.260
APTT at ECMO implantation	65.3 (44.3, 95.8)	54.1 (41.7, 89.8)	67.2 (47.8, 99.6)	0.252
INR at ECMO implantation	1.4 (1.2, 1.7)	1.3 (1.2, 1.6)	1.5 (1.2, 1.9)	0.032
MAP at ECMO implantation	46.0 (39.5, 58.0)	46.0 (40.0, 58.5)	46.0 (38.3, 56.0)	0.540
Lactate at ECMO implantation	7.6 (4.8, 11.1)	6.3 (4.4, 9.0)	8.6 (5.6, 13.9)	0.009
VIS at ECMO implantation	27.0 (17.0, 45.0)	22.0 (16.0, 42.5)	28.5 (18.0, 47.8)	0.222
Precannulation acid buffer	38 (37.6)	15 (30.6)	23 (44.2)	0.218
Post-ECMO pump flow at 24 h (mL/kg/min)	93.6 (76.0, 114.9)	85.5 (69.4, 103.3)	102.4 (80.0, 122.7)	0.008
Complications				
Hemorrhagic	70 (69.3)	30 (61.2)	40 (76.9)	0.130
Infectious	47 (46.5)	16 (32.7)	31 (59.6)	0.009
Mechanical	20 (19.8)	6 (12.2)	14 (26.9)	0.082
Neurological	14 (13.9)	2 (4.1)	12 (23.1)	0.008
Pulmonary	7 (6.9)	1 (2.0)	6 (11.5)	0.113
Renal	74 (73.3)	28 (57.1)	46 (88.5)	0.001
Prediction scores				
PEP model	45.0 (40.0, 56.0)	42.0 (37.0, 50.5)	50.5 (42.0, 60.5)	0.003
Precannulation Pedi-SAVE	49.0 (46.0, 53.0)	50.0 (47.0, 53.0)	49.0 (45.3, 52.8)	0.153
Postcannulation Pedi-SAVE	97.0 (85.0, 110.3)	108.0 (98.5, 119.0)	89.0 (77.5, 97.0)	<0.001
Clinical outcomes				
ECMO duration (h)	123.0 (91.5, 167.0)	101.3 (89.5, 135.5)	145.5 (102.5, 211.8)	0.001
Successful Weaning	70 (69.3)	49 (100.0)	21 (40.4)	<0.001
Hospital length of stay (d)	42.0 (22.0, 63.0)	51.0 (36.0, 84.5)	50.5 (42.0, 60.5)	<0.001
ICU length of stay (d)	28.0 (11.5, 48.0)	33.0 (23.5, 56.0)	14.0 (7.0, 37.3)	<0.001
Ventilation time (h)	494.0 (203.5, 853.0)	567.0 (284.0, 967.5)	289.0 (144.8, 818.0)	0.006

Continuous data are presented as median (interquartile range) and categorical data as n (percent).
ECMO, Extracorporeal Membrane Oxygenation; RACHS-1, Risk Adjustment for Congenital Heart Sugery-1; STAT, Society of Thoracic Surgeons-European Association of Cardiothoracic Surgery; CPB, cardiopulmonary bypass; ECPR, extracorporeal cardiopulmonary resuscitation; MAP, mean arterial pressure; VIS, vasoactive-inotropic score; APTT, activated partial thromboplastin time, INR international normalized ratio; PEP, Pediatric Extracorporeal Membrane Oxygenation Prediction; Pedi-SAVE, Pediatric Survival After Veno-arterial ECMO; ICU, intensive care unit.

TABLE 3 Multivariable logistic regression analysis: independent predictors of in-hospital mortality.

Variables	*P*-value	OR	95% CI
Lactate at ECMO implantation	0.003	1.199	1.064–1.351
Infection during ECMO	0.005	5.169	1.652–16.172

OR, odds ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation.

There were no significant differences in gender, weight, age, cardiac surgery history, preoperative infection, Risk Adjustment for Congenital Heart Sugery-1 (RACHS-1) class, STAT mortality category (20), CPB time, clamp time, MAP, pH, APTT, vasoactive-inotropic score (VIS) (21), or precannulation acid buffer requirement at ECMO implantation between the groups. A greater number of survivors than non-survivors received ECMO for cardiac support ($P = 0.022$). The significant difference between the groups were in lactate ($P = 0.009$), INR ($P = 0.032$) at ECMO implantation, and post-ECMO pump flow at 24 h ($P = 0.008$; Table 2).

Complications and clinical outcomes

The occurrence of infectious ($P = 0.009$), neurological ($P = 0.008$), and renal ($P = 0.001$) complications were positively correlated with in-hospital mortality. All patients had cardiovascular complications. Seven patients suffered pulmonary hemorrhages. Hemorrhagic, mechanical, and pulmonary complications were not significantly associated with mortality (Table 2).

Seventy patients (69.3%) were successfully weaned from ECMO. Forty-nine children survived, and the overall survival rate was 48.5%. Median ECMO duration was 123.0 (91.5, 167.0) hours, and median hospital stay was 42.0 (22.0, 63.0) days. Clinical outcomes were significantly different in ECMO duration, successful weaning rate, mechanical ventilation time, ICU length of stay, and total hospital length of stay.

Risk factors of in-hospital mortality

After univariate logistic analysis, ECMO for cardiac support ($P = 0.015$), pre-ECMO INR ($P = 0.028$), lactate at ECMO implantation ($P = 0.005$), post-ECMO pump flow at 24 h ($P = 0.019$), hemorrhagic ($P = 0.090$), infectious ($P = 0.007$), mechanical ($P = 0.070$), neurological ($P = 0.014$), pulmonary ($P = 0.095$), and renal ($P = 0.001$) complications were all associated with in-hospital mortality. These variates were entered into multivariate analysis. In a multiple logistic regression adjusted for other factors mentioned above, lactate at ECMO implantation and infection during ECMO independently increased the odds of in-hospital mortality (Table 3).

Predictive values of PEP model, Precannulation Pedi-SAVE score, and Postcannulation Pedi-SAVE score

There was a significant difference in the PEP model and Postcannulation Pedi-SAVE score between non-survivors and survivors, while the Precannulation Pedi-SAVE score was a poor predictor of death (Table 2). Observed mortality for the Precannulation Pedi-SAVE score and PEP model tested weakly paralleled expected mortality; the two scores had decreased accuracy in low-risk groups where higher than expected deaths occurred. The correlation was strongest for Postcannulation Pedi-SAVE score, where the data set had a similar distribution of predicted mortality (Figure 1).

In ROC curve analysis, the Postcannulation Pedi-SAVE score demonstrated the greatest predictive ability, with an AUROC of 0.816 (95% CI: 0.733–0.899). The PEP model also showed high discrimination for in-hospital mortality as a risk adjustment tool, with an AUROC of 0.691 (95% CI: 0.565–0.817; Table 4, Figure 2).

We further explored the associations with clinical outcomes among the three prediction models, and the distinguishing values of the PEP model and Precannulation Pedi-SAVE score for various complications. The PEP model showed predictive values for neurological complications [AUROC = 0.676 (95% CI: 0.552–0.801)], and renal complications [AUROC = 0.659 (95% CI: 0.542–0.775)]. Additionally, the PEP model [AUROC = 0.694 (95% CI: 0.578–0.809)] and Postcannulation Pedi-SAVE score [AUROC = 0.769 (95% CI: 0.667–0.870)] demonstrated predictive ability for ECMO weaning failure (Table 4). Hospital length of stay was correlated with the PEP model ($r = -0.293$, $P = 0.003$) and the Postcannulation Pedi-SAVE score ($r = 0.260$, $P = 0.009$). ECMO duration was negatively associated with the Postcannulation Pedi-SAVE score ($r = -0.214$, $P = 0.032$). A weak relationship existed between mechanical ventilation time ($r = -0.252$, $P = 0.011$), ICU length of stay ($r = -0.228$, $P = 0.022$) and the PEP model.

As cardiac support was the most common indication in this cohort, and the two Pedi-SAVE scores established by ELSO were based on this indication, a subgroup analysis of the three predictive scores was done for the 64 patients receiving VA-ECMO for cardiac support. We found that all scores had good discrimination for in-hospital mortality, with the PEP model, Precannulation Pedi-SAVE score and Postcannulation Pedi-SAVE score having an AUROC of 0.649 (95% CI: 0.509–0.789), 0.664 (95% CI: 0.527–0.802), and 0.832 (95% CI: 0.736–0.929), respectively. To reduce selective bias, we supplemented these four patients in the study to investigate the predictive power

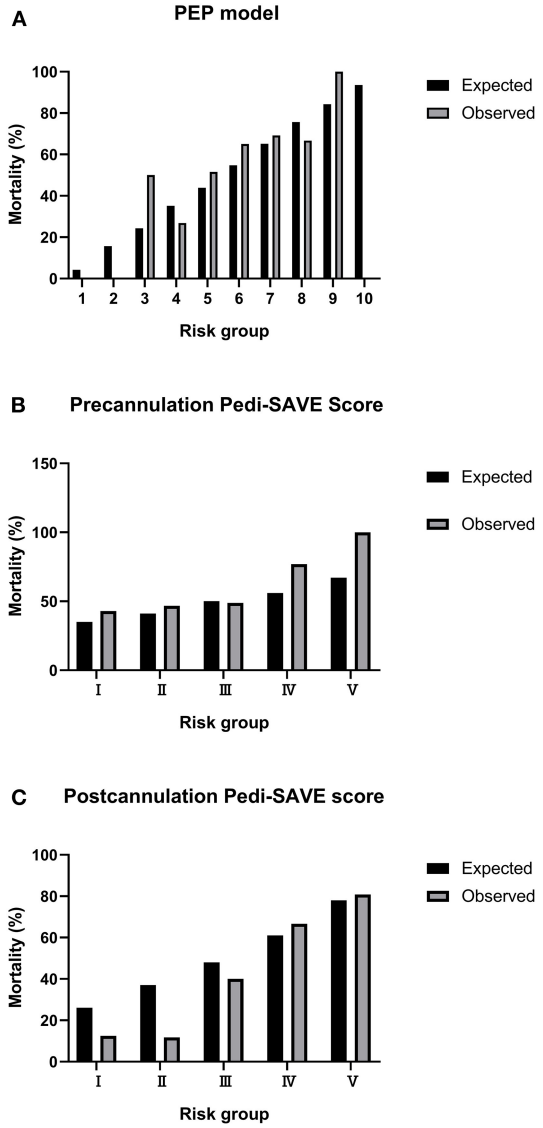

FIGURE 1
Calibration plots for observed to expected mortality. PEP, Pediatric Extracorporeal Membrane Oxygenation Prediction; Pedi-SAVE, Pediatric Survival After Veno-arterial Extracorporeal Membrane Oxygenation. **(A)** PEP model. **(B)** Precannulation Pedi-SAVE score. **(C)** Postcannulation Pedi-SAVE score.

of the three scoring models in 105 consecutive patients during the study period. Patients with no 24-h flow data scored 0 on the corresponding variable in the Postcannulation Pedi-SAVE score. Postcannulation Pedi-SAVE score demonstrated the most excellent predictive power, with an AUROC of 0.823 (95% CI: 0.743–0.903), followed by PEP model, with an AUROC of 0.682 (95% CI: 0.580–0.785). Precannulation Pedi-SAVE score performance was poor, with an AUROC of 0.586 (95 % CI: 0.477–0.696; Supplementary Table 4). In addition, the demographic and clinical variables of the 105 patients were shown in Supplementary Table 5.

Discussion

VA-ECMO can be used as a rescue therapy for failure to wean from CPB, LCOS, cardiac arrest (CA), and acute respiratory distress syndrome (ARDS) after CHD surgery, providing time for cardiopulmonary recovery. However, it is accompanied by high morbidity and mortality; coagulopathies, renal injury, and infection are common complications of pediatric postcardiotomy VA-ECMO (17, 22, 23). Many single risk factors before and during ECMO can predict mortality after VA-ECMO, such as renal failure, lactate level, and clearance (24, 25). However, conclusions are limited to single-center experience and generalizability. Therefore, a prognostic prediction model that simultaneously considers multiple risk factors and assigns corresponding weights according to their relative importance can help us make individualized assessments.

Our study is the first cohort simultaneously validating all currently available prognostic prediction scores for pediatric VA-ECMO. Our results showed that the PEP model and Postcannulation Pedi-SAVE score were significantly associated with survival to discharge, while Precannulation Pedi-SAVE score demonstrated no difference between survivors and non-survivors. The Postcannulation Pedi-SAVE score showed the most potent discriminatory ability in ROC analysis, with an AUROC above 0.8. In this cohort, 48.5% of patients survived to discharge. Lactate at ECMO implantation and infectious complications were independent risk factors for in-hospital mortality.

The PEP model is the first mortality prediction score that can be applied to all pediatric ECMO patients without excluding age or ECMO indication (5). Using our data set from all VA-ECMO subjects, we found that the AUROC of the PEP model for predicting in-hospital mortality was 0.691, lower than the original study's 0.75. Compared with the BATE study (17), our study's population had a lower proportion of neonates (5.0 vs. 51.9%), and a higher proportion of infants (44.6 vs. 23.7%) and children (47.5 vs. 15.6%). More patients received ECMO for cardiac support (63.4 vs. 40.3%) and ECPR (24.8 vs. 13.6%). There were no CDH and MAS; all children were diagnosed with CHD (100 vs. 37.9%). As for laboratory parameters, our subjects had a higher APTT (65.3 vs. 43.7s), while INR (1.4 vs. 1.5), and pH in arterial blood (7.4 vs. 7.3) were similar. Our subjects had no D-BSI prior to ECMO (0 vs. 5.3%), and 8.9% of patients had preoperative respiratory infections. Median ECMO duration (123.0 vs. 120.0 h) was similar for both cohorts. In-hospital mortality was 44.9% in the original study, and 51.5% in our study. The PEP model has eight variables, while our subject data only included 5 parameters: age, indication, pH, APTT, and

TABLE 4 Performance of prediction scores.

Prediction scores	AUROC (95% CI)	Standard Error	HL test *p*-value
In-hospital mortality			
PEP model	0.691 (0.565–0.817)	0.064	0.856
Precannulation	0.582 (0.471–0.694)	0.057	0.522
Pedi-SAVE score			
Postcannulation	0.816 (0.733–0.899)	0.042	0.264
Pedi-SAVE score			
ECMO weaning failure			
PEP model	0.694 (0.578–0.809)	0.059	0.629
Precannulation	0.535 (0.410–0.661)	0.064	0.821
Pedi-SAVE score			
Postcannulation	0.769 (0.667–0.870)	0.052	0.068
Pedi-SAVE score			

AUROC, area under the receiver operating characteristic curve; HL, Hosmer-Lemeshow; PEP, Pediatric Extracorporeal Membrane Oxygenation Prediction; Pedi-SAVE, Pediatric Survival After Veno-arterial ECMO; ECMO, extracorporeal membrane oxygenation.

INR. This may be part of the reason for slightly different results in our center compared to the original study. As all patients required VA-ECMO after cardiac surgery, those who could not be weaned from CPB account for 50%, and coagulopathies are widespread in our subjects. The incidence of hemorrhagic complications is as high as 69.3%. APTT and INR can be used to assess the coagulation status of patients at ECMO implantation. The PEP model was associated with RBC transfusion (mL/kg/d; $r = 0.204$, $P = 0.047$) in our subjects. Thus, this model had a high discrimination ability for in-hospital mortality in our study. Moreover, it was also negatively correlated with recovery indexes: total hospital length of stay, ICU length of stay, and mechanical ventilation time.

Pedi-SAVE scores are tools for risk adjustment and benchmarking in pediatric cardiac patients supported with VA-ECMO to predict survival (16). The C-statistics of the Precannulation Pedi-SAVE score and Postcannulation Pedi-SAVE score in the 6,727 patient development dataset, and 3,364 patient internal validation dataset were 0.62 and 0.64, 0.70 and 0.71, respectively. In our subjects, the discriminative ability of the Precannulation Pedi-SAVE score was significantly lower (AUROC: 0.582), while the Postcannulation Pedi-SAVE score had highly predictive values (AUROC: 0.816). Compared to the ELSO registry, our cohort was older, and included a higher percentage of infants (44.6 vs. 29.0%) and pediatric patients (50.5 vs. 25.2%). Biventricular congenital heart disease (BVCHD; 92.0 vs. 45.4%) was the predominant diagnosis, and there were few patients with single ventricle congenital heart disease (SVCHD; 8.0 vs. 27.8%). All patients in our center were postcardiotomy (100 vs. 40.0%), a larger number of children were in the high-grade STAT mortality category (above 3; 50.5 vs. 35.2%), and more patients required precannulation acid buffer (37.6 vs. 23.9%). Regarding indications, failure to wean from CPB (50.5 vs. 38.5%) and respiratory support percentages (11.9 vs. 3.7%) were higher than in the original study, while LCOS was lower (12.9 vs. 68.2%). After ECMO initiation, a lower median 24-h pump flow (94 vs. 112 mL/kg/min) was found in our study population. Complications, including cardiovascular (100 vs. 68.3%), hemorrhagic (69.3 vs. 46.7%), renal (73.3 vs. 39.5%), and infection (46.5 vs. 9.2%) were much higher than the ELSO multicenter dataset, while mechanical complications (19.8 vs. 34.9%) were lower. Neurologic (excluding brain death; 13.9 vs. 15.9%) and pulmonary (6.9 vs. 7.7%) complications were comparable in both cohorts. Median ECMO duration (123 vs. 113 h) and survival to discharge (48.5 vs. 49.5%) were also not significantly different from the original study. Among the eight pre-ECMO risk factors in the Precannulation Pedi-SAVE score, 92.0% of the patients had BVCHD, 73.3% received primary cardiac surgery, and 70.2% had pre-ECMO pH levels between 7.3 and 7.5. These factors cause the Precannulation Pedi-SAVE score to center around 45–55, and make it difficult to distinguish risk levels effectively. The Postcannulation Pedi-SAVE score included complications that significantly impacted clinical outcomes, and each complication had a different weight. Lack of neurologic, pulmonary, renal, or infectious complications distinctly benefit survival. Our subjects were evenly distributed across the five risk groups of the Postcannulation Pedi-SAVE score, and observed mortality was highly parallel to predicted mortality. Notably, in the cardiac support subgroup excluding ECPR, both Pedi-SAVE scores had high predictive values for in-hospital mortality. Patients undergoing ECPR have varying degrees of persistent hypoperfusion and ischemia-hypoxic injury, so there may be hyperlactatemia and organ damage at ECMO implantation (26). However, the Precannulation Pedi-SAVE score does not include these corresponding risk factors, and has limited application in this population.

As a marker of tissue perfusion, the lactate value can reflect the balance of oxygen demand and supply in macro- and micro-circulation (27). Our study found that lactate at ECMO implantation was predictive of in-hospital mortality, with an AUROC of 0.650 (95% CI 0.543–0.757). The cut-off value was 7 mmol/L (sensitivity 65.4%, specificity 61.2%; $P = 0.009$). This predictor is easily measured for pre-ECMO risk evaluation and may improve patient selection. Hyperlactatemia indicates decompensated oxygen metabolism, which leads to tissue and organ damage. Fux et al. found that arterial lactate level before VA-ECMO initiation was an independent risk factor of 90-day mortality in postcardiotomy cardiogenic shock patients (27). Moreover, an earlier study in our center pointed out that pre-ECMO lactate was a predictor of acute renal failure during pediatric postcardiotomy ECMO (28).

We observed a higher infection prevalence (46.5%) than in other reports (12–42%) (29–31). More than half of the patients in our center who received postcardiotomy VA-ECMO had

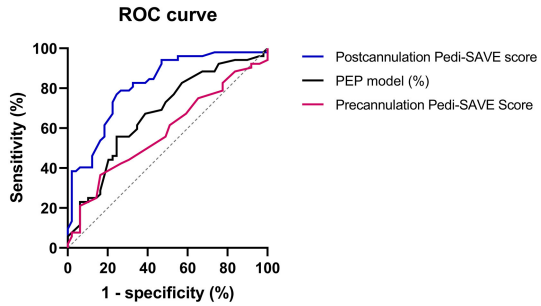

FIGURE 2
The receiver operating characteristic curve of prediction scores. ROC, receiver operating characteristic; PEP, Pediatric Extracorporeal Membrane Oxygenation Prediction; Pedi-SAVE, Pediatric Survival After Veno-arterial Extracorporeal Membrane Oxygenation; ECMO, extracorporeal membrane oxygenation.

delayed chest closure, which increases the risk of infection (29). Positive bacterial cultures of respiratory secretions were the most common type of infection, occurring in 20.8% of our cohort (Supplementary Table 3). The most common pathogen was Gram-negative bacilli, which is associated with ventilator-associated pneumonia (VAP) (32). Nosocomial infections are associated with worse outcomes, particularly with Gram-negative bacteria infection (30, 32, 33). Our findings demonstrate that infectious complications lead to a 5-fold increase in risk of mortality. The epidemiology of infection during ECMO varies widely, and the diagnosis of nosocomial infection remains challenging, with a lack of evidence supporting biomarkers such as procalcitonin and C-reactive protein (34). Although antibiotic prophylaxis is used in half to three-quarters of ECMO centers, its effectiveness needs to be confirmed by research (35–37). The high incidence of VAP in our center suggests that prophylactic antibiotics may not be suitable for all patients.

Limitations of our study include the small number of subjects, and the limited extrapolation value of the results due to variation in clinical practice across centers. A retrospective study analyzing incomplete data may cause potential inaccuracies in the data and potential selection bias.

Conclusion

Pre-ECMO lactate level and mid-ECMO infectious complications significantly increase the odds of in-hospital mortality. The pediatric cardiac ECMO scoring system, including multiple risk factors before and during ECMO, are helpful in our population. The pre-ECMO PEP model and the whole-course Postcannulation Pedi-SAVE score have a high predictive value for in-hospital mortality in pediatric postcardiotomy VA-ECMO. Given the heterogeneity of CHD, prediction scores should not replace individual assessment and prognostication. Further analysis of the risk factors associated with adverse outcomes on pediatric VA-ECMO support is required in the future to create more accurate risk prediction models.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Ethics Board of Fuwai Hospital. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

JL and YJ: conception and design. LB, PZ, YL, PG, and WW: administrative support. XW, JL, and ZF: provision of study material or patients. YJ: collection and assembly of data, data analysis, and interpretation. All authors contributed to the article, manuscript writing and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.967872/full#supplementary-material

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Case report: Cytokine hemoadsorption in a case of hemophagocytic lymphohistiocytosis secondary to extranodal NK/T-cell lymphoma

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We discuss a single case of Hemophagocytic lymphohistiocytosis (HLH) due to NK-type non-Hodgkin lymphoma and Epstein-Barr virus reactivation with multiorgan dysfunction and distributive shock in which we performed cytokine hemoadsorption with Cytosorb ®. A full microbiological panel was carried out, including screening for imported disease, standard serologies and cultures for bacterial and fungal infection. A liver biopsy and bone marrow aspirate were performed, confirming the diagnosis. The patients fulfilled the HLH-2004 diagnostic criteria, and according to the 2018 Consensus Statements by the HLH Steering Committee of the Histiocyte Society, dexamethasone and etoposide were started. There was an associated hypercytokinemia and, due to refractory distributive shock, rescue therapy with cytokine hemoadsorption was performed during 24 h (within day 2 and 3 from ICU admission). After starting this procedure, rapid hemodynamic control was achieved with a significant reduction in vasopressor support requirements. This case report highlights that cytokine hemoadsorption can be an effective since rapid decrease in IL-10 levels and a significant hemodynamic improvement was achieved.

KEYWORDS

hemophagocytic lymphohistiocytosis, cytokine storm, multiorgan dysfunction, cytokine hemoadsorption, shock

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome induced by activated macrophages and cytotoxic T-cells. Secondary (acquired) HLH (1) is the most frequent form in adults, commonly triggered by infections [mainly viruses Epstein-Barr Virus (2) (EBV)], malignancies (mainly malignantlymphoma) (3), macrophage activation syndrome in autoinflammatory or autoinmmune disorders (4) or other causes (for example organ or stem cell transplantation, metabolic, traumatic, immunosupression). Untreated HLH can lead to rapid multiorgan dysfunction and death, so treatment should be started as soon as possible. The pathophysiology of organ dysfunction is led by the cytokine storm, so cytokine hemadsorption could have a potential therapeutic role in this setting.

HLH diagnosis is challenging as its clinical presentation may be indistinguishable from sepsis or autoinflammatory diseases. One of the pillars of treatment includes modulating the cytokine storm (5) responsible for hyperinflammation and multiorgan failure. Treatment should be started as promptly as possible after symptom onset as untreated HLH can lead to multiorgan failure and death. Dexamethasone, etoposide and cyclosporine A are included in the standard HLH treatment protocol (6). In addition, cytokine adsorption can be a potential therapeutical option for the rapid control of cytokine storm. Herein, we report a case of a patient with distributive shock and multiorgan dysfunction due to HLH who underwent cytokine hemoadsorption.

Methods

We discuss a single case of HLH due to NK-type non-Hodgkin lymphoma and Epstein-Barr virus reactivation with multiorgan dysfunction and distributive shock in which we performed cytokine hemoadsorption with Cytosorb ® (Cytosorbents Europe, Berlin, Germany) leading to rapid decrease in several cytokines, such as interleukin 10 (IL-10) and interleukin 6 (IL-6), with significant hemodynamic improvement. Plasmatic levels of IL-6 were measured using the automated quantitative immunoassay Cobas® (Roche diagnostics International Ltd, Switzerland), following the manufacturer's instructions. Circulating levels of IL-10 and soluble CD25 (IL-2Ra) were determined using the microfluidics-based quantitative immunoassay, ELLA® (ProteinSimple, United States of America). The severity of the disease was evaluated with sequential organ failure assessment (SOFA) score (7). We analyzed the plasma concentrations of inflammatory biomarkers, including IL-6, interleukin 10 (IL-10), D-dimer, and C-reactive protein upon ICU admission, immediately before hemoadsorption initiation (pre-hemoadsorption), and after the procedure (post-hemoadsorption). Other laboratory parameters were measured to evaluate organ function. The CytoSorb® filter was connected post-hemofilter *via* a close loop circuit to the Continuous renal replacement therapy (CRRT) pump (Prismaflex, Gambro Lundia AB, Lund, Sweden). CRRT was performed in continuous hemodiafiltration mode (CVVHDF) using a MA 150® hemofilter (Baxter, Illinois, US) at a blood flow rate of 200 ml/min. Anticoagulation was performed with unfractionated heparin.

Results/discussion

A 50-year-old African male patient was admitted to the hospital with a 2-month history of mild epistaxis and diffuse abdominal pain. He presented fever and hepatosplenomegaly at physical exam; laboratory values showed cytolysis with undissociated cholestasis, non-oliguric renal failure, pancytopenia with hemolytic anemia, hyperferritinemia, and hypertriglyceridemia. He required a rapid admission to the Intensive Care Unit (ICU) for hemodynamic and respiratory support. A full microbiological panel was carried out, including screening for imported disease, standard serologies and cultures for bacterial and fungal infection; results came back positive for Epstein-Barr virus with a 7.7 Log viremia. The patient fulfilled the HLH-2004 diagnostic criteria, and according to the 2018 Consensus Statements by the HLH Steering Committee of the Histiocyte Society, dexamethasone and etoposide (8) were started, together with empirical antibiotic treatment with meropenem and amikacin. Simultaneously, a liver biopsy and bone marrow aspirate were performed, confirming the diagnosis of NK-type non-Hodgkin's lymphoma with secondary hemophagocytosis.

Although the patient received broad-spectrum antibiotics and the recommended HLH treatment, he rapidly deteriorated in 48 h with a distributive shock and multiorgan dysfunction (renal, neurological, hemodynamic, respiratory, and hepatic) requiring high doses of vasopressor support, continuous veno-venous hemodiafiltration and invasive mechanical ventilation. There was an associated hypercytokinemia and, due to refractory distributive shock, rescue therapy with cytokine hemoadsorption with Cytosorb® was started on the second day after ICU admission. Cytokine adsorption was performed in parallel to the venovenous hemodiafiltration circuit. Interleukin 6, IL-10 and IL-2Ra were monitored in real time. After starting this procedure, rapid hemodynamic control was achieved with a significant reduction in vasopressor support requirements after only a few hours since the start of cytokine hemoadsorption (Table 1). This therapy was started within 24 hours of ICU admission. Vasopressor support was stopped 37 h after the start of this procedure. Despite this, 6 days after completion of cytokine hemoadsorption and 9 days since ICU admission, the patient died due to thrombotic complications related to the underlying lymphoma with thrombosis of the inferior vena

TABLE 1 Biochemical and clinical parameters.

Variable/Day from ICU admission	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
				Cytosorb®				
IL-10 (RV< 7.8 pg/mL)	4,698	5,643	490	337	36.6	-	-	15.2
IL-6 (RV < 4.3 pg/mL)	165,1	233	91,2	60,8	56,1	-	-	139.8
sCD25 (RV < 2,000 pg/mL)	48,015	65,949	50,667	21,853	15,766	-	-	17,396
Ferritina (RV < 400 ng/mL)	127,055	-	109,983	-	39,493	-	-	-
Bilirrubin (RV <1.2 mg/dL)	18,9	22	13	7,8	11,2	-	-	23,22
NOR (mcg/kg/min)	0	1,5	0,1	0	<0.1	<0.1	<0.1	<0.1
Lactate (RV < 2 mmol/L)	4,7	8,5	10,3	5	2,1	3,7	2,3	1,7
SOFA	11	15	19	16	13	14	13	15
Creatinine (RV < 1 mg/dL)	5,78	7,03	CRRT	CRRT	CRRT	CRRT	CRRT	CRRT
PAFI	-	250	286	215	262	315	272,5	300
AST (RV < 50 UI/L)	926	1,938	2,626	1,625	510	376	246	108
CRP (RV <0.5 mg/dL)	8,8	7,7	5,81	4,94	-	3,3	-	8,44
Platelets (RV 140-400 x 10e9/L)	40,000	49,000	67,000	28,000	33,000	60,000	50,000	22,000

Cytosorb ® therapy was done during 24 h within day 2 and 3 from ICU admission. On Day 2 we describe the worst cytokine record prior to the initiation of therapy; regarding Day 3, we reflect the variables after the completion of the hemoadsorptive therapy.AST, aspartate aminotransferase; CRRT, continuous renal replacement therapy; CRP, C-reactive protein; IL, interleukin; NOR, norepinephrine; PAFI, PaO_2-FiO_2 ratio; SOFA, sequential organ failure assessment; RV, Reference values.

cava, hepatic system, right atrium and partial thrombosis of the thoracic aorta.

The therapeutic strategy of HLH includes a triple approach: organ support measures, trigger resolution and inflammatory response suppression (1). Although dexamethasone, etoposide and cyclosporine A are considered standard HLH treatment, these patients present a cytokine storm that needs rapid control. The pathophysiologic process of HLH is characterized by an uncontrolled activation and expansion of T lymphocytes and macrophages, responsible for the production of a large amount of proinflammatory cytokines, the latter causing a "cytokine storm" (9). Cytokine control could be carried out with drugs such as Tocilizumab (10) or Anakinra (11) but also with extracorporeal blood purification (2).

Several extracorporeal blood purification techniques have been proposed in critical patients with multiorgan dysfunction (12). Cytosorb®, licensed for extracorporeal cytokine removal in the European Union, is a high-flow, low-resistance cytokine adsorbent, containing specially developed polymer beads with a large surface and adsorption spectrum up to 60kDa. Results with Cytosorb indicate not only a broad-spectrum removal of inflammatory mediators, but also significant survival improvement in high-lethality models (13).

In the sepsis cytokine-storm related pattern, IL-6 is the best studied molecule (14), but in secondary HLH the elevation of interferon gamma and IL-10 is more significant (15). Very high levels of interferon gamma and IL-10 with a mildly elevated IL-6 has a high diagnostic accuracy for secondary HLH and could be a useful approach to differentiate HLH from infection (16, 17). In this case, the indication of cytokine hemoadsorption in HLH would have as its main objective the elimination of IL-10 since the inflammatory response is unbalanced toward anti-inflammation.

Experience in the use of cytokine hemoadsorption as adjuvant treatment for HLH is scarce. Greil et al. (18) described a CTLA4-deficient patient who developed secondary HLH due to EBV-induced Hodgkin lymphoma under treatment with abatacept. Their patient also presented multiorgan dysfunction and Cytosorb® was used for 4 days, achieving a reduction in inflammatory parameters and clinical improvement. This case is similar to ours, including the type of technique, since it is performed in parallel with renal hemodiafiltration. Unlike the study by Greil et al. we monitored in real time the plasma concentrations of IL-6 and IL-10 to adjust the duration of hemoadsorption. Once the cytokine levels were controlled and the patient clinically improved (with reduction in vasopressor support), we discontinued hemoadsorption. This system allows us to shorten the hemoadsorption time, an important step since it can alter the concentrations of certain drugs, such as antibiotics (19, 20). Frimmel et al. (21) reported a case of multiorgan dysfunction due to liver failure in a patient with HLH secondary to reactivation of the Herpes simplex virus type 1. In this case, the indication for hemadsorption was a distributive shock due to liver failure. In this patient, there was a very significant elevation of IL-6 but IL-10 concentrations were not reported.

As this is a case report, causality cannot be confirmed, particularly when considering the other treatment interventions (e.g., dexamethasone, etoposide). However, there was a close temporal relationship between the initiation of hemoadsorption and the reduction in cytokine levels and clinical improvement. IL-10 levels were significantly reduced in 24 h and a rapid

improvement in hemodynamic dysfunction was documented 24 h from initiation of therapy, thus controlling the cytokine storm causing distributive shock. The patient's favorable clinical evolution should be attributed to all therapeutic interventions, though the rapid clinical improvement may be related to cytokine elimination by hemoadsorption, as this has not been described as a pharmacological effect of corticosteroids or etoposide. In our institution, we monitor cytokines (IL-6 and IL-10) in real time, which allows us to suspend therapy when a significant clinical and biological improvement (decrease in cytokines) has been achieved.

As we quoted before, haemadsorption therapy has been administered in parallel to conventional treatment of haemophagocytic syndrome. In our case with Etoposide and Dexamethasone. Regarding the administered dose of these immunosuppressive drugs, to date no PK data during Cytosorb is available on this treatment, so we employed conventional dosage (22). Indeed, certain pharmacokinetic consequences of hemoadsorption cannot be ruled out. However, recent studies do not show that plasma concentrations of meropenem (19) are altered, although it could be possible with other antibiotics such as teicoplanin (20). In any case, it is important to monitor antibiotic concentrations, especially when the periods of hemoadsorption are very long.

The use of haemadsorption therapy is a salvage therapy and, in this case, we indicate its use in a situation of distributive shock refractory to conventional treatment, with evolution to multi-organ dysfunction. To date, there is no threshold plasma cytokine level used for initiation or termination of therapy. In this setting, the cytokine storm in HLH is, as in sepsis, also uncontrolled and, especially in its most severe and life-threatening forms, is responsible for inflammation-driven organ damage. In this setting, blood purification techniques can blunt the inflammatory process with a rapidly considerable, nonselective effect on the cytokine storm, potentially translating into survival benefit for the patient (23).

Cytokine hemoadsorption is a safe procedure without relevant associated adverse effects (24). In our case, we did not observe adverse effects.

In our patient, cytokine hemoadsorption was associated with a rapid decrease in IL-10 levels and a significant hemodynamic improvement. This case report highlights that cytokine hemoadsorption can be an effective and safe rescue therapy in patients with HLH and multiorgan dysfunction, complementary to standard protocol treatments. We suggest real-time monitoring of plasma cytokine concentrations as a tool to monitor the biological effect of cytokine hemadsorption, optimizing the duration of this procedure.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to publish this case was obtained and it was recorded in the medical history. Information revealing the subject's identity was avoided.

Author contributions

All authors carry out assistance and research work associated with the Vall d'Hebron Campus, contributed to the article, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Intervention to severe lower trachea obstruction supported by extracorporeal membrane oxygenation in a human immunodeficiency virus patient: A case report and literature review

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Here we reported a case, male, 33 years old, diagnosed with human immunodeficiency virus (HIV) infection 5 months ago, but he didn't take antiretroviral drugs regularly. He was admitted to intensive care unit emergently due to hypoxemia, hypercapnia, and hypotension. CT showed severe lower trachea obstruction caused by soft tissue. After rapid bedside assessment, the patient was considered to need endotracheal operation, but he couldn't tolerate intubation and mechanical ventilation. Extracorporeal membrane oxygenation (ECMO) was used. Hemodynamics improved significantly along with rehydration and low-dose vasoactive drugs. Subsequently, the patient underwent rigid bronchoscopy, airway tumor resection and Y-type silicone stent implantation. Postoperatively protective endotracheal intubation and mechanical ventilation was followed. ECMO was weaned off after the operation, and endotracheal cannula was removed 6 h later. The pathological examination of excisional tissue showed lung squamous cell carcinoma. Finally, the patient was discharged safely and went to local hospital for further treatment. From this case, we conclude that ECMO could play a key role for those who need endotracheal surgery while cannot endure conventional intubation and mechanical ventilation.

KEYWORDS

extracorporeal membrane oxygenation, trachea obstruction, interventional operation, HIV, trachea intubation

Case report

The patient, 33-year-old male, was admitted to Shanghai Public Health Clinical Center on November 22, 2019, with the complaint of "human immunodeficiency virus (HIV) infection for more than 5 months, cough and expectoration for 1 month, aggravation and shortness of breath for 2 days." He was found HIV positive 5 months ago. There were no symptoms such as fever, cough, expectoration, nausea, vomiting, and he refused to accept any antiviral agents. Four month ago, he began to have anorexia and dysphagia. Gradually, he could only take liquid food and drink water. Two month ago, he began to accept antiretroviral drugs, but irregularly. Cough, yellowish white sticky sputum with blood in sputum occurred 1 month ago. Chest CT in local hospital showed that the right upper lung cavity was accompanied by multiple consolidation, and soft tissue density shadows in the trachea. He felt the above symptoms aggravated 2 days ago accompanied with severe shortness of breath, therefore he came to our hospital for further treatment and was admitted through Emergency.

Physical examination after admission found this patient extremely thin. With dyspnea gradually exacerbated, he received nasal catheter oxygen inhalation, transnasal high flow oxygen inhalation (HFNC) and non-invasive ventilator successively. On the 8th day after admission, the patient occurred obvious respiratory distress. Laboratory findings included WBC 12.63 × 10^9/L, HB 125 g/L, PLT 414 × 10^9/L, N 78.4%, L 13.1%, HS-CRP 65.4 mg/L, PCT 0.08 ng/ml, ALT 20 U/L, AST 18 U/L, TBIL 6.1 umol/L, ALB 36 g/L, K 3.7 mmol/L, CL 100 mmol/L, Na 138 mmol/L, UREA 2.95 mmol/L, Cr 49.5 umol/L, Glu 4.83 mmol/L, PT 13.7 S, APTT 41.8 S, FDP 7.1 μg/mL, D-D 2.76 μg/ml, TNI 0.01 ng/ml, pro-BNP 32 pg/ml, CK 40 U/L, HBsAg (-), anti-HCV (-), Anti-TP (-), T-SPOT.TB (-), CD4 195 cell/μl, CD8 597 cell/μl, CEA 0.87 ng/ml, CA125 122 U/ml, G test < 10 pg/ml, HIV 266 copy/ml (reference value < 40). Sputum smear found some coccus and bacillus, but culture was negative. His finger pulse oxygen saturation (SpO_2) fluctuated obviously between 85 and 99%. Blood gas analysis showed pH 7.26, $PaCO_2$ 9.6 kpa and lactic acid 7.65 mmol/L. He was supported by non-invasive ventilation with driving force of 14 cm H_2O and inhaled oxygen concentration of 1.0 and transferred to ICU immediately.

In order to clarify the cause of dyspnea, emergency CT was carried out and showed cavitary lesions in the right upper lung, new organisms in the main trachea near to the carina which almost completely blocked the lumen (the narrowest part is about 2 mm), mediastinal lymph nodes swelling, obvious thickening of the wall of the middle esophagus and obvious expansion of the upper segment (**Figure 1**). This revealed the patient's dyspnea was due to severe stenosis of the trachea and he needed emergent airway operation. An emergent consultation of multiple disciplinary team (MDT) including anesthesia physician, intervention and ECMO team suggested that the patient's vital signs were unstable, and the risk of preoperative anesthesia induction was very high. Meanwhile, due to airway severe obstruction, the conventional endotracheal intubation could not ensure sufficient ventilation. Extracorporeal membrane oxygenation (ECMO) was then considered to start. Bedside ultrasound evaluation found that the diameter of inferior vena cava was 13 mm, the variability 50%, the filling of right ventricle poor, and left ventricular systolic function normal. Fluid resuscitation was carried out and norepinephrine was continuously pumped intravenously (0.3 μg/kg/min) to maintain the stability of blood pressure.

After evaluation of blood vessels with ultrasound, we used Seldinger's method to percutaneously puncture and put the catheters in the right femoral vein and right internal jugular vein. The tube sizes were Fr 21 and Fr 17, respectively. Initial setting of ECMO were rotating speed 3,200 rpm, blood flow 4.0 L/min and air flow 4.0 L/min (FiO_2 1.0). Low dose heparin was used for anticoagulation during catheterization, but anticoagulant agents were not given during ECMO running. With the oxygen supply from ECMO, the SpO_2 increased rapidly from 75 to 100%. With the significant improvement of oxygenation, the real-time invasive arterial blood pressure stabilized at about 120/75 mmHg.

Next, we began to solve the airway obstruction. By inserting the rigid bronchoscope, we found that the neoplastic tissue in the lower part of the trachea lead to severe lumen stenosis. After circumcision of the tumor, a small amount of tissue infiltration could be seen at the opening of the left and right bronchia, and the distal lumen was basically unobstructed. After measuring the length of the neoplastic focus, a Y-shaped silicone stent was cut, sent to the carina, then released and adjusted. The fiberoptic bronchoscopy confirmed that the stent was stable and fit well with the tracheal wall. Withdrew the two scopes, followed by endotracheal intubation and mechanical ventilation. ECMO was weaned off when the operation finished and had been running for a total of 6 h. Ventilator and tracheal cannula were removed another 6 h later. The patient's symptoms were significantly improved. Three days after the operation, bronchoscopy was carried out again and found the stent was in place and the lumen was normal. Pathological examination of excised tissue showed lung squamous cell carcinoma. Laboratory tests showed WBC 16.9 × 10^9/L, N 76.4%, L 15.3%, HS-CRP 95.3 mg/L, PCT 0.89 ng/ml. BALF culture for bacterial (-), fungal (-), tuberculosis (-), and he was treated with antibiotics, expectorants, and atomization therapy. The patient was discharged 1 week later and returned to local hospital for further treatment.

Discussion

Some characteristics of immune system such as decreased CD4 + T lymphocyte counts and impaired natural killer cell (NK) function have been found in HIV patients, which could

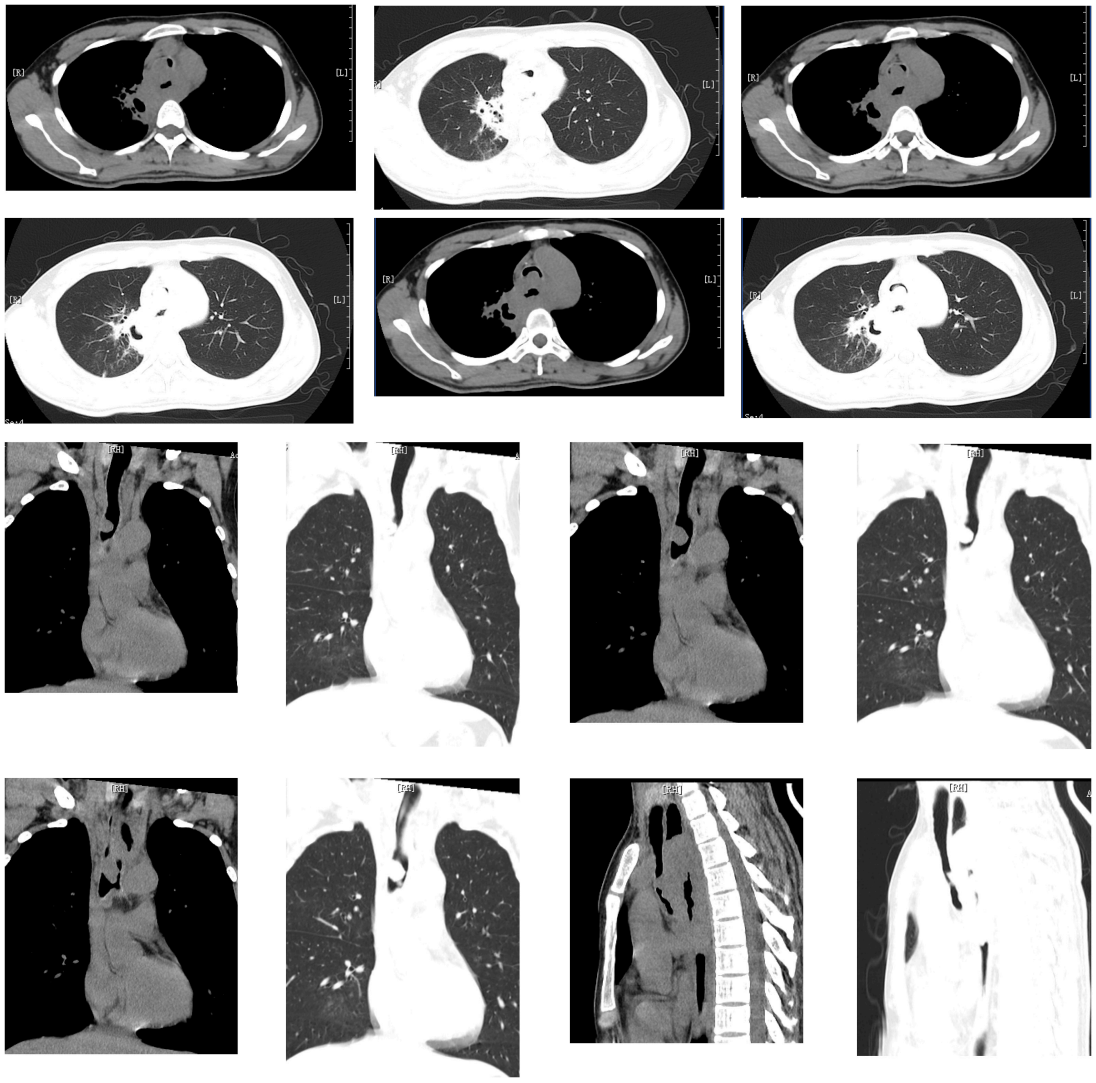

FIGURE 1
Cavitary lesions in the right upper lung, new organisms in the main trachea near to the carina which almost completely blocked the lumen (the narrowest part is about 2 mm), mediastinal lymph nodes swelling, obvious thickening of the wall of the middle esophagus and obvious expansion of the upper segment.

decline the ability of the body to monitor and kill tumor cells. The incidence of Kaposi sarcoma, non-Hodgkin lymphoma (NHL) and invasive cervical cancer show significantly higher in HIV positive patients (1, 2). With the application of antiretroviral therapy (ART), the survival time of HIV carriers has gradually prolonged, the type of tumor changed, and the proportion of non-AIDS defined cancer (NADC) gradually increased (3). The incidence of lung cancer in HIV is about 2–4 times that of non-HIV population, and the tumor is characterized by younger onset age, less typical pathological changes, and stronger invasion (4, 5). The malignant tissue in the airway can lead to obvious lumen stenosis. The swelling of mediastinal lymph nodes caused by tumor or opportunistic mycobacterial infection can worsen insufficient ventilation. Severe hypoxemia and carbon dioxide retention caused by major airway obstruction are life-threatening and usually require emergent disposition (6, 7).

Methods of respiratory support during airway intervention include nasal tube oxygen inhalation, face mask oxygen inhalation, high flow oxygen therapy, non-invasive ventilation, and endotracheal intubation to ensure oxygen supply. However, when severe stenosis occurs near the carina at the lower end of the trachea or bilateral main bronchus concurrently, the above methods might not be able to provide adequate ventilation, or even make it worse. In this situation, ECMO should be chosen to render sufficient oxygen, buy enough time for intervention surgery, and avoid ventilator-associated lung injury (8, 9). In 2015, Kim et al. reported 15 patients with upper respiratory tract

obstruction due to various diseases received ECMO support during the airway intervention treatment. They suggested that ECMO should be considered when bronchoscopy or chest CT indicated the diameter of ventilation lumen was less than 5 mm (10).

In the present case, there was no attempt to intubate, which was the result of MDT discussion, based on the following reasons: 1. CT showed that the patient's ventilation lumen was very small, about 2 mm (showed in lung window). In this case, intubation would reduce the ventilation space and interventional operation would further worsen it. 2. The patient was spontaneously breathing with assistance of non-invasive ventilator. The driving force of the ventilator was 14 cm H_2O and inhaled oxygen concentration was 1.0. From the perspective of oxygen supply, intubation did not benefit the patient more. 3. If intubation and mechanical ventilation were performed, whether to keep the patient's spontaneous breathing was a dilemma. In auxiliary mode with spontaneous breathing, intubation would significantly stimulate his irritability, leading to man-machine confrontation and increase of oxygen consumption. And in controlled mode, oxygen consumption would be reduced after the injection of analgesia and sedative drugs. But with the inhibition of spontaneous breathing, the ventilation of both dorsal parts was severely restricted. The imbalance of ventilation blood flow ratio might lead to further decline of oxygenation. Moreover, if intubation led to further deterioration of oxygenation, it would take an uncertain period of time to switch to ECMO. During this time, the patient was in extremely critical condition. If we chose ECMO, in the process of catheterization, we would not make the current situation worse without touching his airway.

Hong et al. reported that 19 patients with life-threatening hypoxemia caused by severe central airway obstruction underwent venous-venous (V-V) ECMO during intra-airway tumor removal and stent placement, which confirmed that ECMO could play a key role in lifesaving but very dangerous operations (11). Natt et al. reported a female patient who had acute respiratory failure due to severe centripetal stenosis under the cricoid cartilage after tracheotomy. Her physicians determined that the endotracheal intubation might not be successful. Therefore V-V ECMO was used, followed by bronchoscopic balloon dilatation and covered stent implantation. Then intubation and mechanical ventilation were implemented and ECMO was terminated (12). Malpas et al. reported a male patient suffering advanced thyroid cancer complicated with severe glottic stenosis so that tracheal access was difficult to establish. His physicians decided to start venous-arterial (V-A) ECMO under local anesthesia instead, then operated successfully (13).

In cases of airway obstruction caused by intraluminal neoplasm and airway compression caused by extraluminal tumor or lymphadenopathy, the intervention measures include rotary resection of intraluminal tumor or endotracheal stent implantation, or combination of both, which should be carried out based on rigid bronchoscope and high-frequency ventilation to ensure oxygenation (14). Commonly used airway built-in stents include silicone stents and self-expanding metal ones. Silicone stents can cover the fistula caused by malignant tumor, avoid restenosis caused by tumor recurrence, provide opportunities for chemotherapy or radiotherapy, and can be removed when the tumor shrinks after treatment (15).

Analgesic and sedative drugs can lead to breath depression, which could worsen hypoxemia of the patients with large airway obstruction. Local infiltration anesthesia with lidocaine during cannula insertion to keep the patient be awake and breathe autonomously can avoid further decline of oxygenation. Malpas et al. chose local infiltration anesthesia with lidocaine to start V-A ECMO after intravenous injection of midazolam (13). Kim et al. reported to use oxygen storage mask for preoxygenation and infuse remifentanil and dexmedetomidine intravenously for sedation (16). In the present case, we selected lidocaine for local anesthesia during catheterization, and intravenous injection of midazolam, sufentanil and muscle relaxant after ECMO was working. Before ECMO started, non-invasive ventilator was used to ensure oxygen supply with driving pressure of 15 cm H_2O and oxygen concentration of 1.0. It should be noted that when the patient's airway was severely obstructed, no matter what sort of supportive ventilation was used, there was a great risk. The most important thing was to insert the tube and start ECMO as soon as possible.

V-V ECMO was the primary choice while patients suffered from severe hypoxemia caused by critical lung disease. However, when hypotension existed at the same time, V-A ECMO should be considered as an option. In this critical scenario, whether the blood pressure could be controlled quickly became the key to the selection of ECMO mode. Although the patient we reported had shock, the results of rapid bedside assessment showed that his heart filling was not enough, and the systolic function was acceptable. We concluded that the cause of hypotension was partly due to acidosis caused by carbon dioxide retention and lactic acid accumulation, and partly due to insufficient circulating volume. So, the patient's blood pressure could be better after fluid resuscitation and use of vasoactive drugs. Actually, after rapid fluid infusion and intravenous injection of low-dose norepinephrine, his blood pressure was under control. After ECMO started, the blood pressure was further stabilized while hypoxia and acidosis were corrected. However, it should be pointed out that V-A ECMO might be the better choice if the patient's hypoxemia worsened and resulted in more severe shock. Sometimes, when it is uncertain whether V-V ECMO could successfully prevent further deterioration, it is necessary to be geared up for V-A ECMO. Zhang and colleagues placed a catheter in the left femoral artery for rapid conversion to V-A ECMO while inserting cannulas at the right femoral vein and the right internal jugular vein for V-V ECMO to treat a patient with relapsing polychondritis (17).

Anticoagulation is an important part of ECMO management, which is determined by the patient's underlying diseases, coagulation state, the type of pipeline and oxygenator used, ECMO running time and blood flow velocity in the pipeline (18). During ECMO working, increasing blood flow velocity, and decreasing running time can significantly reduce the risk of thrombosis (19). In Hong et al. report, 13 cases received intravenous injection of heparin (3,000–5,000 IU) during blood vessel catheterization, and other 6 cases received nafamostat mesilate infusion. However, anticoagulation was not given during ECMO running in all 19 cases. In the end, 18 patients showed no complications such as bleeding or thrombosis and were discharged alive (11). These research suggested that ECMO could operate safely for a short time without anticoagulation. In the present case, low-dose heparin (50 IU/kg) was given intravenously during catheterization, while no anticoagulants were infused after ECMO started. After the operation, we followed up the coagulation function including D dimer and bedside ultrasound. No obvious bleeding or thrombosis were found during the whole hospitalization.

All in all, for most patients with hypoxemia due to airway obstruction, endotracheal intubation was the primary choice. V-V ECMO should be considered first only in the following cases: 1. The airway stenosis was so severe that the intubation itself had a high risk of exacerbation. 2. Endotracheal intubation had a high risk of failure, and at the same time there was no chance for tracheotomy for various reasons. 3. Patients had severe lung diseases, resulting in the inability of effective gas exchange even with endotracheal intubation, such as diffused pulmonary fibrosis, air leakage syndrome, pulmonary embolism, and extensive alveolar lesions. 4. Patients could tolerate endotracheal intubation, but could not endure endotracheal intervention, because interventional surgery itself might aggravate hypoxia. Preoperative evaluation should be carried out comprehensively to decide ECMO operation mode. The most important thing is to put in the tubes and start the machine at the top speed, and it is safe not to use anticoagulation for a short time. Certainly, patients without systemic anticoagulation should be followed up with coagulation function and ultrasound to assess the risk of thrombosis and bleeding. Weaning ECMO off quickly after the surgery can reduce ECMO related complications after the transition to conventional mechanical ventilation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

XZ, LP, and LW: manuscript writing and results discussion. LL, PZ, and HT: data curation, review, and study supervision. QW and FL: conception and design, formal analysis, and manuscript revision. All authors contributed to the article and approved the submitted version.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Recirculation in single lumen cannula venovenous extracorporeal membrane oxygenation: A non-randomized bi-centric trial

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Background: Recirculation is a common problem in venovenous (VV) extracorporeal membrane oxygenation (ECMO). The aims of this study were to compare recirculation fraction (R*f*) between femoro-jugular and jugulo-femoral VV ECMO configurations, to identify risk factors for recirculation and to assess the impact on hemolysis.

Methods: Patients in the medical intensive care unit (ICU) at the University Medical Center Regensburg, Germany receiving VV ECMO with femoro-jugular, and jugulo-femoral configuration at the ECMO Center Karolinska, Sweden, were included in this non-randomized prospective study. Total ECMO flow (Q_{EC}), recirculated flow (Q_{REC}), and recirculation fraction $Rf = Q_{REC}/Q_{EC}$ were determined using ultrasound dilution technology. Effective ECMO flow (Q_{EFF}) was defined as $Q_{EFF} = Q_{EC} * (1-Rf)$. Demographics, cannula specifics, and markers of hemolysis were assessed. Survival was evaluated at discharge from ICU.

Results: Thirty-seven patients with femoro-jugular configuration underwent 595 single-point measurements and 18 patients with jugulo-femoral configuration 231 measurements. R*f* was lower with femoro-jugular compared to jugulo-femoral configuration [5 (0, 11) vs. 19 (13, 28) %, respectively ($p < 0.001$)], resulting in similar Q_{EFF} [2.80 (2.21, 3.39) vs. 2.79 (2.39, 3.08) L/min ($p = 0.225$)] despite lower Q_{EC} with femoro-jugular configuration compared to jugulo-femoral [3.01 (2.40, 3.70) vs. 3.57 (3.05, 4.06) L/min, respectively ($p < 0.001$)]. In multivariate regression analysis, the type of configuration, distance between the two cannula tips, ECMO flow, and heart rate were significantly associated with Rf [B (95% CI): 25.8 (17.6, 33.8), p < 0.001; −0.4 (−0.7, −0.1), $p = 0.009$; 4.2 (2.5, 5.9), p < 0.001; −0.1 (−0.2, 0.0), p = 0.027]. Hemolysis was similar in subjects with Rf > 8 vs. ≤8%. Explorative data on survival showed comparable results in the femoro-jugular and the jugulo-femoral group (81 vs. 72%, $p = 0.455$).

Conclusion: VV ECMO with femoro-jugular configuration caused less recirculation. Further risk factors for higher R*f* were shorter distance between the two cannula tips, higher ECMO flow, and lower heart rate. R*f* did not affect hemolysis.

KEYWORDS

ECMO, recirculation, ultrasound dilution, cannula, configuration, hemolysis, risk factor

Background

Venovenous extracorporeal membrane oxygenation (VV ECMO) is a method of providing patients with oxygenated blood in the case of severe respiratory failure (1, 2). In VV ECMO, deoxygenated blood is drained from the venous compartment, oxygenated by a membrane lung (ML), and subsequently returned to the venous compartment. Recirculation is evident, when returned fully oxygenated blood is aspirated into the drainage cannula without adding any contribution to systemic oxygenation (3). Recirculation is undesirable because it diminishes the effectiveness of ECMO support and may thus compromise systemic oxygenation.

Peripheral VV ECMO including the jugular vein offers two different configuration options for cannulation with two single lumen cannulae: femoro-jugular and jugulo-femoral. Another peripheral configuration is femoro-femoral. It should be noted that the first part of these terms denotes the site of the drainage cannula and the latter part the site of the return cannula (4). In the femoro-jugular configuration, the tip of the drainage cannula is positioned in the upper inferior vena cava (IVC). In the jugulo-femoral configuration, the tip of the drainage cannula is placed into the right atrium (RA). In both types of configurations, the return cannula is accordingly placed in a large vein on the opposite side of the diaphragm. Placement of the drainage cannula close to the RA as in the jugulo-femoral configuration may result in higher recirculation fraction (R*f*) than achieved with the femoro-jugular configuration.

Both ECMO blood flow (Q_{EC}) and recirculated flow (Q_{REC}) can be measured. The R*f* is defined as $Rf = Q_{REC}/Q_{EC}$, and effective ECMO flow (Q_{EFF}) can be calculated as $Q_{EFF} = Q_{EC} * (1–Rf)$ (5, 6). In the literature, R*f* values range from 2 to 60%, and may depend on various factors such as Q_{EC}, the type of cannula, and the drainage site (6–13). Limited oxygen delivery during VV ECMO can be partly compensated by increasing Q_{EC}, usually at the expense of increasing R*f*. Such increase, however, may expose blood to increased shear forces and the associated risk of hemolysis (14).

Thus, the aims of this study were to investigate the difference in R*f* between the femoro-jugular and the jugulo-femoral configuration, to identify risk factors for R*f*, and to assess the impact on hemolysis.

Abbreviations: ECMO, extracorporeal membrane oxygenation; fHb, plasma free hemoglobin; IQR, interquartile range; IVC, inferior vena cava; ML, membrane lung; PEEP, positive end-expiratory pressure; PaO_2/FiO_2, partial arterial oxygen pressure to fraction of inspired oxygen; Q_{EC}, ECMO blood flow; Q_{EFF}, effective ECMO flow; Q_{REC}, recirculation flow; RA, right atrium; R*f*, recirculation fraction; $S_{PRE}O_2$, saturation pre membrane lung; VV, venovenous.

Methods

Trial design

This non-randomized investigator-initiated bi-centric prospective study compared the R*f* of the femoro-jugular to that of the jugulo-femoral configuration in VV ECMO. The study protocol was reviewed and approved by the local institutional Ethics Committees (Ethical review number: Stockholm: 2014/945-31; Regensburg: 17-737-101). Written informed consent was obtained from all patients. The study was conducted according to the Declaration of Helsinki on Good Clinical Practice.

Study subjects

The study included adult patients (>18 years of age) treated with VV ECMO for severe respiratory failure [PaO_2/FiO_2 < 85 mmHg or refractory respiratory acidosis with pH < 7.25 on optimized positive end-expiratory pressure (PEEP)] at the University Medical Center Regensburg, Germany, between January 2018 to January 2021 or at the ECMO Center Karolinska, Karolinska University Hospital, Stockholm, Sweden, between April 2018 to May 2019. The difference in the two inclusion periods was related to technical malfunction of the measuring device. In addition, patients from a previous study at the ECMO Center Karolinska were considered eligible for the Stockholm cohort due to slow recruitment and failure of measurement probes with delayed delivery in accordance with the ethical committee (6).

Exclusion criteria were VV ECMO configuration other than jugulo-femoral or femoro-jugular configuration, venoarterial,

venopulmonary, or any hybrid mode of ECMO, age <18 years, expected survival of <48 h, and pronounced hemodynamical instability (Figure 1).

Besides demographics, other criteria to be analyzed were cannula specifics (diameter and length), the tip-to-tip distance between the cannulae, ECMO specifics [Q_{EFF}, saturation pre-ML ($S_{PRE}O_2$)], hemolysis [plasma free hemoglobin (fHb) >500 mg/L measured by a commercial available calorimetric assay, C462-0A Catachem, Oxford, CT, USA (14), or HemoCue Plasma/Low Hb, HemoCue, Ängelholm, Sweden], vasoactive inotropic score [dopamine dose (μg/kg/min) + dobutamine (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 50 × levosimendan dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin (units/kg/min) + 100 × norepinephrine dose (μg/kg/min) (15)] ventilation parameters, daily assessment of net fluid balance and survival at discharge from intensive care unit (ICU). Details of ventilation management is presented in the supplement. Cardiac output was measured by means of echocardiography.

Trial procedures and recirculation fraction

In Regensburg, the tip of the femoral drainage cannula was positioned in the IVC, and the jugular return cannula was placed into the superior caval vein (femoro-jugular configuration). The aim was a tip-to-tip distance of ≥15 cm to minimize potential recirculation. After cannulation, the tip position was verified by sonography or radiographic imaging. In general, 21 French (Fr) cannula, 38 cm length was used as drainage and 19 Fr/15 cm as return cannula (HLS, Getinge Cardiovascular, Rastatt, Germany).

In Stockholm, the tip of the jugular drainage cannula was positioned in the RA, and correct placement was confirmed by echocardiography or radiographic imaging. The tip of the femoral return cannula was placed in the iliac vein (jugulo-femoral configuration). By default, the drainage cannula was 25 Fr/38 cm (HLS, Getinge Cardiovascular) and for return 19 Fr/18 cm (Bio-Medicus, Medtronic, Tolochenaz, Switzerland).

In both centers, adaptions were allowed according to the treating physician. Further details for both centers on cannulation strategy have been previously published (6, 16). The distance between the cannula tips was assessed by means of computed tomography or chest X-ray. Further details are presented in the supplements. Recirculation fraction was measured in supine position using ultrasound dilution technology (UDT), (ELSA®, Transonic Systems Inc., Ithaca, NY, USA) as described previously (5, 6). Measurements were allowed any time during ECMO therapy if the patient was hemodynamically stable. One ultrasonic flow probe was applied to the drainage tube in proximity to the patient, the other transducer was placed in proximity to the return cannula. A rapid (<3 s) bolus of 20 mL room tempered saline was injected into the ECMO circuit before the ML. The probes measured ultrasound velocity in the blood and the blood flow rate by means of the Doppler technique. The respective ultrasound velocity data was processed with the ELSA device. The quotient of the drainage to the return curve areas was considered the R*f*. At least two measurements were taken to account for any variability due to breathing efforts. If large differences were observed, further measurements were undertaken, flawed values deleted and the mean of at least two measurements, regarded as valid taken, to chart. For each measurement, Q_{EC}, R*f*, and Q_{EFF} were recorded. Q_{EC} was increased or decreased in steps of 300–500 mL/min. The magnitude and number of respective flow rates in each session depended on the patient status and the prevailing Q_{EC}. After assessment, the Q_{EC} was returned to the clinical baseline setting, and the aggregated saline volume used was added to the daily fluid balance. Vital and ventilatory parameters were recorded with each measurement.

The reproducibility of paired UDT measurements has been reported to differ by 5.6% in children and possibly even less in adults with a greater distance between the two cannula tips and to be similar to other methods using thermodilution and lithium indicator methods (17, 18).

Statistics

Descriptive statistics are presented as numbers (n), range, and fractions (%), and continuous data as median [interquartile range (IQR): 25%; 75%], as appropriate. Continuous data were compared with the Mann-Whitney *U*-test, and categorical data with the Chi² test. A multivariate linear regression model was calculated, including all independent variables with $p < 0.1$ in the univariate model. Multivariate linear regression analyses were conducted to identify risk factors for R*f*, including known possible risk factors such as ECMO and cannula specifics as well as hemodynamic and respiratory parameters as published previously (13). Linear quadratic regression models were used to assess associations between the R*f*, Q_{EC}, and Q_{EFF}. A two-sided $p < 0.05$ was considered statistically significant. Data entry and calculation were done with Microsoft EXCEL365 ProPlus (Microsoft, USA) and IBM SPSS Statistic software version 25.0 (SPSS Inc. Chicago, IL, USA).

Results

Study population

Fifty-five patients were prospectively enrolled in this bi-centric study, 37 received VV ECMO with the femoro-jugular configuration (Regensburg, Germany), and 18 VV ECMO

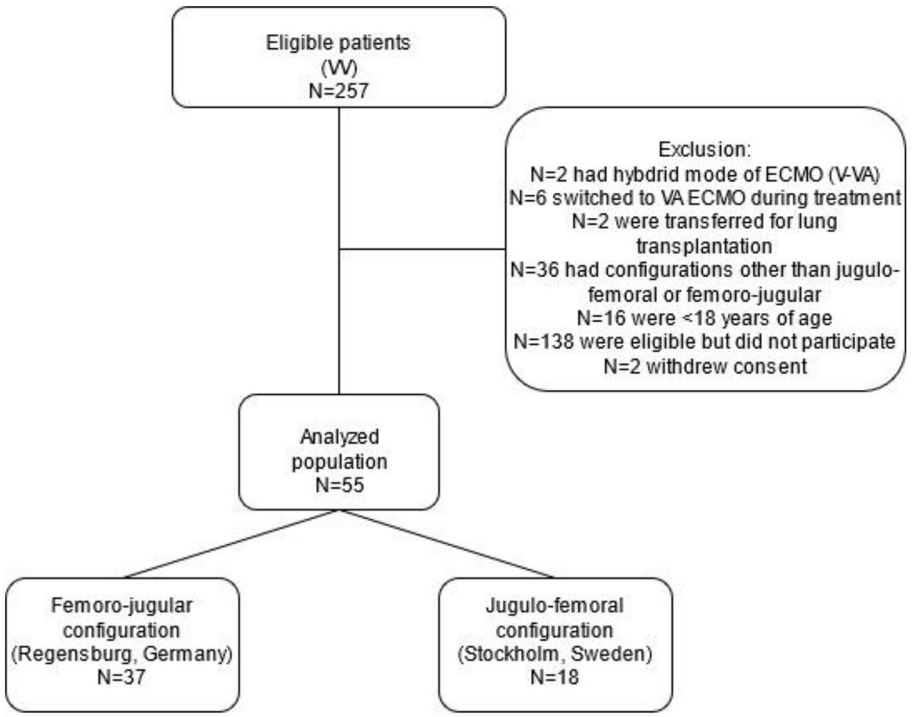

FIGURE 1
Flowchart of the prospective non-randomized bi-centric study comparing the femoro-jugular to the jugulo-femoral configuration in venovenous extracorporeal membrane oxygenation in terms of recirculation. ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous.

with the jugulo-femoral configuration (Stockholm, Sweden) (Figure 1). Patient characteristics were similar between the two groups (Table 1), except for higher PaO_2/FiO_2 ratios, higher doses of norepinephrine and lower bilirubin levels in the femoro-jugular than in the jugulo-femoral group. The most frequent diagnoses at admission to the ICU were bacterial (36%) and viral pneumonia (36%). Median support on ECMO was 17 (9, 26) days in the femoro-jugular group and 13 (8, 22) days in the jugulo-femoral group ($p = 0.468$).

Cannulae

Significantly smaller drainage and return cannulae were used in the femoro-jugular than in the jugulo-femoral group [21 (21, 23) Fr vs. 25 (25, 25) Fr, $p < 0.001$; 18 (17, 19) Fr vs. 19 (19, 20) Fr, $p = 0.003$, Supplementary Table 1]. The drainage cannula was located below the diaphragm in patients receiving the femoro-jugular configuration and above the diaphragm in patients with the jugulo-femoral configuration [−8.3 (−10.0, −4.0) cm vs. 5.5 (4.7, 8.1) cm, $p < 0.001$]. The tip-to-tip distance between the two cannulae was less in the femoro-jugular configuration [19 (17, 21) cm vs. 36 (33, 40) cm, $p < 0.001$] than for jugulo-femoral subjects.

Recirculation fraction

We conducted 826 single-point measurements of recirculation, 595 in the femoro-jugular and 231 in the jugulo-femoral configuration group. Median R*f* of all measurements was 9 [0, 17] %. Extracorporeal flow was lower in the femoro-jugular configuration [3.01 (2.40, 3.70) vs. 3.57 (3.05, 4.06) L/min, $p < 0.001$, Figure 2]. However, since R*f* was significantly lower in femoro-jugular than in jugulo-femoral group [5 (0, 11) vs. 19 (13, 28) %, $p < 0.001$], extracorporeal support in terms of Q_{EFF} was similar between both groups [2.80 (2.21, 3.39) vs. 2.79 (2.39, 3.08) L/min, $p = 0.225$], respectively. Further configuration related data is depicted in Table 2.

Furthermore, higher measurements of Rf were seen in patients with higher Q_{EC}, larger drainage and larger return cannulae, lower heart rate, and more intense mechanical ventilation [i.e., higher peak inspiratory pressure, higher tidal volume and higher respiratory rate (Supplementary Tables 2, 3)].

In univariate analysis, R*f* was associated with Q_{EC}, ECMO configuration, distance between the two cannula tips, mean arterial pressure, heart rate, positive end-expiratory pressure, respiratory rate, tidal volume, size of drainage, and size of

TABLE 1 Patient characteristics and parameters at the time of decision for extracorporeal membrane oxygenation.

Variables	*n*	Femoro-Jugular configuration	*n*	Jugulo-Femoral configuration	*p*-value
Age, years	37	57 [46, 68]	18	55 [44, 66]	0.795
Sex, male	37	24 (65%)	18	11 (61%)	0.786
BMI, kg/m²	37	27.7 [24.7, 34.6]	13	27.0 [24.5, 33.8]	0.732
PaO_2/FiO_2 ratio, mmHg	36	84 [68, 107]	16	50 [45, 66]	**<0.001**
SOFA	37	10 [9, 13]	18	10 [8, 11]	0.363
Norepinephrine, µg/kg/min	33	0.17 [0.07, 0.33]	8	0.0 [0.00, 0.08]	**0.006**
pH before ECMO	36	7.25 [7.16, 7.33]	18	7.28 [7.20, 7.37]	0.279
Lactate before ECMO, mg/dL	37	13 [10, 19]	18	16 [6, 20]	1.000
Days in hospital before ECMO	37	2 [1, 10]	17	7 [3, 10]	0.384
Days on mechanical ventilation before ECMO	37	1 [0, 3]	17	3 [1, 8]	0.135
Days on RRT before ECMO	22	0 [0, 0]	14	0 [0, 5]	0.077
Bicarbonate, mmol/L	35	24.9 [21.4, 28.0]	13	23.0 [21.4, 30.7]	0.991
CRP, mg/L	37	237 [96, 283]	9	283 [40, 411]	0.567
White blood cells, 10^9/L	37	12.9 [8.1, 19.8]	17	14.0 [2.4, 21.1]	0.473
Platelets, 10^9/L	36	227 [138, 326]	17	213 [162, 250]	0.804
Bilirubin, mg/dL	37	0.6 [0.5, 1.1]	17	1.9 [1.2, 5.5]	**<0.001**
Creatinine, mg/dL	37	1.2 [0.8, 2.0]	18	1.3 [1.0, 1.6]	0.647

BMI, body mass index; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction inspired oxygen; PaO_2, arterial partial pressure of oxygen; RRT, renal replacement therapy; SOFA, sequential organ failure assessment. Significant $p < 0.05$ are marked in bold.

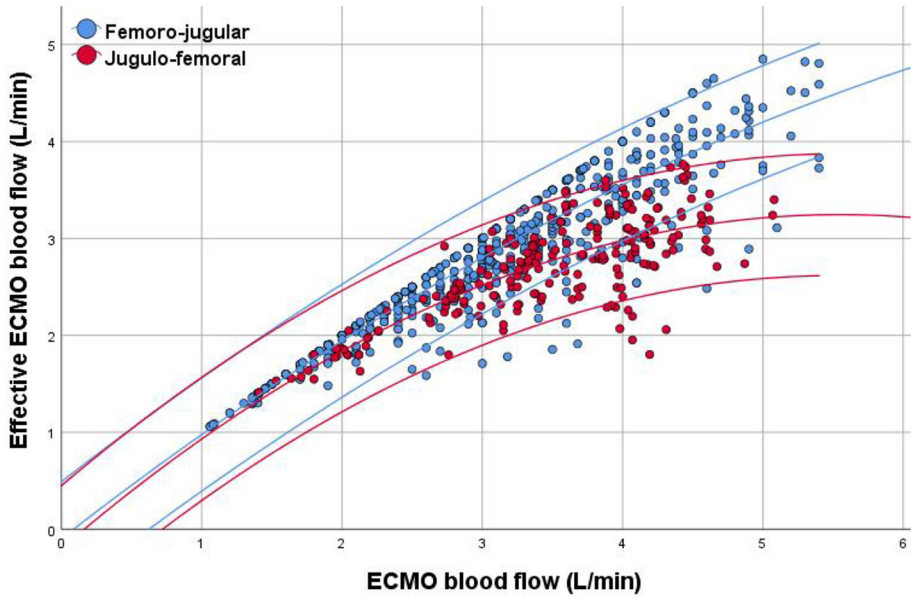

FIGURE 2
Scatter plot of extracorporeal membrane oxygenation (ECMO) blood flow and effective ECMO blood flow. Data are expressed as quadratic regression analysis with a line fitted to the mean and the 95% confidence intervals according to ECMO configuration, demonstrating lower recirculation fraction in the femoro-jugular configuration than in the jugulo-femoral configuration group.

TABLE 2 Characteristics in association with recirculation according to configuration per single point measurement.

Variables	Femoro-Jugular configuration	Jugulo-Femoral configuration	*p*-value
Distance between the two cannulae tips, cm	19 [17, 21]	36 [33, 40]	**<0.001**
ECMO flow, L/min	3.0 [2.4, 3.7]	3.6 [3.0, 4.1]	**<0.001**
Recirculation fraction, %	5 [0, 11]	19 [13, 28]	**<0.001**
Effective ECMO flow, L/min	2.8 [2.2, 3.4]	2.8 [2.4, 3.1]	0.225
Aspartate aminotransferase, U/L	51 [34, 85]	75 [48, 116]	**0.002**
Alanine aminotransferase, U/L	44 [32, 69]	63 [40, 84]	0.061
Lactate dehydrogenase, U/L	378 [296, 502]	432 [345, 612]	**0.019**
Plasma free hemoglobin, mg/L	36 [28, 48]	35 [28, 85]	0.987
Mean arterial pressure, mmHg	72 [64, 78]	71 [66, 76]	0.595
Heart rate, /min	85 [70, 102]	96 [84, 106]	**<0.001**
Cardiac output, L/min	6.1 [5.4, 7.5]	5.7 [4.6, 7.7]	0.426
SaO_2, %	96 [94, 97]	93 [90, 99]	**<0.001**
Saturation pre membrane lung, %	68 [62, 74]	75 [72, 78]	**<0.001**
F_iO_2 (ventilator), %	45 [40, 55]	60 [50, 60]	**<0.001**
Peak inspiratory pressure, cmH_2O	22 [20, 26]	26 [19, 28]	**0.022**
Positive end-expiratory pressure, cmH_2O	11 [8, 15]	8 [5, 10]	**<0.001**
Respiratory rate, /min	13 [10, 16]	20 [15, 25]	**<0.001**
Tidal volume, mL	277 [205, 398]	574 [385, 743]	**<0.001**

Data are expressed as median [25th percentile, 75th percentile]. F_iO_2, fractional inspired oxygen set via ventilator. Significant $p < 0.05$ are marked in bold.

return cannulae (Table 3). Data were robust in multivariate analysis for higher R*f*, which was associated with ECMO configuration (jugulo-femoral approach), higher Q_{EC}, shorter distance between the two cannula tips, and lower heart rate (Table 3). Sensitivity analysis in those with spontaneous breathing yielded comparable results to the overall group, except for ventilatory parameters (Supplementary Table 4). However, in a further sensitivity analysis including only those with measurement of tip-to-tip distance by means of computed tomography or only those with plain X ray measurement, R*f* was only associated with the tip-to-tip distance in the univariate but not in the multivariate analysis (Supplementary Table 5).

Hemolysis and fluid balance

The fHb neither differed between the two types of configurations nor was it related to a R*f* below or above 9% (Table 2, Supplementary Table 3). Negative pre inlet pump pressures were neither different between groups [femoro-jugular: −5 (−23, 5) vs. jugulo-femoral: −10 (– 33, 8), $p = 0.363$] nor associated with fHB (Supplementary Table 6). Total net fluid balance was similar between the two groups on day one of ECMO therapy but differed between configurations from day two of ECMO therapy onwards (Figure 3, Supplementary Table 7).

Discussion

This prospective bi-centric study investigated the impact of the flow direction in VV ECMO on R*f* by means of the femoro-jugular and the jugulo-femoral configuration. The femoro-jugular configuration was superior regarding lower R*f* values because it provided a higher Q_{EFF} at similar Q_{EC} compared to the jugulo-femoral configuration. Factors associated with a high R*f* in multivariate linear analysis were jugulo-femoral configuration, shorter distance between the two cannula tips, higher Q_{EC}, and lower heart rate. The R*f* did not affect hemolysis.

To our knowledge, this is the first study to systematically compare R*f* in two different peripheral VV ECMO configurations in a clinical context. In general, the R*f* in our study was lower than the values published previously (13), eventually due to lower applied ECMO blood flows in comparison to other ECMO centers using ECMO flows of 5-6 l/min. In particular high ECMO flows were associated with higher R*f* (Figure 2). However, ECMO flows of >5 l/min were rarely applied in this study. Moreover, as R*f* and Q_{EFF} were assessed unnecessary high flows were avoided to reduce mechanical blood trauma. The jugulo-femoral configuration has the predestined disadvantage of draining oxygenated blood more easily because the drainage cannula in the RA is placed amidst blood streaming toward the tricuspid valve, even though the design of a multi-staged cannula may partly reduce this effect (6). It is still unknown if recirculation is a limiting factor for jugulo-femoral configuration in relation to hemolysis, morbidity, and mortality in comparison to femoro-jugular configuration.

In 1998, Rich et al. (19) compared the jugulo-femoral to the femoro-jugular configuration, each with two 23 Fr/25 cm cannulae, in nine patients and found higher maximal Q_{EC} with femoro-jugular configuration; R*f*, however, was not assessed. The study was conducted with neuromuscular blockade in the first day of VV support and with a low frequency (6 min^{-1}) inversed ratio pressure control ventilation strategy that may impact central venous volume distribution. Consequently,

TABLE 3 Univariate and multivariate linear regression of recirculation fraction.

	Univariate analysis		Multivariate analysis	
	B (95% CI)	*p*-value	B (95% CI)	*p*-value
Configuration (Center)	13.7 (12.3, 15.2)	**<0.001**	25.8 (17.6, 33.9)	**<0.001**
Distance between the two cannula tips, cm	0.3 (0.2, 0.5)	**<0.001**	−0.4 (−0.7, −0.1)	**0.009**
ECMO flow, L/min	6.3 (5.5, 7.0)	**<0.001**	4.2 (2.5, 5.9)	**<0.001**
Mean arterial pressure, mmHg	−0.1 (−0.2, 0.0)	**0.046**	0.0 (−0.1, 0.1)	0.667
Heart rate, /min	0.1 (0.0, 0.1)	**0.017**	−0.1 (−0.2, 0.0)	**0.026**
Cardiac output, L/min	−1.3 (−2.8, 0.3)	0.106		
Vasoactive inotropic score	0.0 (0.0, 0.0)	0.206		
FiO_2, %	5.5 (−1.5, 12.4)	0.126		
Positive inspiratory pressure, cmH_2O	0.1 (−0.1, 0.3)	0.327		
Positive end-expiratory pressure, cmH_2O	−0.5 (−0.7, −0.3)	**<0.001**	−0.2 (−0.5, 0.2)	0.334
Respiratory rate, /min	0.4 (0.2, 0.6)	**<0.001**	−0.2 (−0.4, 0.0)	0.096
Tidal volume, mL	0.013 (0.007, 0.018)	**<0.001**	−0.006 (−0.014, 0.002)	0.126
Drainage cannula, Fr	3.1 (2.7, 3.5)	**<0.001**	−0.9 (−2.5, 0.7)	0.255
Return cannula, Fr	1.6 (1.0, 2.1)	**<0.001**	−0.5 (−1.5, 0.5)	0.352

ECMO, extracorporeal membrane oxygenation; FiO_2, fraction inspired oxygen. Significant p-values < 0.05 are marked in bold.

several centers switched from the jugulo-femoral to the femoro-jugular configuration to be able to provide higher Q_{EC}. Today, the femoro-jugular configuration is the more commonly used technique (20).

Traditionally, Q_{EC} is adjusted to meet the patient's need for oxygen, whereas removal of carbon dioxide is adjusted by the amount of sweep gas flowing through the ML. Without R*f* measurement, Q_{EFF} will remain unknown, and only indirect signs such as saturation pre-membrane lung or pulmonary arterial oxygen saturation can be used to evaluate this variable (21). In this study, R*f* measurements showed similar Q_{EFF} in both groups, but adequate ECMO support could be provided more effectively, i.e., with a lower $Q_{EC,}$ in the femoro-jugular group.

As R*f* increases, Q_{EFF} may approach a plateau. Beyond an inflection point, arterial oxygen delivery may decrease without the physician noticing it. In our study, recirculation became apparent at higher flows in both configurations, but less pronounced in the femoro-jugular configuration, as supposed to in a simulation model (22). In the same model (22), flow direction and cannula diameter were calculated to have a moderate influence on R*f*. In our multivariate analysis, the size of the cannulae was not associated with R*f*, but jugulo-femoral configuration showed a strong association with higher R*f*, in fact, stronger than any other investigated parameters. Comparable to a computational model, further risk factors with rather modest absolute effects on R*f* were the distance between the two cannula tips and heart rate (22). The higher R*f* with shorter tip-to-tip distance may be reasonable from a pathophysiological perspective because the drainage cannula may easier drain oxygenated blood from the return cannula. In 2018, Togo et al. (23) showed comparable results in an experimental setting in four goats; in their study, the tip-to-tip distance in femoro-jugular configuration was associated with the R*f* as assessed with the limited oxygen saturation calculation method. In an experimental model it was recently shown that a distance of nine to twelve cannula diameters was required for the mix of native venous and ECMO blood to become homogenous (24). Further investigation is necessary with respect to the association of higher Rf with lower heart rate.

Hemolysis and fluid balance

Hemolysis has been described to be associated with blood flow velocity (14). Therefore, the femoro-jugular configuration with lower R*f* compared to the jugulo-femoral configuration may cause less blood trauma. In this analysis, however, neither the R*f* nor the two configurations did affect hemolysis, maybe due to the appropriate choice of cannula size for the applied blood flow (22).

Beside hemolysis, fluid balance might be affected by the type of configuration. In particular, in femoro-jugular configuration chattering of the tubing (relative hypovolemia; drainage problems from the IVC) is regarded by some to be a

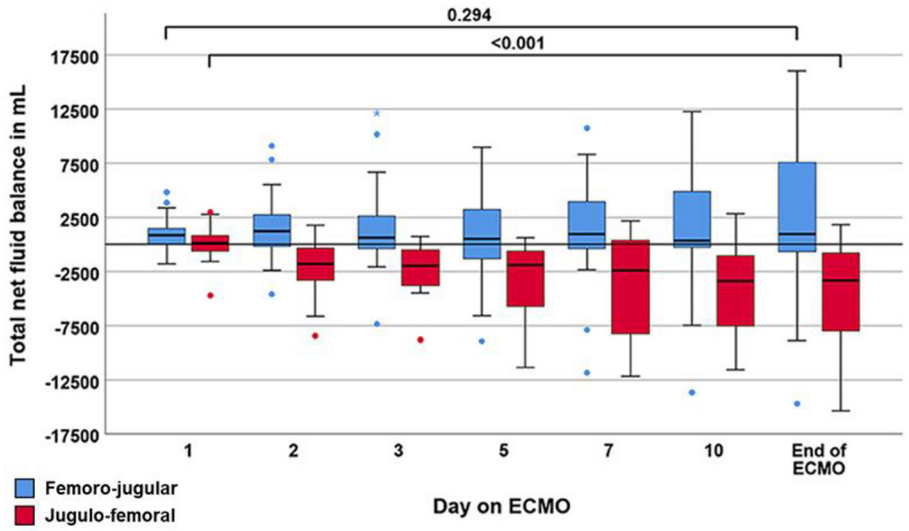

FIGURE 3
Boxplot showing the trajectory of net fluid balance during the course of extracorporeal membrane oxygenation (ECMO). Data are expressed as median, minimum, maximum, 25th percentile, and 75th percentile. Circles and stars represent outliers with more than one and a half times or more than three times the length of the box from either end of the box.

more obvious problem than with jugulo-femoral configuration and thus might explain the differences in fluid states. Similar to a recent retrospective study in 27 patients (25), the results of the current study pointed in the same directions, however, due to differences between the groups in patients' characteristics and ECMO management, e.g., timing of ECMO therapy during course of disease or hemodynamic impairment prior to cannulation, these results have to be considered with caution. However, in a computational fluid dynamic model, the recirculation fraction was very constant across different volume states (22).

This finding of easier and faster accomplishment of negative fluid balance using jugulo-femoral configuration, is hypothesis generating and needs further investigation set in the context of the impact of fluid overload and risk of increased mortality (26, 27).

Limitations

This prospective non-randomized bi-centric study has several limitations restricting the generalizability of its results. The study design was non-randomized and did therefore not account for any possible differences in baseline characteristics, such as requirement of norepinephrine or the number of days on mechanical ventilation before ECMO, which might have particularly affected fluid management. In addition, patients from a previous study at the ECMO Center Karolinska were considered eligible for the Stockholm cohort. The study was conducted by staff with considerable expertise and experience in the use of ECMO, but the general clinical guidelines regarding the care of critically ill patients in the two study centers were neither harmonized nor scrutinized by the study supervisors prior to commencing the study. This may especially be true for the management of volume status. Changes in intrathoracic pressure and venous return due to spontaneous breathing effort may have affected R*f*. The used cannula brands and designs differed between the two centers. ECMO flows >5 l/min were rarely applied. Future studies on R*f* should assess the effect of prone position, intrathoracic and intraabdominal pressures. Patients with femoro-femoral configuration were not evaluated.

Conclusions

VV ECMO with the femoro-jugular configuration results in less recirculation and thus provides equally effective ECMO support as VV ECMO with the jugulo-femoral configuration but at a lower Q_{EC}. Risk factors for higher R*f* were shorter distance between the two cannula tips, higher ECMO flow, and lower heart rate. R*f* did not affect hemolysis. Further studies on the impact of recirculation during VV ECMO are warranted that should include other configurations such as bi-femoral and dual-lumen cannulation.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the local institutional Ethics Committees (Ethical review number: Stockholm: 2014/945-31; Regensburg: 17-737-101). The patients/participants provided their written informed consent to participate in this study.

Author contributions

LB was responsible for the study design and the conception. CF and TM co-designed the concept. LB, CF, and TM were responsible for the hypothesis, delineation, the design of the study as well as for the acquisition of data, the analysis and interpretation of this information, for writing the article, and its revision prior to submission. LB, OP, MS, and CF were responsible for drafting the manuscript were involved in the acquisition of data, the analysis and interpretation of this information, and the critical revision of the article prior to submission. MP, MF, AP, MM, ML, and TM were involved in the acquisition of data, the analysis and interpretation of results, and the critical revision of the article prior to submission. LB and CF are the guarantor of the content of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

MM and LB are advisory board members of the Eurosets Srl., Medolla, Italy. LB is an advisory board member of the Xenios AG, Heilbronn, Germany.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.973240/full#supplementary-material

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Case report: Total percutaneous post-closure of femoral arterial access sites after veno-arterial extracorporeal membrane oxygenation

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Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) which is a form of circulatory and gas exchange support. Following VA-ECMO, total percutaneous closure of the site of femoral arterial puncture with perclose Proglide (PP) has become widespread, enhancing patient comfort and lessening the incidence of wound infections and lymphatic fistulas in a short closure time. The preclose technique with perclose Proglide provides numerous benefits, however, it prolongs extra time during the VA-ECMO procedure, adds additional post-operative care to workloads, and increases the potential for Proglide stitch infection. The modified technique-percutaneous post-closure, described here by a case of a 65-year-old man with heart attack who underwent VA-ECMO, is a simple, rapidly applied technique to wean VA-ECMO also suitable for emergency cannulation. The patient was administered mechanically ventilated and sedated and the femoral artery access site and evaluated by ultrasound for precise positioning, then the VA-ECMO arterial cannula was withdrawn, and a 0.035-in guidewire was left in the artery. The first set of sutures was deployed after the Proglide device was inserted over the guidewire. The second sutures were then replaced in the same way but at a different angle. After hemostasis was achieved, the guidewire was removed, and additional manual compression was used to control any residual blood seeping. No hematoma, pseudoaneurysm, major bleeding, minor bleeding, acute arterial thrombosis, arteriovenous fistula, groin infection, lymphocele, or arterial dissection and stenosis occurred during the periprocedural period or during the 30-day post-procedural follow-up. In conclusion, the standardized algorithm we established, total percutaneous post-closure of femoral arteriotomies utilizing Perclose ProGlide device is feasible and safe with a low incidence of access site complications.

KEYWORDS

Perclose Proglide, arteriotomies, VA-ECMO, suture-mediated closure device, integrated algorithm

Introduction

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) may be of benefit as salvage therapy in select patients who continue to have unstable circulatory and profound gas-exchange abnormalities, which provided encouraging outcomes regarding the efficacy and economic assessment of this strategy (1–3). In general, the common size sheath of 14–20 F is used for ECMO insertion, hemostatic stitches or prolonged manual compression can be used to achieve arteriotomy hemostasis, while large arteriotomy wounds require surgical vascular repair as a standard weaning strategy. As vascular complications following decannulation, to improve patient outcomes after percutaneous decannulation, cannula removal techniques, particularly a standardized procedural technique with a suitable closure device are essential. The ProGlide (4) (Abbott Vascular Inc., Redwood, California) is a suture-based closure device that deploys a suture on either side of the arterial wall at the arteriotomy site, mimicking open surgical closure, designed to access created by large-bore catheters, stopping the blood flow. Since it is a mechanical closure, there are theoretically no limitations to re-access or the administration of antiplatelet and anticoagulant. The ProGlide can track over a standard 0.035-inch (or smaller) wire and accommodate 5- to 21-Fr. arteriotomies, but with a larger than 8-Fr. sheath, at least two devices are required to close the arteriotomy. Therefore, the device facilitates various vascular interventions and the Proglide deployed prior to the insertion of the large bore devices is often referred as "Perclose technique." The preclose technique with perclose Proglide (PP) allows for rapid arteriotomy closure after percutaneous interventions as it is used immediately once the procedure has concluded. They allow early ambulation and discharge after groin puncture and mitigate patient discomfort from extended manual compression (5, 6). Proglide-assisted closure devices in preclosure have been popular proposed and applied to VA-ECMO decannulation (6–9), which minimize invasiveness, shorten procedure time, release post-operative pain, and decrease the risk of wound complications. However, despite the obvious benefits, they have not gained universal adoption among interventionalists, as it prolongs extra time during the VA-ECMO procedure, adds additional post-operative care to workloads, and increases the potential for ProGlide stitch infection. Primarily based on shortcomings or defects, the modified technique has been proposed—percutaneous post-closure. We described a case of percutaneous post-closure for VA-ECMO decannulation, which revealed this technique under the evaluation of ultrasound safely and successfully closed arterial ECMO decannulation sites after arteriotomy wound closure with improved accuracy.

Case description

A 65-year-old man with a myocardial infarction leading to cardiac arrest who underwent VA-ECMO and intra-aortic balloon pumping was deployed bedside percutaneous decannulation by Perclose ProGlide (Abbott Vascular Inc., USA) at the arteriotomy site. The patient was sedated and mechanically ventilated, and local anesthesia was administered at the femoral artery access site. The following steps detail the implementation sequence to close the arteriotomy of VA-ECMO decannulation using two Perclose ProGlide devices.

Preparation phase

Pre-operative imaging should be closely scrutinized for anatomic information regarding the arterial sheath catheter, common and superficial femoral artery, including its diameter, associated occlusive disease, particularly anterior calcification, and the location of the femoral bifurcation relative to the femoral head and inguinal ligament, record Doppler ultrasonic blood flow signal simultaneously. Therefore, femoral artery ultrasound was estimated (Figure 1a) before catheter decannulation and marked when necessary. Then thoroughly sterile preparation for the cannulation area was in place (Figure 1b).

Procedural description

Above all, the arterial and venous cannulas were instantly clamped at the distal part with four tubing clamp forceps (Maquet, Germany, 20 cm) (Figure 1c) before being cut with a scissor. After direct puncture with seldinger technique (Figure 1d) in the proximal portion of the arterial cannula (Maquet, Germany, 23 cm, 19 F), a 0.035-inch guidewire (Terumo Stiff Wire, Terumo, Japan, 150 cm) was advanced cautiously into to ascending aorta (Figure 1e), the VA-ECMO arterial cannula was withdrawn and removed under manual compression at the access by an assistant (Figure 1f). Subsequently, the first Perclose Proglide was inserted through the guidewire and continued to advance the device until a vigorous pulsating flow of blood was plainly obvious from the marker lumen, placed at about 10–11 o' clock (Figure 1g), then deployed the foot by lifting the lever (marker #1), gently pulled the device back, using the other hand to push on the plunger assembly (as shown in marker #2), disengaged the needles by pulling the plunger assembly back (as shown in marker #3) and dislodged the plunger and needles utterly. Pulled back the plunger until the suture was totally taut, then used the QuickCuts to cut the suture. Pushing the lever (marker #4) down to the main body to return the foot to its premier closed position,

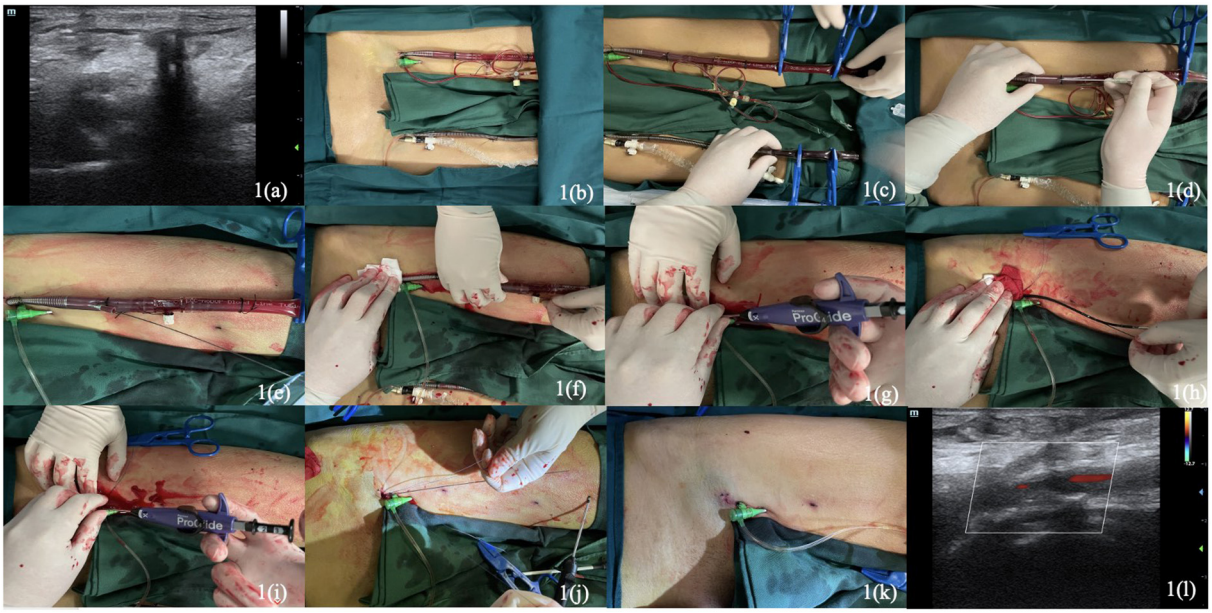

FIGURE 1
Pre-operative ultrasound images **(a)**. Sterile preparation of the operative area **(b)**. The clamping of arterial and venous cannulas at the distal part by four tubing clamp forceps **(c)**. Direct puncture with seldinger technique in the proximal portion of the arterial cannula **(d)**. The insertion of Terumo Stiff guidewire through the cannula **(e)**. Removal of the arterial cannula under manual compression at the access by an assistant **(f)**. Insertion of the first Perclose Proglide and deploying at the direction about 10–11 o' clock **(g)**. Removal of the first Proglide and placement a clamp forcep to hold the two suture limbs together on the right side of the patient **(h)**. Reinsertion of the guidewire to place the second Proglide and deploy at about 1–2 o' clock **(i)**. Wrapping the railed suture limbs tightly around the left index finger to pull it **(j)**. The hemostasis was adequate and cut the suture tails **(k)**. Post-operative ultrasound images with normal blood flow of femoral artery **(l)**.

releasing the suture knot, and continuing to remove the device until the guide wire was visible while holding the two suture limbs pull through the distal end of the proximal guide. Placed a clamp forcep instantly to hold the two suture limbs together on the patient's right side. Reinserted the guidewire (Check-Flo Performer, Cook Medical, USA) maintaining an adequate length inside the artery and removed the first ProGlide (Figure 1h). Repeat aforementioned steps with the second ProGlide, which is placed at about 1–2 o' clock (Figure 1i) toward the patient's left side, and the other clamped suture were placed on the left side. Advanced the guidewire into the artery and irrigated the sutures with heparinized saline. Removed the clamp from the first suture, applied manual pressure proximal to the puncture site and wrapped the railed suture limb tightly around the left index finger to pull it (Figure 1j). Removed the clamp from the second suture and advance the knot using the same technique while ensuring guidewire access. The bleeding was controlled, and the hemostasis was adequate, ultimately cutting the suture tails below the surface of the skin (Figure 1k).

After completing the procedure, we assessed the incision by ultrasound, the blood flow of femoral arterial signals was well-filled with no abnormal signals outside the blood vessels (Figure 1l). Manual compression was continued for at least 5 min, and the puncture site was covered with a pressure bandage for 12 h. Another Doppler ultrasound control was performed 3 days later to exclude hematoma, arteriovenous fistula, or pseudoaneurysm after release of the pressure bandage and estimated again 1 month later. The double Proglide-assisted post-closure technique was successful with adequate hemostasis without extra endovascular or surgical procedures to prevent vessel blood leaking. The hemostatic good control with no sign of access-related complications and other adverse events, such as massive bleeding, acute limb ischemia, lymphocele, groin infection, vessel dissection, occlusion, any stenosis or arterial thrombosis during the periprocedural period, defined as arterial closure within 48 h and 30-day follow-up. More detailed clinical relative information, data, and parameters can be achieved from medical record review during ECMO-inserted.

Discussion

Veno-arterial extracorporeal membrane oxygenation has emerged as the preferred treatment option for patients suffering from cardiogenic shock or cardiac arrest. Regarding ECMO weaning, diverse strategies have been described for achieving hemostasis from cannula removal. Simple manual compression is effective in small puncture sites (4–8 F) in the majority

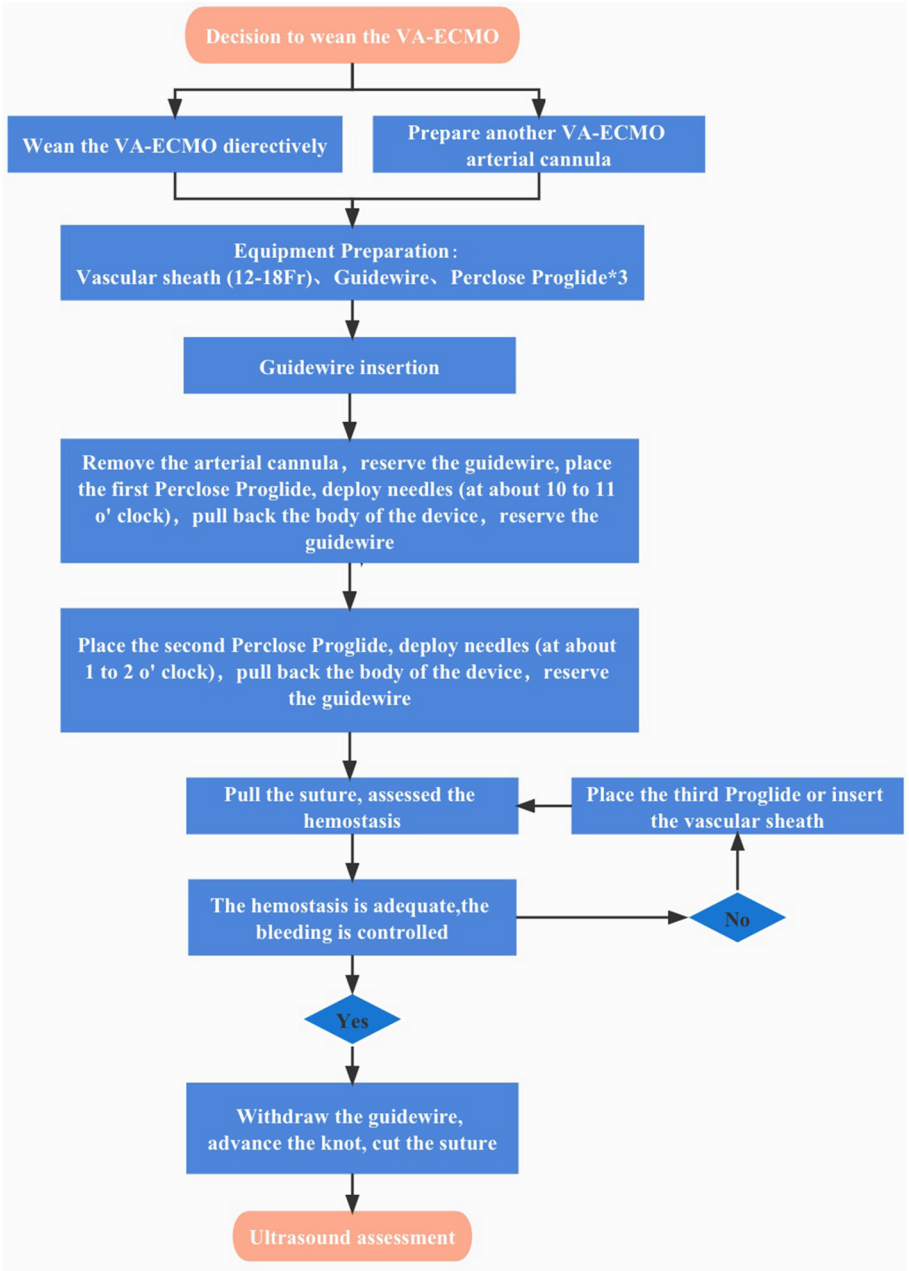

FIGURE 2
Algorithm of total percutaneous post-closure of femoral arterial access sites after Veno-arterial Extracorporeal Membrane Oxygenation.

of cases. The advent of percutaneous technique, especially the Perclose Proglide, the most common vascular closure device, decreased the morbidity of the procedure, minimized the need for compression, address patient complaints, and significantly shortened the bedrest period even further. A prospective randomized study looking at the Perclose Proglide device compared with manual compression showed that there was shorter time to hemostasis, ambulation, and discharge with suture mediated closure, with no difference in overall complication rate between the two treatment groups (10). Practitioners have used the ProGlide device to close much larger puncture sites by placing two Proglide devices through a single puncture site, thus allowing a totally percutaneous method to wean VA-ECMO, which is referred as standard "preclose technique." This technique has been verified to be a convenient, safe, and effective procedure for repairing

arteriotomy sites in quite a bit of procedures (11), including endovascular aortic repair (EVAR) and other percutaneous treatments. These devices may increase the risk of groin infection and leg ischemia but decrease the time needed to achieve hemostasis (4).

Revolutionary precepts using Proglide-assisted closure devices in preclosure have been popular proposed and applied to VA-ECMO decannulation (6, 7). Total percutaneous suture arteriotomy wounds minimize invasiveness compared with femoral cutdown access repair. A most recent single-center study using Perclose ProGlide suture-mediated system with preclose technique shows satisfactory successful closure rates with fewer limb complications and bleeding events and a reduction in total operative time without increasing hospital stay length (5). While we propose that potential defects are the following: (1) Preclose technique increases operational complexity and likelihood of error during VA-ECMO implantation of cannulation and prolongs the whole operating time, which means operators should be adequately strictly trained. There is a learning curve with this device, despite the high technical success rates observed in recent series; (2) Pre-operative imaging for anatomic information must be scrutinized, and small access vessel diameter and anterior wall calcification will become factors of failure, which undoubtedly infeasible in emergency rescue; (3) the Proglide system stitches remain in the large arteriotomy access which may be more vulnerable to infection in the prolonged time, considering the uncertain duration of extracorporeal therapy; (4) the Proglide suture adds extra post-operative care burden of medical staff, tearing, injury, dissection of vessels may occur during repeated care operations. Given several reasons mentioned above, we put forward the innovative techniques and protocols in post-closure technique applying to VA-ECMO decannulation (Figure 2). Some experts are hesitant to the effectiveness and safety reliability of post-closure of large-bore arterial access, it has been suggested that post-closure may increase technical difficulties during VA-ECMO decannulation procedure and be prone to excessive blood loss (6). We further modified this protocol inserting the guidewire by a direct puncture technique without cutting down the arterial catheter. In this case, we successfully wean the VA-ECMO and decannulate the arterial catheter *via* post-closure technique within 10 min coordinated by two experienced vascular surgeons, under routine use of ultrasound guidance to increase the accuracy of arterial access which achieved a shorter procedure time, less post-operative pain, and a lowered risk of wound complications.

The decision to use a closure device on a given access site should be individualized to the patient's anatomy, clinical circumstances, and likelihood of benefit. For a safe and successful decannulation of ECMO catheter, it is critical that high-risk vessels be identified on either pre-operative imaging or initial angiography. Therefore, this may prompt earlier anticoagulation, use of protection devices, or use of smaller catheters and sheaths to prevent adverse outcomes. Moreover, manual compression is commonly held between 5 and 20 min after percutaneous closure device depending on the extent of anticoagulation, the puncture size, and the patient's blood pressure to make sure adequate hemostasis. Overall, this complete percutaneous post-closure perspective of arteriotomies provides an effective, safe, and simple practice for the management of patients facilitating VA-ECMO decannulation even in patients with poor vascular conditions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of The Second Affiliated Hospital of Zhejiang University, School of College. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LT gleaned the patient's detailed information, took the relevant pictures, and compoesd the manuscript. ZJL performed the surgical procedures. NDZ and XX underwent data curation and validation. ZJL reviewed and edited the original draft. All authors contributed to the article and the final manuscript was approved by all of them.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: AngioJet thrombectomy with extracorporeal membrane oxygenation support for acute massive pulmonary embolism in a severe multiple trauma patient

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Acute massive pulmonary embolism (PE) is one of the main leading causes of high cardiovascular mortality, and the prognosis strongly varies, depending on the severity of pulmonary arterial obstruction and its impact on the RV function. Alternative therapy approaches comprise systemic thrombolysis, catheter-directed thrombolysis, catheter embolectomy, catheter-assisted fragmentation techniques, and surgical thrombectomy. The following case study explores a 72-year-old man with severe multiple trauma who suffered from a sudden massive pulmonary embolism and presented with an unstable hemodynamic status. Extracorporeal membrane oxygenation (ECMO) has amply proven its efficacy in supplying cardiopulmonary assistance for this patient shocked by a massive PE with contraindication for thrombolysis. AngioJet catheter embolectomy and ECMO were performed, which finally cleared the massive pulmonary embolism away and improved the patient's hemodynamic status. The use of ECMO was continued during the weaning program, on the fifth day after ECMO decannulation, the patient was extubated and transferred to a local hospital for further recuperation. This case highlights that the AngioJet thrombectomy with the combination use of ECMO may be a potential choice of treatment for unstable PE patients.

KEYWORDS

acute pulmonary embolism, AngioJet thrombectomy system, catheter-assisted embolectomy, fragmentation techniques, ECMO

Introduction

Acute pulmonary embolism (PE) is a partial or complete occlusion of the pulmonary arteries, with hemodynamic consequences determined by the size and location of the embolus, preexisting cardiopulmonary disease, and the severity of ventilation and oxygenation compromise. Annual PE incidence rates range from 39 to 115 per 100,000 population, steadily increasing over the past decades, notwithstanding, both PE-related in-hospital death rates and age-standardized mortality from PE have been dwindling or stagnating in recent years (1). The physical pulmonary arterial obstruction raises pulmonary vascular resistance and right ventricular (RV) afterload, ultimately causing RV failure with a subsequent life-threatening reduction in coronary perfusion and cardiac output. Clinical presentation can manifest as asymptomatic to catastrophic and symptoms are determined by the embolic burden as well as the severity of any accompanying cardiopulmonary disease (2). The standard treatment is systemic anticoagulation, but in the case of high or intermediate-risk PE, treatment can be escalated. Systemic thrombolysis, surgical thrombectomy, and catheter-directed interventions (CDIs) drive experts' attention, and are ready for primetime. Patient selection criteria, hemodynamic conditions, and clinical outcomes are considered to resolve the indications and benefits of invasive interventions. As new technology evolves, up to now, CDIs vary and can be utilized with or without thrombolysis. More specifically, for patients who have absolute contraindications to thrombolysis, this approach with no lytic agents, consisting of thrombus fragmentation and/or aspiration techniques, is properly fitting (3, 4). For patients with fatal bleeding risks such as recent surgical procedures, intracranial hemorrhage, and other contraindications to thrombolysis, anticoagulation, or surgical thrombectomy; the treatment options are of controversial complexity. The AngioJet rheolytic thrombectomy (ART) system provides pharmacomechanical thrombolysis and has been previously attempted for PE, with promising clinical outcomes despite several adverse events reported (5–8). Nowadays, transportable extracorporeal membrane oxygenation (ECMO) assistance systems with percutaneous femoral cannulation may become effective in extreme circumstances, maintaining circulation and oxygenation. It retrieves the sharply failing right heart as well, implementing adequate hemodynamic and respiratory support for patients who experience massive PE until the initial pulmonary conditions are recovered. It has been increasingly used for patients with unstable PE who are not responding to other therapeutic approaches, or as catheter-based or surgical embolectomy media (9). Throughout this case study, we encountered challenges with the catastrophic pulmonary and cardiogenic collapse in a multiple trauma patient, who underwent the AngioJet thrombectomy stabilized by an ECMO system and successfully survived.

Case description

In September 2021, a 72-year-old male falling from a height of 3 m with multiple trauma (right temporal subdural hematoma, subarachnoid hemorrhage, right frontal brain contusion, left temporal bone fracture, left clavicle and left 1–11 ribs, right 1st rib fracture, and hemopneumothorax) and a history of long-term smoking. The patient became progressively short of breath during the local hospitalization, developed wheezing with dyspnea, his oxygenation decreased and consciousness suddenly changed, consequently, he underwent tracheal intubation and ventilator-assisted ventilation. While transferring to our emergency room for further life-saving treatment, his condition aggravated with unstable vital signs. His subsequent examination revealed a large bilateral PE, especially the bifurcation of the main pulmonary artery, the posterior basal segment of the dorsal segment of the right inferior pulmonary artery, and the posterior and external basal segment of the left upper pulmonary artery by computerized tomography pulmonary arterial angiography (CTPA) (Figure 1A). Pervasive deep thrombosis was also visible in the bilateral posterior tibial and calf intermuscular veins by ultrasound Doppler. Electrocardiography (ECG) showed sinus rhythm and atrial premature beat. The arterial blood gas analysis indicated that blood PH of 7.14, blood base excess of −8.50 mmol/L, lactic acid of 20.00 mmol/L, oxygen tension of 379.70 mmHg, carbon dioxide tension of 59.40 mmHg, and potassium of 5.80 mmol/L. Echocardiography showed right-sided heart enlargement and pulmonary hypertension (Table 1). Therewith, the patient experienced severe cardiopulmonary decompensation and sudden cardiac arrest. Following academic discussion, the multidisciplinary team of specialists determined that bleeding risk and other comprehensive elements contributed to the patient's contraindication for systemic thrombolysis or surgical embolectomy. They reached a consensus that AngioJet catheter thrombectomy of the massive PE integrated with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) supports might be a better option. Following the transition of VA-ECMO at 2.9∼3.1 L per minute *via* left femoral and right internal jugular vein to left femoral artery, the patient's hemodynamic indicators ameliorated exacerbation. An AngioJet thrombectomy system—Solent® Omni was used to perform mechanical aspiration thrombectomy on the patient's right pulmonary thrombus. The pulmonary angiograms revealed discontinuities in the trunk of the left main pulmonary artery, with a marginal change in left lower lobe perfusion. The embolus catheter was inserted in the right pulmonary artery and continued to suction for 100 s, then a repeated pulmonary

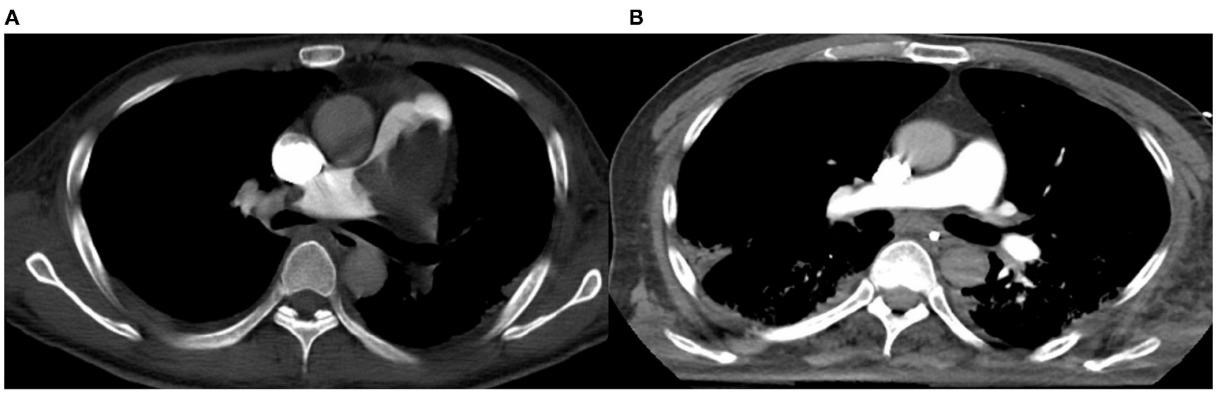

FIGURE 1
(A) Computed tomography pulmonary angiography (CTPA) demonstrates pulmonary embolism (PE). **(B)** Computed tomography pulmonary angiography (CTPA) demonstrates that residual thrombus markedly improved.

TABLE 1 The echocardiographic findings and laboratory results before and after the AngioJet procedure.

	Echocardiographic findings				Laboratory results		
	PA pressure	RV size (ventricular diameter)	Function TAPSE	RV/LV ratio	Pro-BNP	Troponin	Hemoglobin
Before AngioJet	56 mmHg	4.5 cm	2.30 cm	1.4	417 pg/ml	0.016 ng/ml	138 g/L
After AngioJet	44 mmHg	4.9 cm	2.10 cm	1.2	756 pg/ml	0.067 ng/ml	121 g/L

angiogram demonstrated a substantially improved blood flow to the right lung (Figures 2A–C). At this time, the intraoperative echocardiogram demonstrated no dyskinesia of the myocardial wall with otherwise normal function and an ejection fraction of ∼65%. The patient was transferred back to the intensive care ward, and the nurse constantly monitored the ECMO settings and circuit. Upon closer inspection, there were no severe adverse events, nor were there any complications related to the procedure, the patient hemodynamic parameters were stable, and hypoxia was resolute. Furthermore, the reversal of RV failure and pulmonary artery hypertension was assessed using echocardiography after 48 h. Following this initial week, CTPA was repeated to evaluate the residual thrombus, which was markedly improved (Figure 1B). The VA-ECMO was weaned on the fifth day and the patient was transferred to the local hospital for further recuperation. The echocardiography was performed at 4-weeks postoperatively which proved the pulmonary artery hypertension and the reversal of RV failure were in good condition.

Discussion

Massive pulmonary embolism constantly foreshows a fatal outcome, with a mortality rate ranging from 30 to 50% (9). Hemodynamic status is considered a crucial short-term predictive factor for patients with acute PE, according to Antithrombotic Therapy for VTE Disease CHEST Guideline and Expert Panel Report 2016, scholars are of the opinion that for patients at high risk who require immediate reperfusion therapies, mechanical methods can be used alone when thrombus removal is indicated but thrombolytic therapy is contraindicated due to a high-risk of bleeding (10). Thus, emergent revascularization and systemic thrombolysis might be the first alternative for patients with unstable hemodynamics. Multiple technical options targeting rapid clot debulking for unstable patients have been reported in various combinations, particularly when lytics are contraindicated. The AngioJet System creates a local low-pressure zone to entrain, fragment, and aspirate thrombi *via* Bernoulli's principle of fluid dynamics. The largest and latest 7-year single-center study on AngioJet rheolytic thrombectomy in patients with PE revealed that for patients with PE who have various comorbidities and a proclivity to bleed, ART may be considered preferable, resulting in significant improvements in obstructive burden and hemodynamics (8). ART mentioned in most cases or articles (8, 11), instead of using the pulse spray technique and t-PA assisted in increasing the surface area of thrombus to enhance the effectiveness of lytic agents, we chose thrombus fragmentation and aspiration techniques with no lytic agents for this patient who had absolute contraindications to thrombolysis. In addition, some patients who underwent catheter rheolytic thrombectomy died from cardiogenic shock. The patient has to be hemodynamically stable for an extended period of time, allowing for a significant reduction of the thrombus load so as to the rheolytic thrombectomy to be efficacious. Therefore, for patients with PE in unstable status, ECMO can quickly attenuate

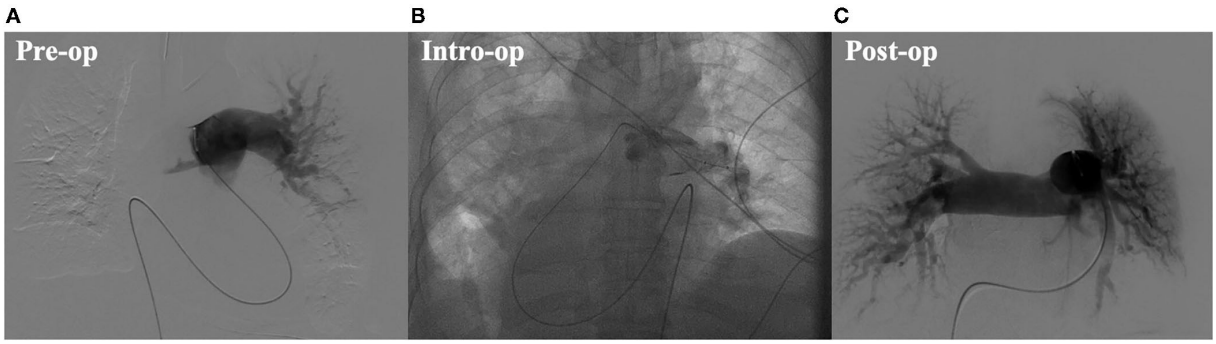

FIGURE 2
(A) Preoperative digital substraction angiography (DSA) image. **(B)** Intro-operative digital substraction angiography (DSA) image. **(C)** Postoperative digital substraction angiography (DSA) image.

hemodynamic collapse and facilitate treatment over several days better than cardiopulmonary bypass and surgical embolectomy.

Patients with massive PE present in extremes and who are too unstable to successfully undergo CDI, with the help of ECMO, can be resuscitated and supported until thrombus removal occurs by using other catheter-directed interventions. With VA-ECMO, venous blood is drained into the inferior vena cava *via* a cannula inserted through the femoral vein, and oxygenated blood is reinfused *via* a cannula inserted through the femoral artery into the thoracic descending aorta. Recently, VA-ECMO has been performed successfully to treat patients suffering from massive PE, some of whom have reported excellent short-term outcomes (12). The prognosis of acute PE strongly varies, many times, physicians will face dilemmas as to what approach will best balance the benefits of surgical invasions against potential risks of cardiopulmonary failure or death. For the treatment of massive PE in this patient with unstable hemodynamic status, considering bleeding risk and contraindications for thrombolysis or surgical embolectomy, catheter embolectomy under the protection of ECMO should be considered as a first-line treatment in the appropriate clinical setting, as a way to provide the benefits and minimize adverse events. As the renovation of novel interventional devices and technology advances, we should underscore the requirement for an integrative multidisciplinary approach flexible enough to evaluate and utilize; the supplement of ECMO combined with the AngioJet catheter thrombectomy may be a good choice of treatment in massive PE. Despite the publication of several case reports, further research, specifically randomized controlled trials, are necessary to confirm its efficacy and safety to become sufficient robust evidence.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University, School of Medicine. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LT collected the patient's information and wrote the manuscript. ZL and LZ performed the surgical procedures. LZ, NZ, XX, and YX underwent data curation and validation. ZL and MH reviewed and edited the original draft. The article was contributed by all of the authors and the final manuscript was approved by all of them.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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