ADVANCES IN EXTRACORPOREAL LIFE SUPPORT IN CRITICALLY ILL PATIENTS

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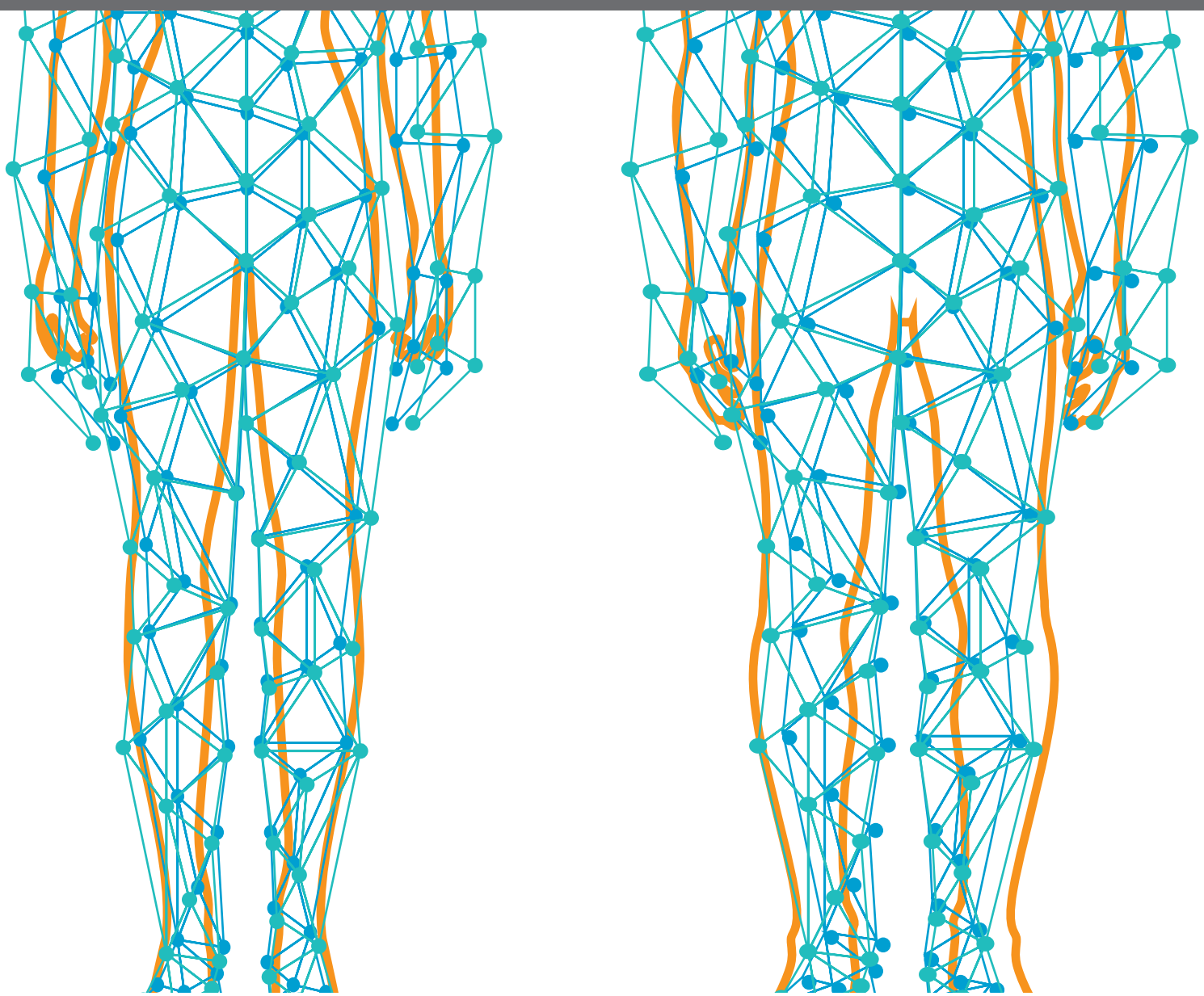

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ADVANCES IN EXTRACORPOREAL LIFE SUPPORT IN CRITICALLY ILL PATIENTS

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Neurological Complications of Veno-Arterial Extracorporeal Membrane Oxygenation: A Retrospective Case-Control Study

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Background: To explore the epidemiology, clinical features, risk indicators, and long-term outcomes of neurological complications caused by veno-arterial extracorporeal membrane oxygenation (V-A ECMO).

Methods: We retrospectively analyzed 60 adult patients who underwent V-A ECMO support in our unit from February 2012 to August 2020. These patients were separated into the neurological complications group (NC group) and the non-neurological complications group (nNC group). The differences in basic data and ECMO data between the two groups were compared. The data of long-term neurological prognosis were collected by telephone follow-up.

Results: Thirty-nine patients (65.0%) had neurological complications. There were significant differences between the two groups in terms of median age, hypertension, median blood urea nitrogen, median troponin I (TNI), median lactic acid, pre-ECMO percutaneous coronary intervention, continuous renal replacement therapy (CRRT), median Sequential Organ Failure Assessment score, median Acute Physiology and Chronic Health Evaluation II score, median peak inspiratory pressure, median positive end expiratory pressure, and median fresh frozen plasma ($P < 0.05$). The median Intensive Care Unit length of stay (ICU LOS), 28-day mortality, median post-ECMO vasoactive inotropic score, non-pulsate perfusion (NP), and median ECMO duration of the NC group were significantly higher than those of the nNC group ($P < 0.05$). Furthermore, multiple logistic regression analysis revealed that TNI ($P = 0.043$), CRRT ($P = 0.047$), and continuous NP > 12 h ($P = 0.043$) were independent risk indicators for neurological complications in patients undergoing ECMO. Forty-four patients (73.3%) survived after discharge, and 38 patients (63.3%) had Cerebral Performance Category score of 1–2. And there were significant differences between the two groups in long-term neurological outcomes after discharge for 6 months ($P < 0.05$).

Conclusion: The incidence of neurological complications was higher in patients undergoing V-A ECMO and was closely related to adverse outcomes (including ICU LOS and 28-day mortality). TNI, CRRT, and continuous NP > 12 h were independent risk

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indicators for predicting neurological complications in ECMO supporting patients. And the neurological complications of patients during ECMO support had significant adverse effect on long-term surviving and neurological outcomes of patients after discharge for 6 months.

Keywords: V-A ECMO, neurological complications, retrospective study, risk indicators, long-term outcomes

INTRODUCTION

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) can replace the roles of the heart and lungs to maintain circulation and respiration and is used to treat acute cardiac or pulmonary failure. However, ECMO support can cause various complications due to the severity of the diseases and longstanding extracorporeal circulation, which may negatively impact patients' survival (1, 2).

The Extracorporeal Life Support Organization (ELSO) registry reported that survival after ECMO had reached to 58% from 1989 (3). Mortality and poor functional outcomes are often induced by neurological injury that results not only from underlying diseases but also from complications associated with ECMO support itself (4, 5). With ECMO being widely used, multiple studies on ECMO have focused on neurological complications, including cognitive dysfunction, hypoxic-ischemic encephalopathy, and even cerebral ischemic stroke and cerebral hemorrhage (6–8). However, a large knowledge gap exists in our understanding and treatment of ECMO-related neurological complications. The data about epidemiology, pathophysiology, and risk indicators of neurological complications is limited, meanwhile, no practice guidelines or management strategies for the neurological care of ECMO patients (9, 10).

Through retrospectively analyzing patients with V-A ECMO support in our unit, we aimed to investigate the epidemiology, clinical features, and risk indicators of neurological complications caused by V-A ECMO supporting.

METHODS

Study Design and Participants

We collected data on all in-hospital and out-of-hospital adult (>18 years old) patients who received V-A ECMO support at the Department of Critical Care Medicine, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, from February 2012 to August 2020. The inclusion and exclusion criteria were determined based upon current reports and the clinical experience of our unit.

Inclusion criteria:

(1) Time nodes: Process of ECMO support, and after weaning from ECMO.
(2) Types of neurologic complications: Short-term or persistent mental and organic diseases observed after stopping sedative for 48 h, including coma, delirium, depression, epilepsy, hypoxic ischemic encephalopathy, ischemic stroke, hemorrhagic stroke and death, that were identified by the Glasgow Coma Scale (GCS < 15, patients with endotracheal intubation < 11), the Cerebral Performance Category (CPC score > 2), the confusion assessment method for the ICU (CAM-ICU), and the neuroimaging examination.

Exclusion criteria

(1) Acute primary craniocerebral injury before admission, or previous neuropsychic symptoms.
(2) Incomplete and missing cases.
(3) Duration of ECMO support < 24 h.

Data Collection

(1) Baseline characteristics: Age; sex; underlying diseases, including hypertension, diabetes, and coronary heart disease (CHD); etiology supporting the use of ECMO; hemodynamic data such as mean arterial pressure (MAP) and Central Venous Pressure (CVP); biochemical indexes (blood gas analysis, blood biochemistry, coagulation function, blood routine) 24 h post-ECMO support; assessment of severity after ECMO support for 24 h, including Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, Sequential Organ Failure Assessment (SOFA) score; and other interventions, including percutaneous coronary intervention (PCI), intra-aortic balloon pump (IABP), mechanical ventilation (MV), and continuous renal replacement therapy (CRRT).
(2) ECMO-related characteristics: Location of ECMO, duration of building ECMO, vasoactive inotropic score [VIS = 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)], duration of non-pulsatile perfusion (NP) after ECMO support, ECMO duration, mechanical ventilation parameters, complications, dosage of blood product [red blood cell (RBC) and fresh frozen plasma (FFP)], and weaning from ECMO
(3) Outcome indicators: Intensive Care Unit (ICU) length of stay (LOS), hospital LOS, 28-day mortality, incidence of neuropathy and mortality after discharge.
(4) Data processing: The epidemiology, clinical features, and related risk indicators connected with the identified neurological complications are discussed through the analysis of the above data.

Extracorporeal Life Support Technology

All patients used the ROTAFLOW centrifugal pump and piping system produced by MAQUET, Germany, and all modes of connection were V-A ECMO. Furthermore, all patients received a peripherally inserted catheter into the femoral artery and femoral vein under ultrasound guidance. The left heart function of ECMO-assisted patients was evaluated via cardiac ultrasound and the circulatory state. An IABP was implemented when

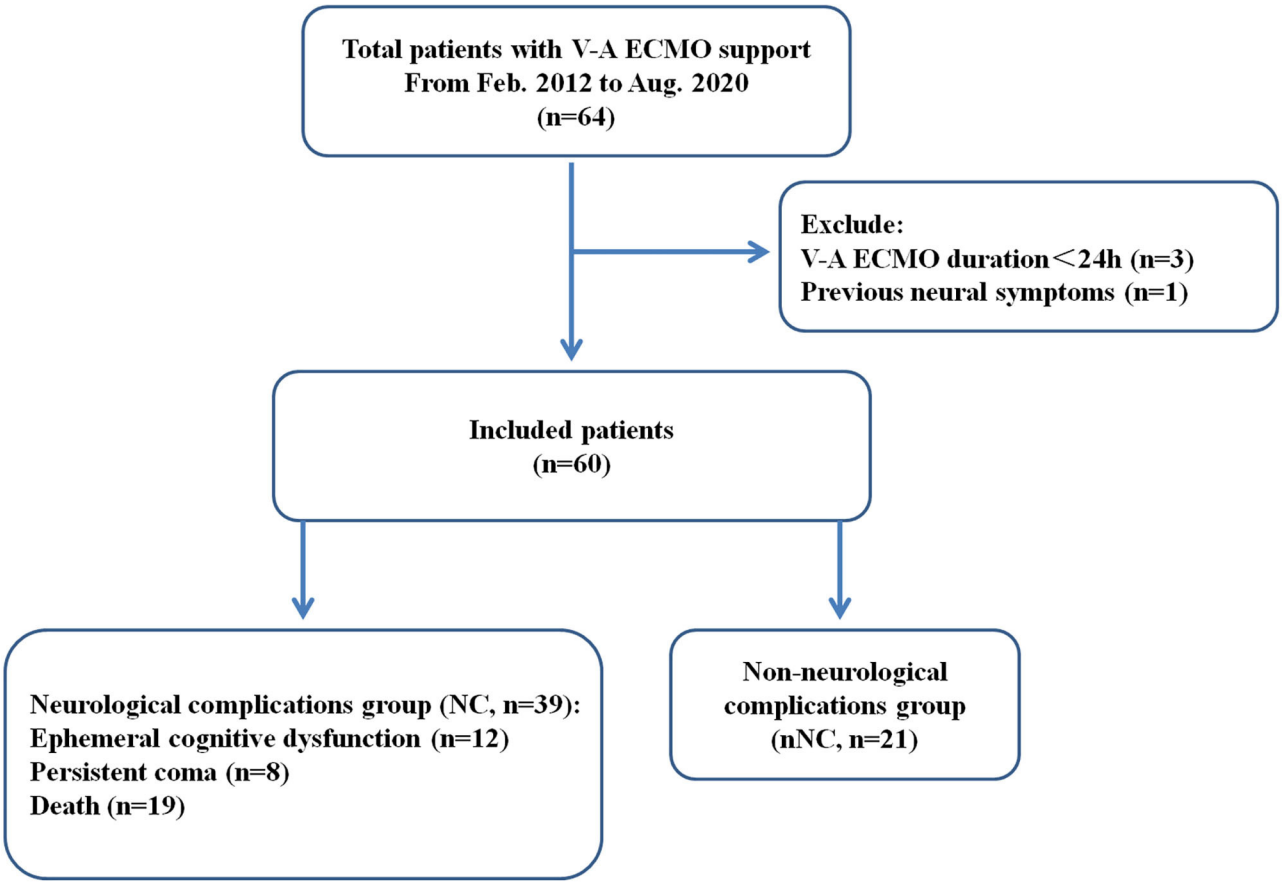

FIGURE 1 | Flow chart of patient cohorts. V-A ECMO, veno-arterial extracorporeal membrane oxygenation; NC, neurological complications group; nNC, non-neurological complications group.

necessary. The application of CRRT depended on renal function, urine volume, and intake and output volume management. All patients received tracheal intubation and mechanical ventilation, and periodical and individualized analgesics-sedatives.

Statistical Analysis

All data were statistically processed using SPSS 25.0 statistical software. Categorical variables and continuous variables are represented as counts (%) and medians [inter quartile range (IQR)]. Chi-square or Fisher's exact test was used for categorical variables, and the student's *t*-test or Mann–Whitney *U* test was used for continuous variables. Multiple logistic regression analysis was used to analyze statistically significant variables to identify independent risk indicators related to neurological complications, which are summarized as odds ratios (OR) and 95% confidence intervals (95%CI). *P*-values < 0.05 were considered statistically significant.

RESULTS

Comparison of Baseline Characteristics of Patients

After excluding four patients, a total of 60 patients with V-A ECMO support were retrospectively screened and assigned to the neurological complications group (NC group) and the non-neurological complications group (nNC group) based on the presence or absence of neurological complications (**Figure 1**). Of these 60 patients, 39 patients (65.0%) suffered neurological complications, including ephemeral cognitive dysfunction ($n = 12$, including brief coma and delirium), persistent coma ($n = 8$, hypoxic-ischemic encephalopathy) and death ($n = 19$) (**Table 1**). The median ages of the patients in the NC and nNC groups were 50 [31, 66] and 30 [24, 35] years old, respectively, with the NC group patients being significantly older than the nNC group patients ($P < 0.01$). But there was not significant statistical difference between the two groups in some pre-ECMO baseline characteristics (**Supplementary Table S2**). In addition, patients were considered to be more likely to develop neurological complications when their etiologies for ECMO support were acute myocardial infarction ($P < 0.001$) and acute fulminant myocarditis ($P < 0.001$), and when the underlying diseases were hypertension ($P = 0.011$) and diabetes ($P = 0.042$). We also found significant differences 24 h post-ECMO support between the NC and nNC groups with respect to the median concentration of blood urea nitrogen (BUN) (8.12 [605, 13.81] vs. 6.43 [4.45, 8.71] mmol/L, $P = 0.012$), median concentration of troponin I (TNI) (16.7 [1.7, 88.8] vs. 5.0 [1.5, 7.5] μg/L, $P = 0.041$), median concentration of

TABLE 1 | Comparison of baseline characteristics of patients.

	All patients	Neurological complications		*P*
	n = 60	Yes (*n* = 39)	No (*n* = 21)	
Age (years)	39 (29, 59.5)	50 (31, 66)	30 (24, 35)	<0.001
Sex, *n* (%)				
Male	36 (60)	26 (66.7)	10 (47.6)	0.176
Female	24 (40)	13 (33.3)	11 (53.4)	
Underlying diseases, *n* (%)				
Hypertension	15 (25)	14 (35.9)	1 (4.8)	0.011
Diabetes	8 (13.3)	8 (20.5)	0 (0)	0.042
CHD	5 (8.3)	5 (12.8)	0 (0)	0.152
Initiate etiology, *n* (%)				
AMI	22 (36.7)	21 (53.8)	1 (4.8)	<0.001
AFM	29 (48.3)	12 (30.8)	17 (81.0)	<0.001
MA	3 (5.0)	2 (5.1)	1 (4.8)	1
CA	29 (48.3)	22 (56.4)	7 (33.3)	0.109
Others	6 (10.0)	4 (10.3)	2 (9.5)	1
24 h post-ECMO				
MAP (mmHg)	79 (72.1, 87.9)	77.7 (71.7, 85.3)	82.3 (73.8, 91.5)	0.059
CVP (cmH_2O)	9 (6, 12)	9.5 (6, 13)	7 (5, 12)	0.371
PH	7.448 (7.409, 7.49)	7.456 (7.409, 7.488)	7.44 (7.408, 7.501)	0.567
PaO_2 (mmHg)	200 (131, 302.9)	193 (129.1, 390.3)	233 (136, 296.1)	0.620
$PaCO_2$ (mmHg)	31.9 (27.5, 34.9)	32.2 (28.3, 35)	31 (23.8, 34)	0.205
$ScvO_2$ (mmHg)	74.5 (66.9, 82.9)	70.9 (66.4, 80.3)	81 (71, 84.7)	0.091
BUN (mmol/L)	7.26 (5.74, 10.14)	8.12 (6.05, 13.81)	6.43 (4.45, 8.71)	0.012
K (mmol/L)	4.31 (4.05, 4.53)	4.32 (4.11, 4.59)	4.29 (4.02, 4.46)	0.426
Cr (μmol/L)	105.5 (84.5, 134)	108 (94, 156)	102 (75, 117.5)	0.083
TBil (μmol/L)	20.1 (13.5, 37.4)	23 (15.1, 37.5)	15.4 (11.2, 26.5)	0.104
GLU (mmol/L)	9.15 (7.32, 10.91)	9.26 (6.69, 10.52)	8.81 (8.38, 11.41)	0.248
Hb (g/L)	94 (77, 117.25)	94 (75, 115)	94 (78.5, 119.5)	0.587
PT (s)	16.3 (14.1, 20.5)	17 (14.3, 21.7)	15.4 (14, 19.7)	0.327
APTT (s)	93.2 (60.8, 141.7)	93.2 (58.5, 134.1)	96.7 (62.3, 157.3)	0.934
TNI (μg/L)	6.71 (1.6, 45.4)	16.7 (1.7, 88.8)	5 (1.5, 7.5)	0.041
LAC (mmol/L)	1.7 (1.2, 2.6)	1.8 (1.3, 3.3)	1.4 (1, 2)	0.03
CRP (mg/L)	61.5 (28.75, 81.75)	67 (32, 92)	52 (18.5, 70)	0.097
PCT (μg/L)	2.59 (0.27, 22.75)	4.28 (0.38, 37.4)	0.69 (0.14, 6.61)	0.052
Pre-ECMO score				
SOFA score	10 (7, 12)	11 (8, 12)	8 (4, 10)	0.004
APACHE- II score	19.5 (12, 25)	22 (18, 31)	12 (6, 16.5)	<0.001
24 h post-ECMO score				
SOFA score	11 (8, 14)	12 (10, 14)	9 (5,10)	<0.001
APACHE- II score	19 (13, 24)	22 (17, 27)	13 (7, 18)	<0.001
Other intervenes, *n* (%)				
Pre-ECMO PCI	7 (11.7)	7 (17.9)	0 (0.0)	0.085
Post-ECMO PCI	12 (20.0)	11 (28.2)	1 (4.8)	0.042
IABP	25 (41.7)	19 (48.7)	6 (28.6)	0.174
Pre-ECMO MV	50 (83.3)	34 (87.2)	16 (76.2)	0.298
Post-ECMO MV	10 (16.7)	5 (12.8)	5 (23.8)	0.298
CRRT	33 (0.55)	27 (69.2)	6 (28.6)	0.003
Outcomes				
ICU LOS (days)	14 (10, 21)	16 (11, 24)	11 (9, 17.5)	0.038
Hospital LOS (days)	19.5 (13, 27)	19 (13, 30)	20 (13, 26.5)	0.981
28-day mortality (%)	20 (33.3)	20 (51.3)	0 (0.0)	<0.001

CHD, coronary heart disease; AMI, acute myocardial infarction; AFM, acute fulminant myocarditis; CA, cardiac arrest; ECMO, extracorporeal membrane oxygenation; MAP, mean arterial pressure; CVP, Central Venous Pressure; $ScvO_2$, Central venous oxygen saturation; PH, Potential of Hydrogen; PaO_2, Arterial oxygen partial pressure; $PaCO_2$, Arterial carbon dioxide partial pressure. BUN, blood urea nitrogen; K, kalium; Cr, creatinine; TBIL, total bilirubin; GLU, glucose; Hb, hemoglobin; PT, prothrombin time; APTT, activated partial thromboplastin time; TNI, troponin I; LAC, lactic acid; CRP, C-reactive protein; PCT, procalcitonin; SOFA, sequential organ failure assessment; APACHE- II, acute physiology and chronic health evaluation II; PCI, percutaneous coronary intervention; IABP, intra-aortic balloon pump; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; LOS, length of stay.

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

	All patients	Neurological complications		*P*
	n=60	Yes (*n*=39)	No (*n*=21)	
ECPR, *n* (%)	29 (48.3)	22 (56.4)	7 (33.3)	0.109
Locations of ECMO, *n* (%)				
OR	7 (11.7)	6 (15.4)	1 (4.8)	0.404
ICU	49 (81.7)	31 (79.5)	18 (85.7)	0.078
ED	4 (6.7)	2 (5.1)	2 (9.5)	0.287
Duration of building ECMO (mins)	53.5 (40, 67.75)	51 (40, 61)	55 (40, 71.5)	0.571
ECMO flow (L/min)				
Initial Flow	3.63 (3.21, 4.18)	3.72 (3.33, 4.15)	3.49 (3.05, 4.35)	0.803
24 h post-ECMO	3.34 (3.00, 3.97)	3.40 (3.00, 4.01)	3.55 (3.00, 3.95)	0.845
48 h post-ECMO	3.48 (3.06, 3.97)	3.44 (3.09, 4.11)	3.55 (2.98, 3.95)	0.607
VIS, mean				
0 h post-ECMO	36 (8.5, 123)	60 (20, 181.1)	15 (4, 57)	0.013
24 h post-ECMO	10 (0, 19.2)	12 (3, 20.8)	3.8 (0, 17.2)	0.094
Continuous NP > 12 h, *n* (%)	15 (25.0)	14 (35.9)	1 (4.8)	0.011
ECMO duration (days)	6 (5, 8)	7 (5, 11)	5 (4, 6)	0.01
MV parameter at 24 h post-ECMO				
FiO_2 (%)	100 (62.5, 100)	90 (70, 100)	100 (50, 100)	0.874
RR (times/min)	12 (12, 16)	12 (12, 15)	12 (12, 17)	0.672
PIP (cmH_2O)	20 (16, 22)	21 (18, 24)	16 (15, 20)	0.003
PEEP (cmH_2O)	8 (7, 10)	10 (8, 10)	7 (5, 8)	0.004
Complication, *n* (%)				
Cannulation site bleeding	42 (70.0)	28 (71.8)	14 (66.7)	0.771
Limb ischemia	6 (10.0)	5 (12.8)	1 (4.8)	0.412
Dosage of blood products				
RBC (U)	4.0 (2.0, 7.0)	4 (2, 6)	3 (0, 9.25)	0.33
FFP (ml)	520 (205, 1035)	660 (250, 1150)	340 (0,925)	0.043
Successful weaning from ECMO, *n* (%)	50 (83.3)	29 (74.4)	21 (100.0)	0.011

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; PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure; RBC, red blood cell; FFP, fresh frozen plasma.

lactic acid (LAC) (1.8 [1.3, 3.3] vs. 1.4 [1.0, 2.0] mmol/L, P = 0.03), SOFA score (12 [10, 14] vs. 9 [5, 10], P < 0.001), and APACHE-II score (22 [17, 27] vs. 13 [7, 18], *P* < 0.001). Meanwhile, the results showed the proportion of patients who underwent PCI after ECMO support (28.2 vs. 4.8%, $P = 0.042$), and the CRRT during ECMO support (69.2 vs. 28.6%, $P = 0.003$) was higher in the NC group than in the nNC group (**Table 1**). Besides, we investigated the ECMO flow, MAP, CVP and blood gas of patients during the phase of pre- and post- ECMO support, and the results did not show significant statistical difference between the groups with and without neurological complications ($P > 0.05$, **Table 2** and **Supplementary Tables S1–2**).

The primary adverse outcome were ICU LOS, hospital LOS, and 28-day mortality. The results showed no significant differences in hospital LOS between the NC and nNC groups. However, we found that the ICU LOS (16 [11, 24] vs. 11 [9, 17.5] days, $P = 0.038$) and the 28-day mortality (51.3% vs. 0, $P < 0.001$) of the NC group were significantly higher than those of the nNC group (**Table 1**).

Comparison of V-A ECMO-Related Characteristics

As shown in **Table 2**, 29 patients (48.3%) underwent extracorporeal cardiopulmonary resuscitation (ECPR), which was not significantly related to the development of neurological complications. The locations of ECMO surgery included the operation room ($n = 7$, 11.7%), ICU ($n = 49$, 81.7%), and emergency department ($n = 4$, 6.7%); the location was not significantly related to the development of neurological complications. However, we found significant differences between the NC and nNC groups with respect to the median VIS (60 [20, 181.1] vs. 15 [4, 57], $P = 0.013$) at the 0h post-ECMO, the median ECMO duration (7 [5, 11] vs. 5 [4, 6] days, $P = 0.01$), and the median FFP dosage (660 [250, 1150] vs. 340 [0, 925] mL, $P = 0.043$) (**Table 2**).

It is worth noting that 15 patients (25.0%) suffered from non-pulsatile perfusion (NP; pulse pressure < 10 mmHg) for more than 12 h after ECMO support, of whom, 14 patients suffered neurological complications, which was significantly higher than control group (35.9 vs. 4.8%, $P = 0.011$). We also investigated

TABLE 3 | Multivariate analysis of neurological complications in V-A ECMO patients.

	OR	95% CI	*P*
TNI	1.038	1.001–1.076	0.043
CRRT	3.884	1.018–14.812	0.047
Continuous NP > 12 h	10.127	1.073–95.564	0.043

TNI, troponin I; CRRT, continuous renal replacement therapy; NP, non-pulsate perfusion.

the mechanical ventilation parameters 24 h post-ECMO, and the results showed that the median peak inspiratory pressure (PIP) (21 [18, 24] vs. 16 [15, 20] cmH_2O, $P = 0.003$) and positive end expiratory pressure (PEEP) (10 [8, 10] vs. 7 [5, 8] cmH_2O, $P = 0.004$) in the NC group were significantly higher than those in the nNC group (**Table 2**).

Multivariate Analysis of Neurological Complications in V-A ECMO Patients

Based on the above bivariate analysis in **Table 1** and **Table 2**, the association were checked in the multivariable model, and after adjustment for age, initiate etiology, SOFA score, and APACHE- II score, the multivariable analysis revealed that the 24 h post-ECMO TNI value (OR, 1.038; 95% CI, 1.001–1.076; $P = 0.043$), CRRT (OR, 3.884; 95% CI, 1.018–14.812; $P = 0.047$), and continuous NP > 12 h (OR, 10.127; 95% CI, 1.073–95.564; $P = 0.043$) were independent risk indicators for predicting the occurrence of neurological complications in V-A ECMO patients (**Table 3**).

Long-Term Follow-Up Outcomes of Survivors After Discharge

As shown in **Table 4**, 44 patients (73.3%) survived 1 month after discharge, with 6 (13.6%) patients had significant neurological damage (CPC score of 3–5). And 4 patients (9.1%) died within one month after discharge because of severe hypoxic ischemic encephalopathy (HIE) or abandoning maintenance treatment. After discharge for 3 and 6 months, 40 (66.7%) and 39 (65%) patients were surviving, with 5.0 and 2.6% of them had significant neurological damage (CPC score of 3–5), respectively. Besides, the main neurological complications at 3 months and 6 months after discharge were Hypomnesia, accounting for 12.5 and 10.3%, respectively. Other neurological complications included HIE, stroke, and peripheral neuropathy (PN) and so on.

A Kaplan–Meier survival analysis further confirmed that the NC group had a significantly poorer 6-month survival than nNC group (HR = 7.900, 95%CI: 1.298∼48.08; $P < 0.05$, **Figure 2**). And the neurological complications of patients during ECMO support had significant adverse effect on long-term neurological outcomes of patients after discharge for 6 months ($P < 0.05$, **Table 5**).

TABLE 4 | Long-term neurological outcomes of survivors after discharge.

	Time after discharge		
	1 month (*n* = 44)	3 months (*n* = 40)	6 months (*n* = 39)
CPC score, *n* (%)			
CPC 1–2	38 (86.4)	38 (95.0)	38 (97.4)
CPC 3–5	6 (13.6)	2 (5.0)	1 (2.6)
Neuropathy, *n* (%)			
HIE	1 (2.3)	1 (2.5)	1 (2.6)
Stroke	1 (2.3)	1 (2.5)	1 (2.6)
Hypomnesia	5 (11.4)	5 (12.5)	4 (10.3)
PN	1 (2.3)	1 (2.5)	1 (2.6)
Others	2 (4.5)	1 (2.5)	1 (2.6)
Death, n (%)	4 (9.1)	1 (2.5)	0 (0.0)

CPC, Cerebral Performance Category; HIE, hypoxic ischemic encephalopathy; PN, peripheral neuropathy.

DISCUSSION

V-A ECMO is a promising rescue therapy for patients with cardiac shock, with or without respiratory failure. Researchers have focused on the neurological complications and adverse outcomes in V-A ECMO supported patients (2, 11, 12). In the present study, we not only evaluated long-term neurological outcomes but also neurological organic lesions and transient psychiatric symptoms during ECMO supporting or within 28 days after. A CPC score of 1–2 was regarded as a good neurological outcome in several of these studies (11, 13). GCS and CAM-ICU were mainly used to recognize short-term neurological complications during the ECMO support. Besides, the transfer of patients with ECMO support between departments inevitably involves high-risk or immediate-threat-of-life situations that have to be dealt with immediately, sometimes within seconds (14). Therefore, the patients were not transferred to the imaging department unless there was a clear indication. In view of this, it is necessary to increase the use of bedside objective indicators, such as craniocerebral ultrasound and bedside Video-electroencephalogram (VEEG), to allow neurological complications to be easily recognized in future. These techniques can identify neurological organic lesions and psychiatric symptoms over time through calculating cerebral blood flow velocity (CBFV) and monitoring brain electrical activity. We will investigate the value of point of care ultrasound (PoCUS) combined with multimodal brain monitoring guided ECMO management in improving the outcomes of patients in future study. Moreover, biomarkers of brain injury (like NSE and S-100β) contribute to the assessment of central nervous system injury (15–17).

Sadhwani et al. described early neurodevelopmental outcomes in children who received ECMO support for cardiac indications, and demonstrated that these patients had significant developmental delays (18). In the present study, 65% patients had neurological complications. Meanwhile, the 28-day mortality of the NC group reached up to 51.3% and was significantly higher than that of the nNC group. We also found a significant difference in ICU LOS but no significant difference in hospital LOS, which further suggested that neurological complications caused by ECMO might impact mid-long-term

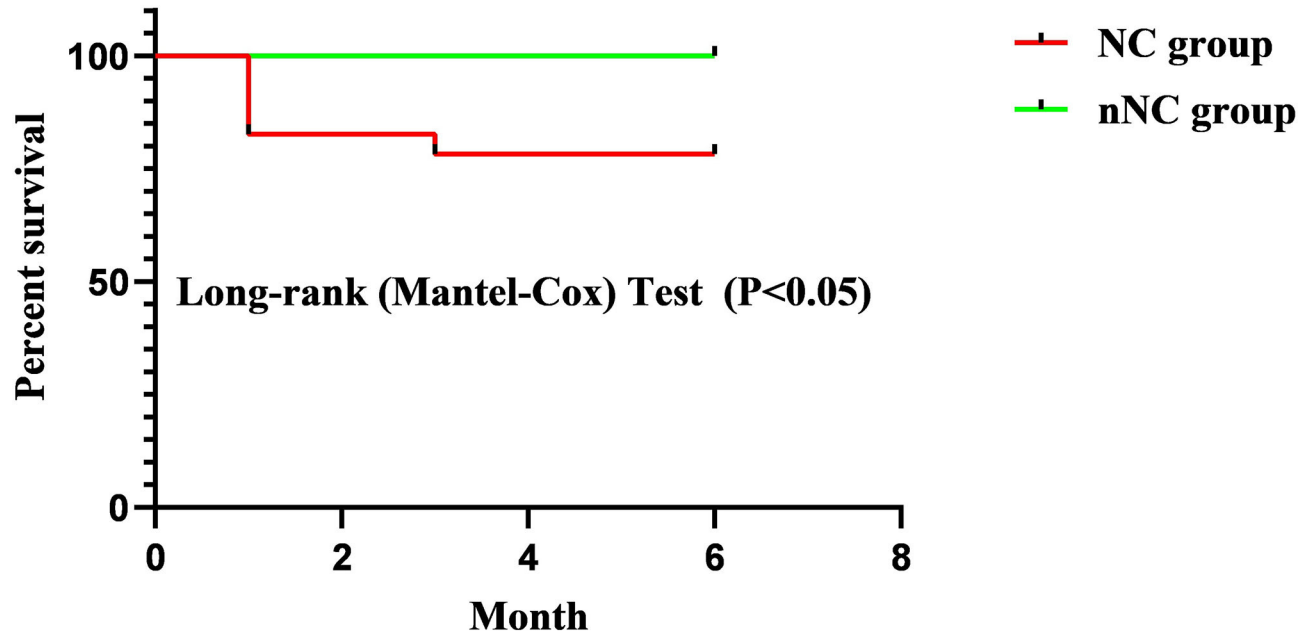

FIGURE 2 | Kaplan–Meier survival analysis of patients after discharge for 6 months. The NC group had a significantly poorer 6-month survival than nNC group (HR = 7.900, 95% CI: 1.298∼48.08; P <0.05). NC, neurological complications; nNC, non-neurological complications group.

TABLE 5 | Effect of neurological complications on long-term neurological outcomes.

Neurological complications	Long-term outcomes after discharge		
	1 month (n = 44)	3 months (n = 44)	6 months (n = 44)
Yes, *n* (%)	11 (25.0)	11 (25.0)	10 (22.7)
No, *n* (%)	3 (6.8)	3 (6.8)	3 (6.8)
P	0.024	0.024	0.049

prognosis and life quality. A recent systematic review and meta-analysis involving 6261 ECPR patients showed that the overall survival rate after ECPR was 29%, with good neurologic outcome achieved in 24% (12). However, as for the ECPR in our study, there was no significant difference between the two groups, which may be due to the small sample size.

Serum TNI is often used for estimating myocardial injury, and serious damage can result in low cardiac output (CO). A previous study of children with myocarditis showed that abnormal TN in the first 72 h of hospitalization was associated with the use of ECMO (19). Another small retrospective study evaluated 34 patients with post cardiotomy ECMO for low CO and found that a plateau in TNI levels at 48 h appeared to indicate a poor outcome due to irreversible myocardial damage (20). In the present study, the median TNI level of the NC group (16.7) was distinctly higher than that of the nNC group (5.0), and we also found there were 12 AMI patients had to undergo PCI with ECMO support because of refractory cardiogenic shock (**Table 1**), of which 11 patients suffered neurological complications ($P < 0.05$). An elevated TNI level in V-A ECMO patients signifies cardiac injury, which results in a drop in CO (20, 21). This reduction in CO causes lowered cerebral blood flow (CBF) and subsequent neurological complications (22).

It has been confirmed that the combination of V-A ECMO and CRRT is feasible and appears to be a safe and effective technique that has the potential to improve the fluid balance and electrolyte disturbances (23–25). A single-center retrospective chart review had found that the mortality rate of patients with combined ECMO and CRRT was higher than that of those receiving ECMO alone (26). A number of studies have indicated that damaged kidneys could have a detrimental effect on the central nervous system in acute kidney injury (AKI), which was also found to be a risk factor for delirium and coma during critical illness (27–29). In the present study, the proportion of CRRT in the NC group (69.2%) was significantly higher than that in the nNC group (28.6%), and CRRT was one of the independent risk indicators for V-A ECMO patients with neurological complications. In the meantime, we also found that the Cr of NC group was significantly higher than that of nNC group at 12, 48 and 72h after ECMO support (**Supplementary Table S3**). Previous study has shown neurological complications exist in the majority of patients with renal failure, and many of their effects are more obvious when renal failure acute attack (30).

Epidemiological studies also exhibited an association between AKI and a subsequent risk for developing stroke and dementia (29). Especially, the dialysis-requiring AKI was associated with a higher risk and higher severity of subsequent stroke events and dementia (31, 32).

It has been reported that V-A ECMO might damage the autoregulation of CBF and result in neurological dysfunction (33, 34). We found that 25.0% patients had a duration of NP of > 12 h; NP was defined as a pulsatile pressure < 10 mmHg during V-A ECMO support, referring to the paper of Yang et al. (35). Blood pressure management is crucial for patients undergoing V-A ECMO. A previous retrospective study evaluated the MAP of 116 patients receiving V-A ECMO, and the results showed that the survival of patients on V-A ECMO was significantly greater, with a higher MAP and without being affected by prolonged vasopressor use (36). Previously, Park et al. and Pappalardo et al. indicated that a higher MAP was an independent predictive factor for survival and successful weaning from V-A ECMO (37, 38). Several studies have confirmed that V-A ECMO combined with IABP could improve outcomes, enhance survival, and facilitate weaning from V-A ECMO during cardiogenic shock and cardiac arrest (39–42). Furthermore, the use of IABP could decrease the CBF with cardiac stun, and increase CBF without cardiac stun during V-A ECMO support (35). Therefore, the abovementioned studies suggested that continuous NP and low CBF might play an important role in the occurrence of neurological complications during V-A ECMO support.

Published data have exhibited persistent functional deficits associated with ECMO support (43–45). The long-term neurological sequelae of patients after weaning from V-A ECMO included hypoxic-ischemic brain injury, ischemic stroke, intracranial hemorrhage, posterior reversible encephalopathy syndrome, intracranial hypertension, seizures and brain death (10). With the overall increase in the use of ECMO, improving outcomes will depend on precisely defining the extent and types of neurologic complications and underlying pathophysiology that are specific to ECMO (10). Currently, we cannot address their etiologies with specific, targeted monitoring techniques and interventions. Furthermore, long-term survival in patients receiving ECMO was acceptable (46–48).

LIMITATIONS

This retrospective case-control study obtained some meaningful results for clinical guidance. However, there remain some limitations. Firstly, it is a single-center retrospective study, with small sample size and lower freedom degree, which might cause statistical bias. In addition, we should add more objective indicators, including PoCUS combined with multimodal brain monitoring and cerebral regional tissue oxygenation (rSO2) monitoring guided ECMO management, to facilitate more accurate and timely recognition of neurological complications. Moreover, the absence of stratification analysis about the influence of pulsate bold flow and MAP on brain perfusion, might also cause statistical bias. Therefore, strict randomized clinical trials or substitutive research designs are necessary to reduce bias further and then clarify the neurological complications caused by V-A ECMO.

CONCLUSION

In this retrospective case-control study, we found that the morbidity of neurological complications in patients receiving V-A ECMO was high, which was closely related with adverse outcomes (including ICU LOS and 28-day mortality). Moreover, TNI, CRRT, and continuous NP > 12 h were independent risk indicators for neurological complications in V-A ECMO patients. And the neurological complications of patients during ECMO support had significant adverse effect on long-term surviving and neurological outcomes of patients after discharge for 6 months. Future work should include strict randomized clinical trials or substitutive research studies and stratification analyses to increase the understanding of the long-term neural prognosis and cognitive function of V-A ECMO patients.

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 Hangzhou First People's Hospital, Zhejiang University School of Medicine. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

All corresponding and first authors contributed to study concept and design. YnL, QG, XW, YwL, and WP: acquisition and analysis of data. YnL: writing of the original manuscript and statistical analysis. WH and SX: revision and editing of the manuscript. YZ and WH: material, technical, and 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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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.698242/full#supplementary-material

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Awake Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: Which Clinical Issues Should Be Taken Into Consideration

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With the goal of protecting injured lungs and extrapulmonary organs, venovenous extracorporeal membrane oxygenation (VV-ECMO) has been increasingly adopted as a rescue therapy for patients with severe acute respiratory distress syndrome (ARDS) when conventional mechanical ventilation failed to provide effective oxygenation and decarbonation. In recent years, it has become a promising approach to respiratory support for awake, non-intubated, spontaneously breathing patients with respiratory failure, referred to as awake ECMO, to avoid possible detrimental effects associated with intubation, mechanical ventilation, and the adjunctive therapies. However, several complex clinical issues should be taken into consideration when initiating and implementing awake ECMO, such as selecting potential patients who appeared to benefit most; techniques to facilitating cannulation and maintain stable ECMO blood flow; approaches to manage pain, agitation, and delirium; and approaches to monitor and modulate respiratory drive. It is worth mentioning that there had also been some inherent disadvantages and limitations of awake ECMO compared to the conventional combination of ECMO and invasive mechanical ventilation. Here, we review the use of ECMO in awake, spontaneously breathing patients with severe ARDS, highlighting the issues involving bedside clinical practice, detailing some of the technical aspects, and summarizing the initial clinical experience gained over the past years.

Keywords: extracorporeal membrane oxygenation, acute respiratory distress syndrome, mechanical ventilation-induced lung injury, spontaneous breath, respiratory drive

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BACKGROUND

For years, invasive mechanical ventilation has been the first-line tool for managing severe acute respiratory distress syndrome (ARDS). However, ARDS patients treated with conventional mechanical ventilation are at high risk of detrimental complications, including ventilator-associated pneumonia (VAP) (1), mechanical ventilation-induced lung injury (VILI) (2), and diaphragm atrophy or myotrauma (3). To avoid iatrogenic injuries to the lungs and extrapulmonary organs associated with intubation and invasive mechanical ventilation, as well as subsequent side effects related to adjunctive therapies of sedatives, opioids, and neuromuscular blocking agents,

venovenous extracorporeal membrane oxygenation (VV-ECMO) has gradually come to be a preferable treatment for refractory respiratory failure (4, 5). Some centers have even pursued the idea of using ECMO as a first-line treatment to rest the heart and lungs, to facilitate protective and even ultraprotective ventilation with low tidal volume, low frequency, low platform pressure, low driving pressure, and low mechanical power (6–10).

In recent years, the new concept of "awake ECMO" has emerged, with ECMO being used for awake, non-intubated, spontaneously breathing patients with respiratory and circulatory failure (11). Although this new technique seems promising as an alternative to mechanical ventilation (12–14), high-quality evidence regarding its safety, feasibility, and efficacy remains sparse. In the present review, we aimed to discuss the pivotal issues and share our initial experience in using VV-ECMO in awake, spontaneously breathing patients with severe ARDS.

POTENTIAL INDICATIONS OF AWAKE ECMO

The first attempt at awake ECMO was reported in a population with an end-stage pulmonary disease as an approach to bridging to transplant (15, 16). With the support of ECMO alone, this group of patients could reserve spontaneous breath and free from symptoms of dyspnea, facilitating early ambulation and rehabilitation, thus being rationale to improve both short- and long-term outcomes (16, 17). Recently, several case series with small sample size reported the use of ECMO in non-intubated, primarily ARDS patients, of which the etiology of ARDS includes perioperative lung injury, multiple trauma, viral pneumonia of influenza and COVID-19, and *Pneumocystis jirovecii* pneumonia (12, 13, 18–21). We reviewed these cases' characteristics and summarized several patient selection criteria combined with our center's experience.

General Criteria

As a complex and resource-consuming intervention, a careful weighing of the potential benefits and risks of ECMO by using predictive survival models and adequate communications between doctors and patients/surrogates before its initiation are crucial (22). As a prerequisite, patient selection should first meet the criteria for conventional ECMO, which, based on the severity of hypoxemia, respiratory mechanics and radiological features as reflected in the Murray score (23), and the patients' outcomes, were usually evaluated by the prognostic scores using PRESERVE, RESP, or PRESET score (24–26). Though any evidence-based guidelines or expert consensus has not recommended it, awake ECMO seems more inclined to benefit ARDS patients at the early phase of the disease (27, 28), as it appears to be safer and more feasible in those with a better level of oxygenation, less accumulation of airway secretions, a smaller area of consolidation, and fewer accompanied dysfunctional organs (29).

Immunosuppressed Patients

As reflected in predictive survival models of ARDS (25, 30–32), immunosuppression independently predicts worse outcomes, with even higher mortality in patients supported by ECMO. A recent retrospective study involving a total of 288 severe ARDS patients requiring ECMO support showed that immunosuppressed ones had both lower survival rates and ventilator-free days (33) despite the diverse survival rate among the different etiologies of immunosuppression. However, it is interesting that immunocompromised ARDS patients are more likely to be selected for awake ECMO (13, 18), and the possible reasons might be as follows: (1) The immunocompromised state in these patients mainly results from HIV infection, hematological malignancies, the transplantation of solid organs, and autoimmune diseases treated with corticoids and/or immunosuppressive therapy (13, 18, 32). These patients are at high risks of opportunistic infections, usually with pathogens such as *P. jirovecii* and cytomegalovirus, which could lead to moderate or severe respiratory failure but less possibly accompanying sepsis, shock, acute kidney injury, or other extrapulmonary organ disorders (34, 35). Moreover, it would be relatively safer and more feasible to adopt awake ECMO in the progressive respiratory failure induced by *P. jirovecii* and cytomegalovirus infections, which are often characterized by bilateral lung diffuse ground-glass lesions without patchy consolidations or much airway secretions. (2) Previous evidence concerning ARDS patients supported by ECMO mainly was obtained from intubated ones, among whom the mortality was mainly associated with VILI and nosocomial infections (36, 37). Of note, poor outcomes were rarely found resulted from the mechanical complication of ECMO (36, 37). Thus, it might be possible that avoiding intubation and invasive mechanical ventilation might substantially improve the outcome of ARDS patients.

ETIOLOGY OF ARDS

The etiology of ARDS and the factors driving acute deterioration of respiratory dysfunction are crucial when choosing the candidate for awake ECMO. Usually, lung function concerning gas exchange can be restored in days or weeks after the alleviation of driving factors in the mild and moderate ARDS population. Under given circumstances, the direct insult of driving factor and the secondary histopathologic changes of lung injury, including diffuse alveolar damage, hemorrhage, and fibrosis, however, would take a prolonged period to recover and even become irreversible. In some patients, hypoxemia and hypercapnia might persist and even progress for the increase of alveolar dead space and intrapulmonary shunt despite effective control of pathogenic stimuli, especially in patients with existing lung disease. One study has shown that pulmonary disorders such as pneumonia, aspiration, or lung contusion might be more prone to induce early lung fibrosis as compared with extrapulmonary disorders (38), which could result in an irreversible progression of the lung lesions, eventually leading to the failure of weaning from ECMO. This group of patients would have no choice but to bridge to lung transplant. Unfortunately, evidence regarding the underlying mechanism of disease exacerbation and how to predict the reversibility of rapid progression of disease

remains scarce (32, 39, 40). Moreover, it is not rare that infections or other pathogenic insults could exacerbate previous pulmonary lesions. Among immunosuppressed ARDS patients, those with anti-synthetase syndrome, rheumatoid arthritis, and Sjogren's syndrome, compared with patients with HIV or solid organ transplantation, were found to be less likely to benefit from ECMO support, perhaps due to a higher probability of existing interstitial lung disease (ILD) in this population and opportunistic infections might drive a rapid but irreversible progression of ILD (32, 41–43). In brief, a careful selection of patients who are suitable for awake ECMO is a crucial issue and high-quality evidence is needed.

MONITORING AND MODULATION OF RESPIRATORY DRIVE

For ARDS patients, the adverse effects of either over strong or weak spontaneous breathing have been widely discussed in the aspect of respiratory drive, the course of the disease, and the severity of lung injury (44–47). Excessive spontaneous breathing, as confirmed in many studies, may lead to "patient self-inflicted lung injury (P-SILI)," especially in ARDS patients with "baby lungs" (2, 48). An appropriate level of spontaneous breathing could help improve oxygenation, optimize ventilation–perfusion matching (49), and avoid diaphragm dysfunction (50). One of the most important goals of the VV-ECMO was to protect the lungs from further injuries by reducing tidal volume, respiratory rate, plateau pressure, driving pressure, and mechanical power.

Control of Respiratory Drive

In the physiological state, the respiratory drive is mainly regulated by the cerebral cortex, metabolic feedback, and chemical feedback, among which chemical feedback of blood $PaCO_2$/pH level plays a dominant role (51). In some cases, however, dyspnea symptoms are not significantly alleviated, even when effective oxygenation and decarbonation are attained with the support of VV-ECMO (52). Crotti et al. reported that only 27% (8/30) of ARDS patients could tolerate awake VV-ECMO in lieu of mechanical ventilation, and 50% of these patients maintained an unexpectedly high respiratory rate even with an increased ECMO sweep gas flow rate as high as 12–15 L/min (29). In severe ARDS patients, the development of an excessively strong respiratory drive might be caused by atelectasis, microthrombosis, or inflammation-induced activation of physiological receptors in the lungs or thorax (53). Other explanations for respiratory control disorders include a separation of the "brain curve" (respiratory drive) and the "ventilation curve" (actual ventilation) and an upwards shift in the metabolic curve (metabolic hyperbola) caused by an elevation in dead space after high-frequency ventilation (54).

Monitoring of Respiratory Drive

Respiratory drive monitoring and modulation are one of the key issues in determining the feasibility of awake ECMO in severe ARDS patients. The intensity and amplitude of the respiratory drive can be accurately evaluated in patients receiving invasive mechanical ventilation by collecting indicators such as respiratory rate, tidal volume, minute ventilation, inspiratory flow rate, the electrical activity of diaphragmatic muscle (EA_{di}), esophageal and gastric pressures, and airway obstructive pressure ($P_{0.1}$). Although there had been fewer monitoring options for awake non-intubated patients than in those receiving invasive mechanical ventilation, it was not difficult to recognize high respiratory efforts by the presence of clinical signs of dyspnea and respiratory distress, a rapid shallow breathing pattern and signs of agitation. Besides, among patients receiving non-invasive mechanical ventilation (NPPV), more objective and quantitative parameters like respiratory rate, minute ventilation, waveforms of dys-synchrony, and $P_{0.1}$ could be monitored. Moreover, with the widespread use of bedside ultrasound, diaphragmatic excursion, and diaphragm thickening fraction can be good parameters to evaluate inspiratory effort in both intubated and non-intubated patients. As there is growing interest in the role of accessory muscles in critical illness, ultrasound might also be of great value in assessing the structure and activity of accessory muscles (55).

MAINTAINING ECMO BLOOD FLOW

Configuration of Cannulation

In most clinical practice, the blood flow of VV-ECMO is generally recommended to establish with two-cannula access-drainage from the femoral vein and reinfusion into the internal jugular vein (56). An ECMO blood flow obtained with a 21–23 Fr venous drainage cannula could reach as much as 60% of the cardiac output in ARDS patients (57). So far, there is no known difference in the drainage efficiency between multistage drainage cannula with side holes and most distal tip drainage cannula (58); however, in some situations with the relative inadequacy of intravascular volume, stable ECMO blood flow might not be easily maintained through a multistage cannula due to the collapse and variability of the inferior vena cava (IVC) if the top of draining cannula is located far away from the right atrium. On the other hand, there could be a potential risk of an unacceptable degree of recirculation as the tops of drainage and inflow cannulas are positioned too close, which could compromise the oxygenating efficiency of ECMO. Thus, alternative single-site access involving the internal jugular vein with a double-lumen cannula (mostly 27–31 Fr) could be recommended in patients receiving awake ECMO because the large lumen provides full oxygenation support through enough drainage and minimizing recirculation if proper positioning and monitoring could be achieved (59, 60). Moreover, awake VV-ECMO with double-lumen cannula enables early rehabilitation and improves outcomes (61).

Heart–Lung Interaction

In VV-ECMO, classic venous drainage is achieved through femoral vein access, with the top advanced at the junction between the IVC and the right atrium. Compared with the ones under spontaneous breathing, a larger end-expiratory lung volume could remain among patients under positive pressure ventilation, resulting in a relatively caudal position of the diaphragm and a consequent better venous drainage (62). For patients undergoing awake VV-ECMO, the tidal volume and

respiratory rate may fall quickly following cannulation and extracorporeal support initiation, resulting in a low residual capacity and even atelectasis. As a consequence of heart–lung interactions (63), the position of the drainage cannula tip moves further away from the right atrium as the diaphragm moves toward the cranial side. Significant IVC collapse, induced by a dramatic shift in intrathoracic pressure during spontaneous breathing, especially in the inspiratory phase (11) or under a relatively conservative fluid management strategy (64, 65), might cause unstable blood drainage of ECMO. Not only does the decreased ECMO blood flow itself aggravate the patient's hypoxia, but the subsequent dyspnea symptoms, in turn, affect the drainage of the inferior cannula. This vicious cycle may eventually lead to the failure of awake VV-ECMO. Therefore, stable ECMO flow relies on both proper cannulation and consideration of the dynamic swings in intravenous volume related to heart–lung interactions.

COMBINED VENTILATION

The periodic opening and closing of alveoli in the physiological state enables gas exchange and participates in the regulation and transportation of lung water (66, 67). Under some pathological conditions, it even helps repair and regenerate lung tissue to a certain degree. Although the function of oxygenation and decarbonation of the native lung can be replaced by ECMO, primary and heterogeneous lesions in the lung tissue, aggregation of lung consolidation, and inflammation after ECMO cannulation may hamper the repair and regeneration of lung tissue (68, 69). In addition, an increase in pulmonary vascular resistance caused by the decrease of lung volume might compromise, or even offset, the benefit of ECMO concerning reversing hypoxemic pulmonary vascular constriction (70) and thus might further compromise the protective effect of VV-ECMO against right ventricular failure (5). So, it raises a question on how to find the balance between lung rest and proper ventilatory load.

Of note, a moderate level of end-expiratory positive pressure (PEEP), ranging from 10 to 20 cmH_2O, is essential in ultraprotective or near-apneic mechanical ventilation to keep the alveoli open and reduce shear damage (6–9, 71). Thus, the proper timing of initiating spontaneous breathing in ARDS patients and the options for combined respiratory support warrant careful consideration (44). ECMO centers favor different combined ventilation options according to their own clinical experience, including initiating awake ECMO without establishing any artificial airway, removing the artificial airway within 24–48 h after ECMO cannulation, or bridging with a tracheotomy and then weaning from positive pressure ventilation (12, 13, 72). So far, there has not been enough evidence to compare the advantages of these options regarding the safety, feasibility, protocols, and effects on survival or VAP/VILI incidence. There has been an increasing agreement on the early weaning of invasive mechanical ventilation during ECMO when doctors could confirm the efficiency of ECMO therapy, optimal hematocrit level, and no hemodynamic instability, neurological deficit, or other catastrophic complications (73). Recently, one study showed that patients taken off mechanical ventilation during support of ECMO had a higher likelihood of survival to discharge and were mobilized in half as many days (74). So far, there has been a paucity of evidence on other alternative modes of respiratory support during awake ECMO, such as high-flow nasal cannula oxygen therapy (HFNC), NPPV, or complete separation from oxygen therapy. With a comprehensive evaluation of the etiology and course of ARDS, the level of airway secretion, and the risks of VILI, we prefer HFNC or NPPV as the combined mode of ventilation in the patients at an early phase of ARDS, especially among the ones where an initiation of ECMO could dramatically decrease the level of respiratory drive. If patients present progressive dyspnea, excessive respiratory secretions, or concomitant organ failure during awake ECMO, early intubation should be considered.

SEDATION AND ANALGESIA

It has been challenging to manage analgesia and sedation in both initiating and running phase of awake ECMO. Local anesthesia and general analgesia and sedation are indispensable to ensure successful cannulation, especially in ARDS patients with dyspneic symptoms due to severe hypoxia. Adequate depths of analgesia and sedation protect patients from pain and anxiety resulting from invasive procedures and discomfort of disease, and promote the level of oxygenation by providing a stable blood flow and reducing systemic oxygen consumption. A proper level of analgesia and sedation also enables patients to preserve proper levels of spontaneous breath and early ambulation. However, an overdose of sedative and analgesic agents may lead to a deteriorating respiratory and circulatory failure and even result in intubation and invasive mechanical ventilation.

Most of the agents used for analgesia and sedation exhibit pharmacokinetic and pharmacodynamic changes in patients on ECMO as a result of both patient- and circuit-related factors (75). On the one hand, as the circuit is considered a separate pharmacokinetic compartment, it may influence drug absorption and sequestration, especially for those lipophilic and highly protein-bound ones, including fentanyl, benzodiazepines, and propofol, which could lead to an underdosing in the initial drug administration period. On the other hand, ARDS patients often present with acute kidney injury, augmented cardiac output, and increased blood volume during ECMO support, leading to changes in analgesia and sedation requirements (76).

Parenteral opioids such as fentanyl and morphine/hydromorphone have often been chosen as the preferred agents in ECMO, and hydromorphone showed less sequestration in ECMO circuits and more days alive without delirium (77). Compared with propofol or benzodiazepines, dexmedetomidine produces sedative effects without amnesia or respiratory depression, making it an attractive option for general sedation in ARDS patients undergoing awake ECMO (78). Other adjunct agents like atypical antipsychotics have also been used in ARDS patients, but the safety and efficacy in awake ECMO

need to be proven. In conclusion, finding a balance between drug concentration and the goal of analgesia and sedation is essential during awake ECMO.

LIMITATIONS

It is important to note that although awake ECMO has its specific advantages compared to conventional ECMO, there have been some potential risks and limitations. First, for a moderate to severe ARDS patient with hypoxemia under the support of HFNC or NPPV, it is more difficult to perform cannulation under the situation of dyspnea, anxiety, and agitation. On the other hand, studies have reported a higher risk of fatal mechanical complications such as decannulation in patients receiving awake ECMO, which are mostly unpredictable and unpreventable but may contribute to a lower survival rate (79). In addition, patients who present with a typical ARDS radiological feature, especially with a substantial amount of consolidation in the gravity-dependent areas of lungs, are more likely to benefit from the prone position strategy (80, 81), whereas keeping awake patients with ECMO in a prone position for a more extended period of time is much more difficult in clinical practice. Finally, concerning the assessment of the native organ's function, we would be lacking some respiratory physiological or respiratory mechanics indicators in awake ECMO patients and would rely more on clinical symptoms and signs and radiological manifestations. Considering the risks of transportation with ECMO, bedside techniques such as portable X-rays and ultrasound seem more accessible.

CONCLUSIONS

In summary, the application of awake ECMO in severe ARDS patients seems promising as it allows several inherent side effects related to conventional mechanical ventilation to be avoided. However, it remains complicated since limited clinical data have been provided so far. By applying strict patient selection criteria, maintaining a stable ECMO blood flow during awake ECMO implementation, closely monitoring interactions between the artificial organ and the patient's native organ, and avoiding underlying fatal complications, awake ECMO could be a strong rationale to achieve organ protection and rest in ARDS patients in the future.

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XY, SG, and ML have designed, written, and reviewed this paper. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Prolonged VV-ECMO (111 Days) Support in a Patient With Severe COVID-19

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Venovenous extracorporeal membrane oxygenation (VV-ECMO) may be a lifesaving rescue therapy for patients with severe coronavirus disease 2019 (COVID-19). However, little is known regarding the efficacy of prolonged ECMO (duration longer than 14 days) in patients with COVID-19. In this case report, we report the successful use of prolonged VV-ECMO (111 days) in a 61-year-old man with severe COVID-19. Given the high mortality rate of severe COVID-19, this case provided evidence for use of prolonged VV-ECMO as supportive care in patients with severe COVID-19.

Keywords: COVID-19, acute respiratory failure, acute respiratory disease syndrome, extracorporeal membrane oxygenation, prolonged maintenance

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INTRODUCTION

As of January 3, 2021, 84,793,806 infections by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and 1,838,440 related deaths had occurred worldwide (1). The mortality rates of patients with severe coronavirus disease 2019 (COVID-19) admitted to intensive care units (ICUs) is high (2–4). Venovenous extracorporeal membrane oxygenation (VV-ECMO) may serve as a lifesaving rescue therapy (5, 6). A recent report from 213 hospitals worldwide based on Extracorporeal Life Support Organization (ELSO) registry data provided a generalizable estimate of about 40% ECMO mortality in patients with severe COVID-19 (7). The median duration of ECMO support was 13.9 days (7). The data supported current recommendations that centers experienced in ECMO should consider its use for refractory COVID-19-related respiratory failure (7, 8). However, little is available regarding prolonged VV-ECMO (duration longer than 14 days) in patients with COVID-19. Here, we report the case of a patient with severe COVID-19 who received prolonged VV ECMO and was successfully decannulated after 111 days.

CASE REPORT

A 61-year-old man with a height of 168 cm and a predicted body weight of 64.2 kg had recently returned from Wuhan. He presented with fever (38.5°C), dry cough, and hypodynamia. Nasopharyngeal swabs obtained at the time of presentation were positive by PCR for SARS-CoV-2. A chest computed tomography (CT) scan demonstrated bilateral air-space infiltrates with consolidation and ground glass opacities consistent with a diagnosis of COVID-19. He had a medical history of sleep apnea hypopnea syndrome, hypertension, and chronic hepatitis B.

The patient's respiratory status deteriorated on Day 10 post-hospitalization, requiring intubation. He was transferred to the ICU of the First Affiliated Hospital of Guangzhou Medical University, the designated center for patients with COVID-19 in Guangdong, China.

INITIATION OF ECMO

On Day 6 post-intubation, the patient's oxygenation level continued to deteriorate despite lung-protective ventilation, high positive end-expiratory pressure (PEEP), deep sedation, and paralysis using neuromuscular blockers. His PaO_2/FiO_2 ratio decreased from 200 to 123 mmHg and his $PaCO_2$ increased from 50 to 64 mmHg. Chest x-ray revealed diffuse opacification in the lung field (**Figures 1A,B**). A decision was made to commence VV-ECMO on Day 6 post-intubation for respiratory failure.

Cannulation was carried out *via* a right femoral–right internal jugular vein approach. Initial ECMO settings were sweep gas flow 1.5 L/min, flow 4.4 L/min, 3,005 RPM, and heparin infusion [with the goal of achieving an activated partial thrombosis time (APTT) of 50–60 s]. Ventilation was set at a tidal volume of 6 ml/kg, PEEP 10 cmH_2O, and a respiratory rate of 20 bpm to keep his plateau pressure <25 cmH_2O.

Chest CT did not show any significant recovery and compliance remained poor over several weeks following initiation of ECMO (**Figure 1C**). Infectious complications included Gram-positive and Gram-negative bacteria and fungi (e.g., *Enterococcus faecium*, *Escherichia coli*, or *Candida albicans*) based on bronchoscopic alveolar lavage and sputum cultures. Antibiotics were administered as required based on the laboratory data from bacterial cultures.

Anticoagulation and ECMO Circuit Change

Coagulation function was reviewed every 3 h after initiation of ECMO and heparin infusion. Heparin (starting at 1 μg/kg/h) was administered and the dose titrated to achieve an APTT ranging from 50 to 60 s. Both bleeding and thrombus formation were monitored to adjust the dosage of heparin. However, active surveillance for hemolysis revealed elevated D-dimer on Day 7 after VV-ECMO initiation. Minimal areas of thrombus formation were observed peripherally on the oxygenator membrane. Meanwhile, the patient was in respiratory distress and laboratory tests showed clear evidence of deterioration of oxygenation. This was resolved following an oxygenator change out and his SpO_2 and PaO_2/FiO_2 ratio improved. However, 4 days after oxygenator change out (ECMO Day 11), his $PaCO_2$ increased and thrombi appeared on the membrane again, again requiring oxygenator change out. In the following days, the membrane oxygenator was changed out four times because of gas exchange failure, apparent thrombus formation on the membrane, and acute D-dimer increases associated with massive clot formation around the hollow-fiber bundles in the oxygenator (**Table 1**; **Figure 2**). The average lifespan of the oxygenators was 11 days.

A tracheostomy was performed on ECMO Day 58. However, bleeding from the tracheal incision and nasal cavity was hard to control under ECMO support with heparin anticoagulation. The dose of heparin had to be decreased, and thrombi again appeared on the membrane. Bleeding of the tracheal incision and nasal cavity was finally controlled using tranexamic acid. Then, the dosage of heparin could be increased, and the infusion of blood products (such as fresh frozen plasma, fibrinogen, and platelets) could be reduced to avoid thrombus formation. We first began trials off ECMO after 66 days of support. The patient again showed a low PaO_2/FiO_2 ratio and a high $PaCO_2$ with decreased ECMO support. A sixth oxygenator exchange had to be performed.

Subsequent Progress

The patient's condition slowly improved when balance was achieved in terms of bleeding, thrombus formation, and fluids. With the appropriate use of antibiotics, analgesia and sedation were gradually reduced. Moreover, there was a major improvement in compliance (**Table 2**). During this time, the patient was awake, alert, intubated, and on light sedation for comfort. After prolonged VV-ECMO support for 111 days, the patient was successfully decannulated. He underwent daily physical therapy and continued physical therapy with the intubated cannula in place. On July 2, 2020, he was successfully weaned off mechanical ventilation. Significant improvement in his chest CT was observed before discharge (**Figure 1D**). Finally, on August 27, 2020, he was discharged from hospital and was able to walk slowly by himself after a prolonged hospitalization of 218 days. The patient was followed up every 3 months without readmission. He received home oxygen therapy about 12 h per day. Significant improvement in his chest CT was observed in mid-January 2021 (**Figure 1E**).

DISCUSSION

The use of ECMO to treat acute respiratory distress syndrome (ARDS) is currently in widespread use (9). As ECMO management is improving, prolonged duration of support is becoming more common. The ELSO registry data showed that 4,361 adult patients who underwent prolonged ECMO for respiratory failure had a mean ECMO duration of 22 days (10). Moreover, previous cases demonstrated that prolonged ECMO support for 265 days without complications was possible; one patient received ECMO for 403 days while waiting for lung transplantation but died soon after decannulation (11, 12). In our case, VV-ECMO was maintained for 111 days and successful weaning and recovery of lung function was achieved in a patient with severe COVID-19.

Several factors may be associated with the successful use of prolonged VV-ECMO in critically ill patients with COVID-19. First, early use of ECMO is recommended in these patients. In the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) study, patients with severe ARDS received immediate VV-ECMO if indicated by one of three criteria: a PaO_2/FiO_2 ratio < 50 mmHg for more than 3 h; a PaO_2/FiO_2 ratio < 80 mmHg for more than 6 h; or an arterial blood pH < 7.25 with $PaCO_2$ > 60 mmHg for more than 6 h (13). However, these criteria may be controversial because of several instances of "late" use of ECMO (14). By contrast with the EOLIA criteria, ECMO was administered in this patient at a relatively "early" point when we observed a rapid

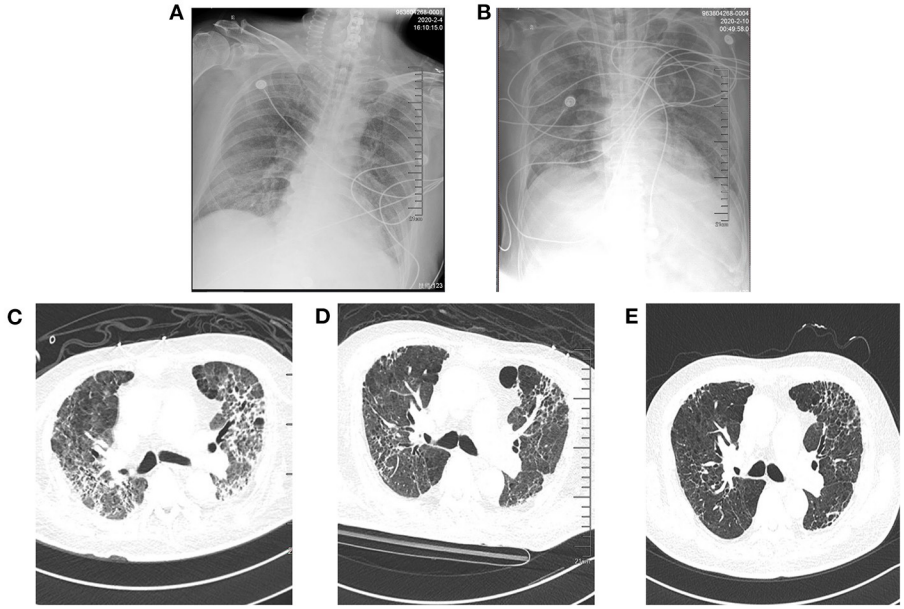

FIGURE 1 | Serial chest radiographs. **(A)** at ICU admission; **(B)** ECMO day 1; **(C)** ECMO day 48; **(D)** Day 44 after extubation before discharge hospital; **(E)** Following up at mid-January 2021.

TABLE 1 | Timeline of medical and ECMO events in a patient with COVID-19.

Event	Date	ECMO Day	Comments
Symptoms began	Jan. 16, 2020	–	–
Hospital admission	Jan. 22, 2020	–	PCR (+)
ICU admission	Jan. 23, 2020	–	Dyspnea
Intubation	Feb. 3, 2020	–	Respiratory failure
Transfer to referring hospital	Feb. 4, 2020	–	–
ECMO cannulation	Feb. 9, 2020	1	Oxygenation and hypercapnia continued to deteriorate
Oxygenator exchange*1	Feb. 15, 2020	7	Oxygenation deteriorate and high D-dimer
Oxygenator exchange*2	Feb. 19, 2020	11	Thrombus on oxygenator membrane and high $PaCO_2$
Oxygenator exchange*3	Feb. 28, 2020	20	Low oxygenation, high $PaCO_2$ and increased D-dimer
Oxygenator exchange*4	Mar. 12, 2020	32	Bleeding, low fibrinogen, and increased D-dimer
Oxygenator exchange*5	Mar. 24, 2020	44	Oxygenation deteriorate and thrombus on oxygenator membrane
Tracheostomy	Apr. 7, 2020	58	–
Orotracheal intubation	Apr. 10, 2020	61	Bleeding of tracheal incision and rhinal nasal cavity
Begin trials off ECMO*1	Apr. 15, 2020	66	Failure of low oxygenation and high $PaCO_2$
Oxygenator exchange*6	Apr. 16, 2020	67	Bleeding and thrombus on oxygenator membrane
Begin trials off ECMO*2	Apr. 25, 2020	76	Gradually decreased analgesia and sedation
Off ECMO support	May. 29, 2020	111	–
Extubation	Jul. 2, 2020	–	Successful Spontaneous Breathing Test on Jun. 30, 2020
Discharge hospital	Aug. 27, 2020	–	–

decline in oxygenation (PaO_2/FiO_2 ratio decrease from 200 to 123 mmHg) and an increase in hypercapnia ($PaCO_2$ increase from 50 to 64 mmHg).

Second, coagulation function was continuously monitored. Thrombotic complications and coagulopathy frequently occur in patients with COVID-19 (15). In addition, bleeding and thrombosis are serious complications during the use of ECMO (16). Taken together, the data suggest that use of ECMO in patients with COVID-19 may be challenging, particularly if prolonged support is needed. In this case,

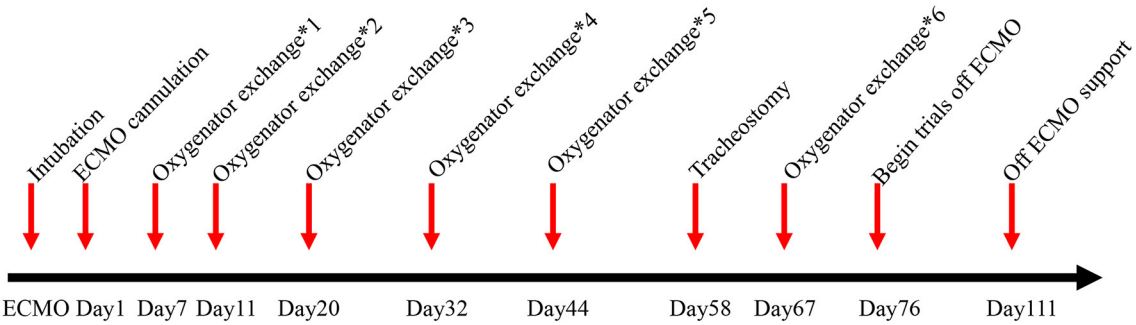

FIGURE 2 | Timeline of ECMO events.

TABLE 2 | Ventilation parameters and respiratory mechanics during ECMO.

Timing	FiO_2	PaO_2 (mmHg)	P/F ratio (mmHg)	VT (ml)	RR (per/min)	PEEP (cmH_2O)	ΔP (cmH_2O)	Compliance (ml/cmH_2O)
Before ECMO	0.7	86.6	123	470	21	11	15	25
ECMO day 1	0.5	84.1	168	400	16	11	12	27
Before decannulation	0.6	119	198	530	25	6	16	30
After decannulation	0.6	121	201	530	25	6	16	36

FiO_2, fraction of inspired O_2; PaO_2, partial pressure of oxygen in arterial blood; P/F ratio, PaO_2/FiO_2 ratio; VT, tidal volume; RR, respiratory rate; PEEP, positive end expiratory pressure; ΔP, driving pressure.

we continuously monitored coagulation (APTT, D-dimer, fibrinogen, and fibrinogen degradation products) to detect thrombotic bleeding and hemolytic complications. Coagulation disorders were the main reason why a change of the oxygenator is required in this patient. Balancing bleeding with risk of thrombus formation was of vital importance in the care of this patient who was bleeding from a tracheal incision and nasal cavity. Antiplasmin therapy (tranexamic acid) may have been critical to the care of this patient. When bleeding was controlled by tranexamic acid, we were able to increase the dosage of heparin and reduce the infusion of blood products (fresh frozen plasma, fibrinogen, and platelets). Decreased administration of blood product also meant reduced risks of thrombosis formation on the oxygenator. Meanwhile, aggressive ECMO circuit changes may improve membrane oxygenator-related coagulation disorders.

Third, infection control was performed according to the ELSO's guideline on patients with COVID-19 (17). The patient was managed in a negative pressure isolation room. ECMO team members received adequate training in the use of PPE including N95/FFP2 masks, gowns, cap, and eye protectors. Antibiotics were administered as required based on laboratory data from bacterial cultures. Moreover, ours was the designated center for patients with COVID-19 in Guangdong, China, and thus we implemented additional level of infection prevention and control measures such as use of closed respiratory suction tubes and disposable bronchoscopy tubes.

Fourth, centers experienced in ECMO are recommended to deliver ECMO to patients with refractory respiratory failure because this strategy is associated with low mortality (18). The ICU of the First Affiliated Hospital of Guangzhou Medical University was the designated center for patients with severe COVID-19 and experienced with ECMO because of the high volume of cases every year (19). Finally, the relatively small number of patients with COVID-19 in Guangdong Province prompted intensive care interventions, and availability of ICU beds may have contributed to enhanced levels of care for patients like the one described here (20, 21).

CONCLUSION

Our patient was aggressively treated by early use of ECMO, and coagulation was continuously monitored to inform the need for circuit change. The patient was ambulatory at the time of discharge despite a prolonged VV-ECMO support of 111 days. Future studies are warranted to determine reversibility of lung injury following use of ECMO in patients with COVID-19.

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 Commission

of the First Affiliated Hospital of Guangzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XiL, ZX, YX, and YL: conception and design. YL and XiL: administrative support. YH, DL, and LZ: provision of study materials or patients. ZX, DL, XuL, and YH: collection and assembly of data. ZX, YX, and XuL: manuscript writing. All authors contributed to the article and approved the submitted version.

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Neurologic Complications in Adult Post-cardiotomy Cardiogenic Shock Patients Receiving Venoarterial Extracorporeal Membrane Oxygenation: A Cohort Study

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Background: This study aims to describe the prevalence of neurologic complications and hospital outcome in adult post-cardiotomy cardiogenic shock (PCS) patients receiving veno-arterial extracorporeal membrane oxygenation (V-A ECMO) support and factors associated with such adverse events.

Methods: Four hundred and fifteen adult patients underwent cardiac surgery and received V-A ECMO for more than 24 h because of PCS. Patients were divided into two groups: those who developed a neurological complication and those who did not (control group). Multivariable logistic regression was performed to identify factors independently associated with neurologic complications.

Results: Neurologic complications occurred in 87 patients (21.0%), including cerebral infarction in 33 patients (8.0%), brain death in 30 patients (7.2%), seizures in 14 patients (3.4%), and intracranial hemorrhage in 11 (2.7%) patients. In-hospital mortality in patients with neurologic complications was 90.8%, compared to 52.1% in control patients (p <0.001). In a multivariable model, the lowest systolic blood pressure (SBP) level pre-ECMO (OR, 0.89; 95% CI: 0.86–0.93) and aortic surgery combined with coronary artery bypass grafting (OR, 9.22; 95% CI: 2.10–40.55) were associated with overall neurologic complications. Age (OR, 1.06; 95% CI: 1.01–1.12) and lowest SBP (OR, 0.81; 95% CI: 0.76–0.87) were correlative factors of brain death. Coagulation disorders (OR, 9.75; 95% CI: 1.83–51.89) and atrial fibrillation (OR, 12.19; 95% CI: 1.22–121.61) were shown to be associated independently with intracranial hemorrhage, whereas atrial fibrillation (OR, 8.15; 95% CI: 1.31–50.62) was also associated with cerebral infarction.

Conclusions: Neurologic complications in adult PCS patients undergoing V-A ECMO support are frequent and associated with higher in-hospital mortality. Identified risk factors of neurologic complications might help to improve ECMO management and might reduce their occurrence.

Keywords: extracorporeal membrane oxygenation, post-cardiotomy cardiogenic shock, neurological complication, lowest systolic blood pressure, in-hospital mortality

INTRODUCTION

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) is an effective technique to rescue patients with refractory cardiogenic shock or cardiac arrest (1–4). Despite the significantly increasing use and experience in recent years, V-A ECMO is still associated with very high in-hospital mortality (40–60%) and high rate of complications. Of these, bleeding, renal failure, infection, and neurologic complications, often result in poor outcomes or permanent disability (5–8). Previous studies have shown that the mortality in V-A ECMO patients associated with neurologic complications was high (9–13). However, the patients enrolled in these studies were from the Extracorporeal Life Support Organization (ELSO) registry or the complication profiles of detailed V-A ECMO indications were well not well-defined or including various V-A ECMO settings (9–13). One of the most common V-A ECMO indications is post-cardiotomy cardiogenic shock (PCS). Better understanding of the neurologic complications in PCS adult patients receiving V-A ECMO support might be meaningful to elucidate this peculiar aspect and improve the ECMO management in this challenging setting.

This study, therefore, aimed to assess the prevalence of cerebral injury and its influence on outcomes in adult PCS patients undergoing V-A ECMO support. Furthermore, independent risk factors of neurologic complications were also investigated.

MATERIALS AND METHODS

ECMO Setting and Patient Profile

The present study was a retrospective cohort study conducted at Beijing Anzhen Hospital, Capital Medical University. Forty-two thousand six hundred and sixty-eight adult patients (>18 years old) received cardiac surgery in our center from January 2006 to December 2016. Four hundred and ninety-six underwent V-A ECMO because of PCS. Of those, 21 patients aged 17 years or younger were excluded. Fifty-eight patients undergoing ECMO for <24 h were excluded because of the lack of complete central nervous system (CNS) assessment. Two patients undergoing more than one ECMO run were also excluded to avoid bias from confounders contributing to the severity of illness. Finally, 415 adult patients requiring V-A ECMO were included in this study. Patients were categorized according to the in-hospital occurrence (the neurological complication group) or absence of neurologic complications (the control group), and the two groups were compared (**Figure 1**). Data were extracted from the prospective institutional registry database of ECMO patients. This study was approved by Beijing Anzhen Hospital human research ethics committee (Ethics number: 2016018X). Because this was a retrospective observational study, the individual patients' consent was waived.

Post-cardiotomy cardiogenic shock patients included: (1) those who could not be weaned from cardiopulmonary bypass (CPB); (2) those presenting low cardiac output syndrome (LCOS) after CPB, cardiac arrest, or arrhythmias and hemodynamic instability despite satisfactory cardiac surgical procedure and conventional anti-arrhythmia therapy in the operating room; (3) those with delayed LCOS or cardiac arrest in intensive care unit (ICU) (14). Postoperative LCOS was defined as a systolic blood pressure (SBP) <90 mmHg for at least 30 min with a severe reduction in cardiac index (<1.8 L/min/m^2) and elevated left or right ventricular filling pressures, or inadequate peripheral organ perfusion (pH < 7.3, serum lactate > 2 mmol/L, cool extremities, urine output <30 mL/h, and altered mental status), acute pulmonary congestion or edema despite adequate/appropriate fluid administration and pharmacologic agents or intra-aortic balloon pump (IABP) (14).

V-A ECMO Implantation Techniques

The decision to use V-A ECMO was made by the cardiac surgeon and ECMO team. V-A ECMO was setup by the experienced ECMO team members. The femoral vessels (vein and artery) were cannulated with Fr 17–21 draining cannulae, and Fr 15–19 perfusion cannulae (Medtronic, Minneapolis, MN) by surgical cut-down. An additional 7F catheter was systematically inserted distally to the cannulated femoral artery site to perfuse the limb. Intrathoracic cannulation strategy has not been used in the 415 patients.

Patient Management

The detailed management of patients under V-A ECMO was previously described (14, 15). Heparin was used for anticoagulation. A heparin bolus (5,000 IU) was injected before cannulation. After V-A ECMO initiation, if surgical site bleeding could be controlled or thoracic drainage was <0.5 ml/kg/min, continuous intravenous infusion of unfractionated heparin was given to the patients as early as possible to maintain the activated clotting time (ACT) between 180 and 220 s, or activated partial thromboplastin time (aPTT) in the range of 60–80 s. Therapeutic hypothermia (32–35°C) was initiated during the first 24 h in case of extracorporeal cardiopulmonary resuscitation (ECPR) patients. The partial pressure of carbon dioxide ($PaCO_2$) was maintained between 35 and 45 mmHg before airway extubation.

Coagulation disorders could occur at any time of the perioperative period. In this study, we analyzed the coagulation disorders, defined as platelets $<20 \times 10^9$/L, fibrinogen <1.5 g/L and prothrombin time <30% of the standard value (16), before and during ECMO support. The definition and/or treatment of ECMO-related complications, such as major bleeding, lower-limb ischemia or compartment syndrome requiring fasciotomy, renal failure requiring renal replacement therapy, and significant infection, were described in the previous reports (14, 17).

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; BMI, body mass index; CABG, coronary artery bypass grafting; CI, confidence interval; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; CRRT, continuous renal replacement therapy; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; FFP, fresh frozen plasma; IABP, intra-aortic balloon pump; ICU, intensive care unit; IQR, interquartile range; LCOS, low cardiac output syndrome; MV, mechanical ventilation; OR, odds ratio; PCS, post-cardiotomy cardiogenic shock; RBC, red blood cells; SBP, systolic blood pressure; VA ECMO, veno-arterial extracorporeal membrane oxygenation.

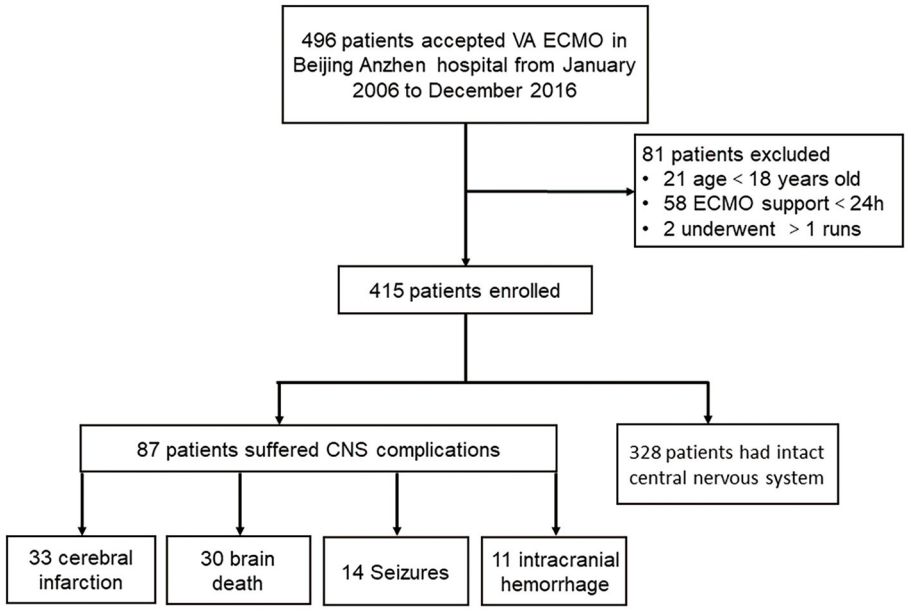

FIGURE 1 | Study flow. CNS, central nervous system.

Definition, Monitoring, and Treatment of Neurologic Complications

We defined neurologic complications as any clinical event occurring during the V-A ECMO support, including any clinical sign suggestive of stroke, brain death, and seizures despite sedation (11–13, 17). Routine neurological examinations were performed at least twice a day by the ICU doctors and the nurses in charge of the patients during sedation interruption or after sedation withdrawal, including response to verbal orders or pain, tendon reflexes, brainstem reflexes, eye movement, and pupil size and their light reflection. When abnormal signs were detected (such as pupil dilatation, convulsion of the limbs, delirium confusion, no awakening after sedation withdrawal, etc.), a cerebral computed tomography (CT) scan was performed within 6 h, and a neurologist was consulted immediately to perform neurocognitive test (18). The diagnosis of cerebral infarction or intracranial hemorrhage was determined by a neurologist analyzing CT scan images. Brain death, an irreversible cessation of the functions of the entire brain, including the brain stem (19) was defined according to the diagnostic criteria set by the American Academy of Neurology (AAN) (19, 20). In addition to neurologic examination, EEG and transcranial Doppler were performed to confirm the electrical activity loss or the loss of cerebral blood flow. Seizures were identified by a neurologist by means of at least 30 min continuous EEG monitoring and clinical features. When a neurological lesion was diagnosed, it would be treated according to the neurologist's consultation.

ECMO Weaning

Weaning from V-A ECMO support was based on the clinical and laboratory evidences of recovery of cardiac and pulmonary function, including that pulsatile arterial waveform was maintained (pulse pressure >20 mmHg) for over 24 h, and LV ejection fraction was >20–25% or not worsened right heart function and no significant arterial blood O_2 saturation when the ECMO flow was reduced to <1.5 L/min according to conventional protocol (15). Cardiac function and blood gas were continuously monitored during the weaning process. V-A ECMO was removed, and the femoral artery was primarily repaired in the operating room. Weaning off ECMO was considered successful when a patient survived V-A ECMO explantation for at least 48 h (15).

Statistical Analysis

Categorical data are reported as numbers and percentages. Continuous variables are expressed as mean ± standard deviations for normally distributed variables, or as median and interquartile range (IQR) for non-normally distributed variables. Normality of distribution was assessed by the Kolmogorov–Smirnov test. Categorical variables were compared with chi-square or Fisher's exact tests. Continuous variables were compared with two-tailed Student's *t*-test or Mann–Whitney *U*-test. Univariable and stepwise multivariate logistic regression analyses of baseline characteristics, pre-ECMO, and ECMO-related risk factors for neurologic complications were performed by calculating the odds ratio (OR) with 95% confidence interval (CI). Variables with $p < 0.05$ during univariable analysis were entered in multivariate logistic regression. Variables were retained in the model if the adjusted *p*-value was <0.05. The maximum value of Youden's index was used to determine the threshold of lowest SBP before VA ECMO initiation. Analyses were performed using IBM SPSS Statistics v22.0 software (IBM Corp, Chicago, IL). $p < 0.05$ defined statistical significance.

TABLE 1 | Demographics, baseline characteristics, and pre-extracorporeal membrane oxygenation information.

Variable	Neurological complication group ($n = 87$)	Control group ($n = 328$)	*p*-value
Demographics and baseline characteristics			
Age (years)	61.0 [51.0, 66.0]	55.0 [45.3, 63.8]	0.002
Older age (≥65 year)	27 (31.0)	80 (24.4)	0.208
Gender (male)	56 (64.4)	225 (68.6)	0.453
Body mass index (kg/m^2)	24.3 ± 3.7	23.7 ± 3.5	0.154
Obesity (BMI ≥ 30)	15 (17.2)	30 (9.1)	0.031
Smoking	35 (40.2)	146 (44.5)	0.460
Comorbidities			
Hypertension	47 (54.0)	117 (35.7)	0.002
Hyperlipidemia	7 (8.0)	23 (7.0)	0.746
Diabetes mellitus	20 (23.0)	63 (19.2)	0.441
Coronary artery disease	48 (55.2)	161 (49.1)	0.325
Peripheral arteria disease	21 (24.1)	36 (11.0)	0.001
COPD	2 (2.3)	4 (1.2)	0.460
Abnormal liver function	0	4 (1.2)	0.300
Atrial fibrillation	3 (3.4)	2 (0.6)	0.031
Preexisting neurological comorbidities	8 (9.2)	25 (7.6)	0.630
Pre-ECMO situation			
Intra-aortic balloon pump	49 (56.3)	187 (57.0)	0.908
CPR history before ECMO	38 (43.7)	68 (20.7)	<0.001
Lowest SBP (mmHg)	70.0 [65.0, 80.0]	80.0 [75.0, 80.0]	<0.001
Blood glucose (mg/dl)	256.0 [198.0, 311.0]	243.0 [189.0, 289.0]	0.177
Pre-ECMO cardiac procedures			
CABG	41 (47.1)	122 (37.2)	0.092
Valve replacement	20 (23.0)	85 (25.9)	0.577
Aortic surgery	7 (8.0)	14 (4.3)	0.153
CHD repair	2 (2.3)	10 (3.0)	0.711
CABG and valve replacement	7 (8.0)	36 (11.0)	0.425
CABG and aortic surgery	6 (6.9)	4 (1.2)	0.002
CABG and CHD repair	0	1 (0.3)	0.606
Valve replacement and CHD repair	0	9 (2.7)	0.118
Valve replacement and aortic surgery	0	5 (1.5)	0.247
CABG combined valve replacement and CHD repair	0	1 (0.3)	0.606
CABG combined valve replacement and aortic surgery	1 (1.1)	2 (0.6)	0.597
CABG combined aortic surgery and CHD repair	0	1 (0.3)	0.606
Heart transplantation	0	23 (7.0)	0.011
Atrial/ventricular thrombus clearance	3 (3.4)	10 (3.0)	0.849
Pulmonary embolism	0	10 (3.0)	0.099
Re-operation	1 (1.1)	9 (2.7)	0.389

Results are expressed as mean ± SD, number (%) or median [27th−75th percentile interquartile range].
CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; SBP, systolic blood pressure, CHD, congenital heart disease.

RESULTS

Two hundred and sixty-eight patients (64.6%) were successfully weaned off V-A ECMO, and 165 patients (39.8%) survived to discharge. Eighty-seven patients (21.0%) suffered from neurologic complications during V-A ECMO support (**Figure 1**). Thirty-three patients had preexisting neurological comorbidities (32 had a history of cerebral infarction, and 1 had suffered intracranial hemorrhage).

Baseline Characteristics

In comparing the baseline characteristics between the neurological complication group and the control group (**Table 1**), we found significant differences in age and body mass index (BMI). Patients experiencing neurological complications were

TABLE 2 | VA-ECMO indications and outcomes.

Variable	Neurological complication group ($n = 87$)	Control group ($n = 328$)	p-value
ECMO implantation			
Failure to wean off CPB	36 (41.4)	181 (55.2)	0.022
LCOS in ICU	27 (31.0)	110 (33.5)	0.659
ECPR	24 (27.6)	37 (11.3)	<0.001
Transfusion			
RBC (U)	26.0 [14.0, 35.0]	23.5 [14.0, 32.0]	0.417
FFP (ml)	2400.0 [1400.0, 3400.0]	2000.0 [1400.0, 3000.0]	0.309
Complications			
Renal failure need CRRT	46 (52.9)	155 (47.3)	0.351
Lower extremities ischemia	15 (17.2)	26 (7.9)	0.010
Femoral artery embolism	1 (1.1)	3 (0.9)	0.842
Cannulate site hemorrhage	4 (4.6)	28 (8.5)	0.221
Retroperitoneal hematoma	0	1 (0.3)	0.606
Major bleeding of other reasons	11 (12.6)	43 (13.1)	0.909
Surgical incision infection	3 (3.4)	28 (8.5)	0.113
Sepsis	16 (18.4)	76 (23.2)	0.327
Lower phlebothrombosis	0	1 (0.3)	0.606
Re-thoracotomy for hemostasis	37 (42.5)	136 (41.5)	0.858
Tracheostomy	41 (47.1)	126 (38.4)	0.141
Outcomes			
Weaning from ECMO	31 (35.6)	237 (72.3)	<0.001
Duration of ECMO (h)	97.0 [50.0, 128.0]	95.5 [65.0, 137.0]	0.388
Survival to discharge	8 (9.2)	157 (47.9)	<0.001
Duration of MV (h)	137.0 [72.0, 216.0]	121.5 [52.5, 210.0]	0.181
ICU length of stay (h)	170.0 [95.0, 245.0]	169.5 [96.0, 264.0]	0.386
Hospital stay (d)	17.0 [12.0, 25.0]	25.0 [17.0, 36.75]	<0.001

Results are expressed as mean ± SD, number (%) or median [27th−75th percentile interquartile range].
CPB, cardiopulmonary bypass; LCOS, low cardiac output syndrome; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; CRRT, continuous renal replacement therapy; RBC, red blood cells, ICU, intensive care unit; FFP, fresh frozen plasma; MV, mechanical ventilation.

older and had a higher ratio of BMI ≥ 30 ($p < 0.05$). The rates of hypertension and peripheral arterial disease were also higher in the neurological complication group ($p < 0.01$). Patients with atrial fibrillation appeared more frequently in the neurological complication group ($p < 0.05$). Patients in the neurological complication group had a higher ratio of cardiopulmonary resuscitation (CPR) before V-A ECMO initiation (43.7 vs. 20.7%, $p < 0.001$), and the lowest SBP before V-A ECMO start was lower in the neurological complication group [70.0 (65.0, 80.0) vs. 80.0 (75.0, 80.0) mmHg, $p < 0.001$]. Receiving aortic surgery combined with coronary artery bypass grafting (CABG) was more common in the neurological complication group (6.9 vs. 1.2%, $p < 0.01$). In our study, no heart transplantation recipients developed neurologic complications ($p < 0.05$; **Table 1**).

ECMO Indications and Outcomes of Patients With and Without Neurologic Complications

The proportion of patients receiving V-A ECMO for failure to wean off CPB was significantly lower in the neurological complication group (41.4 vs. 55.2% in the control group, $p < 0.05$). In addition, there were 61 ECPR patients, the incidence of neurological complications of these patients was 39.3%. The proportion of ECPR patients was significantly higher in the neurological complication group (27.6 vs. 11.3% in the control group, $p < 0.01$; **Table 2**).

Further analysis was performed to detect the differences in the type of neurologic complications among the patients who experienced failure to wean off CPB, LCOS and ECPR. ECPR patients had a higher rate of brain death (18.0 vs. 5.1% in the patients failure to wean off CPB or 5.8% in the patients of LCOS, $p < 0.01$, respectively; **Figure 2**).

Blood transfusion and severe bleeding were similar between the two groups ($p > 0.05$). Lower-extremity ischemia occurred more often in the neurological complication group (17.2 vs. 7.9% in the control group, $p < 0.05$). There were no significant differences in the duration of ECMO, mechanical ventilation (MV), and ICU stay. However, the overall hospital stay in the neurological complication group was significantly shorter than that in the control group [17.0 (12.0, 25.0) days vs. 25.0 (17.0, 36.75) days, $p < 0.001$] (**Table 2**).

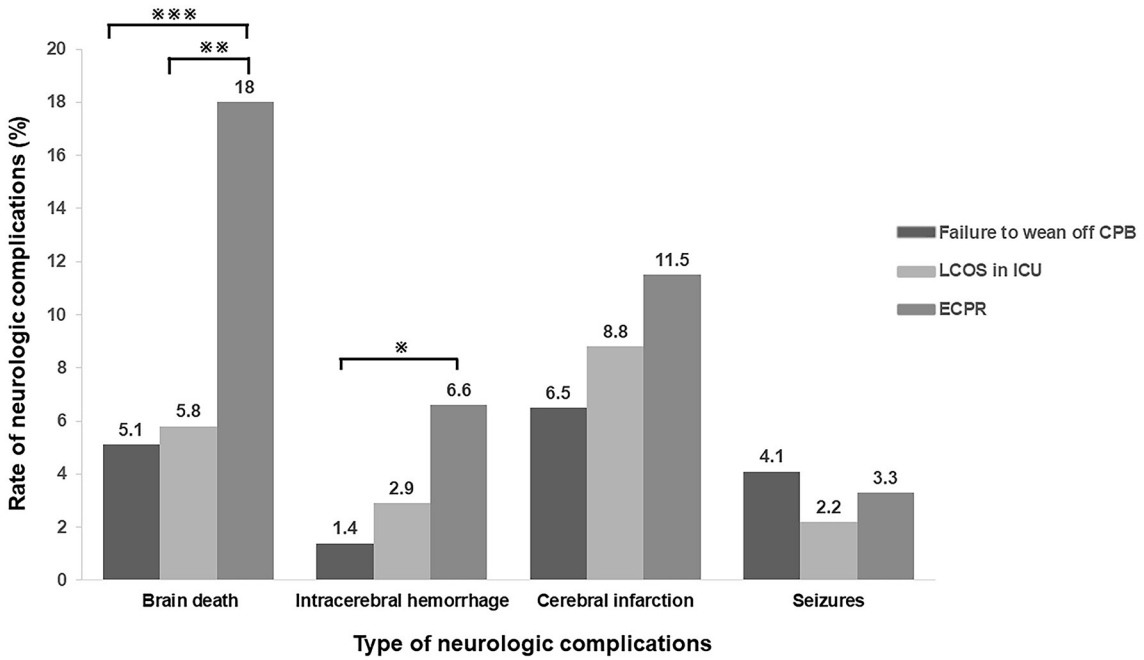

FIGURE 2 | Incidence of neurologic complications in different types of ECMO indications. ECPR patients had a higher rate of brain death, intracranial hemorrhage and cerebral infarction when compared with the patients with other indications. (※$P < 0.05$; ※※$P < 0.01$; ※※※$P < 0.005$) CPB, cardiopulmonary bypass; LCOS, low cardiac output syndrome; ICU, intensive care unit; ECPR, extracorporeal cardiopulmonary resuscitation.

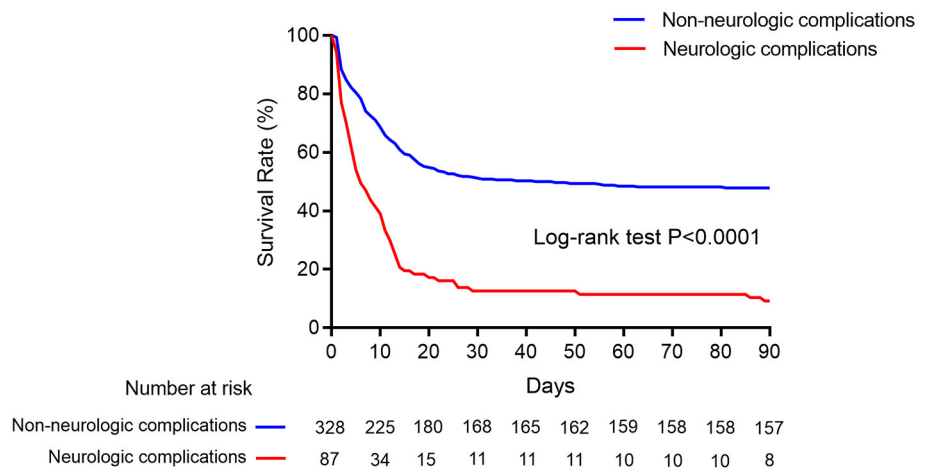

FIGURE 3 | Kaplan–Meier cumulative in-hospital mortality after ECMO initiation. Kaplan–Meier survival curves showed in-hospital mortality in ECMO patients with neurologic complications (red line) and without (blue line).

The rate of successful weaning from ECMO (35.6 vs. 72.3%, $p < 0.001$) and survival to discharge (9.2 vs. 47.9%, $p < 0.001$) in the neurological complication group were significantly lower than those in the control group (**Table 2**; **Figure 3**).

Prevalence and Prognosis of Different Type of Neurologic Complications

Among all kinds of neurologic complications, cerebral infarction was the most frequent (33 patients, 8.0%), followed by brain death (30, 7.2%), seizures (14, 3.4%), and intracranial hemorrhage (11, 2.7%), respectively. Two patients presented two kinds of neurologic complications at the same time.

Poor survival was observed in the patients with brain death, intracranial hemorrhage, and cerebral infarction ($p < 0.001$ compared with the control group). Patients with seizures had similar survival rate as compared to patients in the control group (**Figure 4**).

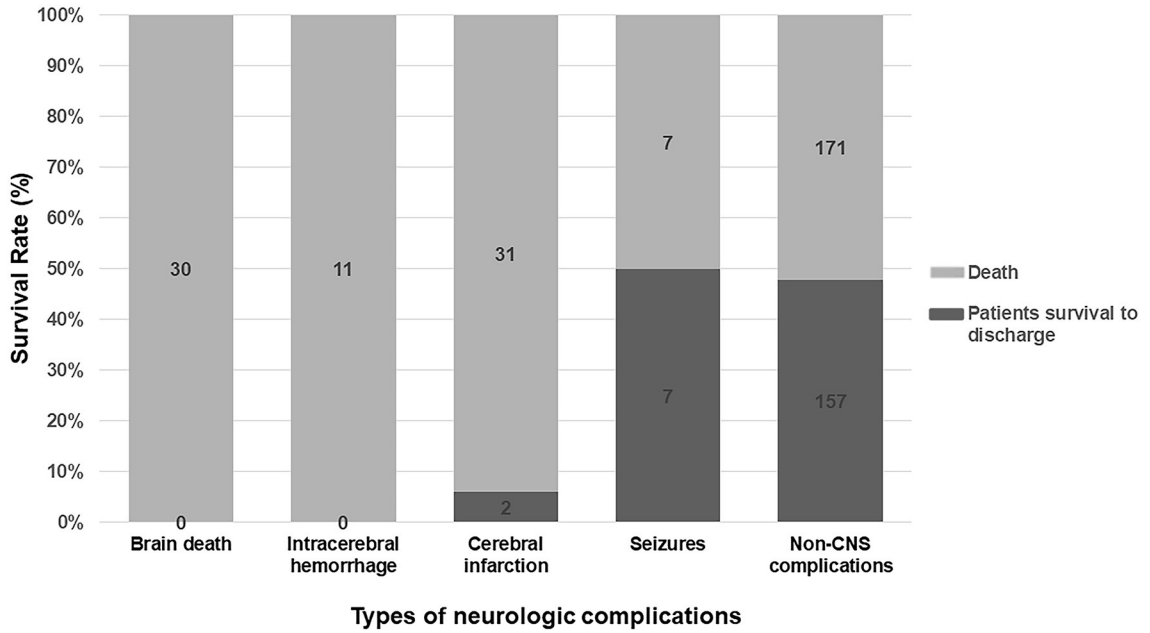

FIGURE 4 | Subgroup analysis for survival rate in different kinds of neurologic complications. Patients with brain death, intracranial hemorrhage, and cerebral infarction had a catastrophic outcome. Patients suffered seizures had a similar prognosis to patients in the control group.

Risks Factors Associated With Neurologic Complications

Multivariate logistic regression analysis showed that the lowest SBP level before VA ECMO initiation (OR, 0.89; 95% CI: 0.86–0.93; $p < 0.001$) and aortic vascular surgery combined with CABG (OR, 9.22; 95% CI: 2.10–40.55; $p < 0.01$) were associated with neurologic complications. Although ECPR was more common in the neurological complication group, it was not a risk factor at multivariable analysis (**Table 3**).

Age (OR, 1.06; 95% CI: 1.01–1.12, $p < 0.05$) and lowest SBP (OR, 0.81, 95% CI: 0.76–0.87, $p < 0.001$) were correlative factors of brain death. Coagulation disorders (OR, 9.75, 95% CI: 1.83–51.89, $p < 0.01$) and atrial fibrillation (OR, 12.19, 95% CI: 1.22–121.61, $p < 0.05$) could influence the incidence of intracranial hemorrhage. The occurrence of cerebral infarction might also be affected by atrial fibrillation (OR, 8.15, 95% CI: 1.31–50.62, $p < 0.05$). Hyperlipidemia patients had increased odds for seizures (OR, 5.75, 95% CI: 1.69–19.60, $p < 0.01$). It is noteworthy that preexisting neurological comorbidities were not risk factors of neurologic complications on ECMO (OR, 1.23, 95% CI: 0.53–2.83, $p > 0.05$; **Figure 5**).

Threshold of the Lowest SBP Level Before V-A ECMO Initiation in the Prediction of Neurologic Complications

In converting the lowest SBP level before V-A ECMO initiation from a continuous to a categorical variable, 72.5 mmHg was chosen as a threshold. It offered a sensitivity and specificity of 86.6 and 50.6% for prediction, respectively. The odds ratio of neurologic complications associated with SBP lower than 72.5 mmHg was 6.61 (95% CI: 3.90–11.19, $p < 0.001$; **Figure 6**).

DISCUSSION

This study shows the neurologic complications in adult PCS patients receiving V-A ECMO support. We found that the rate of successful weaning from V-A ECMO and survival to discharge were significantly lower in patients with neurologic complications. The lowest SBP level pre-ECMO and aortic surgery combined with CABG were identified as correlative factors independently associated with overall neurologic complications in these patients.

In this study, neurologic complications occurred in 21% of cases in adult PCS patients supported with V-A ECMO, a slightly higher rate reported by previous investigations (6–17%) (12, 15, 21, 22). This perhaps was due to the type of cardiac surgery or by neurologic patient examination protocols. In previous studies, owing to the difficulties of getting an imaging examination during V-A ECMO support or patients dying from severe neurologic complications without an imaging examination, the true incidence of neurologic complications might have been underestimated (14–16, 18, 21–25).

Matteen et al. (23) found that increased age was associated with higher rates of death and neurological morbidity. We also found that patients with neurologic complications were older, obese, and with more comorbidities, especially hypertension, hyperlipidemia, and peripheral arterial disease. All of these conditions indicate patients' worse general status and vascular

TABLE 3 | Univariable and multivariable analyses of factors associated with neurologic complications.

Factor	Univariable analysis		*P*-value	Multivariable analysis		*P*-value
	OR	95% CI		OR	95% CI	
Overall neurologic complications						
Age	1.03	1.01–1.05	0.003			
Obesity (BMI ≥ 30)	2.07	1.06–4.05	0.034			
Hypertension	2.11	1.31–3.40	0.002			
Peripheral arterial disease	2.60	1.43–4.75	0.002			
CPR history before ECMO	2.97	1.80–4.89	<0.001			
Lowest SBP	0.89	0.86–0.92	<0.001	0.89	0.86–0.93	<0.001
CABG combined with aortic surgery	6.00	1.65–21.76	0.006	9.22	2.10–40.55	0.003
ECPR	3.00	1.68–5.36	<0.001			
Failure to wean off CPB	0.57	0.36–0.93	0.023			
Brain death						
Age	1.06	1.02–1.11	0.002	1.06	1.01–1.12	0.022
Obesity (BMI ≥ 30)	2.78	1.12–6.90	0.028			
Peripheral arterial disease	3.14	1.35–7.30	0.008			
CPR history before ECMO	6.95	3.14–15.42	<0.001			
Lowest SBP	0.81	0.77–0.86	<0.001	0.81	0.76–0.87	<0.001
CABG	2.89	1.34–6.25	0.007			
ECPR	3.88	1.74–8.63	0.001			
Intracranial hemorrhage						
Coagulation disorders	8.76	1.67–45.85	0.010	9.75	1.83–51.89	0.008
Atrial fibrillation	10.00	1.02–97.71	0.048	12.19	1.22–121.61	0.033
Cerebral infarction						
Atrial fibrillation	8.15	1.31–50.62	0.024			
Seizures						
Hyperlipidemia	5.75	1.69–19.60	0.005			

BMI, body mass index; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; SBP, systolic blood pressure.

condition in our series, which may lead to increased rate of neurologic complications.

We found that the incidence of neurologic complications was associated to pre-ECMO low perfusion situations. ECPR was also frequently present in patients with neurologic complications. The incidence of neurologic complications in ECPR patients was higher than that in the patients failure to wean off CPB or the patients of postoperative LCOS. The reasons may be that the patients failing to wean off CPB (or postoperative LCOS patients) could promptly transition to V-A ECMO and whereas the majority of ECPR patients may have experienced cerebral hypo-perfusion, hypoxia, and reperfusion injury prior to ECMO implantation (23). Moreover, aortic surgery combined with CABG was shown to be an independent risk factor of the neurologic complications in the current study. The possible reason could be that the patients in our study had type A aortic dissection involving coronary artery and multiple organs, requiring intraoperative deep hypothermic circulatory arrest and long CPB times, conditions more likely associated with postoperative neurological injury.

Coagulation disorders can be induced by many factors, including the ECMO circuit, the surgical procedures, and the severity of the disease. Coagulation disorders were important factors affecting the integrity of the neurologic system and might lead to intracranial hemorrhage (12). In addition, we found that a history of atrial fibrillation was an independent risk factor of both intracranial hemorrhage and cerebral infarction. Atrial fibrillation is a well-known reason for thromboembolism in PCS patients (26). On the other hand, the patients with atrial fibrillation need anticoagulants to prevent thrombosis, condition favoring the occurrence of intracranial hemorrhage. Our results are in accordance with the previous literature regarding intracranial bleeding occurring in ECMO patients (27–29). Hyperlipidemia was associated with seizures which may be due to asymptomatic cerebrovascular disease secondary to dyslipidemia, but the underlying mechanism is yet less defined and warrants further research. A threshold of lowest SBP before V-A ECMO initiation, which may predict prognosis and assist doctors in managing patients, was defined in our investigation. When patients' blood pressure cannot be sustained by vasopressors, ECMO should be used prior to severe and refractory hypotension. In the clinical setting, neurologic complications may be induced by multiple factors during V-A ECMO support. Similarly, risk factor identification may help

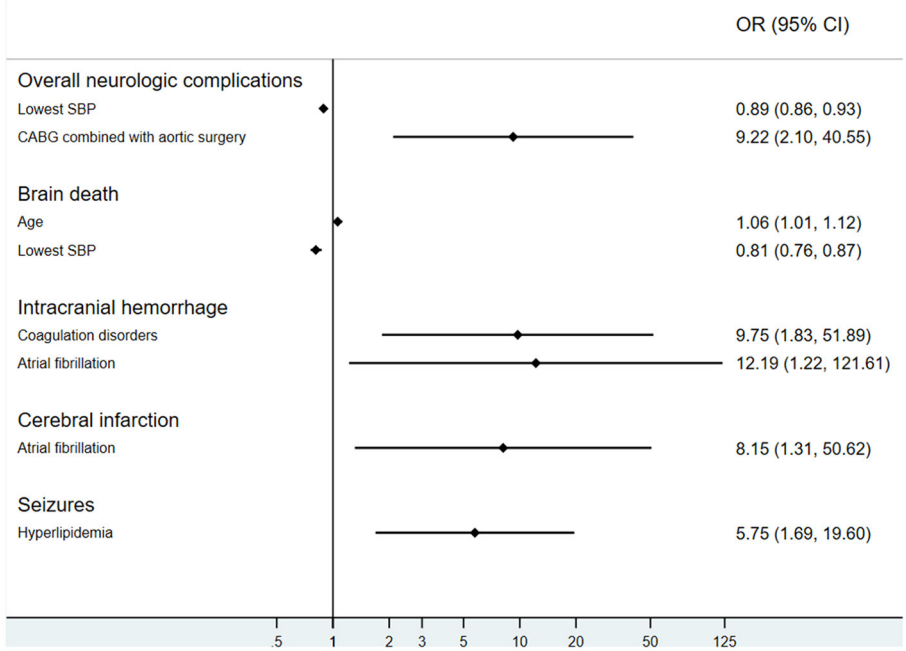

FIGURE 5 | Risk factors of neurologic complications during extracorporeal membrane oxygenation. SBP, systolic blood pressure; CABG, coronary artery bypass grafting.

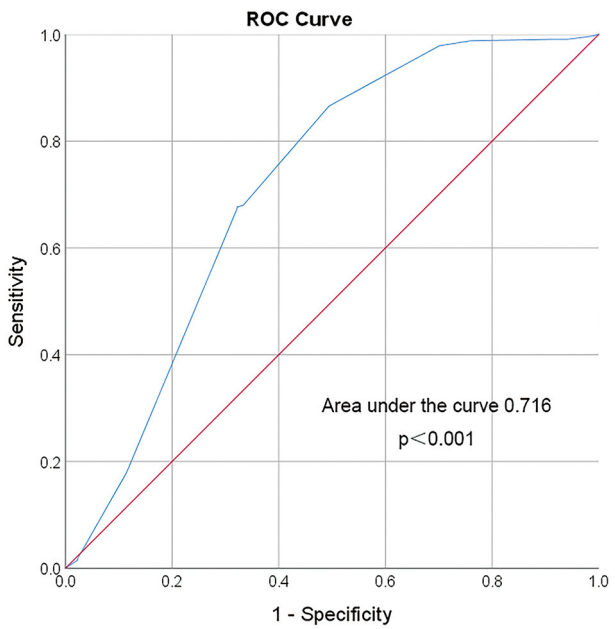

FIGURE 6 | ROC curve of the lowest SBP before VA ECMO initiation. Area under the ROC Curve of the lowest systolic blood pressure (72.5 mmHg) before VA ECMO initiation for predicting incidence of neurologic complications during ECMO is 0.716 (95% CI 0.647–0.786). The red line indicates reference values.

initiate steps to lower the risk of such complications in PCS patients undergoing temporary ECMO assistance.

Limitations

This single-center study is limited by its retrospective nature. The exact timing of neurologic complication in relation to ECMO and information regarding neurologic impairment before ECMO were uncertainty. In addition, full neuroimaging assessment was not performed on every patient. Even though we could perform CT scan, we had no MRI results because of the restrictions of the ECMO device, and, therefore, some subtle abnormalities, such as cerebral microbleeds, might have been not objectivated (30). Therefore, neurological complications were likely underestimated. However, routine neurological examinations were performed at least twice a day by the ICU staffs. It was unlikely to miss neurological complications with positive clinical manifestations in this study. Neurological events after ECMO weaning were not involved in this study, because of confounding factors. Another limitation is that we did not have long-term follow-up on survivors.

CONCLUSIONS

Neurologic complications are frequent in adult PCS patients treated with VA ECMO, and are associated with increased in-hospital mortality. We identified the lowest SBP level before

V-A ECMO initiation, CABG combined with aortic surgery, age, coagulation disorders, atrial fibrillation and hyperlipidemia as independent risk factors for different neurologic complications during V-A ECMO support in PCS patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was approved by Beijing Anzhen Hospital human research Ethics Committee (Ethics number: 2016018X). Because this was a retrospective observational study, the individual patients' consent was waived.

AUTHOR CONTRIBUTIONS

DH and HW participated in the design of the study, analyzed the data, and drafted the manuscript. FY interpreted the data and revised the manuscript. XH conceived the study, participated in its design, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Comparison of Success Rate and Complications of Totally Percutaneous Decannulation in Patients With Veno-Arterial Extracorporeal Membrane Oxygenation and Endovascular Aneurysm Repair

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Background: Total percutaneous closure for the site of femoral arterial puncture using Perclose ProGlide (PP) has become prevalent post-percutaneous endovascular aortic repair (EVAR) and veno-arterial extracorporeal membrane oxygenation (VA-ECMO).

Objective: To evaluate the safety and efficacy of total percutaneous closure of the femoral artery access site post-EVAR compared with VA-ECMO.

Methods: This was a retrospective observational study conducted over 4 years, including 88 patients who underwent EVAR (64 patients) and VA-ECMO (24 patients). Perclose ProGlide devices were used in the femoral artery puncture sites closed percutaneously. In this study, technical success was defined as successful arterial closure of the common femoral artery (CFA) without additional surgical or endovascular procedures to prevent vessel leaking. Access site complications, including overt bleeding requiring transfusion or surgical intervention, minor bleeding, tinea cruris, pseudoaneurysm, and lymphocele, were recorded 24 h and 30 days after arterial closure.

Results: Each group's technical success rates were 95.8% (VA-ECMO) and 92.2% EVAR, respectively. There were no differences in the periprocedural complications of major bleeding, pseudoaneurysm, minor bleeding, acute limb ischemia, and groin infection. Furthermore, we did not observe any complications such as arterial thrombosis, dissection, stenosis, arteriovenous fistula, hematoma, groin infection, or lymphocele at the access site by following-up an ultrasound examination. There was no significant difference in the technical success rate of percutaneous closure by the PP device in the EVAR and VA-ECMO oxygenation groups. Also, no periprocedural or 30-day complications were observed at the access site of the EVAR and VA-ECMO patients.

Keywords: extracorporeal membrane oxygenation, endovascular procedures, vascular closure devices, complications, endovascular aortic repair

INTRODUCTION

Recent studies revealed that Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) as a kind of mechanical circulatory and gas exchange support could benefit patients with shock or without return of spontaneous circulation during cardiorespiratory resuscitation (1–3). Moreover, endovascular aortic repair (EVAR) has spread rapidly as an alternative to treat abdominal aortic aneurysms (4–8). The most frequently accessed site for VA-ECMO is through the common femoral artery (CFA), using either open or percutaneous techniques. Percutaneous closure devices for a femoral arterial access site have been approved for use with up to only 10 French (Fr) sheaths in the past decades (9, 10). However, recently, the Perclose ProGlide (PP) suture-mediated closure technique (Abbott Laboratories, Chicago, IL, USA) has made it possible to close vessels in which larger sheaths are required (11, 12).

The PP percutaneous technique has been extensively used in endovascular therapy. Torsello et al.'s prospective randomized study indicates that compared with traditional surgical cutdown, the PP percutaneous technique showed several benefits, including a lower complication rate at the percutaneous group access site (5). interestingly, total percutaneous closure of CFA access sites highly increases patient comfort while decreases wound infection and lymph fistula rate dramatically (13, 14). Patients are also mobilized and discharged earlier following the use of percutaneous closure devices than compression (15, 16), which implies its promising prospect.

Although studies of the complication and success rates of percutaneous closure devices have accumulated in the past two decades (5, 6, 8, 9, 11, 13, 17–20), there is no data on applying the PP technique VA-ECMO patients. Furthermore, there are no comparisons of the PP method between VA-ECMO and percutaneous EVAR patients. Thus, our study aimed to compare the success rates and complications of the PP suture-mediated closure technique. In patients with these two different pathophysiological conditions.

MATERIALS AND METHODS

Patients who received total percutaneous closure of a femoral access site to wean VA-ECMO or finish EVAR procedures, between February 2015 and October 2018, in The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China, were examined retrospectively. The puncture sites of all patients were evaluated by ultrasound before the procedure. All patients' demographic characteristics, comorbidities, and routine biochemical analyses were utterly documented. At The Second Affiliated Hospital, the ethics committee, Zhejiang University, approved our study protocol.

Each PP closure device was inserted by the same trained and experienced operators into the anesthetized patient. Femoral artery ultrasound was used for the vessel diameter and calcification measurement before the placement of the PP closure device. A small skin incision was made to permit the advancement and deployment of the PP device over a 0.035-inch guidewire. On the VA-ECMO withdrawal day and at the end of EVAR, the arterial sheath was removed, leaving a guidewire in the artery. Two sutures were placed in each arteriotomy using either two 8-Fr PP closure devices sequentially deployed with opposite 30° rotation in a "crosshair" configuration. While one operator manually compressed the puncture site, the other operator tightened the knot with the knot pusher. A third PP device could be applied if necessary. After achieving hemostasis, the guidewire was quickly removed, and additional manual compression was applied as needed for oozing bleeding.

Procedural success was defined as successful arterial closure of the CFA without additional surgical or endovascular procedures to prevent vessel leaking. The Bleeding Academic Research Consortium (BARC) highly suggested using the bleeding classification measurement in our research (21). Access-related complications including periprocedural hemorrhoid, acute hindlimb ischemia, tinea cruris, multiple system/organ failure, femoral arterial stenosis, arterial thrombosis and dissection, pseudoaneurysm, arteriovenous fistula, hematoma, or lymphocele in the following 30 days post-arterial closure of CFA.

Continuous variables were given as mean ± standard deviation (SD) or median (interquartile) for skewed variables, while categorical data were expressed as number and percent as we previously described. The statistical difference for continuous variables was based on the Kolmogorov–Smirnov test, whereas categorical variables were assessed using a chi-square test or Fisher's exact test, as appropriate. The Student's *t*-test or Mann–Whitney U-test was used for comparing the groups' continuous variables according to whether or not they were normally distributed. Results were evaluated within a 95% confidence interval and at a significance level of $p < 0.05$. All statistical analyses were performed using SPSS (version 11.0).

RESULTS

A total of 88 patients, including 24 patients who underwent VA-ECMO and 64 patients who received EVAR treatment, were included in this study. Demographic characteristics and current comorbidities of the patients in VA-ECMO and EVAR subgroups who received PP closure treatment were analyzed. Characteristics at the inception of the study are presented in **Table 1**. The VA-ECMO patients were significantly younger than the EVAR patients. There was no significant difference between the two groups regarding body mass index (BMI), diabetes mellitus, and coronary artery disease (CAD). Compared with the VA-ECMO patients, the EVAR patients were associated with higher hypertension, hyperlipidemia, and smoking. However, compared with the EVAR patients, the VA-ECMO patients were associated with higher heart and respiratory failure incidences.

Most of the CFA access procedures were performed successfully, without conversion to open surgery. However, two patients received immediate surgical intervention due to the failure of the PP closure device. The 64 patients in the EVAR group received percutaneous closure using PP devices in 128 CFAs, whereas all 24 VA-ECMO patients received unilateral CFA access and percutaneous closure (**Table 2**). The patients in the EVAR group were associated with a larger and more severely calcified CFA compared with the VA-ECMO patients. There was no difference in the sheath size in the two groups (**Table 2**). The patients' total success rates in the VA-ECMO and

TABLE 1 | Characteristics of patients undergoing VA-ECMO and EVAR.

Characteristic	VA-ECMO ($n = 24$)	EVAR ($n = 64$)	*P*
Age (years)	42.0 ± 19.5	68.7 ± 10.9	<0.001
Male sex (*n*, %)	10 (47.6%)	51 (79.7%)	0.010
Body mass index (BMI) (kg/m^2)	24.3 ± 3.8	25.6 ± 4.8	0.262
Hypertension (*n*, %)	4 (19.0%)	61 (95.3%)	<0.001
Diabetes mellitus (*n*, %)	2 (9.5%)	4 (6.3%)	0.634
CAD (*n*, %)	1 (4.8%)	16 (25%)	0.059
Hyperlipidemia (*n*, %)	2 (9.5%)	41 (64.1%)	<0.001
Heart failure (*n*, %)	20 (95.2)	2 (3.1%)	<0.001
Respiratory failure (*n*, %)	8 (38.1%)	1 (1.6%)	<0.001
Antiplatelet (*n*, %)	6 (28.6%)	9 (14.1%)	0.185
Smoking (*n*, %)	3 (14.3%)	45 (70.3%)	<0.001

CAD, coronary artery disease; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; EVAR, endovascular aortic repair.

TABLE 2 | Periprocedural characteristics of VA-ECMO and EVAR patients*.

Characteristic	VA-ECMO ($n = 24$)	EVAR ($n = 64$)	*p*-Values
Puncture sites (common femoral arteries)	24	128	
Hospital stay (days)	13.7 ± 10.9	9.2 ± 6.9	0.024
Blood transfusion, % (*n*/*N*)	4/24 (16.7%)	4/64 (6.3%)	<0.001
Periprocedure anticoagulation, % (*n*/*N*)	19/24 (79.2%)	60/64 (93.8%)	0.058
Access site			
CFA diameter (mm)	6.9 ± 0.7	7.1 ± 0.8	0.283
vCFA calcification, % (*n*/*N*)	2/24 (8.3%)	49/64 (76.6%)	<0.001
Sheath size			
<18 Fr, % (*n*/*N*)	6/24 (25.0%)	28/128 (21.9%)	0.791
Technique success rate, % (*n*/*N*)	23/24 (95.8%)	118/128 (92.2%)	0.999
Device failure			
Primary device failure	2/24 (8.3%)	16/128 (12.5%)	0.999
Complete device failure	1/24 (4.2%)	1/128 (0.8%)	0.292
No. of Perclose ProGlide	2.1 ± 0.3	4.3 ± 0.5	<0.001

**CFA, common femoral artery; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; EVAR, endovascular aortic repair.*

EVAR groups were similar (95.8 and 92.2%, respectively). Due to the device failure, 2 VA-ECMO patients and 16 patients who underwent EVAR treatment required a third PP closure device to close the access site fully. One patient in each group had complete device failure and required surgical repair because of FA pseudoaneurysm and hematoma in the vascular access site 3 days post-percutaneous closure (**Table 2**).

There were no differences in the periprocedural complications of major bleeding, pseudoaneurysm, minor bleeding, acute limb ischemia, and groin infection. We did not observe any stenosis, arterial thrombosis, and dissection, pseudoaneurysm, arteriovenous fistula, hematoma, groin infection, or lymphocele by ultrasound test in the access site (**Table 3**).

TABLE 3 | Periprocedural and 30-day complications of VA-ECMO and EVAR patients.

Complications	VA-ECMO	EVAR	*p*-Values
(1) 24-h Vascular Access Complications			
Major complication			
Major bleeding (intervention or transfusion acquired)	1/21 (4.8%)	6/128 (4.7%)	0.999
Peudoaneurysm	1/21 (4.8%)	4/128 (3.1%)	0.537
Minor complication			
Minor bleeding	3/21 (14.3%)	18/128 (12.3%)	0.731
Peudoaneurysm	1/21 (4.8%)	4/128 (3.1%)	0.537
Acute lower limb ischemia (acute arterial dissection/occlusion)	0/21	2/128 (1.6%)	0.999
Groin infection	0/21	2/128 (1.6%)	0.999
(2) 30-Day Vascular Access Complications			
Arterial thrombosis	0/21	2/128 (1.6%)	0.999
Arterial dissection	0/21	0/128	0.999
Pseudoaneurysm	1/21 (4.8%)	4/128 (3.1%)	0.527
Stenosis (>50%)	0/21	2/128 (1.6%)	0.999
Arteriovenous fistula	0/21	0/128	0.999
Hematoma	1/21 (4.8%)	6/128 (4.7%)	0.999
Groin infection	0/21	2/128 (1.6%)	0.999
Lymphocele	0/21	1/128 (0.8%)	0.999

VA-ECMO, veno-arterial extracorporeal membrane oxygenation; EVAR, endovascular aneurysm repair.

DISCUSSION

We revealed that the incidence of PP closure device-related complications and the device technique success rate were similar in EVAR and VA-ECMO patients. The technical success rates of percutaneous closure of vascular access sites in VA-ECMO and EVAR patients are 95.8 and 92.2%, respectively. In all, our research indicated that the necessity of intraoperative and post-operative transfusion is similar in both groups.

The PP closure device system was the first suture-mediated device approved by the United States Food and Drug Administration. Since then, the development of the PP closure device has evolved (22). As the latest generation, the suture-mediated device from Abbot, PP closure device offers a breakthrough in the ease of knot delivery, trimming of the suture, and polypropylene monofilaments sutures, which are non-inflammatory and characterized by higher tensile strength (22). The deployment of the PP device includes several steps that require meticulous care and are prone to failure if operators are not adequately trained. Dr. Balzer et al.'s research uncovered that the learning curve of suture-based closure device's technical

success was steeper and much more enduring than traditional methods (23).

Over the past few decades, EVAR has become the preferred treatment choice for patients with an anatomically suitable abdominal aortic aneurysm (24). Total percutaneous EVAR minimizes invasiveness compared with femoral cutdown access EVAR. Several small single-center studies using various grafts show a reduction in total operative time and hospital stay length (4, 5, 10, 11, 25, 26). Previous studies have reported that vascular access site complications range from 0 to 11% (4, 13). Thus, percutaneous EVAR has been shown to have a higher success rate, shorter operation time, shorter length of hospital stay, and fewer access site complications than cutdown EVAR. Similarly, total percutaneous peripheral VA-ECMO minimizes invasiveness compared with femoral cutdown VA-ECMO with the femoral artery access. Peripheral VA-ECMO remains one of the most widely used and reliable methods as acknowledged for rescuing perfusion in life-threatening circulatory and respiratory failure (27). This extracorporeal support strategy provides immediate restitution of organ perfusion and oxygenation and, therefore, enables clinicians to establish a bridge to decision, recovery, or alternative therapies in various settings. However, there were limited data on the percutaneous closure of the vascular access sites by the PP closure device in VA-ECMO patients. Data from this study demonstrate that the meticulous use by a well-trained surgeon of two PP devices for percutaneous closure of a femoral artery access site in VA-ECMO patients is safe and effective compared to total percutaneous EVAR.

Four VA-ECMO and 24 EVAR patients did, however, have some closure site bleeding. Most of these incidences could be managed by manual compression. Only five patients needed further surgical intervention to stop the bleeding. We found that these five patients, who needed a transfusion and surgical intervention, had severe femoral artery calcification. Fortunately, it was evident that pulsatile bleeding was from the puncture site when the PP device technique failed. Maintaining stiff guidewire access until confirmation of adequate hemostasis is critically important (11, 12, 28), especially in VA-ECMO patients. In cases of PP device failure, the guidewire allows the bleeding to be wholly and immediately stopped with a dilator's simple reinsertion to prevent a life-threatening hemorrhagic complication. This guide wire advantage allows enough time for an unhurried surgical repair of the femoral artery access site to be performed.

In contrast, there were two acute limb ischemic failures in EVAR patients due to an anterior plaque that had fractured and resulted in local dissection occluding the distal flow. These patients received surgical intervention for revascularization before the irreversible injury of the limb. Based on our experience, cannulation of profunda, or superficial FA could be one of the major causes of vessel rupture or occlusion, especially when the arterial puncture site is too low. These complications can be avoided by the identification of the CFA by ultrasound. For example, we detected 50% CFA stenosis by ultrasound in two EVAR patients who did not show obvious limb ischemic symptoms at the 30-day follow-up. However, the ultrasound revealed a posterior plaque fracture that resulted in a local dissection and thrombosis that occluded the distal flow. These patients received a third PP device that was deployed due to primary device failure during the procedure.

There were four pseudoaneurysms in the EVAR patients and one pseudoaneurysm in the VA-ECMO patients. Three of the pseudoaneurysms were related to closure device failure, whereas two were due to mycotic aneurysm, diabetes, and groin infection. Regardless of the pseudoaneurysms' etiology, they all required major arterial reconstructions and were characterized by significant morbidity. These complications emphasized the importance of maintaining strict aseptic techniques and anti-infective therapy in the perioperative period.

Our study design was a retrospective, non-randomized, and observational study with a relatively small number of patients at a single center. Because of the lack of randomization, the surgeon's preference and experience likely played a role in treatment choice. Besides, the database did not provide information on long-term follow-up and prevented us from comparing the incidence of iliofemoral stenosis. Prospective, randomized clinical trials should confirm our findings with a larger population.

In conclusion, this study demonstrated that two PPs for percutaneous closure of femoral artery access site in VA-ECMO and EVAR patients is a safe and effective procedure when used with a well-trained surgeon and careful patient selection. The technical success rate and device-related complications are similar in the EVAR and VA-ECMO patients. Long-term follow-up is still necessary.

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 Human Research 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

ZLiu, MH, BC, and YX: conception and design and final approval of the article. ZLiu, YX, MH, CS, XX, YP, LY, ZL, PH, and LZ: analysis and interpretation. ZLiu, YX, MH, CS, XX, ZL, PH, and LZ: data collection. ZL, YX, and LY: writing the article and statistical analysis. ZLiu, YX, MH, CS, XX, YP, LY, ZL, PH, LZ, MH, and BC: critical revision of the article. ZLiu and LY: obtained funding. ZLiu, MH, and BC: overall responsibility. All authors contributed to the article and approved the submitted version.

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Double Distal Perfusion Catheters for Severe Limb Ischemia on the IABP Side in Patients Who Received Femoro-Femoral VA-ECMO With IABP

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Background: Limited research is available on the pattern of double distal perfusion catheters in patients on venoarterial extracorporeal membrane oxygenation (VA-ECMO) with an intra-aortic balloon pump(IABP). Here, we compared the outcomes of a double distal perfusion catheter and conventional treatment in patients who received VA-ECMO with IABP and had severe lower limb ischemia on the IABP side.

Methods: We reviewed the data of 15 adult patients with postcardiotomy cardiogenic shock who received VA-ECMO via femoral cannulation combined with an IABP in the contralateral artery that was complicated with severe acute limb ischemia (ALI) on the same side as the IABP between January 2004 and December 2016. Patients underwent symptomatic treatment (conventional group, $n = 9$) and double distal perfusion catheterization treatment (DDPC group, $n = 6$). ALI was monitored using near-infrared spectroscopy placed on both calves after double distal perfusion catheters. The outcomes were compared.

Results: All 6 patients who underwent double distal perfusion catheters were successfully decannulated without the development of osteofascial compartment syndrome, amputation, or bleeding and infection of the double distal perfusion catheters. The number of patients who weaned from extracorporeal membrane oxygenation successfully in the DDPC and conventional groups was 6 (100%) and 3 (33%, $p = 0.028$), respectively. The in-hospital mortality rates were 17% and 89% for the DDPC and conventional groups, respectively ($p = 0.011$).

Conclusions: DDPC can be considered a strategy for severe limb ischemia on the IABP side in patients who received femoro-femoral VA-ECMO with IABP.

Keywords: distal perfusion catheter, extracorporeal membrane oxygenation, intra-aortic balloon pump, osteofascial compartment syndrome, severe limb ischemia

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) via femoral arteriovenous cannulation is an established option for adult patients with refractory cardiogenic shock after cardiac surgery. However, acute limb ischemia (ALI) is a common complication and sometimes requires fasciotomy or amputation and is a significant predictor of mortality (1, 2). Although it is controversial whether patients with intra-aortic balloon pumps (IABPs) combined with ECMO have better prognoses (3, 4), they might have an increased risk of ALI (5). ALI is a complication on both the ipsilateral side of the arterial cannula (ECMO side) as well as the contralateral side (IABP side). Conservative treatment is often ineffective in patients with severe ALI, and IABP may even need to be removed. Insertion of a distal catheter may be an effective means to improve the blood supply of the ischemic lower extremity and reserve IABP.

We describe 3 types of establishing perfusion catheters to relieve distal ischemia (**Figure 1**). The oxygenated blood is diverted from the arterial cannula to the distal limb of the ECMO side using a perfusion catheter, called the ECMO side distal perfusion catheter (EDPC). Some centers insert EDPC as a preventive routine to decrease limb ischemia (2, 6), while others implant it as treatment following ALI (7, 8). When patients with EDPC develop IABP side limb ischemia, another distal perfusion catheter is inserted distally on the IABP side, called a double distal perfusion catheter (DDPC). In the present study, we compared the outcomes of DDPC and conventional treatment in ECMO patients with ALI on the IABP side.

METHODS

Study Population

Between January 2004 and December 2016, 451 patients required VA-ECMO support following postcardiotomy cardiogenic shock (PCS), of which 245 patients required combined treatment with IABP. Fifteen patients (6%) who were diagnosed with severe ALI on the IABP side were retrospectively enrolled in this study. Before January 2015, 9 patients underwent conventional treatment. Since January 2015, 6 patients underwent treatment with DDPC. Severe ALI was classified according to the Rutherford system as IIA, IIB or III (9). Category I was excluded because of better prognosis. The study was approved by the institutional ethics committee/review board of the Beijing Anzhen Hospital, Capital Medical University, and the requirement for informed patient consent was waived in view of the retrospective nature of the study.

ECMO Implantation Techniques

The VA-ECMO was placed by trained ECMO team members. ECMO cannulae (Biomedicus, Medtronic; Minneapolis, MN, USA) were inserted through the femoral artery and femoral vein. A 6-Fr EDPC was inserted at the time of ECMO initiation to preserve limb perfusion. An IABP catheter (Datascope Corp., Fairfeld, NJ, USA) was placed percutaneously through the contralateral femoral artery.

Patient Management

Detailed management strategies for patients have been previously described (10). ECMO blood flow was adjusted to maintain a mixed venous oxygen saturation (SvO2) level of 70%. Blood circulation of the lower limbs was observed continuously by trained ICU staff during ECMO support. Medial or/and lateral incisions of a minimum of 15 cm were made when acute compartment syndrome developed (intracompartmental pressure ICP >25 mmHg). Amputation was considered when ischemic tissue was subjected to unmanageable infections and when ischemic rest pain or tissue loss could not be restored by any surgical or non-surgical approaches.

A heparin bolus (5,000 IU) was injected before ECMO insertion. After surgical bleeding was controlled, unfractionated heparin was infused continuously as early as possible to maintain an activated clotting time of 160–180 s. When SLI occurred on the IABP side, intravenous prostaglandin therapy or sympathicolysis was initiated. The vasoconstrictors were reduced gradually following hemodynamic stability. Upon failure to relieve ischemia, IABP was removed (conventional group). After January 2015, we began to insert DDPC in such patients (DDPC group).

DDPC Insertion

A 2–3-cm incision was made 1 cm below the midpoint of the groin. The vasculo-neural sheath was dissected after the subcutaneous tissues and muscles were released. A 6-Fr distal perfusion catheter (Transradial Kit, Cordis Corporation, Miami Lakes, FL, USA) was inserted into the superficial femoral artery at the end of the IABP artery. The distal perfusion catheter was connected to the side hole of the arterial cannula of the ECMO circuit. DDPC decannulation was performed while ECMO was weaning.

NIRS

Continuous monitoring of limb perfusion began immediately after ALI was diagnosed and measured using bilateral near-infrared spectroscopy (NIRS). The Oximeter sensor pads were placed on the bilateral lower limbs midway between the knee and ankle.

Data Collection

All clinical variables of patients were recorded in our institutional database. Tissue saturation (StO2) was detected using near-infrared spectroscopy in the ICU, and persistent ALI was diagnosed until stable conditions were achieved. In addition to lactate and muscle injury markers, StO2 was recorded when ALI was diagnosed 6 and 24 h later. Patients also underwent measurement of the ankle brachial index (ABI) of both legs after DDPC was placed and during the follow-up measurements until ECMO and IABP were removed. Clinical indications of

Abbreviations: ABI, Ankle-brachial index; DDPC, Double distal perfusion catheter; EDPC, Extracorporeal membrane oxygenation side distal perfusion catheter; IDPC, Intra-aortic balloon pump side perfusion catheter; IABP, Intra-aortic balloon pumps; PCS, Postcardiotomy cardiogenic shock; SLI, Severe limb ischemia; ECMO, Extracorporeal membrane oxygenation; StO_2, Tissue saturation; ICU, Intensive care unit; SOFA, Sequential organ failure assessment.

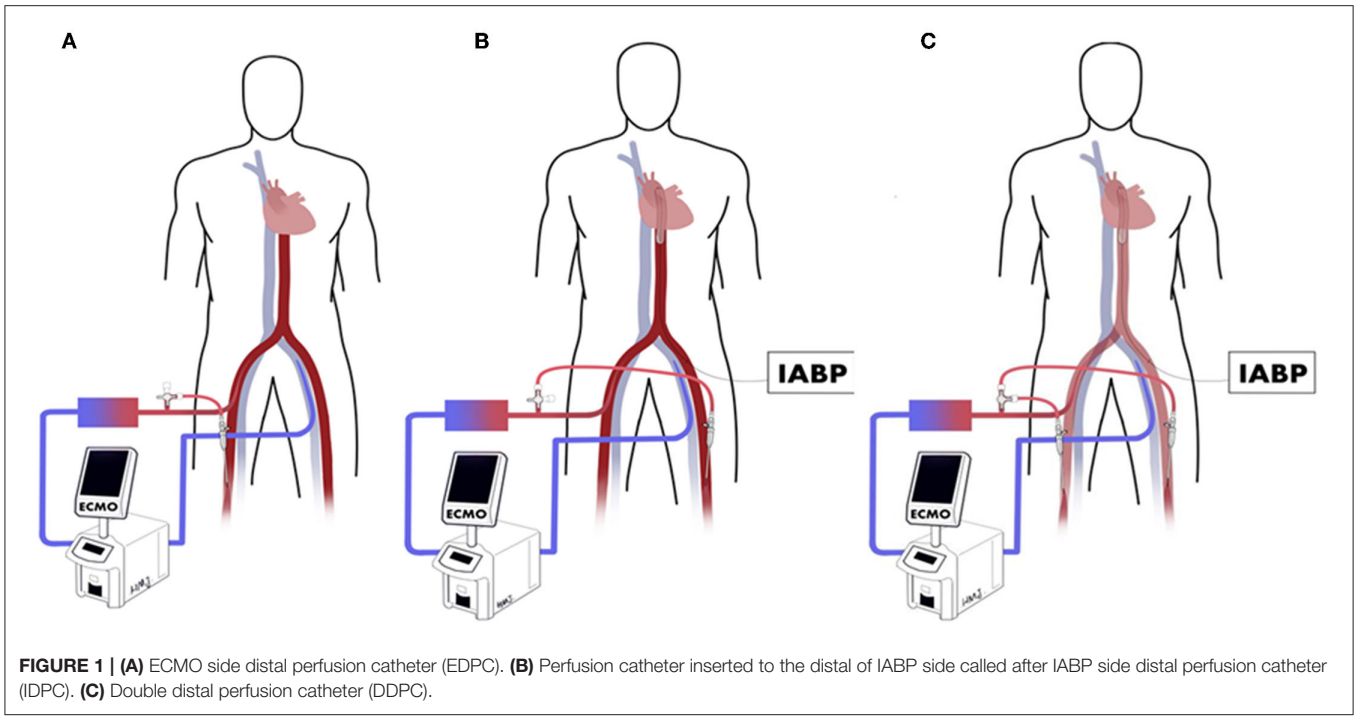

FIGURE 1 | (A) ECMO side distal perfusion catheter (EDPC). **(B)** Perfusion catheter inserted to the distal of IABP side called after IABP side distal perfusion catheter (IDPC). **(C)** Double distal perfusion catheter (DDPC).

TABLE 1 | Demographics and clinical characteristics.

Variables	**No. (%) or median (interquartile range)**		***P*-value**
Group	**DDPC (6)**	**Conventional (9)**	
Age, years	48.2 (16–68)	54.1 (36–63)	0.25
Male	83.3%	77.8%	0.34
BMI[a]	27.2 (22.9–31.5)	24.7 (20.1–30.2)	0.41
Etiology			0.32
CAD	50%	55.6%	
VHD	50%	11.1%	
AD	0%	22.2%	
CHD	0%	11.1%	
Complications			
Hypertension	55.6%	33.3%	0.23
Diabetes mellitus	44.4%	33.3%	0.54
Smoking history	55.6%	66.7%	0.54
Femoral stenosis history	22.2%	16.7%	0.34
SOFA scores (when ALI was diagnosed)	12.9 (12–14)	12.7 (11–15)	0.55
Inotrope scores (when ALI was diagnosed)	61.7 (43–78)	54.4 (40–66)	0.36
ECMO Flow (LPM) (when ALI was diagnosed)	3.5 (3.2–3.8)	3.6 (3.5–3.9)	0.92

BMI, body mass index; CAD, coronary artery disease; VHD, valvular heart disease; AD, aortic disease; CHD, congenital heart disease; SOFA, sequential organ failure assessment; Inotrope scores = dosage of dopamine (in μg/kg/min)+dosages of dobutamine (in μg/kg/min)+[dosages of epinephrine (in μg/kg/min+ norepinephrine (in μg/kg/min)] × 100+dosages of pituitrin (in u/min) × 100+dosages of milrinone (in μg/kg/min) × 15.

hypoperfusion were also recorded, including cold limbs, mottled skin, and pulseless Doppler signaling after DDPC.

Statistical Analysis

SPSS software (IBM Corp., SPSS Version 25, Armonk, NY, USA) was used for statistical analysis. Baseline classification data were expressed as percentages, and continuous data were expressed as medians or averages. The chi-square test was applied to categorical data, and Student's *t*-test or Wilcoxon *t*-test were applied to continuous data. Odds ratios (ORs) with 95% confidence intervals (CIs) were assessed to determine the relationship

TABLE 2 | Clinical outcomes and ischemia indicator.

Variables	No. (%) or mean ± SD		*P*-value
Group	DDPC (6)	Conventional (9)	
ICU stay (days)	10.2 (8–13)	16.8 (3–45)	0.19
Acute compartment syndrome	0%	45.6%	0.03
Amputation	0%	11.1%	0.60
Weaning from ECMO	100%	33%	0.01
mortality	16.7%	88.9%	0.01
StO_2 (IABP side when ALI was diagnosed)	31.5 (23–42)	35.0 (26–38)	1.00
StO_2 (IABP side 6 h later)	61(55-66)+	35.0(28-39)	0.01
StO_2 (IABP side 24 h later)	61.5 (52–63)+	35.0 (25–41)	0.01
Lactate (when ALI was diagnosed,mmol/L)	10.1 (5.7–17.1)	12.3 (5.4–16.6)	0.61
Lactate (6 h later,mmol/L)	9.0 (5.5–15.5)	13.0 (5.3–17)	0.61
Lactate (24 h later,mmol/L)	3.0 (2.5–7.8)*	12.6 (5.7–20)	0.07
Myohemoglobin (when ALI was diagnosed,ng/ml)	3,390.0 (3,390–3,390)	3,390.0 (3,280–3,390)	1.00
Myohemoglobin (6 h later,ng/ml)	3 390 (2,350–3,390)	3,390.0 (3,390–3,390)	1.00
Myohemoglobin (24 h later,ng/ml)	3,390 (1,880–3,390)	3,390.0 (3,106–3,390)	1.00
Myohemoglobin (48 h later,ng/ml)	475 (262–2,512)#	3,390 (578–3,390)	0.01

ALI, acute limb ischemia; StO_2, tissue saturation.
**compare with the Lactate (when ALI was diagnosed).*
+compare with the StO_2 (when ALI was diagnosed).
#compare with the myohemoglobin (when ALI was diagnosed).

between the changes in StO_2, lactate and muscle injury markers. $P < 0.05$ was considered a statistically significant difference.

RESULTS

The characteristics of the 15 patients with complications of limb ischemia on the IABP side are shown in **Table 1**. Normalized single tissue oxygen saturation values, lactate, and myohemoglobin when ALI was diagnosed are shown in **Table 2**. There was no significant difference between the 2 groups.

Overall, the in-hospital mortality for all patients was 60%, with a mean SOFA score of 12.8 ± 0.7. The mortality rate was significantly lower in the DDPC group (16.7, vs. 88.9%, $p = 0.01$). The ratio of successful ECMO weaning was significantly higher in the DDPC group than in the conventional group (100 vs. 33%, $p = 0.01$). Five patients in the conventional group developed osteofascial compartment syndrome and underwent incision and tensioning surgery (0 vs. 56% $p = 0.03$). One patient was amputated in the conventional group (0 vs. 11.1% $p = 0.40$). Furthermore, no recurrence of lower limb ischemia was noted in any patients in the DDPC group.

StO2 was noticeably increased 6 h later in the DDPC group. The lactate level was significantly increased 24 h later in the DDPC group, and the myohemoglobin was significantly reduced 48 h later in the DDPC group. These parameters did not change significantly in the conventional treatment group (**Table 2**; **Figure 2**).

DISCUSSION

In this study, we described a method to manage severe ALI developing on the IABP side in inpatients with ECMO and IABP support. To our knowledge, this is the first study comparing the outcomes of DDPC with conventional treatment in these patients. Our results showed that DDPC is associated with lower mortality. It could also reduce the rate of acute compartment syndrome.

The combined use of IABP in ECMO patients may reverse protracted aortic valve closure and impaired left ventricular unloading (11, 12). It can also increase the cerebral blood flow (13). However, Chen et al. reported that the concomitant use of IABP with ECMO did not appear to be associated with a dramatic change in survival outcomes. It increased the incidence of lower limb ischemia (14). ALI on IABP side patients has a poor prognosis with high mortality and a high incidence of acute compartment syndrome, despite the removal of IABP (15).

Haldun et al. used polytetrafluoroethylene external femoro-femoral bypass grafting in patients assisted with ECMO and IABP (16). However, this approach is complex and demonstrates a higher incidence of infection and thrombogenesis. In this study, we report our experience with DDPC in 6 patients with adult PCS shock receiving VA-ECMO with limb ischemia on the IABP side. This procedure is simple, with no bleeding or infection complications in the groin. None of the patients developed osteofascial compartment syndrome, and none needed amputation. The StO_2 was notably higher 6 h after DDPC. The markers of muscle injury peaked within 48 h with lower limb blood supply improvement. There were no significant differences in SOFA scores or Inotrope

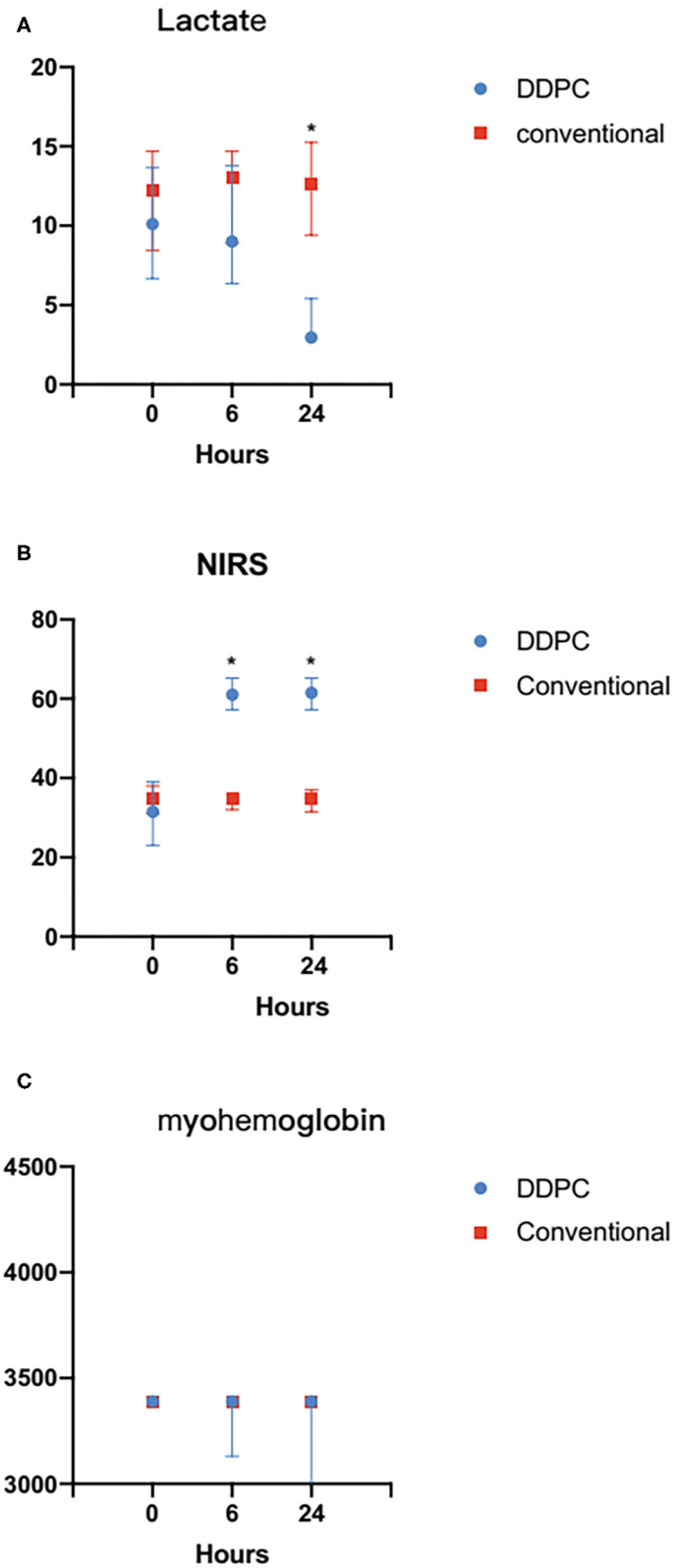

FIGURE 2 | (A) Compared with the conventional treatment group, the StO2 was significantly increased 24 h after ALI in the DDPC group. **(B)** Compared with the conventional treatment group, the Lactate level decreased significantly 24 h after ALI in the DDPC group. **(C)** There was no significantly change in myohemoglobin within 24 h between 2 groups. *$P < 0.05$.

scores between the two groups, indicating that the severity of the disease was similar between the two groups before grouping. There was a significant difference in prognosis between the two groups, and the mortality was significantly reduced in the DDPC group. The StO2 of the DDPC group was significantly increased after DDPC placement, and myoglobin and lactate were also significantly decreased. The results suggested that this might be due to the improvement of lower limb ischemia.

DDPC could be removed safely while ECMO was weaning. Contraction of the peripheral vessels caused by the large doses of vasoactive agents and poor cardiac output may be the main cause of limb ischemia in the early ECMO stage. With the stability of the circulation system and reduced use of vasoactive agents, the blood supply of the lower limbs gradually recovers.

Our study suggests that DDPC is a simple, safe, and effective method. It may play a vital role in patients with complications of lower limb ischemia on the IABP side following ECMO combined with IABP.

The study has several limitations. First, it was a non-randomized, retrospective, and observational study. The treatment strategies and monitoring methods that changed over time might have influenced the results of the study. Second, the number of patients included in this study was small, which may have prevented the detection of significant differences for other risk factors. Further multicenter studies are needed to corroborate the effectiveness of DDPC. Third, although pulse checks are still a routine diagnostic method for lower extremity ischemia in ECMO patients (17), advection perfusion of ECMO certainly has some influence on ABI, and whether this index needs to be corrected in ECMO patients needs further study to confirm.

CONCLUSION

DDPC could be an effective method for lower limb ischemia on the IABP side in patients who received femoro-femoral VA-ECMO and IABP, and was associated with reduced mortality in these 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 author/s.

DISCLOSURE

All authors had freedom of investigation and full control of the design of the study, methods used, outcome parameters and results, analysis of data, and production of the written report.

AUTHOR CONTRIBUTIONS

MX is in charge of writing the articles. XH is in charge of providing idea. XT and LW are in charge of data analysis. HW, JW, and MJ are in charge of research design. DH is in charge of Chart production. All authors contributed to the article and approved the submitted version.

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frontiers in Medicine

REVIEW
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Extracorporeal Membrane Oxygenation for Acute Toxic Inhalations: Case Reports and Literature Review

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Previous studies have shown that poisoning is a major threat to human health. Inhalation of acute toxic gas has been linked to serious health consequences. Among the antidotes for poisoning currently used, supportive care is the most common intervention in clinical practice. Severe acute respiratory distress syndrome (ARDS) and/or refractory cardiogenic shock or cardiac arrest caused by toxins are associated with high mortality and are difficult to treat. Extracorporeal membrane oxygenation (ECMO) is an aggressive supportive measure used to manage severely poisoned patients. This study presents two cases of acute toxic gases inhalation, severe ARDS and circulatory instability induced by bromine inhalation, and ARDS induced by nitric acid inhalation which were successfully treated with ECMO. The ECMO techniques used in the animal models and in human cases to treat severe poisoning are described as well as the indications, contraindications, complications, and weaning of ECMO.

Keywords: extracorporeal membrane oxygenation, acute toxic inhalation, poisoning, ARDS, cardiogenic shock, cardiac arrest

INTRODUCTION

Poisoning causes a detrimental effect to human health. The 37th Annual Report of American Association of Poison Control Center's (AAPCC) National Poison Data System (NPDS) showed that there were 2,148,141 cases of human toxicological exposure in 2019. In addition, 2,048 out of 2,619 deaths were identified as exposure-related fatalities whereas 1,688 (81.4%) of the 2,048 fatalities were identified as drug exposure cases. The main exposure routes were ingestion (80.1%), inhalation/nasal (8.15%), and parenteral (5.24%). Furthermore, the most human toxic exposures were unintentional (76.6%) (1). The Centers for Disease Control and Prevention (CDC) reported that the incidence of mortality due to poisoning has been increasing in the past decade (2).

The previous studies define acute toxicity as the adverse effects of a substance resulting either from single or multiple exposures in short periods of time (usually less than 24 h) (3, 4). Acute toxic inhalation is considered an emergency in clinical practice. The previous studies have established that smoke, gases, and vapors are the most frequently inhaled substances (4, 5). Acute inhalation of toxic substances often occurs during the production, operation, storage, transportation, and other human factors. A National Occupational Exposure Survey (NOES) conducted from 1981 to 1983 estimated that more than 1,000,000 million workers in the United States were at risk of exposure

to respiratory irritants annually. However, the data from poison control centers have suggested that exposure to the toxic substances occurs more frequently in the home environment than at workplaces (6).

Inhalation of gases, mists, aerosols, fumes, or dust may irritate the lungs, cause acute respiratory distress syndrome (ARDS), asphyxiation, and cardiogenic shock (5). Respiratory failure or cardiogenic shock or cardiac arrest caused by acute toxic inhalation are related to significant mortality (7–9). Several antidotes have been used to control the damage caused by some toxins, such as hydroxocobalamin for cyanide, fomepizole for methanol, pralidoxime chloride, and atropine for organic phosphorus pesticide poisoning, and oxygen for carbon monoxide. However, such antidotes are not effective in all the cases. Extracorporeal membrane oxygenation (ECMO) is an external device that can provide cardiopulmonary support for patients. The previous studies reported successful use of ECMO in the treatment of severe ARDS (10, 11) and refractory cardiogenic shock or cardiac arrest (12–14) following its introduction. The studies have also reported the use of ECMO in both animal models and human cases with refractory shock and/or ARDS induced by intoxication or toxicant exposure (15–19). The randomized trials of ECMO in the poisoned patients with acute toxic inhalation have not yet been undertaken. The available evidence has been generated from observational cohorts, case series, and case reports (20). The previous studies have, however, reported that early initiation of ECMO can improve the outcome of severely poisoned patients when optimal conventional treatment failed (18, 21, 22). Therefore, ECMO is a potential treatment option for patients with acute toxic inhalation with refractory circulatory shock and/or ARDS. The previous studies have shown that ECMO helps in the recovery from acute incidents, or transition to or candidacy for long-term advanced therapies, such as surgical ventricular assist devices or transplants (14, 23, 24).

In the current study, two successful ECMO support cases for acute toxic gases inhalation with severe ARDS were elaborated. In addition, the current study described the ECMO techniques, an application of ECMO in poisoned patients, indications, contraindications, complications of use, and weaning of ECMO.

CASE REPORTS

Case 1

A 44-year-old man, working in a chemical plant, was accidentally exposed to bromine gas (Br_2). The worker became unconscious for 15 min and was transferred to an open-air setting by the colleagues, where the man gained consciousness after 10 min.

Upon admission to a local hospital, the man presented with several symptoms, such as dyspnea, vomit, fatigue, cough, pharyngalgia, and mental confusion. The patient remained conscious with the following vital signs: blood pressure 92/63 mmHg, pulse rate 94 beats/min, respiratory rate 22 breaths/min, temperature 36°C, oxygen saturation (80–85%) supported by mask ventilator assisted ventilation with inhaled 100% oxygen concentration. Arterial blood gases obtained before intubation were: pH 7.309, partial pressure of oxygen (PaO_2) 8.18 kpa, partial pressure of carbon dioxide ($PaCO_2$) 6.73 kpa, and bicarbonate concentration −0.9 mmol/L (P/F oxygen ratio was 61.5 mmHg). Despite inhaling 100% oxygen, the status of dyspnea did not improve but progressively worsened accompanied with profuse sweating and irritability. Moreover, a pronounced stridor could be heard. The physical examination revealed cyanosis of the lips and mouth, shortness of breath, three concave signs, and increased bilateral vesicular sounds. Because of laryngeal edema caused by Br_2 irritation and potential retention of secretions in the lower respiratory tract with a probable need for more than a week of respiratory support, a tracheotomy was performed immediately. A large amount of pinkish foamy secretions was discharged from the patient's mouth after tracheotomy. The clinical and laboratory investigations indicated that the pulse oxygen saturation (SpO_2) was less than 90% after assisted mechanical ventilation. A chest x-ray showed pulmonary edema with fluid-filled bilateral lungs (**Figure 1**). Subsequently, a single dose of methylprednisolone (80 mg) was administered intravenously. Considering the severity of the Br_2-induced injury, the patient was transferred to critical care center 4 h after Br_2 inhalation for definitive treatment.

At the critical care center, the patient received synchronized intermittent mandatory ventilation (SIMV), with initial settings of positive end-expiratory pressure (PEEP) of 12 cmH_2O, fraction of inspired oxygen (FiO_2) of 1.0, respiratory rate (*RR*) of 16 bpm, tidal volume (V_T) of 4 ml/kg, and plateau pressure (Pplat) $\leq$ 25 cmH_2O. In addition to the routine critical care, initial management included absolute bed rest, intravenous methylprednisolone, anticoagulation, energy and vitamin supplements, maintenance of water, electrolytes, and acid-base balance. However, the condition of the patient worsened. Arterial blood gases recorded 48 h after mechanical ventilation were: pH 7.26, PaO_2 6.13 kpa, $PaCO_2$ 4.97 kpa, and bicarbonate concentration 2.4 mmol/L (P/F oxygen ratio was 46 mmHg). Thereafter, the patient was initiated on ECMO. Two cannulas were placed percutaneously by vessel puncture, guidewire placement, and serial dilation. One cannula (Edward 24F, Edwards Lifesciences Corp., CA, USA) was advanced into the right femoral vein; another (Edward 16F) into the right internal jugular vein. The assembled circuit (PLS heparin-coated ECMO kit, Edward) was primed. Initial ECMO flow settings were: blood flow of 4 L/min, sweep gas flow of 2 L/min, FiO_2 of 1.0, and temperature of the water bath was set at 36.8°C (adjusted according to arterial blood gas). The ventilator settings immediately pre-ECMO were: P-SIMV, PEEP 12 cmH_2O, FiO_2 0.5, RR 8 bpm, V_T 4 ml/kg, Pplat $\leq$ 25 cmH_2O. The patient was sedated with fentanyl and midazolam during cannulation and management for the first 12–24 h. Richmond Agitation-Sedation Scale (RASS) was −5. The neurologic examination was performed daily to ensure that the sedation was sufficient. Once the patient had stabilized on ECMO, all the sedatives and narcotics were stopped and resumed depending on the levels of anxiety and discomfort of the patient. Heparin (50–100 units per kg) was administered at the time of cannulation and continuously infused during ECMO. Heparin infusion was regulated to keep the activated partial thromboplastin time

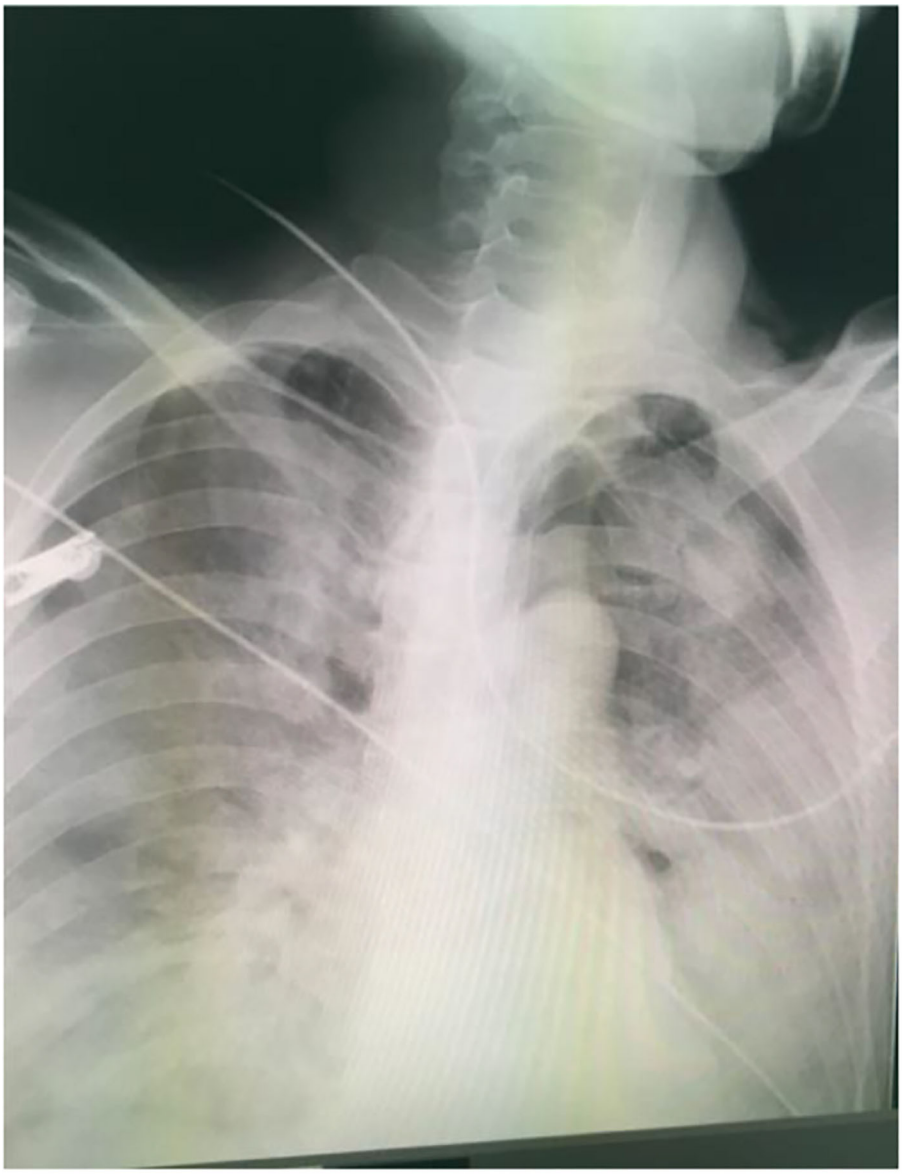

FIGURE 1 | Chest x-ray revealed pulmonary edema with fluid-filled bilateral lungs.

(APTT) at designated levels (usually 1.5 times the normal values for the APTT measurement system). Hemoglobin levels, blood platelet counts, and lactic acid accumulation were regularly detected to monitor the development of complications. The rest settings during ECMO support were: Ppeak 20–25 cmH_2O, PEEP 10–15 cmH_2O, RR 10 bpm, and FiO_2 0.4.

In addition to ECMO support, the pharmacologic diuresis and antibiotic treatment were administered. Respiratory parameters of the patient improved and the chest CT images showed that the bilateral infiltrations had regressed after 7 days of therapy. The patient was weaned off ECMO upon shock reversal and attaining stable condition. The arterial blood gases were analyzed when the patient was extubated: pH 7.47, PaO_2 98.3 mmHg, $PaCO_2$ 38.7 mmHg, and SpO_2 99%. The chest CT was performed on 2nd and 7th day after weaning (**Figure 2**). It was found that the lung edema had resolved. Follow-up chest CT after discharge from the hospital showed progressive improvement in the affected lung regions.

Case 2

A 41-year-old man with a history of hepatitis B, who was taking tenofovir disoproxil fumarate drugs, presented with the complaint of chest stuffiness and shortness of breath immediately after inhaling mixed chemical gas during unloading of concentrated nitric acid. The man was generally healthy with a normal hepatic function. However, the serum HBV-DNA level of

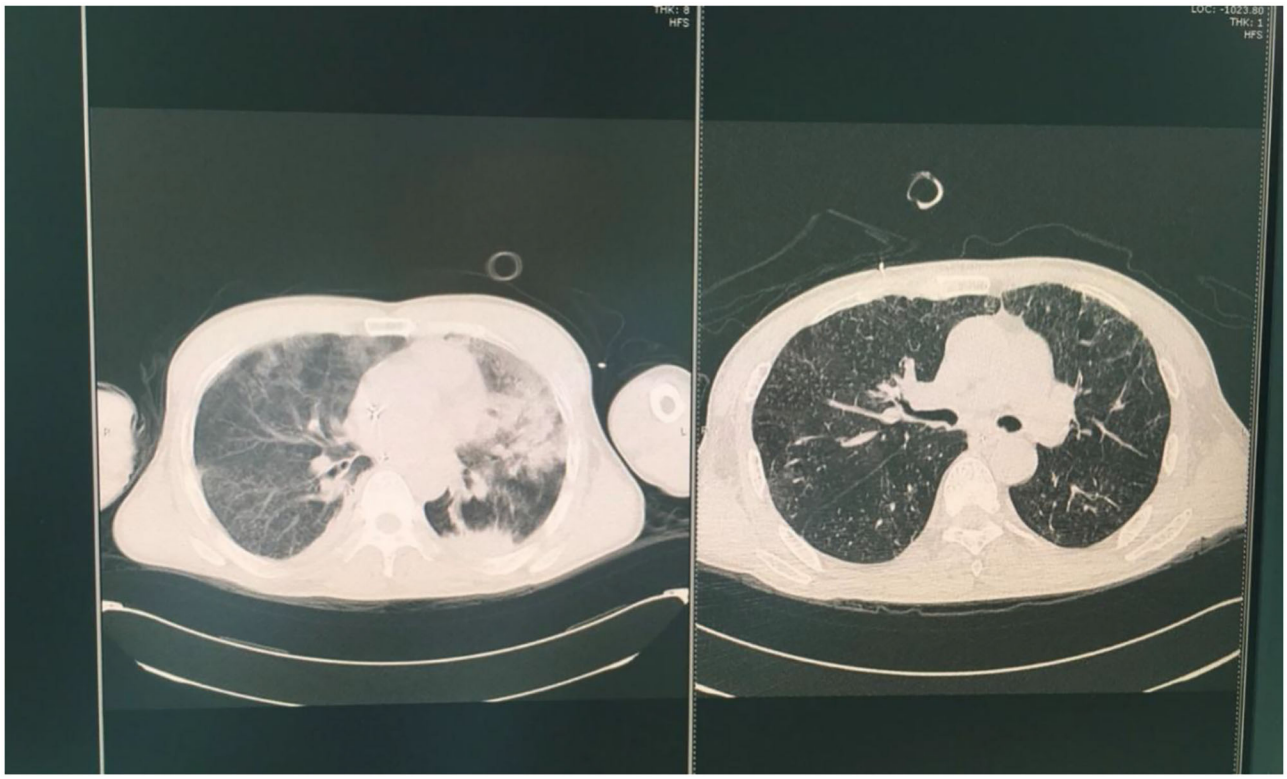

FIGURE 2 | The chest CT images on the second **(left)** and seventh day **(right)** after weaning.

this man was lower than the detection limit. Based on the reports from the factory, the mixed gas mainly comprised of NO_2, NO, and HNO_3, with a small amount of benzene.

Upon admission to a local hospital, the oxygen saturation was 94% after receiving nasal cannula oxygenation at a flow rate of 2 L/min. The symptoms of shortness of breath worsened 2 h after the nasal cannula oxygenation. Chest CT showed scattered exudation in bilateral lower lungs (**Figure 3A**). The patient was transferred to a local tertiary hospital where the man received high-flow oxygenation. Non-invasive ventilation was administered 14 h following the failure of high-flow oxygenation. At 9 h after admission to the intensive care unit (ICU), the patient was orotracheally intubated and mechanically ventilated due to progressive hypoxemia. However, the partial pressure of oxygen (PaO_2) dropped to 50 mmHg (P/F oxygen ratio was 62.5 mmHg) 4.5 h after mechanical ventilation. Chest CT showed extensive exudation and pleural effusion in bilateral lungs (**Figure 3B**). These findings indicated ARDS and veno-venous-ECMO (VV-ECMO) was performed immediately.

Two cannulas (23-19Fr) were advanced percutaneously *via* the right femoral vein for drainage and the right internal jugular vein for reinfusion. The assembled circuit (PLS heparin-coated ECMO kit, Maquet, Germany) was primed. The initial ECMO flow settings were: blood flow of 4.5 L/min, sweep gas flow of 4.5 L/min, FiO_2 of 1.0, temperature of the water bath was set at 36°C (adjusted according to arterial blood gas). The ventilator settings immediately pre-ECMO were: P-SIMV, PEEP 10 cmH_2O, FiO_2 0.3,RR 10 bpm, V_T 4 ml/kg, and Pplat $\leq$ 25cmH_2O. The patient was sedated with remifentanil and midazolam during cannulation and management for the first 12–24 h. RASS was −5. The neurologic examinations were done daily to ensure that the sedation was sufficient. Heparin (50–100 units per kg) was administered at the time of cannulation, and then through continuous infusion during ECMO. Heparin infusion was regulated to keep APTT within designated levels (usually 1.5 times normal for the APTT measurement system). The hemoglobin levels, blood platelet counts, and lactic acid accumulation were measured regularly to monitor the occurrence of complications. The rest settings during ECMO support were: Ppeak 20–25 cmH_2O, PEEP 10–15 cmH_2O, RR 10 bpm, and FiO_2 0.4.

In addition to ECMO, the patient received intravenous methylprednisolone, prone ventilation, and nasogastric gavage with N-acetylcysteine and pirfenidone. The patient was weaned off successfully 71 h after ECMO support and was extubated 16 h later. Chest CT (**Figure 3C**) showed that the diffuse exudation and pleural effusion in bilateral lungs had significantly resolved. The chest CT revealed progressive remission of exudative lesions in bilateral lungs 2 days after weaning (**Figure 3D**). The patient was discharged from the hospital 4 days after weaning. At 54 days after discharge, a follow-up chest CT showed that the lesions in bilateral lungs had almost resolved (**Figure 3E**). Lung

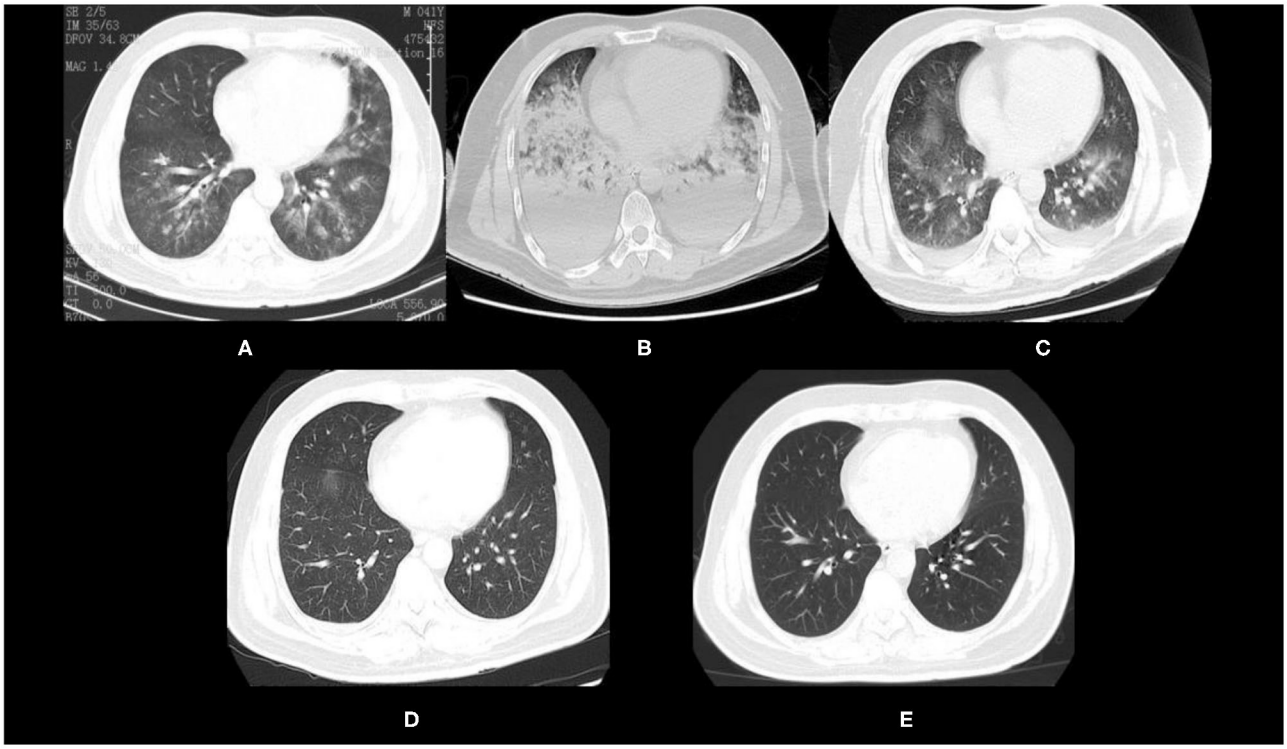

FIGURE 3 | Chest CT of the patient after mixed chemical gas inhalation. **(A)** Chest CT 2 h after inhalation. **(B)** Chest CT 20 h after ECMO initiation. **(C)** Chest CT after ECMO was weaned off. **(D)** Chest CT 2 days after weaning. **(E)** Chest CT 54 days after discharge.

function of the patient was normal 20 months later. The patient currently continues running and is said to have completed a full marathon recently.

ECMO TECHNIQUES

Extracorporeal membrane oxygenation, an auxiliary technique for respiratory and circulatory support, is increasingly being applied in clinical practice. ECMO drains the hypoxic blood from the venous system through the venous cannula. Then, the blood is oxygenated by a membrane oxygenator and pumped back to the patient through a second cannula (9, 25, 26). There are two ECMO modalities; VV-ECMO and veno-arterial-ECMO (VA-ECMO). In VV-ECMO, the blood is drawn from the peripheral vein, often femoral vein, oxygenated and decarboxylated in a dedicated extracorporeal rotor/oxygenator device and pumped back to the right atrium through a cannula. However, VV-ECMO only provides respiratory support and is primarily used in ARDS patients (9, 26). In VA-ECMO, hypoxic blood is drawn from the vicinity of the right ventricle through a large bore cannula, which is usually percutaneously placed through the right jugular or femoral veins. The femoral vein is especially useful in emergency settings, for example, when cardiopulmonary resuscitation (CPR) is performed and chest compressions prevent proper, hygienic placement of the catheter through the right jugular vein. Then, the blood is pumped through the oxygenator and returned to the aorta *via* a large arterial catheter. VA-ECMO provides both respiratory and circulatory support and can be used in hemodynamically compromised patients. Therefore, ECMO is a potentially effective treatment modality for severely poisoned patients with severe ARDS and refractory cardiogenic shock or cardiac arrest.

ECMO FOR ACUTE TOXIC INHALATION

In toxicological studies, ECMO has shown positive effects in both the animal experiments and clinical cases. In the 1990s, this technique was found to significantly improve the survival of animals undergoing cardiac arrest after drug intoxication. Freedman et al. (16) reported that all lidocaine-induced cardiac arrest dogs survived through ECMO support, while the dogs treated with standard resuscitation had a mortality rate of 75%. In recent years, ECMO has also achieved promising results for the treatment of chemical gas poisoning-induced cardiac arrest animals. Simonsen et al. (27) treated carbon monoxide (CO)-poisoned pigs with ECMO and conventional mechanical ventilation, and found that ECMO significantly reduced the incidences of cardiac arrest and mortality in CO-poisoned pigs, when compared with the conventional mechanical ventilation group. Furthermore, after sequential ECMO treatment, the survival rates of conventional mechanical ventilation group were found to have improved. In a previous study, the Danish scientists successfully cannulated and established VA-ECMO for CO-induced cardiac arrest in the porcine models during airborne transportation (28). Although the animal study findings show that ECMO is effective in toxic gas-induced cardiovascular

compromise, the experiments using these models are not the same as real clinical settings. Therefore, the role of ECMO in the treatment of acute toxic inhalation should be explored further in the clinical studies.

The animal model as well as human case reports and case series have shown that ECMO has favorable outcomes for acute toxic inhalation. Smoke is a common toxin that causes acute inhalation injuries and ARDS that requires ECMO support. The cases of ECMO support for fire-induced smoke inhalation injuries (29–35) and zinc chloride inhalation from smoke bombs have been reported (36). Electronic cigarettes (e-cigarettes) are battery-powered devices that aerosolize various substances for inhalation, such as nicotine, tetrahydrocannabinol, cannabidiol, and flavoring agents that may contain diacetyl. However, e-cigarettes should be evaluated further because they also cause pulmonary toxicity (37). As of November 13, 2019, a total of 2,172 "e-cigarette or vaping product use-associated lung injury" (EVALI) cases had been reported to the CDC of the Unites States, with 42 confirmed deaths (1). Landman et al. (38) reported a case of vaping-associated severe acute bronchiolitis, which caused near-fatal hypercapnic respiratory failure requiring intubation and ECMO in a 17-year-old male. The patient was weaned from VV-ECMO and ventilator, tracheostomy tube removed, and was discharged after 47 days in hospital. Accidental powder inhalation is a potential problem for infants. Panarello et al. (39) reported a case of severe ARDS due to accidental inhalation of rice starch powder in a 17-month-old girl. The girl was successfully treated with VV-ECMO. Metal fume inhalation also causes an acute respiratory and circulatory failure, and ECMO has been successfully applied for the severely poisoned patients (40, 41). Toxic gas inhalation causes lung damage. ECMO is a salvage therapy for inhaled toxic gases, such as, ammonia (42), hydrofluoric acid (43), hydrochlogen chloride (44), volatile hydrocarbons (45), carbon monoxide (46, 47), phosgene (48), chlorine (49–51), humidifier disinfectants (52), nitric and hydrofluoric acids (53, 54), and aluminum phosphide (55).

We report two cases of successful ECMO treatment for toxic volatile chemical inhalation. Br_2, which is a reddish-brown fuming liquid with a unique odor and volatile at room temperature, is widely used as the raw material for the synthesis of pharmaceutical compounds, flame retardants, dyes, photographic chemicals, bleaches, and disinfectants. Br_2 causes damage to the eyes, skin, central nervous system, and respiratory system (56–58). Br_2 and hypobromous acid (HOBr), its hydrolysis product, are strong oxidants that initially react with antioxidants in the lung epithelial lining fluid after inhalation. The depletion of antioxidant stores promotes the reaction of Br_2 and HOBr with plasma membranes of lung epithelial cells to form reactive intermediates, such as brominated lipids, which injure the distal sites. Moreover, Br_2 inhalation promotes the intravascular hemolysis. The ensuing elevated free heme causes acute lung injury due to increased acute oxidative stress and inflammation in the lung tissues (59–61). During ECMO, we regularly monitored the hemoglobin levels, however, we did not observe intravascular hemolysis. Maybe, the heme levels could have been elevated, but the elevated level did not attract our attention. The inflammatory responses due to Br_2 exposure worsens the initial pulmonary and systemic injuries, which in turn, aggravates the lung damage due to released inflammatory mediators. Inhalation of Br_2 leads to various pulmonary symptoms, such as cough, dyspnea, hypoxia, or even death due to respiratory failure in the adults (56). There is no specific antidote for Br_2 inhalation. Therefore, the first intervention step is to quickly move the patient out of the toxic environment, followed by the administration of appropriate therapies for symptomatic and supportive care, such as assisted ventilation, bronchodilators, and antibiotics. In our case, the patient was unresponsive to the conventional treatment, which prompted the initiation of ECMO for cardiopulmonary support. After 7 days of ECMO treatment, the condition of the patient improved and then, was successfully weaned off the treatment. To the best of our knowledge, this is the first reported case of successful ECMO treatment for Br_2 inhalation-induced ARDS.

Nitric acid is a strong acid and an oxidizing agent for various applications. One of its main uses include the production of ammonium nitrate in the fertilizer industry and other industrial applications. Pure HNO_3 is a colorless liquid with a boiling temperature of 84.1°C and can partially decompose to form nitrogen dioxide (NO_2). When exposed to air, pure HNO_3 releases white fumes while HNO_3 admixed with NO_2 liberates reddish-brown vapors (62, 63). The applications of HNO_3 generate various oxides of nitrogen, such as nitic oxide (NO), dinitrogen trioxide (N_2O_3), dinitrogen tetroxide (N_2O_4), and dinitrogen pentoxide (N_2O_5) (63). The inhalation injuries attributed to HNO_3 and its oxidized derivatives have been shown to cause acute local tissue inflammation within the lower respiratory tract (63). With regards to the human exposure, NO_2 is the most important nitrogen oxide. Specific mechanisms leading to lung injury following HNO_3 exposure have not been fully elucidated. However, it has been postulated that these injuries are due to a combination of free radical injuries, NO_2 generation of nitric acid after mucosal membrane contact, decrease in α-1-progease inhibitor, lipid peroxidation, thiol oxidation, and 3-nitrotyrosine formation (64). These deleterious effects lead to slough of tracheobronchial mucosa and are frequently accompanied by the direct toxic effects to the airways at the cellular level, which trigger the inflammatory cascade responses. The symptoms of HNO_3 inhalation injury have been generalized into three phases, namely, acute, subacute, and delayed onset phases (63). In this study, acute exposure led to an immediate onset of chest tightness and shortness of breath. Subsequently, the patient presented with subacute symptoms, such as dyspnea and generalized weakness. Then, within 24 h after exposure, the patient quickly presented with delayed symptoms, such as dyspnea, tachypnea, bronchospasm, and cyanosis, which indicated pulmonary edema and ARDS. The symptomatic treatment of lung inhalation injury from HNO_3 has been shown to be largely supportive, and it remains unstandardized (63). Kido et al. (65) reported a case of HNO3-induced pulmonary injury with improvement after corticosteroid administration. Meaden et al. (63) reported a case of pulmonary edema occurring after HNO_3 inhalation, which improved after the bronchodilator treatment. We report the

first case of successful ECMO treatment for ARDS after HNO_3 inhalation, thereby, providing a new treatment modality for HNO_3 inhalation-induced ARDS.

Of note, differences in the application of VV-ECMO for the management of toxic gas inhalation and other conditions should be noted. The patients with toxic gas inhalation are more prone to secondary infection and sepsis due to damage of the respiratory tract caused by the toxic gases compared with the patients with other ECMO indications. Therefore, monitoring body temperature, complete blood count, procalcitonin (PCT), and other infection indicators should be carried out during ECMO management. Full caloric and protein nutritional support are essential. High-dose, short-course methylprednisolone was administered in the early stages of both the cases. Although there was no evidence of reduced mortality, it improved the conditions of patients in our cases. In case 1, the patient was subjected to tracheostomy for laryngeal edema, therefore, the patient was at risk of infections. Appropriate antibiotics were administered to prevent the infections. Pharmacologic diuresis is important for edema clearance. In case 2, the patient was subjected to prone ventilation, which may have a positive effect on the rapid recovery from ARDS. The percutaneous cannulations were performed through the right femoral vein and the right internal jugular vein. Heparin was administered at the cannulation time and continuously infused during ECMO. Two patients were sedated. After the patient had stabilized on ECMO, all the sedatives and narcotics were stopped and resumed depending on the levels of anxiety and discomfort of the patient.

Although an increasing number of cases report the successful use of ECMO for acute toxic inhalations, evidence is majorly from the case reports and case series. We conclude that, when optimal conventional treatments fail, ECMO is a potential treatment modality for severe ARDS induced by acute toxic inhalations. However, large observational studies and randomized clinical trials should be conducted to support the effects of ECMO.

INDICATIONS, CONTRAINDICATIONS, AND COMPLICATIONS FOR ECMO IN POISONED PATIENTS

Extracorporeal membrane oxygenation provides effective gas exchange, reduces mechanical ventilation intensity, allows adequate lung rest, and improves patient outcomes. With the increasingly mature clinical applications of ECMO, there are many successful applications of ECMO in patients with irritant gas poisoning. ECMO improves the prognostic outcomes for severe hypoxemia and severe decompensated hypercapnia under optimal mechanical ventilation. Currently, this technique is a popular treatment option for medical toxicologists. However, it is not a standard treatment alternative as it lacks therapeutic evidence from large poisoning-based observational studies and randomized clinical trials. Indications for the poisoned patients are still under investigation. It has been recommended that ECMO can be initiated as soon as severely poisoned patients become unresponsive to optimal conventional interventions and have no contraindications for ECMO support.

Indications

Veno-venous-extracorporeal membrane oxygenation is recommended for respiratory failure when cardiac function is adequate or moderately depressed in the poisoned patients. It is also indicated for when the risk of mortality is greater than or equal to 80% (66). Approximately 80% mortality is associated with $PaO_2/FiO_2 < 100$ on $FiO_2 > 90\%$ and/or Murray score 3–4, age-adjusted oxygen index (AOI) >80, age, PaO_2/FiO_2 ratio, and plateau pressure (APSS) of eight despite optimal care for 6 h or less (66–69). VA-ECMO is recommended for poisoned patients with refractory cardiogenic shock or cardiac arrest and/or ARDS who are unresponsive to resuscitation, high-dose of vasopressors, transcutaneous cardiac pacing, and intra-aortic balloon pump (IABP), to provide cardiopulmonary support and maintain end-organ perfusion.

Contraindications

Few absolute contraindications for ECMO have been reported. They include severe irreversible non-cardiac organ failure limiting survival (e.g., severe anoxic brain injury or metastatic cancer), and irreversible cardiac failure if the transplantation or long-term ventricular assist devices are not considered (70). Moreover, ECMO treatment is absolutely contraindicated in the preexisting or acute conditions that are incompatible with recoveries, such as neurologic injury or end-stage malignancy that preclude a meaningful chance of intermediate-term survival or functional recovery (14). The relative contraindications for ECMO include severe coagulopathy or contraindications for systemic anticoagulation, such as advanced liver disease. Limited vascular access (severe peripheral arterial disease, extreme obesity, and amputated limbs), central as well as axillary cannulation are considered alternatives. Unrepaired aortic dissection, in which VA-ECMO flow may cause the additional fenestrations or propagate dissection flaps, should be cautiously performed, and acute aortic insufficiency that cannot be surgically corrected almost immediately is prohibited (14). Other relative contraindications include mechanical ventilation at high settings ($FiO_2 > 90\%$, plateau pressure > 30 cmH_2O) for 7 days or more and major pharmacologic immunosuppressions (absolute neutrophil count $<400/mm^3$). Even though the increasing age is associated with increased risks, no specific age contraindications have been reported (69).

Complications

Although ECMO has many clinical benefits, it also has notable complications. Severe potential complications include bleeding, thromboembolism, neurological injury, infection, limb ischemia, acute kidney injury, and homolysis (9, 14, 70–72).

WEANING

There is no universal method for determining whether ECMO can be successfully weaned and decannulated, however, some general principles apply.

In VV-ECMO, ECMO flow is decreased in steps to 1 L/min at sweep FiO_2 100% or decreased to 2 L/min, then sweep FiO_2 is decreased to maintain $SaO_2 > 95\%$. When SaO_2 is stable in these settings, trial off by adjusting the ventilator to lung protective ventilation settings (rate, plateau pressure, PEEP, and FiO_2). Maintain blood flow and anticoagulation, stop the sweep gas, and cap off the oxygenator. If SaO_2 >95% and $PaCO_2 < 50$ mmHg $\times$ 60 min, the cannulas can be removed whenever the patient is ready, but ideally after heparin has been turned off for 30–60 min (69).

In VA-ECMO, the first step is a holistic evaluation of the clinical status of the patient. Stable pulmonary status and euvolemia are particularly important (14). ECMO flow is decreased by approximately 1 L/h over a period of 3–4 h, although the slower rates of weaning at 0.5 L every 6–24 h have been reported (70, 73). The patient should be able to maintain mixed venous saturation >65%, and arterial saturation of >90% with an ECMO flow <1.5 L/min (70). In case of decompensation signs, the bridge is clamped, and the patient is placed back on full support (70, 74).

CONCLUSIONS

An increasing number of successful ECMO treatment cases for acute toxic inhalations have been reported. However, the randomized clinical trials are needed to elucidate the survival benefits and to help develop the clinical guidelines and indications for ECMO initiation in acute poisoning. Although the evidence for the clinical applications of ECMO is mainly derived from the retrospective studies, case reports, and case series, we conclude that ECMO is a potential salvage therapy for severe ARDS and refractory cardiogenic shock or cardiac arrest induced by severe toxicological exposures. However, it should be noted that ECMO is a bridge to recovery, to a more durable bridge, to a definitive treatment, or to a better clinical decision, and is a powerful tool that should be used judiciously. Furthermore, all the caregivers involved in the poisoning treatment should be educated on the potentially lifesaving ECMO technology, its indications, complications, and weaning.

AUTHOR CONTRIBUTIONS

DY, ZL, and SJ conceptualized and wrote the manuscript. ZXL, PL, LF, ZL, and SJ treated the patient as described in this study. ZL and SJ revised the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Extracorporeal Membrane Oxgenation for Rapidly Progressive Interstitial Lung Disease Associated With Clinically Amyopathic Dermatomyositis in a Post-partum Woman

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Background: Clinically amyopathic dermatomyositis (CADM) presented with rapid progressive interstitial lung disease (RP-ILD) is rare. Here, we present a case of a post-partum female with CADM complicated by severe RP-ILD managed with venovenous extracorporeal membrane oxygenation (V-V ECMO).

Case Summary: A 36-year-old woman was referred to a local hospital with cough and fever. She had a history of facial erythema and cough since an induction of labor for a stillborn fetus 2 months ago. Her status developed into RP-ILD with mediastinal emphysema and subcutaneous emphysema after admission, and V-V ECMO was initiated. After several failed attempts to wean the patient from ECMO, a decision was made to place the patient on the lung transplant waitlist. She underwent a double lung transplant on ECMO day 31 and received tacrolimus as an immunosuppressive regimen. The patient presented with positive anti-MDA5 and anti-Ro-52 antibodies and a high ferritin level, all of which indicated the presence of clinically amyopathic dermatomyositis (CADM). The patient was weaned from ECMO at 3 days after transplantation, but the patient's state of consciousness deteriorated, and head CT was considered for posterior reversible encephalopathy syndrome (PRES). After the temporary cessation of calcineurin inhibitors and a dosage reduction, the patient's state of consciousness returned to normal. Because of another disturbance of consciousness, the patient declined further treatment and was discharged 14 days after transplantation.

Conclusion: Early recognition of CADM can effectively improve patients' prognosis. ECMO should be considered as a supportive therapy in patients in acute respiratory failure secondary to RP-ILD.

Keywords: amyopathic dermatomyositis, extracorporeal membrane oxygenation (ECMO), interstitial lung disease (ILD), lung transplantation, posterior reversible encephalopathy syndrome (PRES), case report

INTRODUCTION

Clinically amyopathic dermatomyositis (CADM) is defined as the presence of typical cutaneous manifestations of dermatomyositis (DM) along with absent or minimal muscle weakness in DM (1). Population-based data suggest that CADM occurs in ∼20% of all adult DM cases (2), and the incidence of CADM is estimated to be 2.08 per 1 million persons (3). Patients with CADM have an increased risk of interstitial lung disease (ILD), and especially severe cases are complicated by life-threatening rapid progressive ILD (RP-ILD) (4), emphasizing the necessity and significance of early recognition and management of the disease. ILD more frequently occurs in patients with CADM and positive anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody, and these patients are more likely to progress to RP-ILD and refractory acute respiratory failure and often have a poorer prognosis than those with negative anti-MDA5 antibody (5).

For RP-ILD patients with critical hypoxemia or respiratory acidosis despite conventional therapies, particularly that accompanied by other respiratory complications, venovenous extracorporeal membrane oxygenation (VV-ECMO) may be a perfect choice. The treatment is sometimes a bridge to recovery, but limited options exist for CADM patients with refractory hypoxemia who fail to wean from ECMO (6). However, with no lung transplant consideration, using ECMO in such cases has been felt to be "bridge to nowhere" (7) due to the limited treatment response and overall options. The immunosuppressants used after transplants inevitably introduce complications; posterior reversible encephalopathy syndrome (PRES) is a common complication that manifests as various neurological symptoms (8). Tacrolimus, an important immunosuppressive drug for organ transplantation patients, is a major risk factor for PRES (9).

Here, we present the case of a post-partum female with CADM complicated by severe RP-ILD managed with VV-ECMO. Due to refractory respiratory failure, bilateral lung transplantation was eventually performed, but the patient ultimately developed posterior reversible encephalopathy syndrome.

CASE PRESENTATION

A 36-year-old previously healthy female visited a local hospital presenting with cough and fever. She had a history of spontaneous abortion twice and underwent induction of labor for a stillborn fetus 2 months before. Subsequently erythema on her face was noticed, accompanied by continuous cough, but no phlegm. Allergic disease was considered, and anti-allergic treatment was given, but her symptoms did not improve. Her condition was then managed with oral prednisolone for 10 days, and the facial erythema and cough disappeared. The patient's clinical course is shown in **Figure 1**.

On admission, the patient showed no cutaneous and muscular manifestations. Computed tomography (CT) of the chest showed bilateral ground glass opacities (**Figure 2A**). Anti-MDA5 antibody was not measured because there was no consideration of CAMD and ILD. After receiving antibiotic therapy for 12 days, the patient's status did not improve and worsened in later stages; the clinical manifestations were shortness of breath and dyspnea. CT of the chest showed bilateral pulmonary patchy infiltrates, and interstitial pneumonia was considered (**Figure 2B**). Shortly thereafter, the patient presented with acute hypoxemic respiratory failure (PaO_2/FiO_2: 68 mmHg), and intubation and mechanical ventilation were subsequently performed 3 days after admission. Using next-generation sequencing (NGS) of the bronchoalveolar lavage fluid (BLF) sample and cultured isolates from the patients, *Pseudomonas aeruginosa, Stenotrophomonas maltophilia,* and *Pneumocystis jirovecii* were found. Sulfamethoxazole (SMZ) was added for the treatment of pneumocystis pneumonia (PCP) caused by *Pneumocystis jirovecii*. The patient' s respiratory status continued to deteriorate, and mediastinal emphysema and subcutaneous emphysema developed 4 days after invasive ventilation.

VV-ECMO *via* the right internal jugular and right femoral vein cannulation was initiated on ventilator day 4, and she was then referred to the ECMO center. Laboratory investigations revealed that serum anti-Ro-52 was positive via ELISA, and serum ferritin (SF) was significantly higher without elevated serum muscle enzymes. NGS of BLF also showed *Pneumocystis jirovecii* and *Acinetobacter baumannii*; thus, antibiotic therapy and SMZ were continued. Considering the COVID-19 epidemic in China, the patient received a nucleic acid test for COVID-19, but the result was negative. CT of the chest showed bilateral pulmonary extensive infiltrates and lobular interstitium thickness, and pulmonary fibrosis was considered (**Figure 2C**). CT of the head was normal (**Figure 3A**), and the patient was conscious after withdrawal of the sedative. Although lung protective ventilation, recruitment maneuver and prone position ventilation were implemented, she did not tolerate attempts to wean from ECMO within 28 days of ECMO. She required continuous sedation and analgesia because of patient-ventilator asynchrony.

Therefore, a decision was made to place the patient on the lung transplant waitlist, and she was subsequently transferred to the transplantation center for lung transplant evaluation. Anti-MDA5 antibody was tested by ELISA, and the result was positive. Based on these findings, the patient was diagnosed with CADM and ILD. At 31 days of ECMO, the patient underwent a successful sequential double lung transplant and received tacrolimus as an immunosuppressive regimen after the transplant. Her explant pathology showed extensive consolidation of lung tissue and pulmonary interstitial fibrosis (**Figure 4**). The patient's respiratory status gradually improved, and CT of the chest showed bilateral pulmonary scattered infiltration (**Figure 2D**), which was improved compared with previous imageological diagnosis. ECMO was weaned successfully 3 days after transplant, and the patient's oxygenation status did not deteriorate with ventilator support. The patient's state of consciousness deteriorated, and she presented with coma. Head CT showed bilateral parieto-occipital low-density lesions, which were considered to be due to PRES (**Figure 3B**). Since the condition was considered to be related to immunosuppressive agents, tacrolimus was suspended for 1 day, and the dosage was gradually reduced to 0.5 mg/day, after which the patient's consciousness returned. Unfortunately, the patient developed a disturbance of

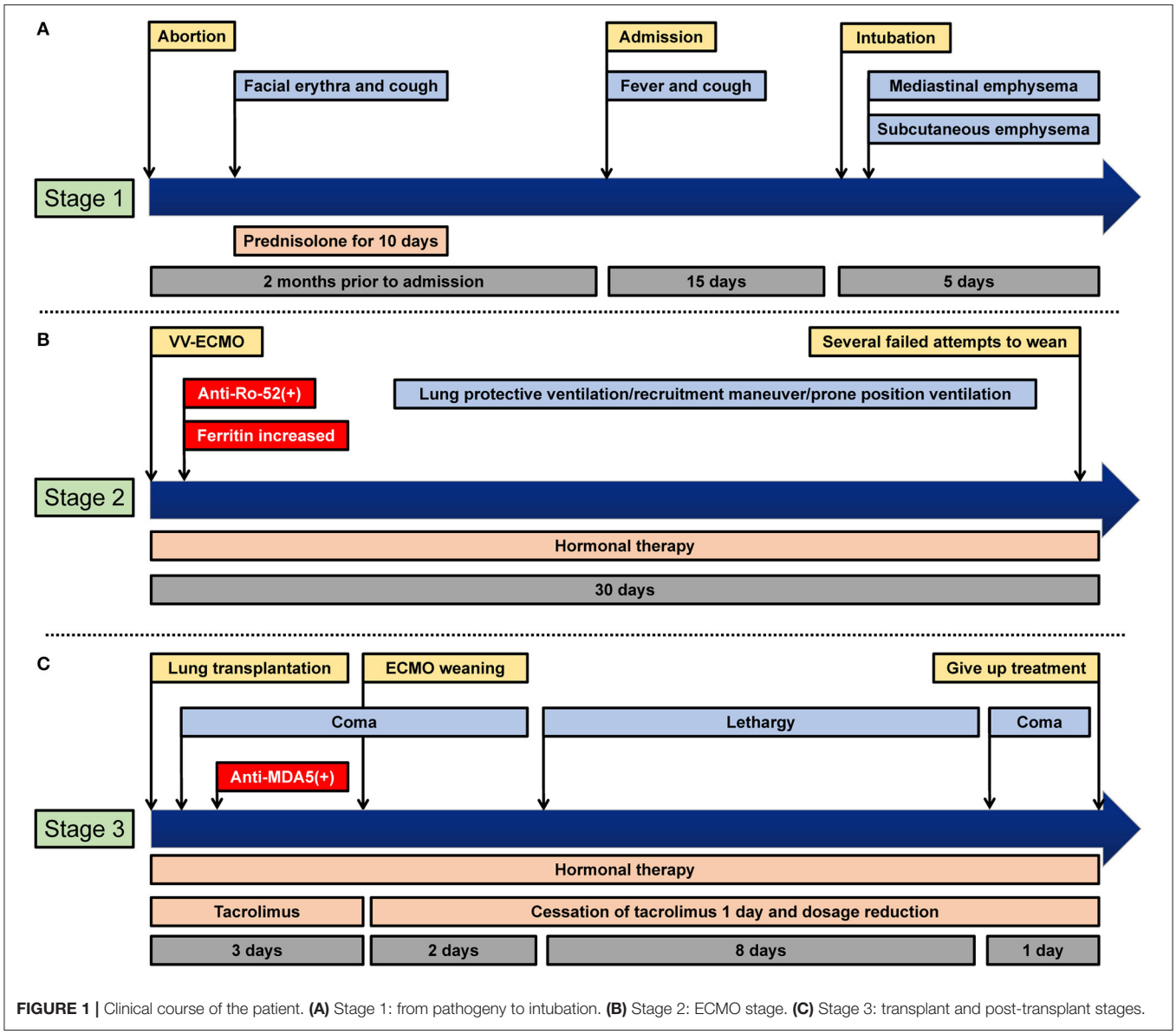

FIGURE 1 | Clinical course of the patient. **(A)** Stage 1: from pathogeny to intubation. **(B)** Stage 2: ECMO stage. **(C)** Stage 3: transplant and post-transplant stages.

consciousness once more after hemodynamic instability, which may be related to implant infection; consciousness did not return after active treatment. After 14 days of lung transplant, the patient declined further treatment for financial reasons and was discharged.

DISCUSSION

CADM typically presents with characteristic cutaneous manifestations of classic dermatomyositis without muscle involvement; almost all patients with CADM present at least one characteristic skin lesion (1). In our present case, because of the absence of traditional muscle findings and atypical skin lesions after hospitalization, the diagnosis of CADM can be a challenge. In this case, facial erythema was noticed after induction of labor for a stillborn fetus, and the symptom vanished after oral prednisone administration. Meanwhile, the patient presented with no myalgia, and her creatine kinase level was normal during subsequent hospitalization. Unfortunately, this patient's symptoms were neglected in the local hospital for the first visit, leading to misdiagnosis. For pregnant and post-partum women, we may need to pay more attention to patients' autoimmune diseases, so as to provide patients with the proper diagnosis and treatment timely.

Patients with CADM are often combined with ILD. It is known that RP-ILD is more common in the CADM subset. Main common strategies for CADM include glucocorticoid pulse therapy and immunosuppressive therapy. Both drugs are often used together and considered to be valid. Furthermore, calcineurin inhibitors, plasma exchange, and hemoperfusion can be alternatives to these drugs when the combination therapy didn't work well. The patient initially presented with interstitial

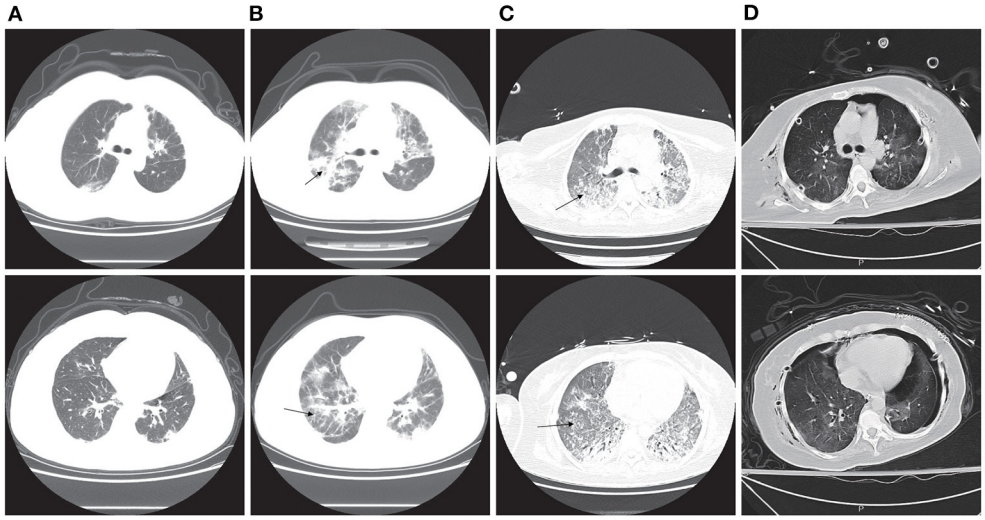

FIGURE 2 | Computed tomography (CT) image of the chest. **(A)** CT of the chest shows bilateral ground glass opacities 9 days before intubation. **(B)** CT of the chest shows bilateral pulmonary patchy infiltrates, which was considered as interstitial pneumonia 3 days before intubation (arrowheads). **(C)** CT of the chest shows bilateral pulmonary extensive infiltrates and lobular interstitium thickness, which was considered as pulmonary fibrosis 23 days after ECMO (arrowheads). **(D)** CT of the chest showed bilateral pulmonary scattered infiltration 3 days after lung transplantation.

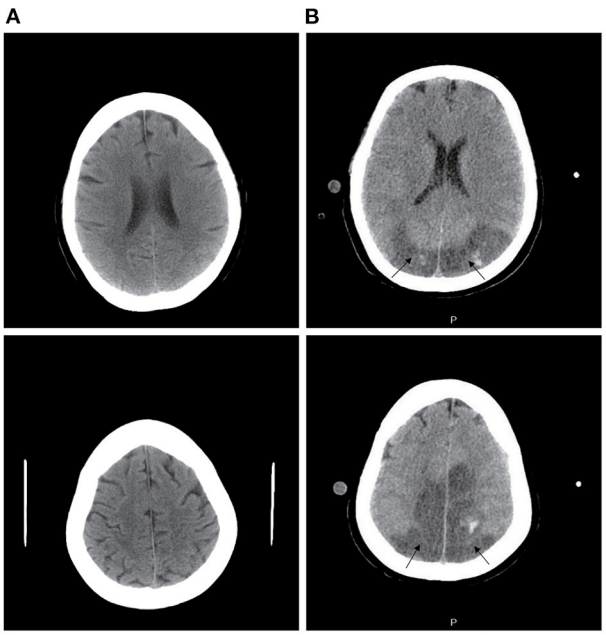

FIGURE 3 | Computed tomography (CT) image of the head. **(A)** CT of the head is normal at the ECMO stage. **(B)** CT of the head shows bilateral parieto-occipital low-density lesions at day 3 after transplantation (arrowheads).

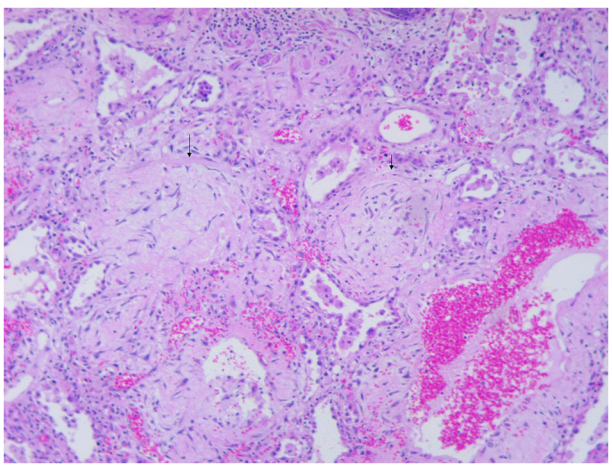

FIGURE 4 | Microscopic examination of the explanted lung (hematoxylin-eosin stain, ×50) shows extensive consolidation of lung tissue and pulmonary interstitial fibrosis (arrowheads). Ring fibrosis connecting alveolar orifice rings and inflammatory cell infiltration into the alveolar walls with pneumocyte hyperplasia and squamous metaplasia.

pneumonia and then developed refractory respiratory failure very quickly. Despite maximum respiratory support and the corresponding treatment, the patient's status was aggravated continuously with a life-threatening hypoxemia. The mechanism of onset of RP-ILD is ill-informed; reports have suggested that the condition is highly correlated with CADM and MDA5 antibody positivity (10). High SF has been shown to be another important indicator of poor prognosis of RP-ILD in CADM. The SF levels are reported to be higher with positive anti-MDA5 antibody than with negative anti-MDA5 antibody and higher in non-survivors than in survivors (11). Furthermore, anti-Ro-52 is also a risk factor for ILD in CADM (12). The patient experienced pneumomediastinum and pneumothorax with the development

of CADM and RP-ILD. Pneumomediastinum has also been reported to be more common in CADM patients with positive anti-MDA5 antibody than in patients with negative anti-MDA5 antibody (13). These reports indicate that our patient had a high anti-MDA5 antibody titer, a high anti-Ro-52 antibody titer, a high ferritin level, and the complications of pneumomediastinum and pneumothorax, all of which indicated the diagnosis of clinically amyopathic dermatomyositis and showed a poor prognosis.

ECMO provides temporary cardiopulmonary support in patients with severe but potentially reversible cardiac and/or respiratory failure unresponsive to maximal conventional management. While it does not reverse the underlying lung disease, it acts as a bridge to recovery by offering patients more time for treatment therapies to take effect. It can also reduce ventilator-induced lung injury and oxygen toxicity caused by mechanical ventilation, which can add further damage to already damaged lungs. Last, chronic systemic disease or refractory end-stage pulmonary disease, which was resistant to conventional therapy, was considered a contraindication to ECMO in the past. Pulmonary interstitial fibrosis associated with RP-ILD in CADM is a rare indication for lung transplantation. However, ECMO can provide additional time for these patients who are being considered for lung transplant, and there are some reports of lung transplantation for RP-ILD (14). In the course of this patient, decreasing oxygenation index (PaO_2/FiO_2) and pneumomediastinum are clear indications of ECMO initiation in this patient, with oxygenation index showing collapsing pulmonary diffusion function and pneumomediastinum indicating the patient's own extreme breathing effort. On the other hand, ventilator maintenance of nearly 4 days prior to ECMO initiation avoids irreversible lung damage from prolonged mechanical ventilation.

Although after lung protective ventilation strategy, lung recruitment maneuver and prone position were all performed to support ECMO, pulmonary interstitial fibrosis gradually occurred, and the patient did not tolerate attempts to wean from ECMO. Our case indicates that ECMO has shown to be a valid rescue therapy in acute refractory respiratory failure secondary to RP-ILD and made further diagnosis and treatment possible. Although this patient did not completely recover her health in the end, ECMO added time to make an accurate diagnosis and offered the patient the opportunity for a lung transplantation.

Tacrolimus, a calcineurin inhibitor, is an effective immunosuppressive agent for the prevention of organ transplant rejection. Whereas, PRES is a rare and serious neurologic complication of tacrolimus. With binding to immunophilins to inhibit the calcineurin-mediated calcium-dependent signaling pathways, tacrolimus can activate T cells and IL-2. Meanwhile, calcineurin is also a mediator of neuronal function and drug toxicity is supposed to occur through impaired vasoconstriction of cerebrovascular vessels and dysregulation of the blood-brain barrier (9). Temporary cessation of tacrolimus and gradual reduction of the dosage may be effective strategies for managing PRES. However, these managements include risks of reducing immunosuppression, thereby leading to acute rejection. In our case, the strategy is to suspend tacrolimus for 1 day and gradually reduce the dosage to 0.5 mg/day. During the therapy, this patient's tacrolimus blood concentration was monitored once a day after lung transplantation and ranged from 2.7 to 18.6 ng/ml. The patient's neurological symptoms improved temporally, and signs of acute rejection were absent.

In conclusion, when patients experience RP-ILD for no apparent reason, CADM should be considered, especially in post-partum patients who are positive for anti-MDA5 and anti-Ro-52 antibody and have a high ferritin level and complications of pneumomediastinum and pneumothorax. ECMO should be considered as a supportive therapy and initiated early in patients in acute respiratory failure secondary to RP-ILD since it could provide a true opportunity to improve survival for such a rare disease and its potentially deadly complications. In cases of refractory respiratory failure and pulmonary fibrosis, lung transplant may be an option. PRES is not very common, but more attention should be paid to the patients who are using immunosuppression drugs. Our findings suggest that temporary cessation of tacrolimus and dosage reduction may be effective management strategies for PRES. The results of our case are frustrating, but more experience and further studies are needed to evaluate the true value of this method.

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) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Safety and Efficacy of a Novel Centrifugal Pump and Driving Devices of the OASSIST ECMO System: A Preclinical Evaluation in the Ovine Model

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Background: Extracorporeal membrane oxygenation (ECMO) provides cardiopulmonary support for critically ill patients. Portable ECMO devices can be applied in both in-hospital and out-of-hospital emergency conditions. We evaluated the safety and biocompatibility of a novel centrifugal pump and ECMO device of the OASSIST ECMO System (Jiangsu STMed Technologies Co., Suzhou, China) in a 168-h ovine ECMO model.

Methods: The portable OASSIST ECMO system consists of the control console, the pump drive, and the disposable centrifugal pump. Ten healthy sheep were used to evaluate the OASSIST ECMO system. Five were supported on veno-venous ECMO and five on veno-arterial ECMO, each for 168 h. The systemic anticoagulation was achieved by continuous heparin infusion to maintain the activated clotting time (ACT) between 220 and 250 s. The rotary speed was set at 3,200–3,500 rpm. The ECMO configurations and ACT were recorded every 6 hours (h). The free hemoglobin (fHb), complete blood count, and coagulation action test were monitored, at the 6th h and every 24 h after the initiation of the ECMO. The dissection of the pump head and oxygenator were conducted to explore thrombosis.

Results: Ten sheep successfully completed the study duration without device-related accidents. The pumps ran stably, and the ECMO flow ranged from 1.6 ± 0.1 to 2.0 ± 0.11 L/min in the V-V group, and from 1.8 ± 0.1 to 2.4 ± 0.14 L/min in the V-A group. The anticoagulation was well-performed. The ACT was maintained at 239.78 ± 36.31 s, no major bleeding or thrombosis was observed during the ECMO run or in the autopsy. 3/5 in the V-A group and 4/5 in the V-V group developed small thrombus in the bearing pedestal. No obvious thrombus formed in the oxygenator was observed. The hemolytic blood damage was not significant. The average fHb was 0.17 ± 0.12 g/L. Considering hemodilution, the hemoglobin, white blood cell, and platelets didn't reduce during the ECMO runs.

Conclusions: The OASSIST ECMO system shows satisfactory safety and biocompatibility for the 168-h preclinical evaluation in the ovine model. The OASSIST ECMO system is promising to be applied in clinical conditions in the future.

Keywords: extracorporeal membrane oxygenation, centrifugal pump, critical care, ovine model, preclinical evaluation

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) has rescued many patients by providing pulmonary or cardiopulmonary support (1), especially during the COVID-19 pandemic (2). The ECMO circuit usually consists of a blood pump and its driver, an oxygenator, tubing and cannula, and several monitors (3). As a conventional ECMO system is composed of complex components, it is not always applicable on some special occasions, such as ECMO transportation and in-/out-of-hospital emergency conditions. Therefore, some portable devices were developed. Among those, Centrimag ECMO system (Levitronix LLC, MA, USA), Cardiohelp (Maquet Cardiopulmonary AG, Hirrlingen, Germany), Lifebox (Sorin, Milan, Italy), and Lifebridge B2T (Lifebridge Medizintechnik AG, Ampfing, Germany) were mostly used (4, 5). STMed has developed a novel portable ECMO system - the OASSIST ECMO System (Jiangsu STMed Technologies Co., Suzhou, China), consisting of a control console, a pump drive, and a single-use centrifugal pump. The pump was previously evaluated in hydraulic experiments, hemodynamic numerical simulations, and standard *in vitro* hemolysis experiments, showing good hydraulic performance and blood biocompatibility (6).

The purpose of this study was to evaluate the safety and biocompatibility of the OASSIST ECMO system in a 168-h ovine ECMO model.

MATERIALS AND METHODS

Study Plan

All animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC) of Fuwai Hospital [NO. 0101-2-20-HX(X)] and all procedures followed the NIH *Guide for the Care and Use of Laboratory Animals*. The experiment was completed at Beijing Key Laboratory of Pre-clinical Research and Evaluation for Cardiovascular Implant Materials, Animal Experimental Center of Fuwai Hospital (registration number: CNAS LA0009). All animals were subjected to routine quarantine and clinical examination before the experiment.

Ten healthy male Small Tailed Han sheep (Beijing Jinyutongfeng Trading Co., LTD, Beijing, China), 12–24 months old, were included in the study. All sheep had surgical implantation of the OASSIST ECMO system (Jiangsu STMed Technologies Co., Suzhou, China). Five underwent V-V ECMO (V-V group, $N = 5$) and five underwent V-A ECMO (V-A group, $N = 5$). The sheep were supported on ECMO for 168 h.

The OASSIST ECMO System

The OASSIST ECMO system consists of three components: the control console, the pump drive (OASSIST STM001), and the disposable centrifugal pump (STM CP-24 I) (**Figure 1**). The size of the control console is 290 × 260 × 210 mm, and the size of the pump drive is 200 × 190 × 110 mm. The control console sets pump speed and monitors operating parameters. The pump drive offers redundant direct control of the pump speed and flow/bubble detection, the battery of which could support for at least 180 min when alternating-current supply was interrupted. The centrifugal pump (**Figure 2**), driven by magnetic coupling, has a priming volume of 24 ml. The rotor of the pump has a contentious intersection area design to improve hydrodynamic efficiency, with a diameter of 45 mm. The rotating speed of the pump rates 1,000–5,500 rpm, and the optimal flow rate ranges from 3.0 to 5.0 L/min with a pressure head from 300 to 500 mmHg. And the pump could achieve a maximum flow rate of 8 L/min. The pump is designed to maximize its hydrodynamic efficiency and minimize shear stress.

Oxygenator and Cannula

Commercial membrane oxygenators with hollow polymethyl pentene (PMP) fibers were used for both V-V and V-A ECMO. For V-V ECMO, the oxygenator kit was Hilite7000LT (XENIOS, Heilbronn, Germany); the 23 Fr Avalon Elite (Maquet, Rastatt, Germany) double-lumen cannula (DLC) was used. For V-A ECMO, the oxygenator kit was Hilite7000LT (XENIOS, Heilbronn, Germany) and BE-PLS 2050 (Maquet, Rastatt, Germany); the 18 Fr arterial cannula (Edwards Lifesciences, Irvine, CA, USA) and 24 Fr venous cannula (Edwards Lifesciences, Irvine, CA, USA) were used.

Surgical Procedure

Anesthesia was induced with propofol (3–5 mg/kg) and maintained by isoflurane inhalation (2–3%) via mechanical ventilation and propofol injection (8–10 mg/kg/h). The right jugular vein of the V-V group; the right jugular vein and artery of the V-A group were exposed. A single-lumen central venous catheter was placed in the left jugular artery (arterial line), and a three-lumen central venous catheter was placed in the left jugular vein (venous line). Then, the initial systemic anticoagulation was induced by 120 IU/kg heparin. The target activated clotting time (ACT) of cannulation was higher than 250 s. The DLC was inserted under transthoracic echocardiography through the right internal jugular vein, with the tip positioned in the inferior vena cava. The arterial cannula was inserted through the right internal jugular artery, with the cannula descending 10–15 cm, while the venous cannula was inserted through the right jugular vein to the right atrium. Then, the pre-primed centrifugal pump head and

FIGURE 1 | Macro-inspection the OASSIST ECMO system. **(A)** The macro-inspection of the pump drive. **(B)** The macro-inspection of the control console. **(C)** The pump drive hold by a staff. **(D)** The control console hold by a stuff.

the oxygenator were connected to the cannula. The animals were extubated immediately when consciousness returned.

Measurement of the OASSIST ECMO System

The pre-set rotational speed was 3200-3500 rpm. An ultrasonic flowmeter (FBS 3/8" × 3/32") was located between the pump outlet and the oxygenator. Three pressure probes were located before the pump inlet (pre-pump pressure), between the pump outlet and the oxygenator (post-pump pressure), after the oxygenator (post-oxygenator pressure), respectively. The adaptive temperature probe can be inserted into the oxygenator.

Postoperative Care

The scheduled experiment duration was 168 h (h). The sheep were kept in the cage, conscious and feeding independently. A linen with four holes to put four legs in. And movement of the sheep's neck was restricted by another clause. The oxygenator was fixed to the cage, while the control console and the pump drive were placed on a cart (**Figure 3**). The heater-cooler was set at 38.5°C to maintain the normal body temperature of the sheep. In the first 24 h, flurbiprofen axetil (1–2 mg/kg) and dexmedetomidine (0.2–0.3 ug/kg●h) were administered intravenously. No sedation was needed after 24 h. Heparin was infused continuously to maintain ACT between 220 and 250 s. The initial heparin dose was 4–16 U/kg●h, and it was adjusted according to the ACT. Hemodynamic monitoring, intravenous fluids, drug injection, and blood sampling were conducted from the arterial and venous lines. After ECMO was weaned as scheduled, all sheep were euthanized by venous administration of potassium chloride (100 mg/kg) under the sedation of propofol (20 mg/kg).

Biocompatibility Measurements

The vital signs, ECMO parameters (including speed, flow rate, pre-pump pressure, post-pump pressure, post-oxygenator pressure), and ACT (Hemochron Signature Elite, Hemochron, MA, USA) were recorded every 6 h. The free hemoglobin

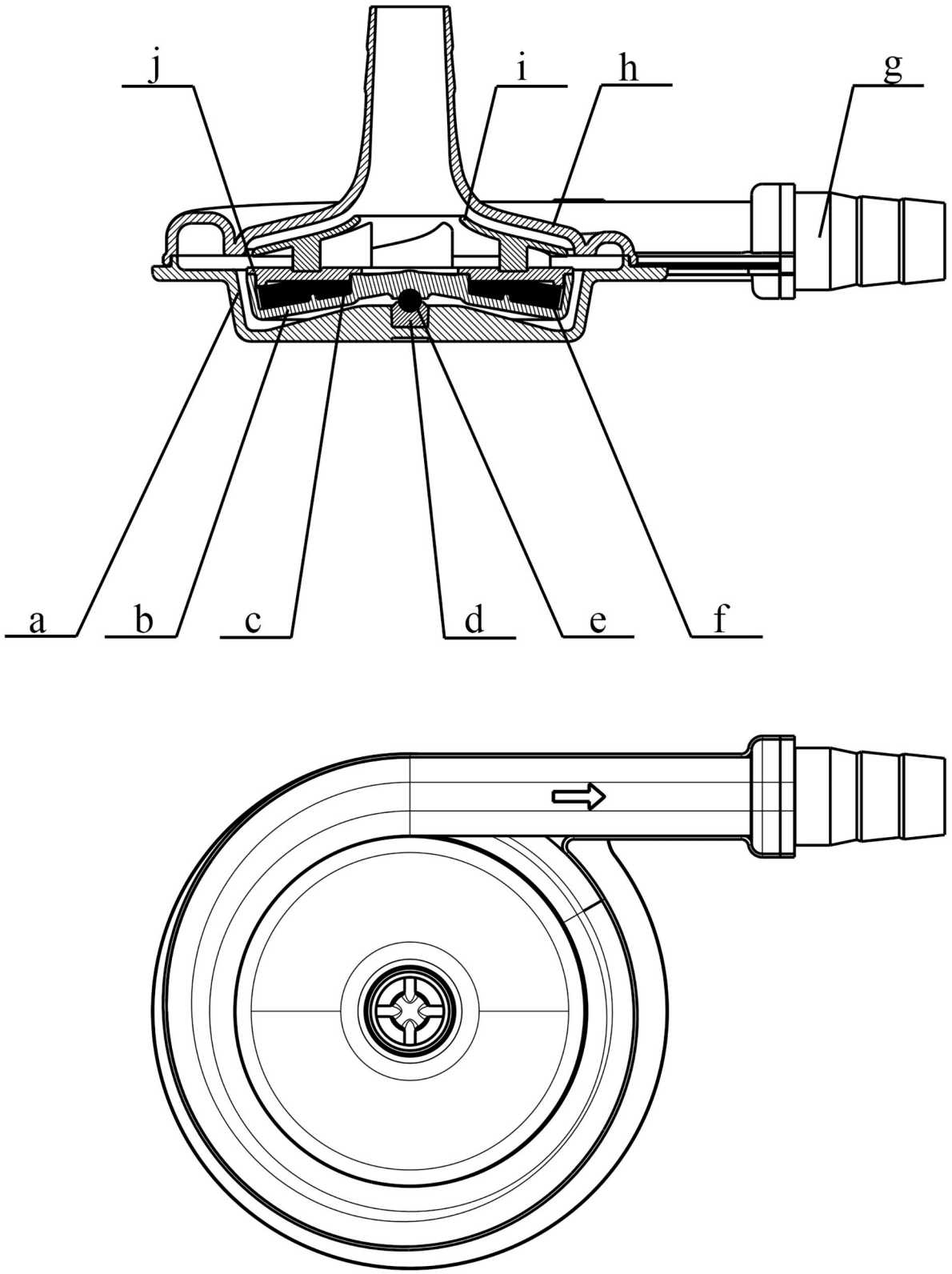

FIGURE 2 | Schematic view of the pump head (STM CP-24 I) of the OASSIST ECMO system. a. the lower case of the volute; b. rotor; c. supporting ring; d. bearing pedestal; e. bearing; f. internal magnet; g. connector; h. the upper case of the volute; i. impeller; j. cap.

FIGURE 3 | The sheep stayed conscious. The oxygenators were fixed to the cages, while the control console and the pump drive were placed on a cart.

(fHb) (DiaSpect T Low Hemoglobin Analyzer, DiaSpect Medical GmbH, Sailauf, Germany), complete blood count (ADVIA 2120i, Siemens Healthcare, Erlangen, Germany), and coagulation action test (Fully Automated Coagulation Analyzer SF-8050, Beijing Succeeder Technology Inc, Beijing) were monitored at the 6th h and every 24 h after the initiation of the ECMO. After 168 h, the sheep were sacrificed, and autopsies of major organs were performed to explore internal embolism, thrombosis, or bleeding. After washing with 0.9% saline solution, the pump head, and oxygenator were dissected to explore the thrombosis.

Statistical Analysis

All values were expressed as mean ± SD. Shapiro–Wilk test was used to test the normality of continuous variables. Normally distributed continuous variables were compared by Student's *t*-test and pairwise *t*-test, and non-normally distributed continuous variables were compared by the Mann–Whitney U-test or Wilcoxon test. All statistical testing was two-sided, and a p-value < 0.05 was considered significant. All statistical analyses were performed using GraphPad Prism 8 (GraphPad Prism, RRID:SCR_002798) and SPSS Version 26.0 (IBM SPSS Statistics, RRID:SCR_019096).

RESULTS

Overall Performance of the OASSIST ECMO System

Ten sheep successfully completed the study duration without device-related accidents. One oxygenator and pump in the V-V group were changed at the 28th h after the initiation of the ECMO, due to the coagulation following the primary thrombosis formed in the cannulation site during the surgical procedure.

The pumps ran stably, the ECMO flow ranged from 1.6 ± 0.1 to 2.0 ± 0.11 L/min in the V-V group, from 1.8 ± 0.1 to 2.4 ± 0.14 L/min in the V-A group. The average pre-pump pressure was −52 ± 14.81 mmHg, and the average post-pump pressure was 169 ± 17.67 mmHg during the ECMO run (**Table 1**; **Figure 4**).

Coagulation Status

The anticoagulation was well-performed. The baseline ACT was 165.88 ± 16.88 s. After systemic anticoagulation, the ACT was maintained at 239.78 ± 36.31 s, and there was no difference between V-V and V-A group [241.67 ± 41.69 vs. 237.89 ± 30.35, $p = 0.558$ (Mann– Whitney U-test)].

No major bleeding or thrombosis was observed during the ECMO run or in the autopsy. Thrombosis around the cannulation site in the V-V group occurred more frequently compared to that in the V-A group (4/5 in the V-A group and 3/5 in the V-A group), but no vascular occlusion or stenosis was observed. 3/5 in the V-A group and 4/5 in the V-V group developed small thrombus in the bearing pedestal of the pump, and no obvious thrombus formed in the oxygenator was observed (**Figure 5**).

Hemolytic Blood Damage Results

No sheep received blood product transfusion. The hemolytic blood damage was not significant. The fHb baseline was 0.26 ± 0.08 g/L. In a total of 80 tests of fHb after the initiation of ECMO, the average fHb was 0.17 ± 0.12 g/L. The fHb between the baseline and the 168th h was not statically different (0.26 ± 0.08 g/L vs. 0.18 ± 0.06 g/L, $p = 0.066$, Wilcoxon test). Considering hemodilution, we compared the hemoglobin, white blood cell (WBC), and platelets between the 6th h and the 168th h. No difference was observed in hemoglobin [101.2 ± 18.83 g/L vs. 95.9 ± 13.17 g/L, $p = 0.536$ (pairwise *t*-test)]. WBC and platelets elevated after 7-day ECMO [5.95 ± 3.52 × 10^3/L vs. 12.01 ± 5.47 × 10^3/L, $p = 0.013$ (Wilcoxon test); 204.3 ± 76.37 × 10^9/L vs.

TABLE 1 | Summary of ten sheep.

No.	Configuration	Weight (kg)	Duration (h)	Termination	Rotational speed (rpm)	Flow (L/min)	Pre-pump pressure (mmHg)	Post-pump pressure (mmHg)	Transmembrane pressure (mmHg)
VV1	V-V	56	168	Scheduled	3,497 ± 1	1.9 ± 0.03	−66.45 ± 7.06	170.03 ± 5.9	26.58 ± 1.15
VV2	V-V	60	168	Scheduled	3,498 ± 105.08	2 ± 0.11	−60.19±6.12	164.68 ± 8.17	23.48 ± 3.21
VV3	V-V	63	168	Scheduled	3,498 ± 0.59	1.7 ± 0.07	−69.06 ± 6.22	172.55 ± 7.63	33.71 ± 8.16
VV4	V-V	59	168	Scheduled	3,499 ± 217.62	1.9 ± 0.14	−60.68 ± 5.56	162.94 ± 19.94	30.77 ± 5.81
VV5	V-V	60	196	Scheduled	3,497 ± 122.5	1.6 ± 0.1	−57.77 ± 12.41	162.77 ± 18.38	41 ± 11.99
VA1	V-A	58	168	Scheduled	3,499 ± 0.69	2.4 ± 0.14	−41.74 ± 12.78	197.23 ± 5.77	34.23 ± 4.08
VA2	V-A	54	168	Scheduled	3,198 ± 159.73	2 ± 0.29	−38 ± 9.14	166.48 ± 13.55	12.74 ± 1.48
VA3	V-A	55	168	Scheduled	3,501 ± 118.18	2.1 ± 0.22	−31.58 ± 6.32	178.52 ± 13.08	16 ± 2.7
VA4	V-A	56	168	Scheduled	3,248 ± 69.64	1.8 ± 0.14	−55.1 ± 5.69	162.06 ± 13.92	11.74 ± 2.5
VA5	V-A	57	168	Scheduled	3,198 ± 138.51	1.9 ± 0.24	−40.32 ± 6.13	149.06 ± 15.64	8.65 ± 2.24

$346.7 \pm 168.13 \times 10^9$/L, $p = 0.022$ (Wilcoxon test)]. **Figure 6** shows how fHb, hemoglobin, WBC, and platelets varied.

DISCUSSION

This preclinical research shows that the centrifugal pump and ECMO device of the OASSIST ECMO system met safety and biocompatibility requirements satisfactorily, demonstrating three major results: First, the hemodynamic performance of the system was stable with no device-related accident (including pump stop, severe thrombosis, and severe hemolysis); Second, continuous heparin infusion provided sufficient anticoagulation, and no major bleeding or thrombosis was observed during ECMO run or in the autopsy; Third, blood damage revealed by fHb, RBC, WBC, and platelets was negligible.

In one experiment in the V-V group, the pump head and oxygenator had to be changed. Because during the cannulation attempt of the VV5 sheep, the cannula was punctured by the scalpel, and massive air was seen returning into venous line and centrifugal pump. The cannulation process was prolonged, and heparin was not supplemented in this process. During the first 28 h after the initiation of the ECMO, we found the transmembrane pressure increased precipitously (from 35 to 89 mmHg), indicating oxygenator thrombosis. Therefore, the occluded oxygenator and pump head were changed at the 28th hour. Long and narrow belt-shaped thrombus were found in both pump head and oxygenator, indicating it might be formed along the cannula and tubing near the punctuated site. Then, the pump ran for another 168 h.

Considering hemolytic blood damage, we tested fHb at baseline, the 6th h, and every 24 h after the initiation of ECMO. The fHb between the baseline and the 168th h was not statically different. However, the pre-ECMO fHb was slightly higher than every test after the ECMO run (**Figure 6A**), which may be caused by the different ways of blood sampling. A three-lumen central venous catheter was placed in the left jugular vein during the procedure, so the blood was collected through this venous line after the ECMO run. Comparatively, a syringe with a needle was used to draw blood at baseline. The needle may contribute to higher fHb.

The OASSIST ECMO System Was Highly Portable

ECMO supports cardiac and respiratory failure and is frequently used as a bridge to transplantation, long-term mechanical circulatory support devices, and recovery, which has saved many critically ill patients. The OASSIST ECMO system is a compact heart-lung support system, composed of a single-use centrifugal pump, a pump drive, and a control console. The pump drive of the OASSIST ECMO system can be used independently with primed circuits in some emergency conditions, such as ECMO transportation and in-/out-of-hospital emergency treatment. The size of the pump drive is 200 × 190 × 110 mm and weighed 3 kg, which could be easily lifted and manipulated by any trained personnel. Since the system was much smaller than conventional ECMO devices, it could be applicable on more experimental and clinical occasions.

The OASSIST ECMO System Provided Certain Hemodynamic Support

The pump head was optimized to support 3.0–5.0 L/min under the pressure of 300–500 mmHg. Fujiwara et al. evaluated a magnetically levitated, centrifugal blood pump on calves, the flow was around 3 L/min by central cannulation (7). Shankarraman et al. tested Levitronix® Centrimag® adult ECMO circuit on ovine acute pulmonary hypertension model, the average flow was 2.2 ± 0.1 L/min (8). Akiyama et al. also evaluated an ultra-compact durable ECMO system in sheep, and the flow rate ranged from 2.2 ± 0.7 L/min to 2.5 ± 0.1 L/min under the pump speed of higher than 4,000 rpm (9). In our experiment, the speed was set at 3,200–3,500 rpm. The ECMO flow ranged from 1.6 ± 0.1 L/min to 2.0 ± 0.11 L/min in the V-V group and from 1.8 ± 0.1 L/min to 2.4 ± 0.14 L/min in the V-A group (**Table 1**). We cannulated the V-V group by 23 Fr DLC because it was easier to fix and contributed to sheep's mobility. As is previously tested in the DLC evaluation sheep model, the 27 Fr DLC can provide around 2.0 L/min flow (10). Therefore, the OASSIST ECMO system can

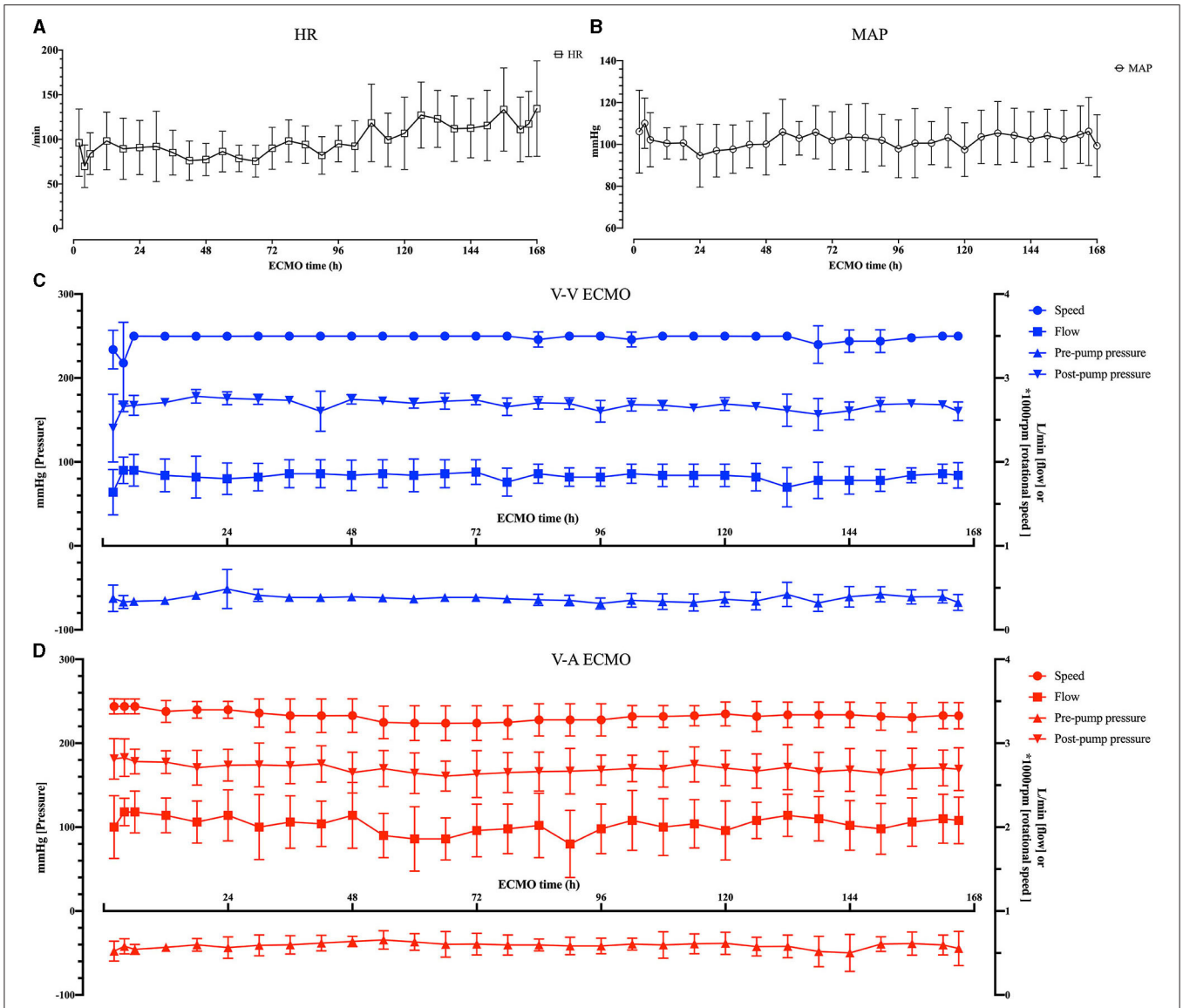

FIGURE 4 | The vital signs of the sheep and the ECMO configurations. **(A)** The heart rate (HR) of the sheep. **(B)** The mean arterial pressure (MAP) of the sheep. **(C)** The rotational speed, flow, pre-pump pressure and post-pump pressure of the OASSIST ECMO system in the V-V group. **(D)** The rotational speed, flow, pre-pump pressure and post-pump pressure of the OASSIST ECMO system in the V-A group.

provide hemodynamic support that is comparable to previous animal studies. Although the JACC Scientific expert panel stated the flow of V-A ECMO should reach 4–6 L/min when supporting human patients (11), 2.0 L/min could satisfy hemodynamic needs in a healthy sheep model with a functional native heart.

The OASSIST ECMO System Can Provide Durable Heart-Lung Support

STMed previously conducted *in vitro* durability tests (**Supplementary Figure**), the experiment system of which consisted of the control console, the disposable pump head driven by the pump drive, the tubing, and several monitors. Ten *in vitro* circuits (primed with 0.9% NaCl and glycerol) ran for 14 days, and no pump stop or other malfunction occurred. The durability tests were conducted under the supervision of National Institutes for Food and Drug Control. The OASSIST ECMO system can run for consecutive 14 days without any mechanical failure. Besides, when used independently without alternating-current supply, the pump drive can support for at least 180 min. The scheduled ECMO duration of previous preclinical evaluations ranged from several hours to at most 4 weeks (10, 12–14). Taken the previous samples and the durability of the PMP oxygenator together, we tested the single-use pump and ECMO device for 7 days in the ovine model. Thrombus formation remains a significant adverse event in mechanical circulatory support (MCS), including ECMO and ventricular assist devices (VADs) (15, 16). After the dissection of the pump and oxygenator,

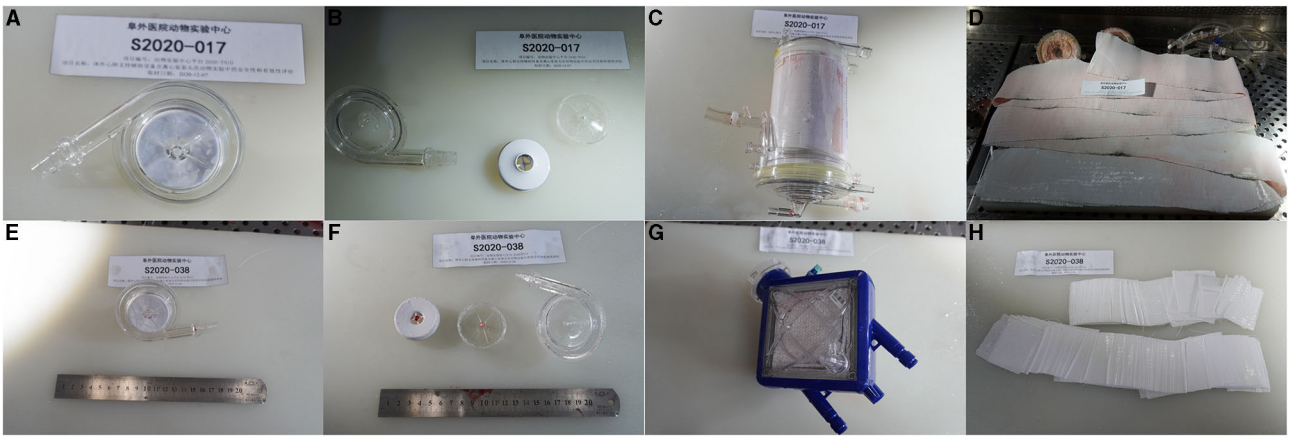

FIGURE 5 | The representative picture of the pump head and oxygenator after 7-day ECMO. **(A)** A representative pump head that developed no obvious thrombus in the V-V group. **(B)** The dissection inspection of **(A)**. **(C)** The oxygenator that formed no obvious thrombus in the V-V group. **(D)** The membrane inside **(C)**. **(E)** A representative pump head that developed small thrombus in the bearing pedestal in the V-A group. **(F)** The dissection inspection of **(E)**. **(G)** The oxygenator that formed no obvious thrombus in the V-A group. **(H)** The membrane inside **(G)**.

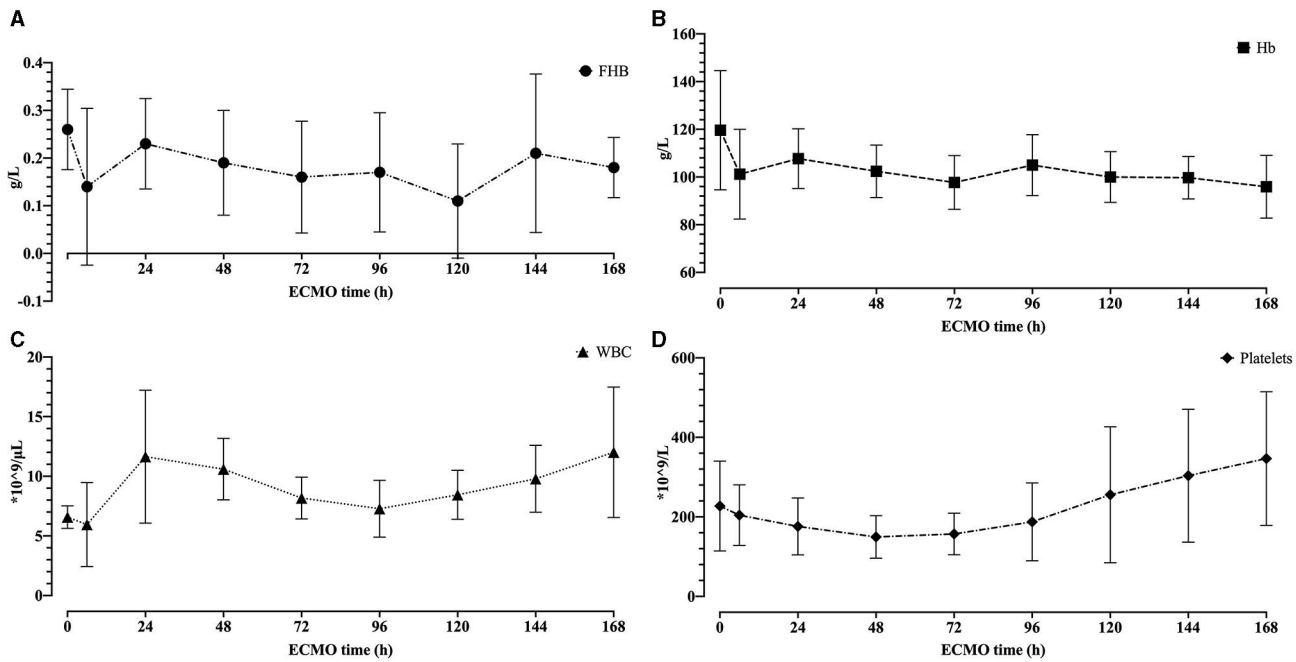

FIGURE 6 | The hemolytic blood damage results. **(A)** The free hemoglobin for 7 days. **(B)** The hemoglobin for 7 days. **(C)** The white blood cell for 7 days. **(D)** The platelets for 7 days.

7/10 pumps developed small thrombus in the bearing pedestal. But researchers didn't observe abnormal vibration or noise, intravascular hemolysis, or hemoglobinuria, which represented significant pump head thrombosis (17). Besides, no pump head was changed due to the primary pump thrombosis and the hemolytic blood damage was not significant. The combined results shows the system can run stably for at least 7 days.

Limitations

Several limitations existed. First, the evaluation study didn't set a control group. To balance the preciseness with cost-effectiveness, the researchers designed a single-arm study. Second, the commercial PMP oxygenator was not the same between the V-V group and the V-A group due to availability, which may cause some bias when analyzing data. But on the other hand, this setting tested the compatibility of the OASSIST

ECMO system with different oxygenators. Third, the animal model did not include a model of disease, as healthy sheep cannot completely be compared to patients with ARDS or cardiogenetic shock. By consulting experts on the animal experiment and researching previous studies, we found the success rate of disease model (such as acute lung injury and cardiogenic shock) was not controllable. Therefore, the healthy sheep model is more suitable for device evaluation.

CONCLUSIONS

The OASSIST ECMO system shows satisfactory safety and biocompatibility during the 7-day preclinical evaluation in sheep. The OASSIST ECMO system could step to clinical evaluation and is promising to be a supportive device in critical and emergency medical conditions in the future.

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 animal study was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Fuwai Hospital.

AUTHOR CONTRIBUTIONS

YL, BG, BJ, and WW conceived and originally designed the research, then approved the final manuscript. SG and WW conducted the experiment and wrote the draft of the manuscript. SG analyzed the data. JQ, WY, and QZ extracted data from the electronic and paper databases. GL and SY conducted the experiment and revised the discussion section of the manuscript. JW, YT, CZ, and QW conducted the experiment and revised the materials and methods section of the manuscript. 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.2021.712205/full#supplementary-material

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Sex Differences in In-hospital Mortality of Patients With Septic Shock: An Observational Study Based on Data Analysis From a Cover Sheet of Medical Records in Beijing

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Background: The goal of our study was to evaluate the association of sex and in-hospital mortality in patients with septic shock in Beijing, China.

Materials and Methods: We analyzed 3,643 adult patients with septic shock from January 1, 2019, to Dec 31, 2019, in all secondary and tertiary hospitals in Beijing. Study data were retrospectively extracted from the Quality Control Center of Beijing Municipal Health Commission.

Results: There were 2,345 (64.37%) male and 1,298 (35.63%) female patients. Compared to male patients, female patients with septic shock had a higher in-hospital mortality rate (55.54 vs. 49.29%, $p < 0.01$).The median length of hospitalization stay for male patients was 22.71 days, while that for female patients was 19.72 days ($p > 0.01$). Male patients had a higher prevalence of pulmonary infection (68.8 vs. 31.2%, $p < 0.01$). The B values of sex in univariate and multivariate logistic regression were −0.251 and −0.312, respectively. Men had a lower likelihood of hospital mortality than women (OR = 0.732, 95% CI = 0.635–0.844, $p = 0.000$).

Conclusions: Female patients with septic shock had a higher risk of dying in the hospital than male patients.

Keywords: septic shock, sex, in-hospital mortality, risk factor, cover sheet of medical records

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INTRODUCTION

Sex is increasingly recognized as a key factor in trauma (1), coronary heart disease (2), autoimmune disease (3), cancer, mental disorder (4) and other medical conditions. A number of studies suggest that a patient's gender may influence both the provision of care as well as outcomes. Critical care is not immune to such bias (5).

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (6). Septic shock is a complex inflammatory crisis associated with a high rate of mortality (7). Sepsis and septic shock are major health care problems, affecting millions of people around the world each year, resulting in the death of as many as one in four patients (and often more) (6). Recently, several

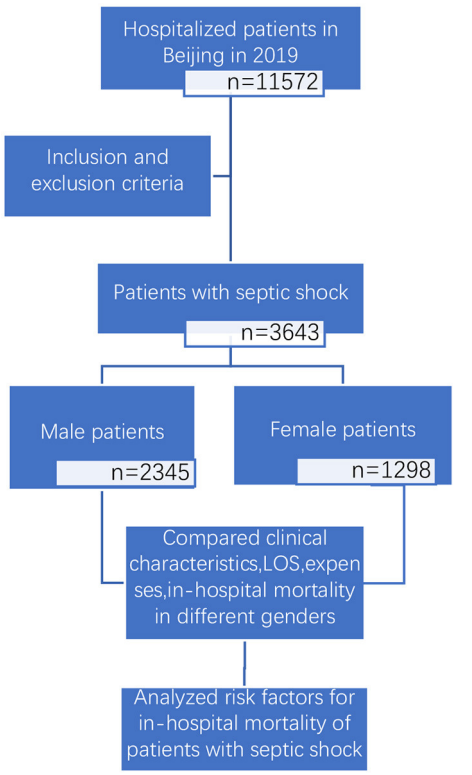

FIGURE 1 | The study flow chart.

studies have evaluated the effect of gender for patients with sepsis or septic shock. However, reports on the sex and mortality of sepsis/septic shock have shown conflicting results (8–11). The goal of this study was to evaluate the association of sex and in-hospital mortality in patients with septic shock in Beijing, China.

MATERIALS AND METHODS

Study Population

We conducted a retrospective and observational study (study flow chart shown in **Figure 1**). Based on the principal discharge diagnosis, patients with septic shock based on the sepsis-3.0 definition were enrolled by reviewing the inpatient lists from January 1, 2019, to Dec 31, 2019, in all secondary and tertiary hospitals in Beijing. The only exclusion criterion was an age <18 years old. This study was approved by the ethics committee of Beijing Friendship Hospital (No. 2021-P2-184-01) and granted a waiver of informed consent.

Data Collection

Study data were retrospectively extracted from the Quality Control Center of Beijing Municipal Health Commission. Data elements were collected from the cover sheet of medical records, including patient' demographics, medical history, expenses, length of hospital stay, hospital level and diagnosis discharge form.

Abbreviations: LOS, length of hospital stay; ICU, Intensive care unit.

Study Variables

Discharge forms included the following: recovered and discharged, discharged without recovery, referral, and death. We defined the first three conditions as "alive" and calculated the in-hospital mortality of patients with septic shock.

The race of patients was categorized as "Han" or "non-Han". Hospital levels were categorized as "Tertiary hospitals" or "Secondary hospitals" which were determined officially.

The insurance of patients was categorized as "medical insurance" or "self-pay". "Medical insurance" included Urban Employee Basic Medical Insurance and Urban Resident Basic Medical Insurance, New Rural Cooperative Medical Insurance or Business insurance.

Comorbidities included hypertension, diabetes mellitus, ischemic heart disease, chronic kidney disease, liver disease, chronic pulmonary disease and malignant tumors. Hypertension was defined as having a history of hypertension, receiving antihypertensive therapy, or having a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on admission. Diabetes mellitus was defined as having a previous or new diagnosis of diabetes mellitus, receiving oral hypoglycemic drug therapy or insulin therapy, or having a fasting blood glucose level ≥7.0 mmol/L (126 mg/dL) or hemoglobin A1c level ≥6.5%. Ischemic heart disease included angina pectoris and myocardial infarction. Chronic kidney disease (CKD) was defined as abnormal kidney structure or function persisting for longer than 3 months. Liver disease included viral hepatitis and autoimmune, metabolic or alcohol-related liver disorders. Chronic pulmonary disease included chronic respiratory disease, cor pulmonale and pulmonary circulatory disease.

The site of infection included the pulmonary, skin, urinary tract, gastrointestinal tract, abdominal cavity and bloodstream.

The primary endpoint in the study was in-hospital mortality, which was defined as death during hospitalization. The hospital length of stay (LOS) and expenses were selected as the secondary outcomes.

Statistical Methods

Categorical variables are presented as frequencies (n) and percentages (%). Continuous variables that conformed to a normal distribution are expressed as the mean ± standard deviation, and those that did not conform to a normal distribution are expressed as the median (interquartile range). An unpaired *t* test or Mann–Whitney *U* test was used to assess the statistical significance of differences between means or medians, where appropriate. The significance of differences for categorical variables was analyzed using the Chi-squared test. To evaluate the relationship between sex and in-hospital mortality, univariate and multivariate logistic regression analyses were performed. All statistical analyses were performed using SPSS version 25.0. Two-sided $P < 0.01$ were considered statistically significant.

TABLE 1 | Clinical characteristics of the septic shock patients at discharge.

	Total (n = 3,643)	Men (n = 2,345)	Women (n = 1,298)	Test value	p value
Age [years, M(P25-P75)]	77.00 (62.00,85.00)	78.00 (62.00,85.00)	77.00 (63.00,84.00)	−1.257	0.209
Marital status				0.214	0.644
Unmarried (*n*, %)	228	150 (65.8%)	78 (34.2%)		
Married (*n*, %)	3,415	2,195 (64.3%)	1,220 (35.7%)		
Race				1.807	0.179
Han (*n*, %)	3,642	2,345 (64.4%)	1,297 (35.6%)		
Non-Han (*n*, %)	1	0	1 (100%)		
Insurance				3.283	0.070
Medical insurance (*n*, %)	3,304	2,142 (64.8%)	1,162 (35.2%)		
Self-pay (*n*, %)	339	203 (59.9%)	136 (40.1%)		
Level of hospital				0.958	0.328
Second hospital (*n*, %)	399	248 (62.2%)	151 (37.8%)		
Tertiary hospital (*n*, %)	3,244	2,097 (64.6%)	1,147 (35.4%)		
Comorbidity					
Hypertension (*n*, %)	1,803	1,174 (65.1%)	629 (34.9%)	0.861	0.354
Ischemic heart disease (*n*, %)	1,632	1,058 (64.8%)	574 (35.2%)	0.271	0.603
DM (*n*, %)	1,351	872 (64.5%)	479 (35.5%)	0.029	0.866
CKD (*n*, %)	1,201	809 (67.4%)	392 (32.6%)	6.986	0.008※
Malignant tumor (*n*, %)	707	498 (70.4%)	209 (29.6%)	14.086	0.000※
Liver disease (*n*, %)	1,347	917 (68.1%)	430 (31.9%)	12.807	0.000※
Chronic pulmonary disease (*n*, %)	180	120 (66.7%)	60 (33.3%)	0.435	0.509

※ *means that the differences is statistically significant (P value < 0.01).*

TABLE 2 | Site of infection in different genders.

Site of infection	Total (n = 3,643)	Men (n = 2,345)	Women (n = 1,298)	Test value	p value
Pulmonary (*n*, %)	933	642 (68.8%)	291 (31.2%)	10.782	0.001※
Skin (*n*, %)	74	46 (62.2%)	28 (37.8%)	0.161	0.689
Urinary tract (*n*, %)	802	518 (64.6%)	284 (35.4%)	0.021	0.884
Gastrointestinal tract (*n*, %)	94	61 (64.9%)	33 (35.1%)	0.012	0.914
Abdominal cavity (*n*, %)	418	272 (65.1%)	146 (34.9%)	0.101	0.750
Blood stream (*n*, %)	74	46 (62.2%)	28 (37.8%)	0.161	0.689

※ *means that the differences is statistically significant (P value < 0.01).*

TABLE 3 | Sex-Based Differences in clinical outcomes of patients with septic shock.

Clinical outcome	Total (n = 3,643)	Men (n = 2,345)	Women (n = 1,298)	Test value	p value
Death (*n*) and in-hospital mortality (%)	1,877 (51.52)	1,156 (49.29)	721(55.54)	13.070	0.000※
LOS [days, M (P25–P75)]	21.64 (6.00, 25.00)	22.71 (6.00, 25.00)	19.72 (6.00, 24.00)	−1.713	0.087
Expenses [rmb, M (P25–P75)]	100,064.21 (13,857.64, 123,022.83)	102,804.68 (33,063.69, 125,903.69)	95,113.20 (26,739.77, 118,980.72)	−4.274	0.000※

※ *means that the differences is statistically significant (P value < 0.01).*

RESULTS

Patient Characteristics

Among 3,643 patients with septic shock who were included in this study, 2,345 (64.37%) were male, and 1,298 (35.63%) were female. The clinical characteristics of the study population are summarized in **Table 1**.

The mean ages of male and female patients were 78.00 (62.00, 85.00) and 77.00 (63.00, 84.00) years, respectively. Men had a higher prevalence of malignant tumors (70.4 vs. 29.6%, $p < 0.01$), chronic kidney disease (67.4 vs. 32.6%, $p < 0.01$) and liver disease (68.1 vs. 31.9%, $p<0.01$).

Site of Infection in Different Genders

The main site of infection leading to septic shock was the pulmonary system. Men had a higher prevalence of pulmonary infection (68.8 vs. 31.2%, $p < 0.01$) (see **Table 2**).

TABLE 4 | Risk factors for in-hospital mortality in patients with septic shock.

	Total	Survival	Death	Test value	*P* value
Gender (*n*, %)	3,643	1,766	1,877	13.070	0.000※
Men (n, %)	2,345	1,189 (50.7%)	1,156 (49.3%)		
women (*n*, %)	1,298	577 (44.5%)	721 (55.5%)		
Age [years, M (P25–P75)]	77.00 (62.00, 85.00)	74.00 (64.00, 85.00)	79.00 (63.00, 84.00)	−9.268	0.000※
Expense [rmb, M (P25–P75)]	100,064.21 (13,857.64, 123,022.83)	102,804.68(33,063.69, 125,903.69)	95,113.20 (26,739.77, 118,980.72)	−2.321	0.020
LOS [days, M (P25-P75)]	21.64 (6.00, 25.00)	22.71 (6.00, 25.00)	19.72 (6.00, 24.00)	−5.167	0.000※
Marital status	3,643	1,766	1,877	35.404	0.000※
Unmarried (*n*, %)	228	154 (67.5%)	74 (32.5%)		
Married (*n*, %)	3,415	1,612 (47.2%)	1,803 (52.8%)		
Race	3,643	1,766	1,877	1.063	0.302
Han (*n*, %)	3,642	1,765 (48.5%)	1,877 (51.5%)		
Non-Han (*n*, %)	1	1 (100%)	0		
Insurance	3,643			29.585	0.000※
Medical insurance (n, %)	3,304	1,554 (47.0%)	1,750 (53.0%)		
Self-pay (*n*, %)	339	212 (62.5%)	127 (37.5%)		
Level of hospital				6.181	0.013
Second hospital (*n*, %)	399	170 (42.6%)	229 (57.4%)		
Tertiary Hospital (n, %)	3,244	1,596 (49.2%)	1,648 (50.8%)		
Comorbidity					
Hypertension (*n*, %)	1,803	852 (47.3%)	951 (52.7%)	2.134	0.144
Ischemic heart disease (*n*, %)	1,632	745 (45.6%)	887 (54.4%)	9.460	0.002※
DM (*n*, %)	1,351	672 (49.7%)	679 (50.3%)	1.374	0.241
CKD (*n*, %)	1,201	581 (48.4%)	620 (51.6%)	0.007	0.932
Malignant tumor (*n*, %)	707	291 (41.2%)	416 (58.8%)	18.803	0.000※
Liver disease (*n*, %)	1,347	664 (49.3%)	683 (50.7%)	0.573	0.449
Chronic pulmonary disease (*n*, %)	180	43 (23.9%)	137 (76.1%)	45.833	0.000※
Site of infection					
Pulmonary (*n*, %)	933	477 (51.1%)	456 (48.9%)	3.523	0.061
Skin (*n*, %)	74	36 (48.6%)	38 (51.4%)	0.001	0.976
Urinary tract (*n*, %)	802	467 (58.2%)	335 (41.8%)	39.165	0.000※
Gastrointestinal tract (*n*, %)	94	57 (60.6%)	37 (39.4%)	5.714	0.017
Abdominal cavity (*n*, %)	418	203 (48.6%)	215 (51.4%)	0.001	0.969
Blood stream (*n*, %)	74	36 (48.6%)	38 (51.4%)	0.001	0.976

※ *means that the differences is statistically significant (P value < 0.01).*

TABLE 5 | Logistics regression on the indicators of in-hospital death.

Characteristic	Univariate analysis			Multivariate analysis		
	OR	95 %CI	*p* value	OR	95 %CI	*p* value
Gender	0.778	(0.679, 0.892)	0.000※	0.732	(0.635, 0.844)	0.000※
Age	1.019	(1.016, 1.023)	0.000※	1.026	(1.021, 1.031)	0.000※
LOS	1.000	(0.999, 1.001)	0.395			
Marital status	0.430	(0.323, 0.571)	0.000※	1.663	(1.125, 2.457)	0.011
Insurance	1.880	(1.493, 2.367)	0.000※	1.390	(1.080, 1.789)	0.010
Ischemic heart disease	0.814	(0.714, 0.928)	0.002※	1.035	(0.887, 1.207)	0.663
Chronic pulmonary disease	0.317	(0.224, 0.449)	0.000※	0.349	(0.244, 0.499)	0.000※
Malignant tumor	0.693	(0.587, 0.818)	0.000※	0.640	(0.538, 0.761)	0.000※
Urinary tract infection	1.655	(1.412, 1.939)	0.000※	2.072	(1.745, 2.460)	0.000※

※ *means that the differences is statistically significant (P value < 0.01).*

The Differences in Clinical Outcomes by Sex

We analyzed the clinical outcomes in male and female patients with septic shock (see **Table 3**). The in-hospital mortality rate was higher in women than in men (55.54 vs. 49.29%, $p < 0.01$). Meanwhile, male patients had higher hospital expenses ($p < 0.01$) and longer stays ($p > 0.01$) at the hospital.

Sex and In-hospital Mortality

We divided patients with septic shock into two groups according to different clinical outcomes (death or survival in the hospital) and compared the data of the two groups (see **Table 4**). We found that sex, age, length of stay, marital status, medical insurance status, chronic pulmonary disease, malignant tumor, ischemic heart disease, and urinary tract infection were significantly different between the two groups ($p < 0.01$).

We then performed univariate and multivariate logistic regression on the above different indicators (see **Table 5**). To examine the association between sex and in-hospital mortality, logistic regression models were used to adjust for patients' clinical characteristics, including sex, age, length of stay, marital status, medical insurance status, chronic pulmonary disease, malignant tumor, ischemic heart disease, and urinary tract infection.

In univariate logistic regression, the B value of gender was −0.251, whereas in multivariate regression the B value of sex was −0.312. The results suggested that after adjusting the covariates, the correlation between gender and in-hospital death was greater. Male patients had a lower likelihood of hospital mortality than female patients (OR = 0.732, 95% CI = 0.635–0.844, $p = 0.000$).

DISCUSSION

In this large, hospital-based registry for male and female patients discharged with septic shock in Beijing China, we observed that men with septic shock were more likely to suffer from chronic diseases (such as hypertension, DM, ischemic heart disease, chronic kidney disease, chronic pulmonary disease, liver disease, malignant tumor) and had higher hospital expenses and longer stays at the hospital. However, the in-hospital mortality rate of male patients with septic shock was lower than that of female patients.

Previous animal and human studies indicated that females have advantageous immunologic and cardiovascular responses during infectious challenge, which means a higher sepsis incidence in males than in females. However, clinical studies on sex and mortality among critically ill sepsis patients have shown conflicting results (12). This may be related to the differences in study design, sample sizes, population included in the studies (ICU patients or non-ICU patients) and the research methods.

To explain the results in our study, we tried to analyze the following possible mechanisms. Estrogens have been proven to have a direct protective effect on vascular endothelial cells (13), inhibit endothelial cell apoptosis, induce endothelial cell proliferation and migration, and promote microvessel regeneration (14). However, estrogens also have physiologic actions that could be detrimental in sepsis (15). In studies of gender-specific responses to endotoxin, there were higher estrogen concentrations in elderly critically ill women than in younger critically ill women, as well as elevated estrogen concentrations in critically ill men, plus the association of higher estrogen levels with higher mortality in both women and men (16, 17). Non-biological explanations for our findings must also be considered. Previous studies (5, 18, 19) suggest that female patients with sepsis/septic shock received less medical care than male patients, and the proportion of withheld or withdrawn treatment was greater for female than for male patients. Although our study did not include data about treatment, it may also be one of the reasons why the in-hospital mortality of female patients with septic shock is higher than that of male patients (20). Sex differences in sites of infection were observed in the study, but similar to the hospital mortality difference, it is unclear whether they originate from gender differences in biology, comorbidity, or medical assessment and care.

The study was a large retrospective study of sample size, making the results credible. Many previous studies (18–21) indicated that the authors only had access to data for patients who presented with sepsis in the ED or ICU. However, in clinical practice, not all patients with septic shock receive treatment in the ED or ICU, so some cases may be missed. Our study included all patients with septic shock in all departments compared with other studies.

Limited by our current capabilities and the extent to which the database can be used, our research discovered a phenomenon but cannot fully explain its pathophysiological mechanism. Information on medical care during hospitalization cannot be fully indicated. Whether to adopt standardized treatment is very important for clinical prognosis. The results of this study can provide ideas and evidence for follow-up research. The patients in our study were middle-aged or elderly, which may not fully represent the characteristics of the entire adult population. This is a limitation of retrospective research. In our study, the death group was older than the alive group. As age increased, mortality also increased. We should consider the impact of age on mortality. However, there was no statistically significant difference in age between male and female patients. The impact of sex on in-hospital mortality was adjusted by logistic regression. In multivariate logistic regression, the B value of sex was greater than that in univariate regression. Based on this, we believe that the conclusions are valid.

CONCLUSION

In this study, female patients with septic shock had a higher in-hospital mortality than male patients. This difference remained after multivariable adjustment.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing Friendship Hospital Ethics Committee (No. 2021-P2-184-01). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MLD and XZ contributed to conception and design of the study. ZL, PL, and NZ organized the database. NZ and XZ performed the statistical analysis. XZ wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, 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.2021.733410/full#supplementary-material

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Levosimendan to Facilitate Weaning From Cardiorespiratory Support in Critically Ill Patients: A Meta-Analysis

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Background: Cardiopulmonary support, as extracorporeal membrane oxygenation (ECMO) or mechanical ventilation (MV), is crucial for ICU patients. However, some of these patients are difficult to wean. Therefore, we aimed to assess the efficacy and safety of levosimendan in facilitating weaning from cardiorespiratory support in this patient population.

Methods: We searched for potentially relevant articles in PubMed, Embase, China National Knowledge Infrastructure, Wanfang, and the Cochrane database from inception up to Feb 30, 2021. Studies focusing on weaning data in MV/ECMO adult patients who received levosimendan compared to controls were included. We used the Cochrane risk of bias tool or the Newcastle-Ottawa Quality Assessment Scale to evaluate the study quality. The primary outcome was the weaning rate from MV/ECMO. Secondary outcomes were mortality, duration of MV, and ICU stay. Subgroup analysis, sensitivity analysis, and publication bias were also conducted.

Results: Eighteen studies with 2,274 patients were included. The quality of the included studies was low to moderate. Overall, levosimendan effectively improved weaning rates from MV/ECMO [odds ratio (OR) = 2.32; 95%CI, 1.60–3.36; $P < 0.00001$, $I^2 = 68\%$]. Subgroup analyses confirmed the higher successful weaning rates in ventilated patients with low left ventricular ejection fractions (OR = 4.06; 95%CI, 2.16–7.62), patients with ECMO after cardiac surgery (OR = 2.04; 95%CI, 1.25–3.34), and patients with ECMO and cardiogenic shock (OR = 1.98; 95%CI, 1.34–2.91). However, levosimendan showed no beneficial effect on patients with MV weaning difficulty (OR = 2.28; 95%CI, 0.72–7.25). Additionally, no differences were found concerning the secondary outcomes between the groups.

Conclusions: Levosimendan therapy significantly increased successful weaning rates in patients with cardiopulmonary support, especially patients with combined cardiac insufficiency. Large-scale, well-designed RCTs will be needed to define the subgroup of patients most likely to benefit from this strategy.

Keywords: cardiopulmonary support, extracorporeal membrane oxygenation, mechanical ventilation, levosimendan, weaning

INTRODUCTION

In the intensive care unit (ICU), cardiopulmonary support is the most common and essential therapy. Mechanical ventilation (MV) is a well-established supportive therapy for patients suffering from various forms of respiratory failure (1). Extracorporeal membrane oxygen (ECMO) is increasingly used to treat patients with intractable hypoxemia or circulatory failure (2, 3). However, long-term cardiopulmonary support is not without its risks. Prolonged MV/ECMO can increase the risks of pneumonia, lung injuries, and skeletal muscle atrophy. Delayed weaning is also associated with increased morbidity, mortality, and length of stay in ICU or hospital (4). Therefore, appropriate early weaning from cardiopulmonary support is pretty necessary.

However, some ICU patients are difficult to wean from cardiopulmonary support (5, 6). The weaning failure is related to various causes of diaphragmatic weakness, especially in patients with cardiac or pulmonary comorbidities (7). The weaning procedure increases left ventricular filling pressures and pulmonary artery pressures, and the resulting increased cardiac burden may be one of the main reasons for weaning failure (8).

Levosimendan is a novel positive inotropic drug that effectively treats acute and chronic decompensated heart failure and is becoming used for weaning from cardiopulmonary support in recent years (9–12). Unlike the traditional inotropic drugs, such as epinephrine, dobutamine, or dobutamine, levosimendan increases cardiac output without adding myocardial oxygen consumption (13). Besides, similar to the myocardium, levosimendan can also strengthen the contraction of respiratory muscles, thereby promoting weaning (14).

Several publications have recently emerged on levosimendan use in ICU patients who undergo weaning from MV/ECMO, with discrepancies among the results (10, 12, 15–17). Therefore, we sought to conduct a systematic review and meta-analysis by pooling available studies to investigate the levosimendan's efficacy and safety in ICU patients during MV/ECMO weaning.

METHODS

We performed this systematic review and meta-analysis following the PRISMA guidance (18) (**Additional File 1**), and our protocol has been registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols database (Registration number: INPLASY 202170024) and is available in full on inplasy.com (https://doi.org/10.37766/inplasy2021.7.0024). Ethical approval was not required for our work.

Search Strategy

Two authors (J-CL and CM) independently searched for eligible studies in the PubMed, Embase, Cochrane Library database, China National Knowledge Infrastructure, and Wanfang Database before Feb 30, 2021, which was the last search. We limited our language to English and Chinese. Details in the literature search terms were summarized in **Additional File 2**. The search strategy was restricted to RCTs and observational studies with matched groups (cohort studies with two-arms or case-control studies). We also evaluated the reference lists of relevant studies to ensure the inclusion of all potential studies.

Study Selection

Studies were assessed for eligibility if they fulfilled the following criteria: (1) comparing levosimendan to control (i.e., placebo, any other drug or no drug) in patients undergoing MV/ECMO; (2) reporting data on the successful weaning rate from MV/ECMO. We excluded studies conducted in pregnant women and studies conducted in review, case reports, or case series.

Data Extraction and Outcomes

The two authors (CM and J-CL) extracted the data independently on the first author's name, study design (retrospective/prospective, RCT/cohort/case-control), year of publication, inclusion criteria, characteristics (age, male or female, and disease severity), levosimendan and control regimens as well as predefined outcomes. The primary outcome was the ECMO or MV weaning. Secondary outcomes included MV duration, length of stay in ICU, overall mortality at the longest following-up available, and adverse events. Discrepancies were identified and resolved through discussion.

Quality Assessment

CM and J-CL independently evaluated the methodological quality of the individual studies using the Cochrane risk of bias tool for RCTs (19) and the Newcastle-Ottawa Quality Assessment Scale (20) for case-control/cohort studies. We evaluated publication bias by visually inspecting funnel plots when at least 10 studies were included in this meta-analysis.

Statistical Analysis

The results from all relevant studies were combined to estimate the pooled odds ratio (OR) and associated 95% confidence intervals (CI) for dichotomous outcomes. As to the continuous outcomes, weighted mean differences (WMD) and 95 % CI were estimated as the effect results if they were measured on the same scale and the difference among the means and standard deviation of these outcomes is not significant, otherwise standardized mean difference (SMD) and 95%CI were used. For studies that reported median with accompanying interquartile range (IQR) as the measure of treatment effect, we estimated the mean from median and standard deviations (SD) from IQR using the methods described in previous studies before data analysis.

We used the I^2 statistic to test the heterogeneity. An $I^2 < 50\%$ was considered as insignificant heterogeneity, and a fixed-effect model was used, whereas a random-effect model was used in cases of significant heterogeneity ($I^2 > 50\%$) using the Mantel-Haenszel method (21). To test the robustness of the primary outcome and explore the potential influence factors, we conducted sensitivity analyses to investigate the influence of a single study on the overall pooled estimate of each predefined outcome. Additionally, subgroup analysis was performed separately by pooling trials focusing on cardiopulmonary support types (MV or ECMO) and cardiac

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygen; ICU, intensive care unit; LVEF, left ventricular ejection fractions; MD, mean difference; MV, mechanical ventilation; RR, risk ratio; RCTs, randomized controlled trials; SD, standard deviations.

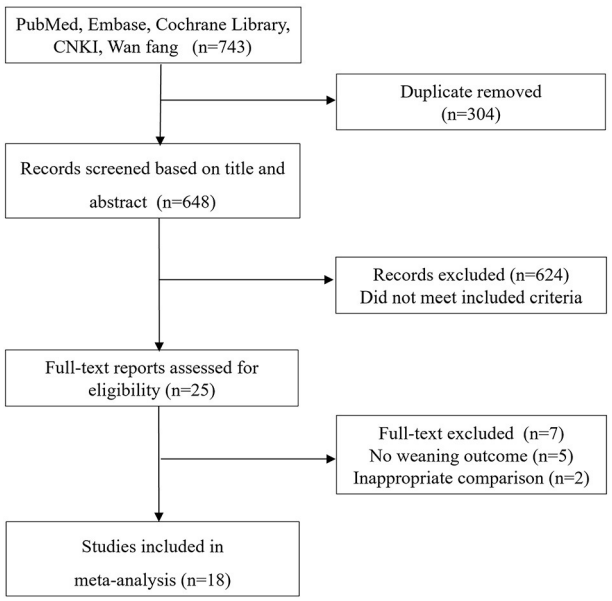

FIGURE 1 | Selection process for studies included in the meta-analysis.

function (low or preserved ejection fraction) for the predefined outcomes. We performed all analyses using Review Manager, Version 5.3.

RESULTS

Searching Results

The electronic search yielded 743 records, of which 25 full-text were considered for review. Finally, 18 studies (9–12, 15–17, 22–32) with 2,274 patients met the inclusion criteria and were selected for the final analysis (**Figure 1**). The details of the search strategy were summarized in **Additional File 2**.

Studies Characteristics and Quality Assessment

The main characteristics of included studies and predefined outcome measures are shown in **Table 1** and **Additional File 3**. Fourteen observational studies (9–11, 15–17, 22–26, 30–32) and four RCTs (12, 27–29) were included, which were conducted between 2009 and 2021. All but two studies (12, 28) were single-center studies. Eight (12, 16, 23, 26–29, 31) of the 18 included trials focused on MV weaning, with or without low LVEF of the recruited patients. The remaining ten studies (9–11, 15, 17, 22, 24, 25, 30, 32) focused on ECMO weaning, with five enrolling patients after cardiac surgery (11, 17, 24, 30, 32) and six enrolling patients suffering from cardiogenic shock (9, 10, 15, 22, 25, 32). Most included studies reported the detail of the levosimendan therapy regimen. As to the control group, two studies (24, 27) used milrinone while others used a placebo or no use.

We evaluated the included studies' risk of bias using the Newcastle-Ottawa Quality Assessment Scale for the 14 observational studies (9–11, 15–17, 22–26, 30–32) and the Cochrane risk-of-bias tool for the four RCTs (12, 27–29) (**Additional File 4**). The quality of case-control/cohort studies was moderate to high, and the risk of bias in RCTs was low in all critical domains. Assessment of publication bias using visually inspecting funnel plots showed no potential publication bias among the included studies (**Additional File 5**).

Primary Outcome

All 18 studies reported MV/ECMO weaning rates. The pooled analysis showed that, compared with control, levosimendan improved MV/ECMO weaning (n = 2,274; OR = 2.32; 95%CI, 1.60 to 3.36; $P < 0.00001$), with high heterogeneity (I^2 = 68%) among the studies. In the sensitivity analysis, excluding any single trial did not significantly alter the overall combined OR (P-value ranging from <0.00001 to <0.0001). Similarly, subgroup analyses confirmed the higher successful weaning rates in patients with low LVEF and MV (27–29, 31), patients with ECMO after cardiac surgery (11, 17, 24, 30), and patients with ECMO and cardiogenic shock (9, 10, 15, 22, 25) (**Figure 2**). However, levosimendan showed no beneficial effect on patients with MV weaning difficulty than the control group (12, 16, 23, 26) (**Figure 2**).

Secondary Outcomes

There was no significant differences between the levosimendan and control groups in duration of MV/ECMO (s studies, n = 1,003; SMD = −0.03 days; 95% CI, −0.41 to 0.36; I^2 = 86%; P = 0.90) (9, 15, 17, 22, 28–30) (**Figure 3**) and length of stay in ICU (3 studies, n = 141, SMD = −0.29 days; 95% CI, −0.05 to 0.62, I^2 = 18%; P = 0.10) (22, 24, 28) (**Figure 4**). Nine studies reported specific data on outcome of overall mortality, and pooled results showed no significant difference between the groups (9 studies, n = 1,225; OR = 0.81; 95% CI, 0.63–1.04; I^2 = 71%; P = 0.10) (9–12, 22, 24, 25, 28, 29) (**Figure 5**). We further conducted subgroup analyses based on ECMO or MV for the secondary outcomes. We found that the use of levosimendan was associated with a significant reduction in mortality rate in patients receiving ECMO [6 studies, 596 patients, 0.66 (0.53, 0.81), P = 0.0001] but not MV therapy. Meanwhile, subgroup analyses also showed no differences in the duration of MV/ECMO, ICU, or hospital LOS between the groups, either in the ECMO patients or in the MV patients. Only three studies (10, 12, 22) reported the advert events summarized in **Additional File 6**. There was no statistically significant difference in the incidence of complications (ARF requiring RRT, bleeding, ECMO-related complications, pneumonia, bleeding, ischemic stroke, hemorrhagic stroke, tracheostomy, acute liver failure, arrhythmia, myocardial infarction, or acute coronary syndrome) between the groups (all $P > 0.05$).

DISCUSSION

This study evaluated the effect of levosimendan on successful weaning from MV and ECMO in critically ill patients. The quality of the included studies was low to moderate. The pooled data showed that: (1) Levosimendan effectively improved ICU

TABLE 1 | Characteristics of the included studies.

Study	Study design	Population	Patient characteristics (Levosimendan group/Control group)						
			Sample	Mean age (yesrs)	Male (%)	Disease severity, mean	Levosimendan	Control	Form of support
Shaker (29)	RCT, SC	Patients of abdominal malignancy, EF <35% and CHF	30/30	62/60	60/73	ASA III: 22/20 ASA IV: 8/10	Infusion at 0.1 μg/kg/min or placebo for 24 h	Infused placebo at 0.1 μg/kg/min for 24 h	MV
Pan (23)	P, SC	Patients of weaning difficulty	50/50	67/67	54/58	NA	Infusion of 12.5 mg for 24 h	None	MV
Huang (27)	RCT, SC	Patients with RF and AHF	30/30	74/69	57/53	NA	Infusion of 12.5 mg for 24 h	Infusion milrinone of 12.5 mg for 24 h × 7 days	MV
Eriksson (28)	RCT, MC	Patients undergoing CABG with impaired LVEF < 0.5	30/30	64/64	93/87	Euro-SCORE: 5/5	12 μg/kg bolus, followed by an infusion of 0.2 μg/kg/min	Infused placebo with 12 μg/kg bolus, followed by an infusion of 0.2 μg/kg/min	MV
Vlasova (31)	R, SC	Patients undergoing CABG with low LVEF	17/29	64/60	NA	NA	Infusion of 12.5 mg for 24 h	None	MV
Gordon (12)	RCT, MC	Patients with sepsis	215/218	67/69	NA	APACHE II:25/25 SOFA:10/10	Infusion of 0.05–0.2 μg/kg/min for 24 h	Infusion of placebo at 0.05–0.2 μg/kg/min for 24 h	MV
Chen (16)	P, SC	Patients of weaning difficulty	45/38	NA	NA	NA	Infusion of 12.5 mg for 24 h	None	MV
He (26)	P, SC	Patients of weaning difficulty	37/31	NA	NA	NA	Infusion of 12.5 mg for 24 h	None	MV
Zipfel (25)	R, SC	Patients with refractory cardiogenic shock	37/49	NA	NA	NA	NA	NA	ECMO
Affronti (22)	R, SC	Patients with cardiogenic shock	6/11	57/56	67/63	NA	Infusion of 12.5 mg for 24 h	None	ECMO
Vally (9)	R, SC	Patients with cardiogenic shock	51/99	54/53	71/63	SAPS II: 59.2/55.5	Infusion of 12.5 mg for 24 h	None	ECMO
Distelmaier (30)	R, SC	Patients after cardiac surgery	179/61	65/65	74/63	Euro SCORE 11/9	Infusion of 12.5 mg for 24 h	None	ECMO
Jacky (24)	R, SC	Patients after cardiac surgery	26/38	66/63	81/76	SAPS II: 53/49	Infusion rate of 0.1 mg/kg/h	Infused milrinone at 10 mg/min	ECMO
Kevin (11)	P, SC	Children after cardiac surgery	54/91	0.7/0.96	48/56	NA	12.5 μg/kg bolus; following 0.2 mg/kg/min	None	ECMO
Guilherme (15)	R, SC	Patients with refractory cardiogenic shock	53/147	54/53	62/65	SAPS II: 53.5/51.7 SOFA:11.5/11.8	Infusion of 0.1 μg/kg/min for 1 h; followed 0.1–0.2 μg/kg/min for 24 h	None	ECMO
Deschka (17)	R, SC	Patients after cardiac surgery	78/198	NA	NA	NA	NA	NA	ECMO
Alonso-Fernandez-Gatta (10)	R, SC	Patients with circulatory compromise	23/100	60/62	74/73		Infusion of 12.5 mg with rate of 0.1 μg/kg/min	none	ECMO
Haffner (32)	R, SC	Patients of cardiogenic shock or following cardiotomy	27/36	NA	NA	NA	NA	NA	ECMO

AHF, acute heart failure; APACHE II, acute physiology and chronic health evaluation II; CABG, Coronary Artery Bypass Grafting; CHF, chronic heart failure; ECMO, Extracorporeal Membrane Oxygenation; Euro SCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; MV, mechanical ventilation; MC, multicenter; P, prospective; R, retrospective; SAPS II, simplified acute physiology score II; SC, single center; SOFA, sequential organ failure assessment.

patients' weaning from VA-ECMO therapy. (2) Levosimendan showed benefits in improving the weaning rate from MV in patients with low LVEF but not in those with preserved LVEF. (3) Subgroup-analyses showed that use of levosimendan was associated with a significant reduction in mortality rate in patients receiving ECMO but not MV therapy. Additionally, no differences were found in other secondary outcomes between groups.

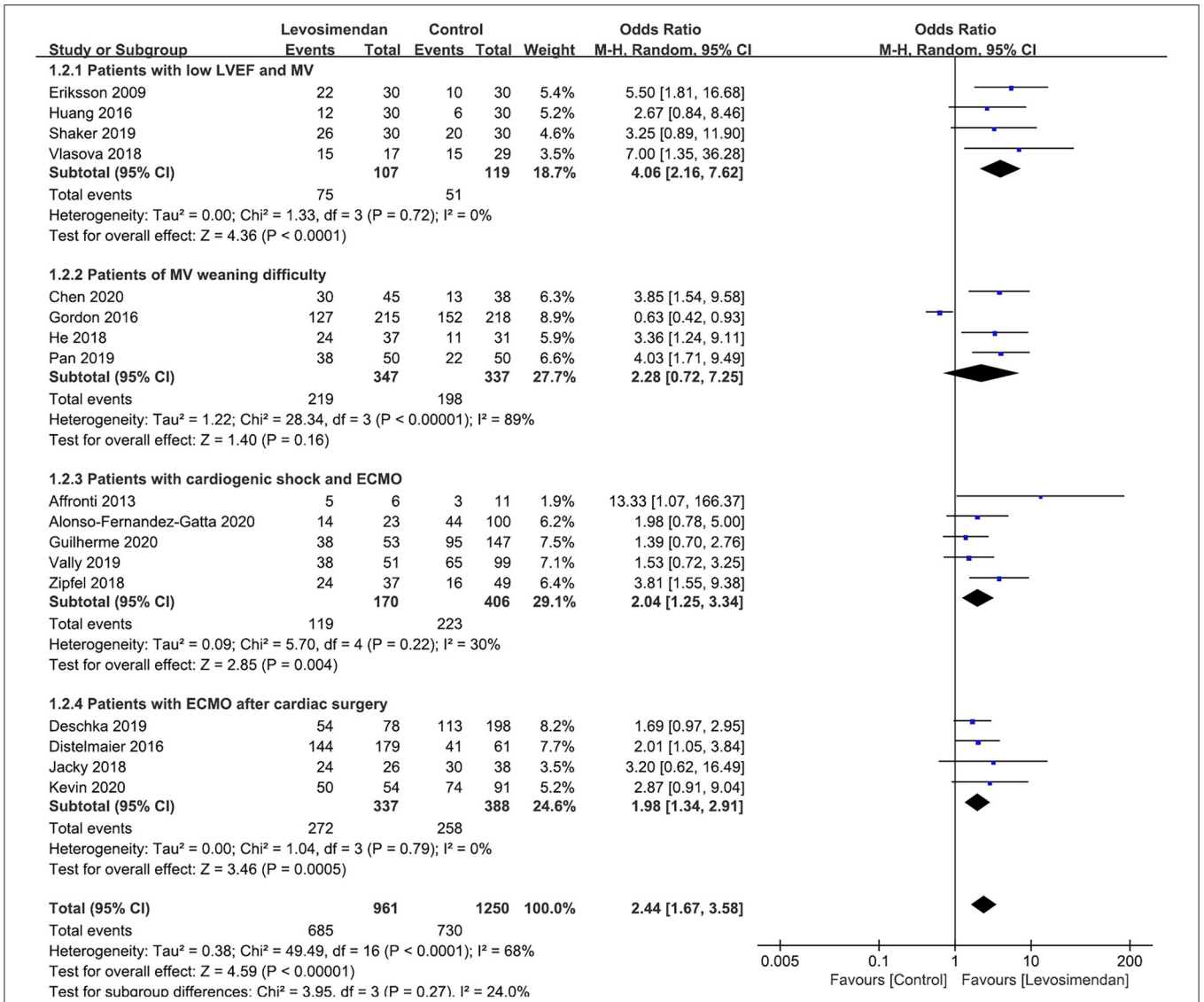

FIGURE 2 | Forest plots of the levosimendan therapy on weaning rates from cardiopulmonary support.

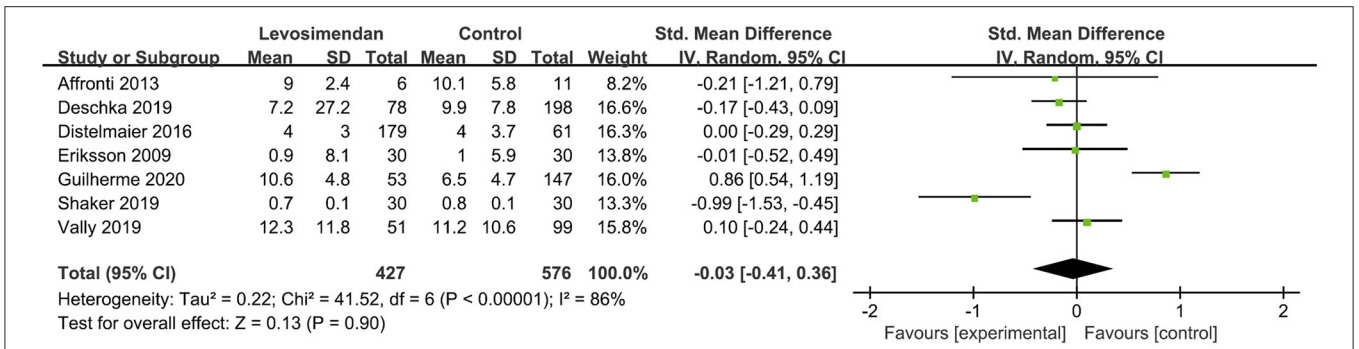

FIGURE 3 | Forest plots of the effects of levosimendan therapy on duration of mechanical ventilation.

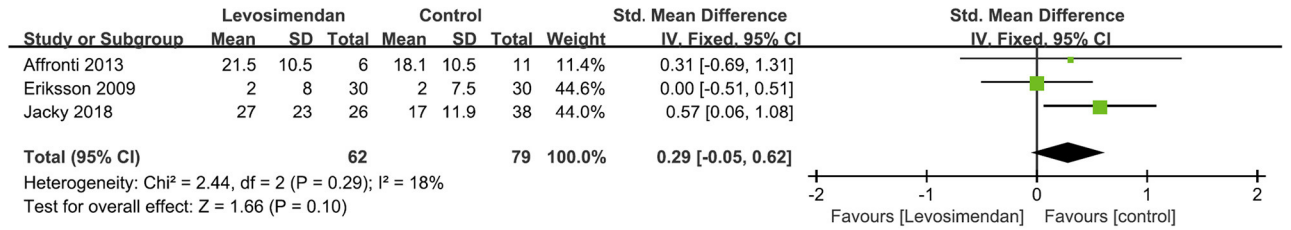

FIGURE 4 | Forest plots of the effects of levosimendan therapy on the length of stay in intensive care unit.

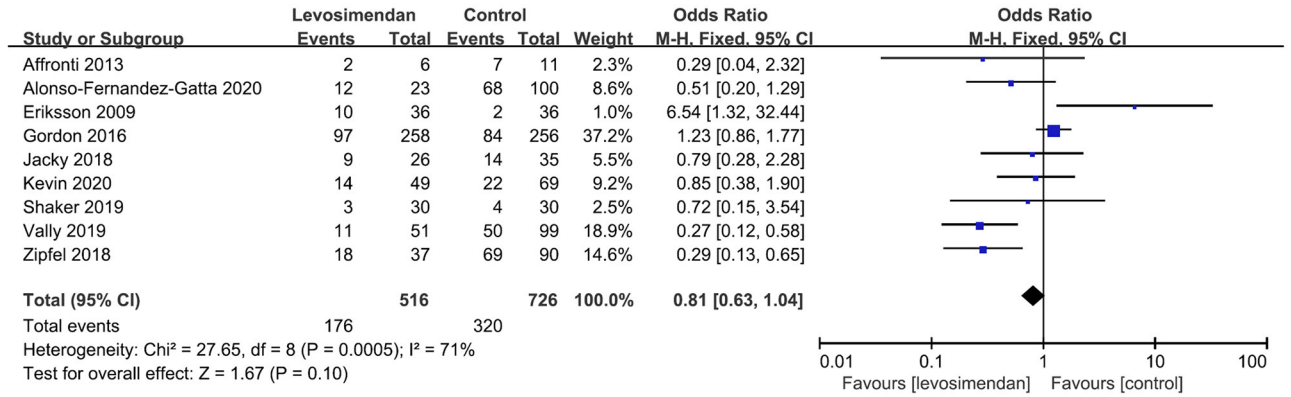

FIGURE 5 | Forest plots of the effects of levosimendan therapy on overall mortality.

Levosimendan in Weaning From ECMO

We found levosimendan facilitates the weaning from ECMO and reduces mortality rate, which is consistent with the findings of two previous meta-analyses (33, 34). Both meta-analyses reported levosimendan could improve weaning from ECMO based on five ($N = 557$) (34) and seven ($N = 630$) (33) studies, respectively. Our study added several newly published studies based on the previous meta-analyses with a large sample size of 1,336 patients, which allowed for better statistical efficacy and allowed subgroup analyses to verify our results' robustness.

VA-ECMO is increasingly being used in the short-term management of refractory circulatory failure. The main indications are myocarditis, cardiac arrest, refractory cardiogenic shock, and post-cardiotomy cardiac failure in high-risk patients with reduced LVEF (35, 36). However, this patient population still has high weaning failures. Our results show that ∼40% of patients cannot successfully wean from VA-ECMO treatment under the conventional weaning process. Therefore, clinical research concerning improvement in the weaning rate of ECMO is rising (10, 15). After all, a successful weaning is a prerequisite for patient survival.

In the present study, we found that the successful weaning from VA-ECMO based on levosimendan was 80%, significantly higher than that of 60% in the control group. Some properties of levosimendan may explain its benefit for weaning from VA-ECMO. The most important thing is the sensitization of calcium ions, the positive inotropic effect without a significant increase in oxygen consumption in the myocardium (13). Second, levosimendan is an effective vasodilator. By opening ATP-dependent potassium channels in vascular smooth muscle, levosimendan has various protective effects against ischemic myocardium (preconditioning, post-processing, anti-coma, and anti-apoptotic effects) (37). Compared with other cardiotonic drugs, the effect of levosimendan is not affected by the combined use of β-blockers, and it lacks an arrhythmia-promoting effect. In addition, the long-lasting effects of its circulating active metabolites (up to 8–9 days) allow it to allow gradual weaning and provide continuous support during the critical period after ECMO (38).

Levosimendan in Weaning From MV

About 26–42% of ICU intubated patients have difficulty weaning from MV, increasing morbidity, mortality, and healthcare costs (5, 12, 16, 29). Diaphragm dysfunction is one of the critical factors contributing to weaning failure in such a patient population (7). Currently, no explicit drugs help restore diaphragm function. Therefore, whether levosimendan can improve diaphragm function, as it does in the myocardium, has aroused widespread interest. Some published studies supported such a hypothesis (14, 39). An *in vitro* study (39) showed that by increasing calcium sensitivity, levosimendan could enhance the contractility of diaphragm muscle fibers in patients with or without COPD. In the RCT by Doorduin et al. (14), the authors recruited 30 healthy volunteers who underwent an inspiratory loading task and found that levosimendan significantly improved neuromechanical efficiency and contractile function ($P < 0.05$) than placebo.

However, the results of our meta-analysis of clinical studies did not fully confirm this hypothesis. Patients who gained benefits from levosimendan during MV weaning are still those with concurrent low LVEF (27–29, 31). For such a patient population, cardiac function is the most critical factor of weaning. During the weaning process, abrupt transfer from MV to spontaneous breathing may significantly increase left ventricular filling pressure and pulmonary artery pressure (8). Simultaneously, sympathetic excitation induces the release of catecholamines, leading to peripheral vasoconstriction and increased cardiac workload. These mechanisms can cause heart failure and weaning failure, especially in patients with previous cardiac or pulmonary comorbidities.

In contrast, pooled studies focusing on patients without low LVEF showed no benefits of levosimendan on weaning from MV (12). Some explanations might help understand this failure. Firstly, most studies enrolling patients who already met the criteria for difficult weaning from MV. Besides heart function, the reasons for weaning difficulty in the ICU setting are respiratory, psychological, and psychomotor nutritional, while these factors are often combined to complicate the weaning process (5). Secondly, the patient's disease can influence the effect of levosimendan. As shown in the leoPARD study (12), the authors enrolled patients with sepsis/septic shock without septic myocardial suppression and found levosimendan was associated with a lower weaning rate from MV (HR 0.77, 95%CI 0.60–0.97, $P = 0.03$). The reason may be that levosimendan can cause peripheral vasodilation, resulting in the need for more norepinephrine to maintain blood pressure and cause increased adequate arterial elasticity to increased afterload. Therefore, the mechanicals might diminish the benefit of enhanced myocardial contraction from levosimendan. Moreover, the increased incidence of side effects of levosimendan, such as rapid supraventricular arrhythmias, might also contribute to the weaning failure (12).

Additionally, we found no levosimendan benefit in the length of stay in ICU or hospital. This may be because, for critically ill patients, ICU or hospital discharge was not always determined by the condition of the patients. The hospital policy to accept or refuse critically ill patients in general wards and the availability of beds for patients requiring long-term rehabilitation therapy may affect the length of ICU or hospital stay.

Study Limitation

Our research has some limitations. First of all, most of the included are retrospective studies, especially studies on ECMO. This greatly affected the causality of our research conclusions. At present, some evaluations aim to assess whether the administration of levosimendan is related to RCT studies that reduce the weaning failure, such as the LEVOECMO trial (NCT04728932), is ongoing. The results of these studies will further verify our conclusions. Second, in the included studies, there is significant heterogeneity in the standard setting of patient weaning and the usage of levosimendan. Third, the study we included did not find any patients treated for VV-ECMO. Finally, the included ICU patients have different underlying diseases. However, due to the number of studies, we cannot conduct a subgroup analysis to clarify this further.

CONCLUSION

In summary, based on the current evidence, levosimendan is significantly associated with successful weaning rates from cardiopulmonary support in ICU patients, especially those with a combination of cardiac insufficiency. However, further well-designed RCTs will be needed to define the subgroup of patients most likely to benefit from this strategy.

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.

AUTHOR CONTRIBUTIONS

W-HZ and CM searched the scientific literature and drafted the manuscript. J-CL helped to collect the data and performed statistical analyses. HZ, G-WT, and YX participated in the design of the study and performed the statistical analysis. H-BH and ZL contributed to the conception, design, data interpretation, manuscript revision for critical intellectual content, and supervision of the study. All authors read and approved the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.741108/full#supplementary-material

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CASE REPORT
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Extracorporeal Membrane Oxygenation in Severe Acute Respiratory Distress Syndrome Caused by *Chlamydia psittaci*: A Case Report and Review of the Literature

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Background: Infection of *Chlamydia psittaci* (*C. psittaci*) could lead to serious clinical manifestations in humans, including severe pneumonia with rapid progression, adult respiratory distress syndrome (ARDS), sepsis, multiple organ dysfunction syndromes (MODS), and probably death. Implementation of extracorporeal membrane oxygenation (ECMO) in the patient with severe ARDS gives a promising new method for recovery.

Case Presentation: We report our successful use of venovenous (VV) ECMO in a 48-year-old man who manifested with severe respiratory distress syndrome, acute kidney injury, and septic shock caused by a diagnosis of pneumonia. After the combination of therapy including anti-infection, mechanical ventilation, and continuous renal replacement therapy (CRRT), acute inflammatory syndrome developed. However, his respiratory status rapidly deteriorated. Then, venoarterial (VA)-ECMO support was placed on the patient as suddenly slowing of the heart rate. Harlequin (North-South) syndrome occurred after ECMO initiation. A series of the process could not relieve hypoxia in the upper body. At last, transition to VV-ECMO improved hypoxia. The duration of VV-ECMO was 7 days and the mechanical ventilation was weaned on the next day. On the day of ECMO weaning, nanopore targeted sequencing (NTS) of bronchoalveolar lavage fluid (BALF) reported the presence of *C. psittaci*. After 19 days of critical systemic rehabilitation and combination therapy, the patient fully recovered from *C. psittaci.*

Conclusion: This is the first reported case of the patient receiving ECMO for *C. psittaci* pneumonia. ECMO puts the lungs on temporary rest, promotes the recovery of pulmonary function, and also wins time for finding the pathogens, which is crucial in the treatment of rare pathogens.

Keywords: *Chlamydia psittaci* (*C. psittaci*), pneumonia, extracorporeal membrane oxygenation (ECMO), next-generation sequencing (NGS), infection

BACKGROUND

Chlamydia psittaci is a type of bacteria that often infects birds. The bacteria can also infect people exposed to the infected birds and cause a disease called psittacosis. Those who have contact with pet birds and poultry, including the people who work in bird-related occupations, are at an increased risk of infection. In 2018, a multistate psittacosis outbreak occurred among the poultry workers that had 13 laboratory confirmed cases (1). A study found that out of the 311 parrots examined in China, 35.37% were seropositive and species, gender, age, season, and geographical location were identified as the risk factors (2). The occurrence of *C. psittaci* genotype A in the droppings of the two pet parrots in China suggests potential environmental contamination with *C. psittaci* and may raise public health concerns (2). A few isolated cases or outbreaks of psittacosis have been reported, usually presenting with severe pneumonia.

Extracorporeal membrane oxygenation (ECMO) is used to treat patients with severe, life-threatening conditions of the heart and lungs, but some diseases may lead to progressive organ dysfunction such as liver failure or severe neurologic injury. Then, these conditions with a poor prognosis may warrant a discussion about discontinuing ECMO support (3). An ECMO study in the United Kingdom found that 95% of the patients with severe respiratory failure had venovenous (VV) ECMO alone (4). The survival rate at ECMO intensive care unit (ICU) discharge was 74% including 71% for the patients with respiratory failure (4). VV-ECMO support is an established treatment of acute respiratory distress syndrome (ARDS) and enables to minimize ventilator-induced lung injury (VILI) as rescue therapy in ARDS patients (5, 6). But, the successful use of ECMO to treat patients with psittacosis has not been published yet.

Therefore, the use of ECMO in patients with psittacosis needs further study and discussion. However, the timing of ECMO initiation, ECMO model [VV, venoarterial (VA) or the other types], and length of ECMO also need to be studied.

CASE PRESENTATION

This was a case of a 48-year-old community inspector with a history of possible hemorrhoids (hematochezia) for 2 months, gastric ulcer, cervical spondylosis, and penicillin allergy, who presented in January 2021 with fever, diarrhea, chest pain, fatigue, and syncope. The patient, who lived in a central urban area of Wuhan, China, had dizziness for 3 days and fell three times before being admitted to the hospital. Fever, diarrhea, and chest pain appeared 1 day before with chest pain subsided 5 min later. Physical examination: Temperature was 39.6°C, heart rate was 126 beats/min, breath rate was 20 breaths/min, blood pressure was 148/77 mm Hg, oxygen saturation (SpO_2) was 98%, and lung auscultation was clear. Other physical examinations were negative. CT scan of the chest showed left upper zone consolidation (**Figure 1**). Blood tests indicated a white blood cell count 2,910/mm^3, neutrophil count 2,630/mm^3, lymphocyte count 100/mm^3, hemoglobin 82 g/l, platelet count 7,300/mm^3, C-reactive protein 193.9 mg/l (normal value < 10 mg/l), serum amyloid A (SAA) protein > 300 mg/l (normal value < 10 mg/l), and procalcitonin (PCT) 6.51 ng/ml. Galactomannan enzyme immunoassay (GM-EIA) shows 0.12 (normal value 0–0.49) and fungus (1→ 3)-β-D-glucan test shows <37.50 pg/ml (normal value < 70 pg/ml). Blood and sputum culture were performed. The patient was diagnosed with community-acquired pneumonia and empirical intravenous antibiotic therapy was started with ceftazidime. 1 day later, he fainted suddenly with SpO_2 80–90%, partial pressure of oxygen (pO_2) 71 mm Hg, and then transferred to the ICU due to deterioration of respiratory status, severe desaturation, and delirium. At the same time, wet and dry rales could be heard in both the lungs, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA) scores were 18 and 8, respectively (**Table 1**). Tracheal intubation and mechanical ventilation were performed with positive end-expiratory pressure (PEEP) 10 mm Hg and a fraction of inspired oxygen (FiO_2) 100%. Flexible bronchoscopy was performed and showed pulmonary edema without the other abnormalities. To get more information on etiology, bronchoalveolar lavage fluid (BALF) samples were obtained for nanopore targeted sequencing (NTS) and sputum culture. The results of echocardiography showed the size of the ventricles and atria were normal, the thickness and amplitude of movement of the ventricular septum and the free wall of the left ventricle, the morphology and activity of the valves, and the opening and closing of the valves were normal. Simultaneously, antibiotic therapy was changed to meropenem and ganciclovir. In the following days, he presented with progressive worsening of the bilateral pulmonary infiltrates, high ventilatory parameters, and increasing serum PCT and creatinine levels with the signs

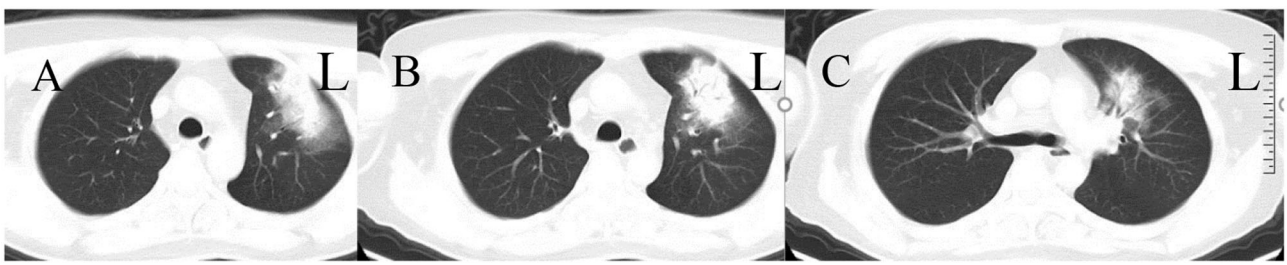

FIGURE 1 | CT scan of the patient (**A–C** show CT scans on the 0th day after admission).

TABLE 1 | Characteristics of the patient and the methods of treatment.

	Feature
Age, yr	48
Sex	Male
Clinical features	Fever, diarrhea, chest pain, fatigue, and syncope
Smoke	No
Drink	No
Surgery	No
Hormone/immunosuppressive therapy	No
Chronic diseases	
Hypertension	No
Diabetes	No
Kidney failure	No
Chronic bronchitis	No
Treatment	
Vasoactive drugs	Yes
Arterial puncture	Yes
ECMO	Yes
Tracheotomy	Yes
CVC	Yes
Nasogastric tube	Yes
Urinary catheters	Yes
CRRT	Yes
SARS score	56
APACHE II	18
SOFA	8
Mechanical ventilation duration(days)	16

CVC, central venous catheter; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy.

of septic shock. Ultrafiltration was required for oligoanuria and severe fluid was overload. On the fourth day after intubation, pO_2/FiO_2 was reduced to 59 and bronchoscopy showed severe airway mucosal edema. Then, ECMO was commenced on day 5 in the ICU. VV-ECMO was planned originally; VA-ECMO with the initial flow set at 4 L/min was finally performed as the heart rate of the patient sharply dropped before the inserting tubes. Then, the patient experienced intermittent episodes of significant hypoxemia with SpO_2 ranging from 41 to 81% corresponding to right radial artery partial pressure of arterial oxygen (PaO_2) ranging from 49 to 58 mm Hg. To find out the reason for hypoxemia, we raised the flow rate of ECMO from 4.0 to 4.5 L/min. This adjustment could not eliminate hypoxemia. The PaO_2 of the right radial artery was 60 mm Hg, while the PaO_2 of the right dorsal foot artery was 400 mm Hg. A severe North-South syndrome was presented as differential cyanosis. This cannot be eliminated by venoarterial venous (VAV)-ECMO with the presence of an internal jugular venous shunt of 18 Fr arterial cannulas. After the confirmation of ultrasound, the function of the heart was normal and at last, we converted to VV-ECMO. On day 2 (day 6) of ECMO, nucleic acid screening of the pharyngeal swab showed chlamydia. Antibiotic therapy with azithromycin was administered. Methylprednisolone pulses and respiratory physiotherapy were implemented. Improvement of pulmonary infiltrates was observed in the following days. After 7 days, ECMO support was discontinued (day 12) and ventilation was converted to high flow humidification oxygen therapy on the next day (day 13). On the 13th day after admission, the NTS results from the third sample of BALF showed the presence of *C. psittaci* and the readings of the sequences were 96. Therefore, the antibiotics were changed to meropenem and doxycycline accordingly. Signs of infection were improved after combined dialysis, nutrition, and other treatments. X-ray and CT scan of the chest demonstrated improved diffuse ground-glass infiltrates. Multiple cultures of blood and BALF were negative. The patient was weaned off the ventilator on the 17th day after the admission. Throughout the course of treatment, the indicators of infection and renal function tended to improve (**Table 2**). He regained some kind of consciousness, but could not give the exact answer and the vasoactive drugs were significantly downregulated.

DISCUSSION

Chlamydia psittaci is a gram-negative, obligate intracellular parasite that is mainly transmitted to humans through contact with the infected birds (such as parrots and poultry), inhalation of aerosols, feces, or feather dust from the nasal secretions of the infected birds. The disease caused by *C. psittaci* infection is called psittacosis, which is considered a rare cause of pneumonia. A meta-analysis of an observational study found that about 1% of the community-acquired pneumonia was caused by *C. psittaci* (7). Probably due to the lack of routine detection of *C. psittaci* and the sensitivity and specificity of the common diagnostic methods, it is difficult to determine the accurate incidence and prevalence of *C. psittaci* (8, 9). Contact with the birds or poultry is the main risk factor for psittacosis. It has been reported that among 1,136 patients, 72% of the patients had pets or had contact with birds or poultry in a domestic environment and 6% had exposure to wild birds, 12% are poultry workers, and only 10% have no relevant contact history (10, 11). In addition to the parrots, poultry is also an important source of infection of *C. psittaci*. A study found that the seropositivity rates of *C. psittaci* in the chickens, ducks, and pigeons sold in Northwest China were 13.3, 38.9, and 31.1%, respectively (12).

In this case study, a positive environmental link has been identified. During the same period, the Chinese news outlets reported psittacosis cases in Changsha, Hunan province, and Zhongshan, Guangdong province. Although this case lived in an urban area, there were large forests and birds in the community. Therefore, the patients with a history of exposure to the birds or poultry should be alert to the possibility of atypical infection of the pathogen, especially *C. psittaci*. The incubation period ranges between 5 and 14 days. In a study of 135 patients, all the patients had a fever as the main manifestation and 61% of patients were accompanied by chills. Although 82% of the patients complained of cough, it often appeared later (13). Its typical clinical manifestations are fever, chills, headache, cough

TABLE 2 | Ventilator and the ECMO parameters, indicators of infection, and renal function.

	D1	D2	D3	D5	D7	D8	D9	D12	D17
FiO_2	100%	60%	60%	100%	100%	40%	40%	35%	35%
PEEP (cmH_2O)	10–8	8	8–5	8–10	8–10	5	5	5	3–5
Pplat	18	15	16	18	18	15	14	12	8
CL (ml/mmHg)	35	38	42	33	38	41	49	56	65
Vt (ml)	300–400	400–450	400–450	300	300–400	300–400	400–45–	400–500	400–500
PCO_2 (mmHg)	30	32	42	42	42	55	36	38	34
PO_2 (mmHg)	71	97	167	59	439	96	102	71	80
P/F ratio (mmHg)	71	161	228	59	439	192	240	177.5	228.6
ECMOration rate (revolutions/min)	–	–	–	3,000	3,200	3,200	3,200	2,200	–
ECMO flux (3 L/min)	–	–	–	3.3	3.3	3.3	3.3	1.4	–
ECMO FiO_2	–	–	–	100%	100%	100%	100%	40%	–
Dosage of vasoactive drugs	NE 20 ug/min	NE 15 ug/min	NE 15 ug/min	NE 30 ug/min DFA 55 ug/min	NE 15 ug/min DFA 30 ug/min	NE 15 ug/min DFA 30 ug/min	NE 15 ug/min DFA 30 ug/min	–	–
Antibiotics	Meropenem and ganciclovir	Meropenem and ganciclovir	Meropenem and ganciclovir	Meropenem and ganciclovir	Meropenem, ganciclovir and azithromycin	Meropenem, ganciclovir and azithromycin	Meropenem, ganciclovir and azithromycin	Meropenem and doxycycline	Doxycycline
W.B.C (mm^3)	3,830	6,090	10,950	13,290	6,270	7,820	7,650	5,760	2,770
PCT (ng/ml)	6.51	60.1	58.7	35.9	16	9.23	5.2	1.38	0.84
Cr (umol/L)	178	243	180	242	180	139	199	171	209
Urine volume (ml)	1,450	2,060	1,400	300	70	50	30	40	1,700

FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; VT, tidal volume; Pplat, platform pressure; CL, lung compliance; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; WBC, white blood cell; PCT, procalcitonin.

without sputum, and gastrointestinal symptoms. In severe cases, severe pneumonia, endocarditis, jaundice, and neurological complications may be developed. Since *C. psittaci* is difficult and dangerous to culture and is highly infectious, serological examination is usually used for the diagnosis. Among them, the most sensitive and specific is a microimmunofluorescence assay showing antibody titers at least 4-fold higher than the upper limit of normal in the duplicate serum samples or the titer of the IgM antibody is $\geq$1:16. The development of the PCR has greatly simplified DNA analysis and shortened the laboratory time to detect *C. psittaci*. This method can quickly and specifically identify the pathogens and perform genotyping at the same time, but many authors described the assays that were less sensitive and detected only when the high loads were observed during the acute phase of the disease. Nowadays, the microbiology laboratories do not routinely screen the above tests, but only in the specialized laboratories, so it is difficult for clinicians to diagnose psittacosis. Through the development of the second-generation metagenomic intervention technology [metagenomic next-generation sequencing (mNGS)], a variety of the pathogens in the different specimens can be quickly and accurately identified including atypical pathogens, viruses, and fungi that are difficult to cultivate. Thus, mNGS, also known as deep sequencing, is widely favored because of its rapid detection. This technology is based on collecting the human genes followed by the amplification and sequencing of pathogen nucleic acids and then high-throughput sequencing, machine-learning algorithms, and bioinformatics pipelines were performed. Its versatile detection has an advantage for the diagnosis of rare pathogenic bacteria in difficult cases. mNGS technology was done to diagnose *Chlamydia pneumoniae* by the BALF samples when the situation deteriorated in our procedure. With rapid analysis, this approach can quickly detect most of the pathogens and overcoming conventional culture-independent evaluation of the little clinical samples (microliter volumes) or prior antibiotic exposure. mNGS also provides additional data

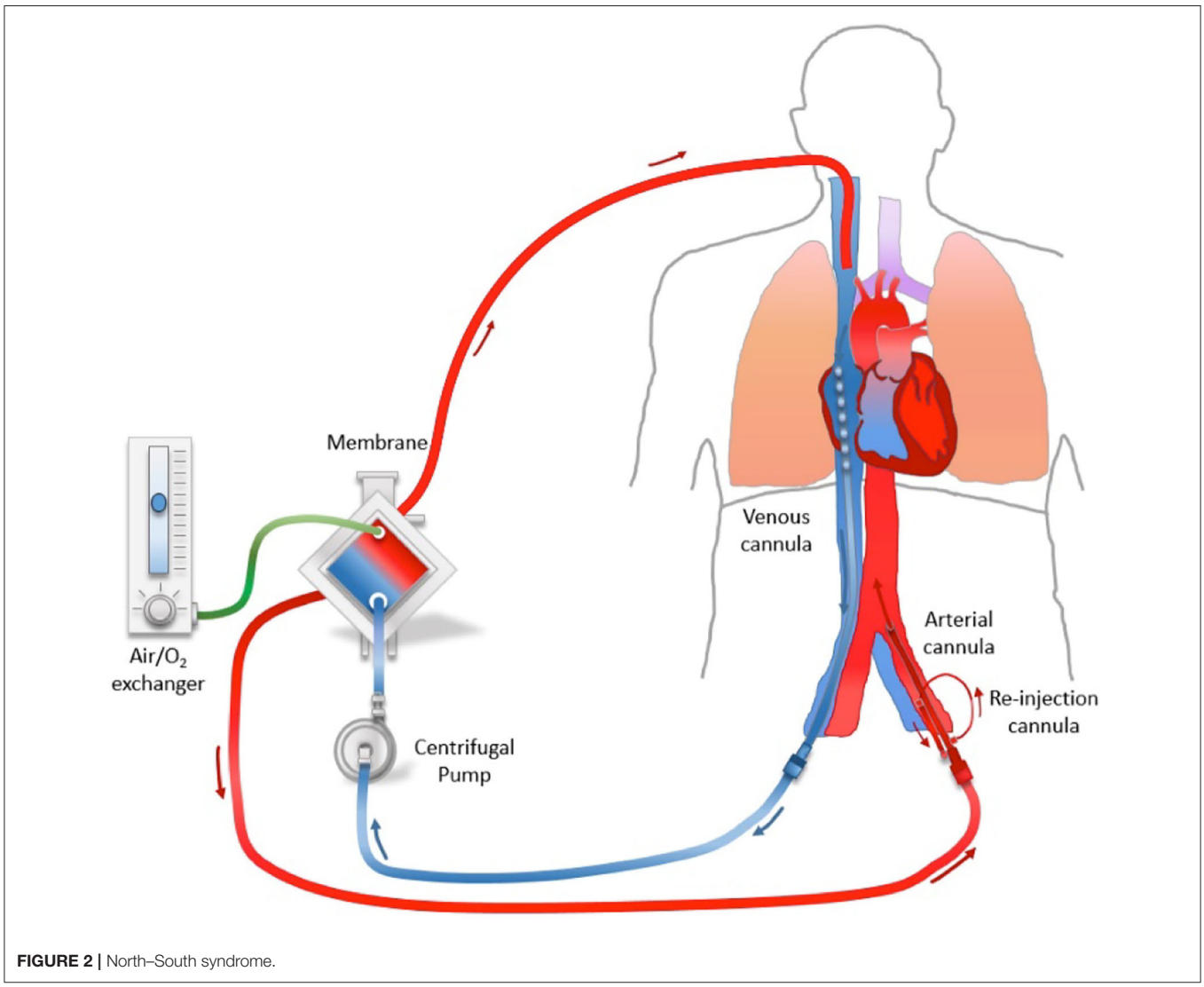

FIGURE 2 | North–South syndrome.

including bacterial DNA burden and community diversity that may help to identify pathogenic bacteria. New technology for performing targeted screening of NTS is a type of mNGS (14); therefore, it was developed to detect *C. psittaci*. Studies have shown that NTS is sensitive for detecting respiratory viruses (15), but its use in the detection of *C. psittaci* is less reported, so its rapid detection could be very beneficial for the early diagnosis and treatment of patients with parrot fever. In this case study, three BALF samples were sent to analyze by NTS technology. Only the last one reported *C. psittaci*. Nevertheless, we only found *C. psittaci* in the third test of NTS after we deeply discussed this case with the laboratory staff and the readings of the sequences were extremely low that is easy to ignore. In consistent with previously reported (16), the difference between blood and BALF may be due to the fewer effective cells in the BALF. Therefore, to obtain a meaningful diagnosis, the doctors need to consider the analysis of NTS combined with the clinical manifestations. NTS also has other disadvantages that limit its public application such as without drug sensitivity, the cost, and unavailable in mostly small hospitals, which increases the possibility of missed or misdiagnosis of the rare pathogenic bacteria in difficult cases.

Chlamydia psittaci belongs to the Chlamydia family (13) and tetracyclines, macrolides, and quinolones which suppress DNA and protein synthesis could be the appropriate antibacterial drugs (17). The first-line medication is tetracycline drugs for at least 3 weeks in order to avoid recurrence. If tetracyclines are restricted in some patients, such as children, pregnant women, or allergies, macrolides can be selected as an alternative treatment. In some cases, quinolones are effective but are less effective compared to tetracyclines and macrolides (18). The patient was presented in this study had used azithromycin and meropenem according to the nucleic acid test of pharyngeal swab that showed *Chlamydia*, but the patient still had fever with pulmonary function deterioration, which means poor efficacy or insufficient treatment. These two drugs are supposed to be second-line treatment and in effect (19, 20), but, at first, the condition of the patient progresses too fast and the disease is too severe. After NTS of BALF reported *C. psittaci,* timely adjustment of the antibacterial treatment based on doxycycline minimized the prognosis time and disease process. At the same time, NTS testing did not report other pathogens, thereby reduced the use of the unnecessary antibacterial drugs, effectively reduced the hospitalization costs, and avoided the emergence of the drug-resistant bacteria.

In the case of ventilator treatment, the condition of the patient deteriorated on the 5th day and the adjustment of ventilator parameters could not meet the needs of the patient, so ECMO treatment was given. In ECMO, blood is pumped outside of the body to a heart-lung machine, which removes carbon dioxide and fills oxygen into the blood back to the tissues in the body, which could be an effective technology to improve organ oxygenation when positive-pressure ventilation and prone position are inadequate to improve the blood oxygen saturation. There are two types of ECMO. The VA-ECMO is connected to both a vein and an artery and is used when there are problems with both the heart and lungs. In most cases of ECMO for severe acute respiratory failure, VV-ECMO is selected from which blood is pumped and returned to a central vein. ECMO allowed further reduction in ventilation-induced lung damage and the search of a diagnostic procession that included culture and mNGS making the patient to the definitive diagnosis, specific antibiotics, immunosuppressive treatment, and recovery. In the present case study, we first described the patient with psittacosis complicated by refractory respiratory failure and rescued with VV-ECMO. In this case study, VA-ECMO cannulation was selected because of the risk of hemodynamic collapse after a sharp reduction of heart rate. This choice leads to the North-South syndrome soon afterward, which is a form of Harlequin syndrome. North-South syndrome occurs in 38% of ECMO operations (21). Some scientists argue that draining from the superior vena cava (SVC) via a multistage cannula inserted in the right internal jugular vein is neutralized (22), but drainage of the internal jugular vein (also called VAV-ECMO) seems do not solve the problem in this case. In the VAV-ECMO circuit, with drainage from a cannula inserted in the femoral artery and then return of a cannula inserted in the internal jugular vein (tip in the SVC next to the right atrium) and the femoral vein (tip in the inferior vena cava), the blood volume of the upper body reduced with insufficient supply of oxygen and low blood pressure. It is also indicated that the patient had a severe pulmonary infection and poor oxygenation (**Figure 2**).

CONCLUSION

In summary, this is the first case of pulmonary infection with ECMO occurring in a patient in China suggesting that ECMO plays an increasing role as an opportunistic pathogen in immunocompromised patients. With the consent of the patient (supply figure), this case provides a reminder that the clinicians should expect the unexpected in terms of the infectious agents and emphasizes the importance of the microbiological diagnostic procedures.

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

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

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Severe Patients With ARDS With COVID-19 Treated With Extracorporeal Membrane Oxygenation in China: A Retrospective Study

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Background: The novel coronavirus disease 2019 (COVID-19) pandemic has become a global health crisis affecting over 200 countries worldwide. Extracorporeal membrane oxygenation (ECMO) has been increasingly used in the management of COVID-19-associated end-stage respiratory failure. However, the exact effect of ECMO in the management of these patients, especially with regards to complications and mortality, is unclear.

Methods: This is the largest retrospective study of ECMO treated COVID-19 patients in China. A total of 50 ECMO-treated COVID-19 patients were recruited. We describe the main characteristics, the clinical features, ventilator parameters, ECMO-related variables and management details, and complications and outcomes of COVID-19 patients with severe acute respiratory distress syndrome (ARDS) that required ECMO support.

Results: For those patients with ECMO support, 21 patients survived and 29 died (mortality rate: 58.0%). Among those who survived, PaO_2 (66.3 mmHg [59.5–74.0 mmHg] and PaO_2/FiO_2 (68.0 mmHg [61.0–76.0 mmHg]) were higher in the survivors than those of non-survivors (PaO_2: 56.8 mmHg (49.0–65.0 mmHg), PaO_2/FiO_2 (58.2 mmHg (49.0–68.0 mmHg), all $P < 0.01$) prior to ECMO. Patients who achieved negative fluid balance in the early resuscitation phase (within 3 days) had a higher survival rate than those who did not ($P = 0.0003$).

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Conclusions: In this study of 50 cases of ECMO-treated COVID-19 patients, a low PO_2/FIO_2 ratio before ECMO commencement may indicate a poor prognosis. Negative fluid balance in the early resuscitation phase during ECMO treatment was a predictor of increased survival post-ECMO treatment.

Keywords: coronavirus (COVID-19), severe acute respiratory syndrome, extracorporeal membrane oxygenation (ECMO), China, management

BACKGROUND

Coronavirus disease 2019 (COVID-19) is a newly emerging disease caused by the novel SARS-CoV-2 virus. It was first reported in Wuhan, China in December 2019 and soon it spread all over the world (1). The World Health Organization (WHO) declared the COVID-19 a pandemic in March 2020. It is now affecting 213 countries and territories globally. As of April 2021, more than 193 million cases have been identified with over 2.9 million fatalities. Typical coronavirus infection causes respiratory symptoms. Common signs and symptoms include fever, cough, shortness of breath, fatigue, and dyspnea (2). Many COVID-19 patients have mild-to-moderate symptoms. However, elderly patients and those with existing chronic medical conditions, for example, diabetes, hypertension, chronic liver, and kidney disease, etc., are at higher risk of serious illness that may require intensive care unit (ICU) admission and are predisposed to severe acute respiratory distress syndrome (ARDS) (3). It has been shown that ARDS contributes to a mortality rate of 50% in ICU patients (4). A very recent report further demonstrated that 15% of patients infected with SARS-CoV-2 develop ARDS, with a resultant mortality rate in this group of 61.5% (5, 6).

The general treatment recommendations for ARDS from WHO interim guidelines indicate that ECMO may serve as a potentially life-saving strategy, providing circulatory and pulmonary support for patients with ARDS (7). During the 2009 influenza A (H1N1) winter pandemic, ECMO was used in treating H1N1–associated respiratory failure (8); however, because of insufficient evidence of decreasing mortality rate, the beneficial effect of ECMO remains controversial (9). Although a few reports have indicated the use of ECMO in the current pandemic (10–12), the exact role of ECMO in the management of COVID-19 is unclear. Importantly, ECMO is a very expensive and highly resource-demanding form of life-rescuing support. Therefore, recognizing and accurately selecting ECMO-appropriate candidates with SARS-CoV-2 pneumonia-associated ARDS would optimize the utilization of limited medical resources.

The principal aim of the study was to describe the clinical features, ECMO-related variables, technical characteristics of extracorporeal management, complications, and outcome of patients with COVID-19-associated end-stage respiratory failure who were treated with ECMO. To the best of our knowledge, this is the largest retrospective study of ECMO-treated COVID-19-induced ARDS in China.

METHODS

Study Design and Patients

This retrospective study was approved by the institutional ethics committee of the West China Hospital, Sichuan University (ID: 2020-717). The institutional ethics review boards at all other participating centers approved the study protocol. All committees waived the need for informed consent because this is a non-interventional retrospective study and only electronic health records were used to extract data.

In this retrospective observational study, we included all adult COVID-19 patients (age from 35 to 91) from Beijing, Sichuan, Guangxi, Hunan, and Hebei province in China who received ECMO support between February 3, 2020, and January 23, 2021. Diagnosis of COVID-19 was confirmed by the use of real-time reverse transcription-polymerase chain reaction (RT-PCR) kits. All these critically ill patients were confirmed SARS-CoV-2 virus-positive and the severity of illness for COVID-19 patients was defined according to the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (version 7.0) (13). ARDS was diagnosed according to the Berlin definition (14). If the PaO_2/FiO_2 ratio of the ARDS patient was <150 mmHg, the lung protective strategies and the prone position were applied. Patients who were unresponsive to conventional ARDS rescuing therapies were eligible for ECMO support if they met the following clinical criteria: (1) developed a refractory severe ARDS; (2) Lung Injury Murray Score $\geq$ 3;(3) developed uncompensated hypercapnia with pH $<$ 7.25 or $PaCO_2 >$ 60 mmHg over 6 h; (4) $PaO_2/FiO_2 <$ 80 over 6 h; (5) $PaO_2/FiO_2 <$ 50 mm Hg over 3 h. Patients with refractory severe multiorgan failure and/or significant neurological injury were excluded.

After initiating ECMO, all the patients received an optimal lung-protective strategy, i.e., FiO_2 was set to 40–70% to maintain SaO_2 over 90 or PaO_2 over 60 mmHg, tidal volume 4–6 ml/kg ideal body weight, Pplat 25–30 cmH_2O, PEEP 5–15 mmH_2O, respiratory rate 4–10 breaths per minute, with transpulmonary driving pressure <14 cmH_2O.

We used heparin as an anticoagulant therapy during ECMO treatment. Heparin was continuously infused intravenously at 5–25 ug/kg.h. Therapeutic strategies were defined as the activated clotting time (ACT) of 180–200 s, the activated partial thromboplastin time (**a**PTT) of 40–60 s. ACT and aPTT were monitored every 2–4 h daily.

Data Collection

A case report form was used for data collection by experienced clinicians. Two researchers cross-checked the collected data to ensure data accuracy and integrity. We obtained the following

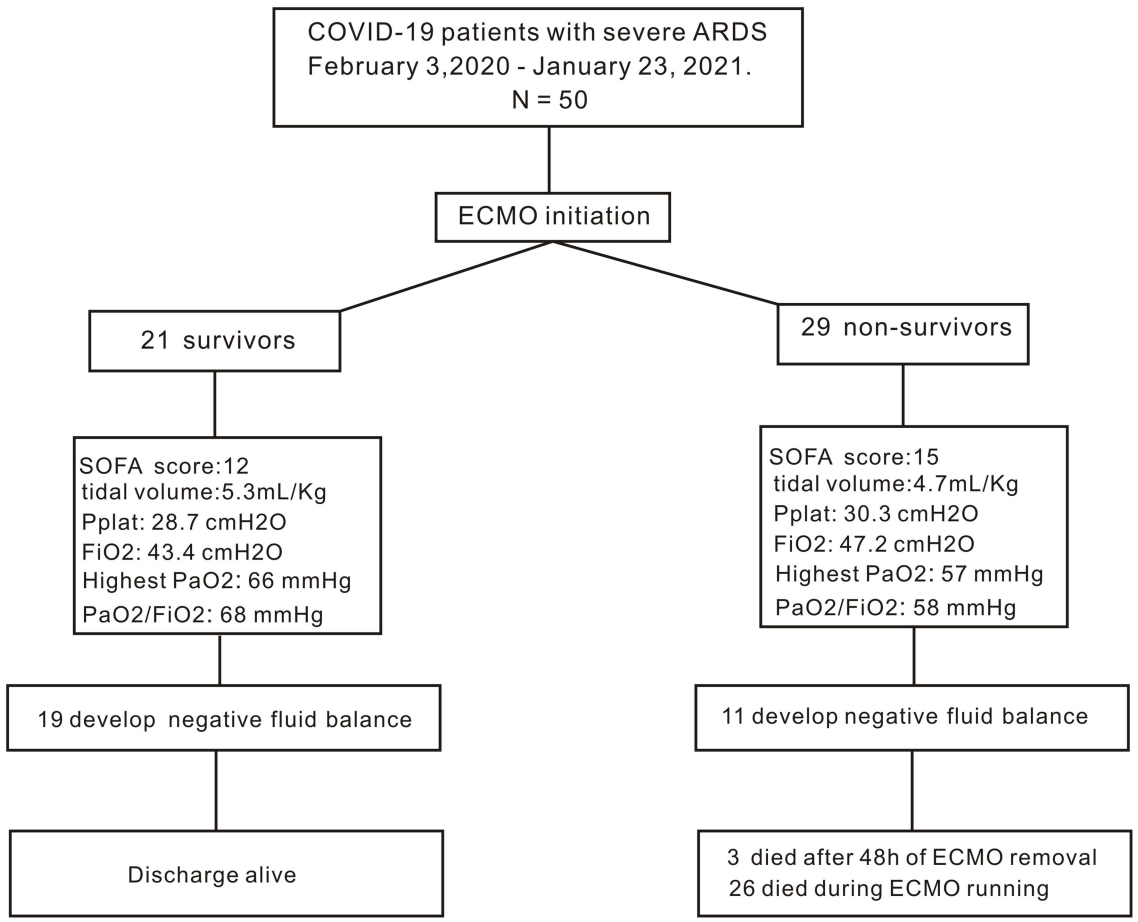

FIGURE 1 | Flow diagram of the study. PaO_2, arterial partial pressure of oxygen; PaO_2/FiO_2, the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; FiO_2: the fraction of inspired oxygen.

retrospective data from electronic medical records: demographic data, including age, gender, body mass index (BMI); predefined comorbidities, including high blood pressure, diabetes, and hyperthyroidism; pre-ECMO laboratory data, including hemoglobin, leukocyte, CREA, alanine aminotransferase (ALT), and total bilirubin. Sequential Organ Failure Assessment (SOFA) score was calculated in both groups within 24 h after admission. We also recorded information on the timing of onset of symptoms, commencement of mechanical ventilation, and ECMO treatment. Data on baseline lung functions, including pH, PO_2, PaO2/FiO_2, PCO_2, and lactate before ECMO placement were also recorded. Ventilator settings, e.g., mode, FiO_2, positive end-expiratory pressure (PEEP), respiratory rate, tide volume, and plateau pressure (Pplat) were recorded either prior to or after ECMO initiation. We collected ECMO-related treatment details, including; (1) ECMO mode, ECMO duration, and ventilation mode during ECMO support; (2) whether patients received protective mechanical ventilation, were placed in a prone position, had bronchoalveolar lavage and daily sputum suction, and/or used vasoactive drugs. We also collected data of PaO_2 and $PaCO_2$ after 24 h of ECMO treatment. Complications associated with ECMO, the characteristics of mortality cases, and the causes of death were documented.

The primary outcomes were survival rate or mortality. Patients who died during ECMO treatment were classified in the latter category, as were those who were weaned off ECMO but died within 48 h post-ECMO (three patients). The 21 patients who were successfully discharged after ECMO treatment were classified as survivors.

Statistical Analysis

Continuous variables were expressed as median with interquartile range (IQR) and were compared using Wilcoxon rank-sum tests. Categorical variables were reported as frequency and percentage. Fisher's exact test was employed to compare the number of patients falling into one of the two ECMO survivor or non-survivor groups. Statistical analyses and survival curves were generated using GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, California, USA). $P < 0.05$ was used to indicate statistical significance.

TABLE 1 | General characteristics of patients with extracorporeal membrane oxygenation.

Parameters	Total ($n = 50$)	Survivors ($n = 21$)	Non-survivors ($n = 29$)	*P*-value
Age	65.3 (58.8–73.0)	61.2 (54.5–70.0)	68.2 (62.0–75.0)	0.07
Gender:male, *n* (%)	34 (68.0)	12 (57.1)	22 (75.9)	0.22
Gender:female, *n* (%)	16 (32.0)	9 (42.9)	7 (24.1)	0.22
Body Mass Index (BMI)	25.3 (23.1-27.8)	25.8 (23.3–29.0)	25.0 (22.7–27.4)	0.48
High blood pressure, *n* (%)	22 (44.0)	6 (28.6)	16 (55.2)	0.09
Diabetes, *n* (%)	15 (30.0)	4 (19.0)	11 (37.9)	0.21
Leukocyte ($\times 10^9$/L)	13.5 (11.5–15.8)	13.3 (11.8–15.7)	13.7 (11.2–16.3)	1
Hemoglobin (g/L)	104.1 (88.0–126.0)	108.5 (97.0–129.0)	100.9 (86.0–125.0)	0.16
CREA (μmol/L)	60.9 (36.8–71.9)	68.6 (39.0–74.5)	55.3 (35.7–70.5)	0.29
Alanine aminotransferase (U/L)	42.7 (22.0–54.3)	45.8 (27.5–61.5)	40.4 (22.0–53.0)	0.27
Total bilirubin (μmol/L)	24.1 (11.9–32.8)	20.5 (12.5–27.5)	26.7 (11.3–35.0)	0.64

p-values: survivors vs. non-survivors.

TABLE 2 | Lung function and treatment before the commencement of extracorporeal membrane oxygenation.

Parameters	Total ($n = 50$)	Survivors ($n = 21$)	Non-survivors ($n = 29$)	*P*-value
SOFA score	13.7 (12.0–15.0)	12 (11–14)	1 (514–16)	<0.0001
Highest PaO_2, mmHg	60.8 (52.0–70.0)	66.3 (59.5–74.0)	56.8 (49.0–65.0)	0.0033
PaO_2/FiO_2, mmHg	62.3 (52.0–73.3)	68.0 (61.0–76.0)	58.2 (49.0–68.0)	0.0051
Highest $PaCO_2$, mmHg	60.2 (54.0–67.6)	57.6 (47.0–67.8)	62.1 (55.1–68.6)	0.34
Lowest PH	7.3 (7.2–7.3)	7.3 (7.2–7.4)	7.3 (7.2–7.3)	0.97
Lactate, mmol/L	2.9 (1.8–3.1)	2.3 (1.8–2.9)	3.2 (1.8–3.8)	0.35
Highest PEEP, cm H_2O	11.4 (10.0–12.0)	11.7 (10.0–12.5)	11.2 (10.0–12.0)	0.53
Pplat, cm H_2O	30.5 (26.0–34.0)	29.3 (24.5–33.5)	31.3 (28.0–35.0)	0.5
Choice of ventilation mode of P/C	23 (46.0)	9 (42.9)	14 (48.3)	0.78
Choice of ventilation mode of A/C	27 (54.0)	12 (57.1)	15 (51.7)	0.78
Duration of onset of symptoms to MV, median (IQR), d	13.6 (5.0–20.3)	11.8 (5.0–16.5)	14.9 (4.5–21.0)	0.54
Duration of onset of symptoms to ECMO, median (IQR), d	18.3 (7.0–25.3)	15.5 (7.5–21.0)	20.4 (6.5–27.0)	0.38
Duration of MV to ECMO, median (IQR), d	5.2 (1.0–9.3)	3.8 (1.0–5.0)	6.2 (1.5–11.0)	0.38

MV, mechanical ventilation; Pplat, airway plateau pressure; PEEP, positive end expiratory pressure; P/C, pressure control mode; A/C, volume control mode; p-values: survivors vs. non-survivors.

RESULTS

General Characteristics of Patients Treated With ECMO

The study population comprised 50 confirmed patients with COVID-19 who were admitted to the hospital between February 3, 2020, and January 23, 2021, and were placed on ECMO (**Figure 1**). **Table 1** depicts patient demographic data of both survivors and non-survivors, as well as their laboratory examinations after hospitalization. The median age of these patients was 65.3 years (IQR: 58.8–73.0), ranging from 35 to 91 years. Although not statistically significant, the patients in the non-survivor group had a higher age as compared with the survivor group. A total of 34 male patients and 16 female patients were included in the study, accounting for 68 and 32% of the total patient population, respectively. The median body mass index was 25.3 (IQR: 23.1–27.8) and was not different between survivors and non-survivors. Various comorbidities were investigated in the current study. The most common associated predefined comorbidities were high blood pressure and diabetes mellitus in 22 patients (44%), and 15 patients (30%), respectively. There were no statistically significant differences

between survivors and non-survivors regarding the incidence of high blood pressure ($P = 0.0857$) or diabetes mellitus ($P = 0.21$). As for laboratory tests, all the patients developed leukocytosis, with an increased WBC count of 13.5×10^9/L (IQR: 11.5–15.8 $\times 10^9$/L). SARS-CoV-2 coronavirus also attacks red blood cells, resulting in a reduced hemoglobin concentration (104.1 g/l, IQR: 88.0–126.0 g/l). The creatinine level was within the normal range. Liver damage was seen in all the patients infected with COVID-19, as evidenced by elevated levels of ALT and total bilirubin. Meanwhile, we did not find any difference between the survivors and non-survivors with respect to blood chemistry (all $P > 0.05$).

Characteristics of Patients and Mechanical Ventilation Protocol Before Initiation of ECMO

Details of the severity of illness before initiation of ECMO are shown in **Table 2**. Generally, all these COVID-19 patients developed severe ARDS with deteriorated lung function. The SOFA score was calculated within 24 h after admission. The mean SOFA score was higher in non-survivors than that in survivors ($P < 0.0001$). PaO_2 was low in all the patients with a median of 60.8 mmHg (IQR: 52.0–70.0 mmHg) and was lower in the non-survivors (56.8 mmHg, IQR: 49.0–65.0 mmHg) when compared with survivors (66.3 mmHg, IQR: 59.5–74.0 mmHg, $P = 0.0033$). Accordingly, the median PaO_2/FiO_2 ratio was 62.3 mmHg (IQR: 52.0–73.3 mmHg), and survivors (68.0 mmHg, IQR: 61.0–76.0 mmHg) had significant higher PaO_2/FiO_2 ratio as compared with the non-survivors (58.2 mmHg, IQR: 49.0–68.0 mmHg, $P = 0.0051$). All the patients had retention of carbon dioxide in the blood, with no statistically significant differences between non-survivors and survivors ($P = 0.34$). Both the survivors and non-survivors had low pH. Serum lactate was slightly elevated with a median of 2.3 mmol/l in survivors and a median of 3.2 mmol/l in non-survivors ($P = 0.35$). The mechanical ventilator settings before ECMO treatment are listed in **Table 2**. Generally, there were no differences in the ventilator settings (i.e., PEEP, Pplat, and ventilation mode) between survivor and non-survivor groups (all $P > 0.05$). Although not achieving $P < 0.05$, there was a trend toward a shorter time between the onset of symptoms and initiation of mechanical ventilation in the survivors vs. non-survivors (11.8 days, IQR: 5.0–16.5 vs.14.9 days, IQR: 4.5–21.0 days, respectively; $P = 0.54$) or the initiation of ECMO (15.5 days, IQR: 7.5–21.0 vs. 20.4 days, IQR: 6.5–27.0 days, respectively; $P = 0.38$), as well as the duration between the start of mechanical ventilation and ECMO (3.8 days, IQR: 1.0–5.0 vs. 6.2 days, IQR: 1.5–11.0 days, respectively; $P = 0.38$).

Extracorporeal Membrane Oxygenation Treatment Details

As shown in **Table 3**, the median duration of ECMO support was 17.9 days (IQR: 6.0–22.0 days), and no difference was found between survivors and non-survivors ($P = 0.95$). All the patients received lung-protective strategy after ECMO initiation in our study. Veno-venous (VV) ECMO was used in 94.0% of patients with the rest (6.0%) of the patients treated with veno-arterial (VA) ECMO. Regarding mechanical ventilator settings, pressure control (P/C) ventilation mode was used in 62.0% of patients during ECMO treatment, while 38.0% of patients have ventilated in volume control (A/C) mode. There were no differences in ventilation modes between survivors and non-survivors (P/C: $P = 0.26$; A/C: $P = 0.26$, respectively). Meanwhile, there is no difference between survivors and non-survivors regarding the respiration rate ($P = 0.25$), driving pressure ($P = 0.15$), and the highest PEEP ($P = 0.16$). However, the FiO_2 was lower ($P = 0.04$), and tidal volume was higher in survivors ($P = 0.014$), accompanied by the reduced Pplat value ($P < 0.0001$) indicating that the patients with better lung compliance had better survival rate. After 24 h of ECMO treatment, significant improvement in oxygenation was observed in all patients as evidenced by increased PaO_2 (93.1 mmHg, IQR: 75.8–109.3 mmHg). Survivors appeared to have higher PaO_2 than non-survivors, although this difference did not reach statistical significance ($P = 0.3$). Accordingly, the average $PaCO_2$ decreased to 38.5 mmHg (IQR: 34.5–42.5 mmHg) after ECMO treatment. However, no difference in $PaCO_2$ was found between survivors and non-survivors ($P = 0.79$). Thirty-nine patients (78%) were subjected to prone positioning during ECMO treatment (90.5% survivors and 69.0% non-survivors, $P = 0.09$). We also studied the influence of fluid balance and found that within the first 3 days of ECMO, more survivors achieved negative fluid balance (19 survivors, 90.5% vs. 11 non-survivors, 37.9%, $P = 0.0003$). During the entire ECMO treatment period, patients underwent a series of therapies, including daily sputum suction (23 out of 50 patients, 46%) and bronchoalveolar lavage (39 out of 50 patients, 78.0%). A combination of vasoactive drugs during ECMO offered no discernible benefit to the patients ($P = 1$).

Complications and Patient Outcomes

As shown in **Table 4**, in our study, of the 50 patients studied, 21 (42.0%) were weaned from ECMO successfully and were discharged. The total mortality rate was 58.0% (29 out of 50 patients). Twenty-six of the non-surviving patients died when they were on ECMO support (89.7%), while three died during the first 48 h of ECMO decannulation (10.3%). The median duration between onset of symptoms and death was 38.2 days (IQR: 25.5–45.0 days). Primary reasons for death were bleeding (9 out of 29 deaths, 31.0%), respiratory failure (4 out of 29 deaths, 13.8%), sepsis (14 out of 29 deaths, 48.3%), multiple organ failure (18 out of 29 deaths, 62.1%), and heart failure (4 out of 29 deaths, 13.8%). ECMO-related complications are presented in **Table 4**. Briefly, of the 50 patients, 13 had decreased platelet counts (26.0%), 39 exhibited bleeding (78.0%), 16 had infections (32.0%), three exhibited thrombus (6.0%), and three exhibited pneumothorax (6.0%).

DISCUSSION

The current COVID-19 pandemic has now infected more than 137 million people worldwide. Approximately 15–30% of COVID-19 patients developed severe respiratory compromise. Mortality for patients with COVID-19-related ARDS is substantial (15). ECMO is an external artificial lung device and a life-saving rescue strategy for patients with severe lung disease

TABLE 3 | Lung function and treatment details after commencement of ECMO.

Parameters	Total ($n = 50$)	Survivors ($n = 21$)	Non–survivors ($n = 29$)	*P*-value
ECMO running days	17.9 (6.0–22.0)	19.1 (7.5–24.0)	17.0 (5.5–22.0)	0.95
Initial ECMO mode of VV, *n* (%)	47 (94.0)	21 (100)	26 (89.7)	0.25
Initial ECMO mode of VA, *n* (%)	3 (6.0)	0 (0.0)	3 (10.3)	0.25
choice of ventilation mode of P/C during ECMO treatment, *n* (%)	31 (62.0)	11 (52.4)	20 (69.0)	0.26
choice of ventilation mode of A/C during ECMO treatment, *n* (%)	19 (38.0)	10 (47.6)	9 (31.0)	0.26
Respiration rate, BPM	10.3 (10.0–10.0)	10.5 (10.0–11.0)	10.1 (10.0–10.0)	0.25
driving pressure, cm H_2O	13.5 (13.0–14.0)	13.7 (13.0–14.0)	13.4 (13.0–14.0)	0.15
Highest PEEP, cm H_2O	8.8 (8.0–10.0)	8.6 (8.0–9.0)	9.0 (8.0–10.0)	0.16
tidal volume, ml/kg	4.9 (4.4–5.6)	5.3 (4.8–6.0)	4.7 (4.0–5.0)	0.014
Pplat, cm H_2O	29.6 (29.0–30.0)	28.7 (28.0–30.0)	30.3 (30.0–31.0)	<0.0001
FiO_2, mmHg	45.6 (40.0–50.0)	43.4 (40.0–50.0)	47.2 (40.0–50.0)	0.04
Highest PaO_2 after 24 h of ECMO treatment, mmHg	93.1 (75.8–109.3)	96.9 (79.0–116.3)	90.3 (74.3–105.0)	0.3
Highest $PaCO_2$ after 24 h of ECMO treatment, mmHg	38.5 (34.5–42.5)	38.6 (34.0–44.0)	38.3 (34.3–42.0)	0.79
Prone positioning during ECMO treatment, *n* (%)	39 (78.0)	19 (90.5)	20 (69.0)	0.09
Development of negative fluid balance at the end of the first 72 h of ECMO treatment, *n* (%)	30 (60.0)	19 (90.5)	11 (37.9)	0.0003
Daily sputum excretion during ECMO treatment, *n* (%)	23 (46.0)	9 (42.9)	14 (48.3)	0.78
Bronchoalveolar lavage during ECMO treatment, *n* (%)	39 (78.0)	17 (81.0)	22 (75.9)	0.74
Using vasoactive drugs during ECMO treatment, *n* (%)	43 (86.0)	18 (85.7)	25 (86.2)	1

P/C, pressure control mode; A/C, volume control mode; VV, veno–venous mode; VA, veno–arterial mode; Pplat, airway plateau pressure; PEEP, positive end expiratory pressure; p-values: survivors vs. non-survivors.

(7). However, the use of ECMO remains controversial for the following reasons: it requires highly specialized medical staff, bears high economic costs and limited ECMO resources, and is associated with a high risk of potentially lethal complications, including bleeding, infection, or thrombus (16).

Although ECMO remains controversial in patients with severe ARDS, ECMO has been used previously to treat virus-induced respiratory failure, such as H1N1 flu in 2009 (8). While the efficacy of ECMO in the setting of COVID-19 has been unclear, the resemblance of COVID-19 to seasonal virus influenza-related respiratory syndrome suggests possible benefits for the use of ECMO in COVID-19 patients with severe and refractory respiratory failure, as it aims to provide sufficient oxygen to the body and helps the lungs to recover (17). At the time of writing, the Extracorporeal Life Support Organization (ELSO) showed that 8080 suspected or confirmed COVID-19 patients received ECMO support, with 52% discharged alive globally (by July 2021).

In our study, the patient population comprised 50 confirmed COVID-19 patients who were admitted to the hospital and were placed on ECMO. The pathological features of patients suffering from the COVID-19 viral disease resemble those observed in Middle Eastern Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) coronavirus infection (18), all of which were characterized by severe pulmonary fibrosis and inflammation. Patients with severe COVID-19 meet the ARDS Berlin definition criteria with respect to the symptoms of pulmonary depression and severity of hypoxemia (14). The criteria for the initiation of ECMO include the levels of PaO_2 and PaO_2/FiO_2 ratio, i.e., PaO_2/FiO_2 <80 mmHg for over 6 h or PaO_2/FiO_2 <50 mmHg for over 3 h.

We found in our study that patients who had lower SOFA scores and better oxygenation, as reflected by higher PaO_2 and PaO_2/FiO_2 ratios (> 70 mmHg) before ECMO treatment, were more likely to survive. Meanwhile, during the lung-protective mechanical ventilation, survivors who had better pulmonary compliance were associated with a larger tide volume and lower plateau pressure. In addition, there was a trend toward a shorter duration of onset of symptoms to mechanical ventilation and mechanical ventilation to ECMO in the survivors, albeit these differences did not achieve statistical significance because of the finite patient availability. A possible explanation for this difference is that

TABLE 4 | Complications of patients treated with extracorporeal membrane oxygenation.

Characteristics of mortality	
Mortality, *n* (%)	29 (58.0)
death during ECMO running, *n* (% of total death)	26 (89.7)
death after 48 h of ECMO removal, *n* (% of total death)	3 (10.3)
Duration of onset of symptoms to die, median (IQR), d	38.2 (25.5–45.0)
Cause of death, *n* (% of the total 29 death)	
Bleeding, *n* (%)	9 (31.0)
Respiratory failure, *n* (%)	4 (13.8)
Sepsis, *n* (%)	14 (48.3)
Multiple organ failure (MOF), *n* (%)	18 (62.1)
Heart failure, *n* (%)	4 (13.8)
Complications, *n* (% of the total 50 patients)	
Decreased platelet counts	13 (26.0)
Bleeding	39 (78.0)
Infection	16 (32.0)
Thrombus	3 (6.0)
Pneumothorax	3 (6.0)

ECMO-treated non-survivors typically had the more severe disease when compared with ECMO-treated survivors, thus, perhaps needed greater rescue efforts and longer time. Therefore, although our data may provide evidence that earlier exertion of respiratory intervention techniques may result in better outcomes, these findings need to be substantiated with larger patient cohorts.

Fluid balance is a strategy for balancing fluid output and input of the patients. Clinicians and researchers have already realized the negative impact of fluid overload in patients admitted to ICUs. It has been shown that altered fluid balance is associated with increased mortality and worse clinical outcomes in patients with acute kidney injury (19), septic shock (20), and lung injury (21). During ECMO, large-volume intravenous fluid infusions are required, especially in the early resuscitation phase to maintain sufficient ECMO blood flow (22). Studies have also shown that proper fluid management may improve patient outcomes (23). However, there is no established optimal fluid balancing protocol for ECMO patients, and debates exist regarding the impact of positive (fluid output is lower than the input) vs. negative (fluid volume deficit) fluid balance on mortality in critically ill patients. A majority of studies showed the beneficial effect of negative fluid balance. For example, in a large cohort study including 1,000 patients with lung injury, a negative fluid balance was shown to be associated with improved lung function (24). Moreover, Schmidt et al. also demonstrated that the patients with negative fluid balance had a higher survival rate than those with positive fluid balance in adult patients treated with ECMO (23). Negative fluid balance was, however, previously found to be associated with increased mortality in ICU patients (25). In addition, a positive fluid balance was found to be associated with increased hospital mortality in adult patients treated with ECMO (23, 26). To the best of our knowledge, no previous studies have addressed the issue of fluid management regarding the critically ill COVID-19 patients treated with ECMO. Our study is the first to describe the effects of fluid balance in the COVID-19 patient treated with ECMO and we found that there was a significant difference in achieving negative fluid balance in the early resuscitation phase (within 3 days of resuscitation) between survivor and non-survivors ($P = 0.0003$). Future large-cohort prospective or retrospective studies on the impact of negative fluid balance in the long-term ECMO treatment (over 3 days) will provide further invaluable information on this subject.

There are several limitations to our study. First, our study of 50 ECMO-treated patients cannot prevent type 2 errors due to the small sample size and limited statistical power. Second, we only collected fluid information during the early part of the resuscitation phase; therefore, whether negative fluid balance affects mortality during the long-term ECMO treatment remains unknown. Moreover, we are not certain whether VV and VA ECMO subgroups may have responded differently to fluid therapy because that portion of this study is underpowered to detect meaningful differences between these two subgroups.

CONCLUSION

This multicenter, retrospective study demonstrates that pre-ECMO low PO_2/FiO_2 ratio indicates poor prognosis, as occurred in most cases of ECMO-treated non-survivors with the COVID-19. Meanwhile, more survivors achieved negative fluid balance in the early resuscitation phase during the ECMO treatment than non-survivors did.

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 West China Hospital, Sichuan University. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

WL, SL, ZH, and YK conceptualized the paper. WL, SL, ZD, XM, JL, and YK collected the data. WL and ZH conducted data analysis. ZH wrote the initial draft. WL, SL, ZD, XM, JL, and YK helped to revise the manuscript. WG and GA revised manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Research Trends and Hotspots of Extracorporeal Membrane Oxygenation: A 10-Year Bibliometric Study and Visualization Analysis

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Objective: To determine the research hotspots and trends in the field of extracorporeal membrane oxygenation (ECMO), and to provide a reference for further and wider research in the future.

Methods: The literatures on ECMO from January 2011 to July 2021 in the Web of Science Core Collection (WOSCC) database were searched, and Citespace5.8.R1 software was used to conduct bibliographic and visual analysis on the literature by country, institution, author and keywords.

Results: A total of 5,986 articles were enrolled. According to an observation, the number of articles published in the past decade has increased, especially from 2019 to 2020. The USA had the largest number of publications, while less ECMO related studies were conducted among non-developed countries. The University of Michigan (Univ Michigan) was the institution that had the largest number of publications and the highest centrality, and Daniel B was the author who had the largest number of publications. However, more inter-institutional cooperation among author teams was needed. The focus of existing ECMO research has primarily been on the treatment of patients suffering from severe cardiopulmonary failure, and the prevention and management of complications during the application ECMO.

Conclusion: Inter-regional and inter-institutional cooperation and exchanges should be carried out among ECMO research teams and institutions. The suggested research direction is to further broaden the application scope of ECMO, while determining the ways to reduce the incidence of complications and the cost, cultivate specialized team talents, and promote the application thereof.

Keywords: ECMO, visualization analysis, bibliometric study, research trends and hotspots, COVID-19

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO), an artificial *in vitro* support system, is commonly used to treat refractory heart and respiratory failure (1, 2). As a form of extracorporeal life support system, ECMO can support the respiratory function of patients with respiratory failure, so as to alleviate circulatory hypoxemia in patients developing cardiopulmonary failure. Therefore, the function of ECMO is not limited to extracorporeal circulation support. ECMO has been extensively applied in clinical cardiac surgery, respiratory diseases and critical care medicine for the past 50 years. In particular, the outbreak of Coronavirus disease 2019 (COVID-19) in late 2019 has posed a significant threat to human health and a huge challenge for global public health security (3, 4). ECMO plays an important role in saving lives as a rescue therapy for COVID-19 patients (5–7). Due to the precise therapeutic effects thereof, ECMO technology has become mature in clinical practices rapidly, and a large number of studies have been performed at the same time. Bibliometrics, an interdisciplinary science, involves mathematical and statistical tools to identify trends, as well as research themes or areas of focus (8, 9). In bibliometrics, based on multiple indicators such as references, authors, journals, countries and institutions, visualizations are generated, which provides an in-depth assessment of thematic trends and priorities in a given field (10–12). Most previous studies on ECMO have centered on theoretical research and experience sharing. Meanwhile, quantitative and visual analysis methods have not been adopted to explore the vertical and horizontal characteristics, development and multiple impacts of the present topic. As such, in the present study, the bibliometric analysis software (CiteSpace) was used to conduct statistics and analysis of ECMO related literatures in the past 10 years, and to generate visual graphics for the exploration of the hot spots and future development trends in the present research field, so as to facilitate further research in the future.

METHODS

Data Acquisition and Search Strategy

Web of Science Core Collection (WOSCC) was used as the source for retrieval and screening, with literatures on ECMO from January 2011 to July 2021 being retrieved. The key words included "Extracorporeal Membrane Oxygenation" and "ECMO." The inclusion criteria included literatures with "ECMO" as the main research content. The exclusion criteria are as follows: newspapers; advertisements; scientific and technological achievements; books and conference papers; repeated publications; and literature with incomplete information. The subjects and abstracts were read independently in pairs and screened on the basis of inclusion and exclusion criteria. If the title and abstract of a study could not be determined, the full text was read, and then a third researcher would be consulted to help decide whether such study should be included or not.

Analysis Software

The included literatures were exported in TEXT format, and then imported into Citespace5.8.R1 software that was used for data visualization analysis and bibliometric analysis. The overall visual analysis process was shown in **Figure 1**. The span of literature in the present study was selected as 1 year. By adjusting corresponding parameters, co-occurrence analysis, cluster analysis and visualization map were performed for countries, authors, institutions and keywords. Frequency was applied to represent the number of countries, institutions and authors. To measure the importance of nodes in the network, the centrality was used, with a higher centrality representing a higher degree of importance. Different nodes in the visualization represent different countries/regions, institutions, authors, or keywords. The size of the node marks the frequency or centrality of the literature. A line between nodes refers to a cooperative network.

Statistical Methods

Frequency, the main metric, was used to identify the core countries/territories, institutions, authors, and keywords. Centrality means betweenness centrality that is an indicator to measure the importance of nodes in the network. This indicator was used by Citespace to discover and measure the significance of various kinds of literatures and purple circles were utilized to highlight such literatures. Pieces of literatures with high betweenness centrality were usually the key hubs connecting two different fields. It is also called a turning point in Citespace. This method of calculating the importance of nodes was proposed by Freeman in 1977. Betweenness centrality is calculated as follows:

$$BC_{\mathrm{i}} = \sum_{s \neq i \neq t} \frac{n_{st}^{i}}{g_{st}} \tag{1}$$

In the formula, g_{st} is the number of shortest paths from node s to node t, and means the number of shortest paths through node i among g_{st} shortest paths from node s to node t. From the perspective of information transmission, the higher the betweenness centrality is, the greater the importance of the node is. The result of clustering analysis is a keyword co-occurrence network. The cluster view emerges the distribution of fields from a different point of view. The timeline view primarily reveals solicitude to delineate the relationship between clustering results and concentrates on the historical span of literatures in a clustering result.

RESULTS

A total of 9,806 studies were obtained through preliminary retrieval, and 5,986 studies were included after screening according to the inclusion and exclusion criteria.

Annual Publication Trend of Literature

In the past 10 years, the number of published studies on ECMO exhibited an overall upward trend, especially during the period from 2019 to 2020 (**Table 1**; **Figure 2**). The number of literatures published in 2020 was five times that of 2011 due to the outbreak

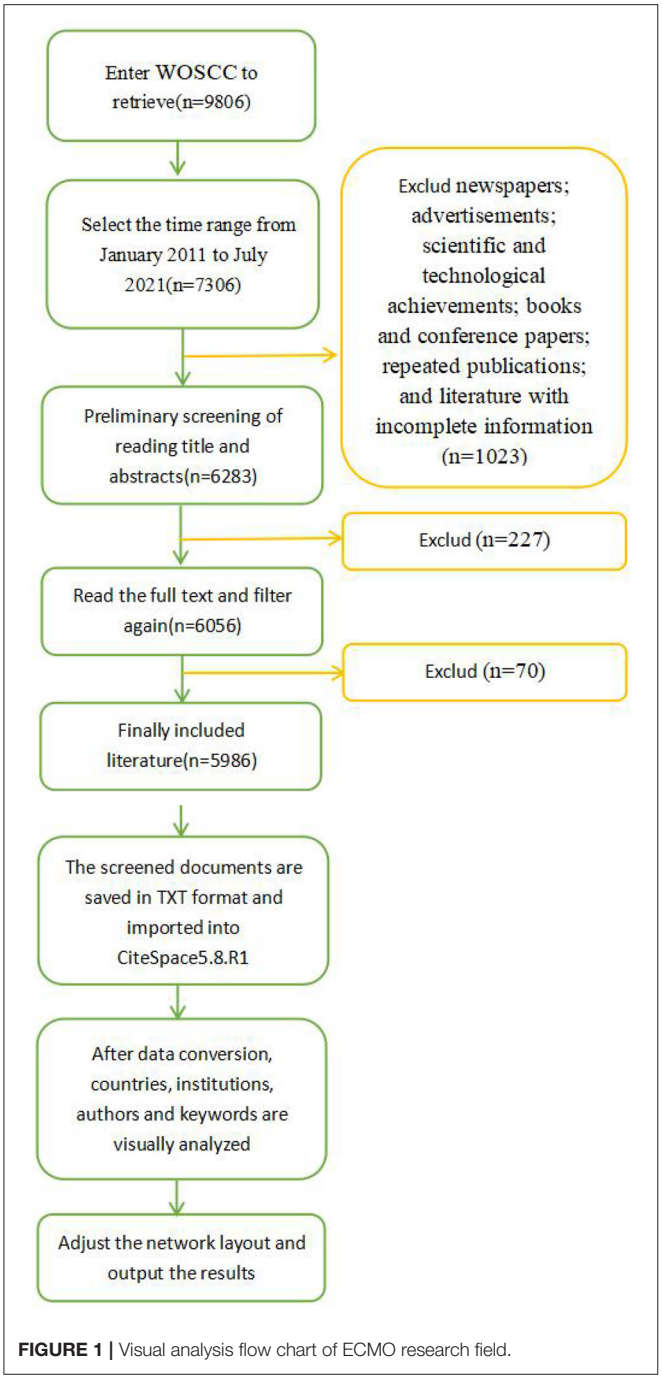

FIGURE 1 | Visual analysis flow chart of ECMO research field.

of COVID-19 in late 2019. ECMO has obtained worldwide attention as an effective treatment, and extensive studies have been conducted on the indications and efficacy thereof.

State Issuance of Documents

According to the frequency of publication and centrality, the countries that published the included literatures were analyzed and ranked, respectively. The top 10 countries were listed in **Table 2**, in which the USA ranked the first in the frequency of publication and centrality. Each node in the country visualization map represents a country, the size of the node stands for the amount of output, and the lines between the nodes are the partnerships between countries (**Figure 3**).

TABLE 1 | Literature annual distribution.

Year of publication	Record	% of 5,986
2021	736	12.30
2020	1,191	19.90
2019	768	12.83
2018	704	11.76
2017	588	9.83
2016	516	8.62
2015	451	7.53
2014	313	5.23
2013	297	4.96
2012	220	3.68
2011	202	3.37

Institutional Publication Status

Research institutions were ranked by publication frequency and centrality, and an institution visualization map was created (**Figure 4**). The top 10 institutions are listed in **Table 3**, in which the University of Michigan (Univ Michigan) ranked first with 144 papers, and also ranked first with 0.13 centrality.

Author Publication Status

The authors were ranked by publication frequency and centrality, and an author visualization map was created (**Figure 5**). The top 10 authors are shown in **Table 4**, in which the results reveal that Daniel B ranked first with a publication frequency of 73 and a centrality of 0.13.

Keywords Clustering Timeline and Keyword Bursts

Cluster analysis was formed on the basis of keyword co-occurrence, and seven clusters were formed in total: acute respiratory distress syndrome, pharmacokinetics, cardiogenic shock, anticoagulation, congenital diaphragmatic hemia, lung transplantation, and cardiac arrest. TimeLine View was used to draw a timeline for keywords after clustering, and the length of the horizontal line corresponding to each cluster represents the time span of the cluster, as shown in **Figure 6**. TimeLine View mainly reveals the relationship between description clustering results, and focuses on the historical span of literature in the clustering results. CiteSpace was further used to detect bursts of keywords with high frequency, as shown in **Figure 7**.

DISCUSSION

Analysis of Countries

In the present study, the top 10 countries in ECMO related fields were found to be mainly developed countries such as the United States, Germany, Italy and others. Both in terms

FIGURE 2 | Annual publications.

TABLE 2 | Top 10 countries by publication frequency and centrality.

No.	Country	Frequency	Country	Centrality
1	USA	1,882	USA	0.22
2	Germany	646	France	0.16
3	Italy	384	Italy	0.14
4	China	313	England	0.12
5	France	304	Germany	0.10
6	England	241	Japan	0.07
7	South Korea	234	Australia	0.05
8	Japan	233	Canada	0.04
9	Australia	223	China	0.01
10	Canada	188	South Korea	0.00

FIGURE 3 | Country visualization map.

FIGURE 4 | Institution visualization map.

of quantity and quality, developed countries have obvious advantages in research strength. At the same time, the problem of geographical imbalance in research is also reflected. Only three Asian countries, China, Japan and South Korea, were in the top 10 list (**Table 2**). Studies have shown that despite being effective, ECMO is considerably expensive (13). A study in Turkey also revealed that current ECMO resources are inadequate (14). Hence, ECMO related studies are rarely conducted in non-developed countries, which may be related to the high cost of ECMO. The economic strength of hospitals in non-developed countries is insufficient, and the economic bearing capacity of the majority of patients is also low, so the promotion is difficult to some extent.

Analysis of Authors and Institutions

The results reveal that many authors collaborated closely with each other and formed several research teams. Among those teams, the top two research teams of Daniel B and

Alain C both focused on the treatment and management of acute respiratory distress syndrome (ARDS) with ECMO. From the perspective of the cooperative network of scientific research institutions, Univ Michigan and Columbia University (Columbia Univ) have conducted more research on ECMO, and the centrality of Univ Michigan ranked first. Such results could be attributed to the strong academic atmosphere, strong scientific research foundation and sufficient funds of the two universities. However, the cooperation between institutions is only limited to the cooperation between institutions and the hospitals with which institutions are closely connected, such as

TABLE 3 | Top 10 institutions by publication frequency and centrality.

No.	Institution	Frequency	Institution	Centrality
1	Univ Michigan	144	Univ Michigan	0.13
2	Columbia Univ	124	Univ Toronto	0.08
3	Univ Maryland	81	Childrens Hosp Philadelphia	0.07
4	Karolinska Univ Hosp	75	Univ Pittsburgh	0.06
5	Univ Pittsburgh	74	Columbia Univ	0.04
6	Univ Toronto	73	Emory Univ	0.04
7	Emory Univ	68	Karolinska Inst	0.03
8	Karolinska Inst	67	Karolinska Univ Hosp	0.02
9	Childrens Hosp Philadelphia	64	Mayo Clin	0.02
10	Mayo Clin	63	Univ Maryland	0.01

TABLE 4 | Top 10 authors by publication frequency and centrality.

No.	Author	Frequency	Author	Centrality
1	Daniel B	73	Daniel B	0.13
2	Alain C	60	Alain C	0.08
3	Alois P	50	Roberto HB	0.08
4	Thomas M	45	Thomas M	0.06
5	Adriano P	41	Alois P	0.04
6	Guillaumel L	37	Adriano P	0.03
7	Matthieu S	36	Matthieu S	0.03
8	Pascal L	36	Guillaumel L	0.01
9	Matthew B	33	Matthew B	0.01
10	Roberto HB	33	Pascal L	0.00

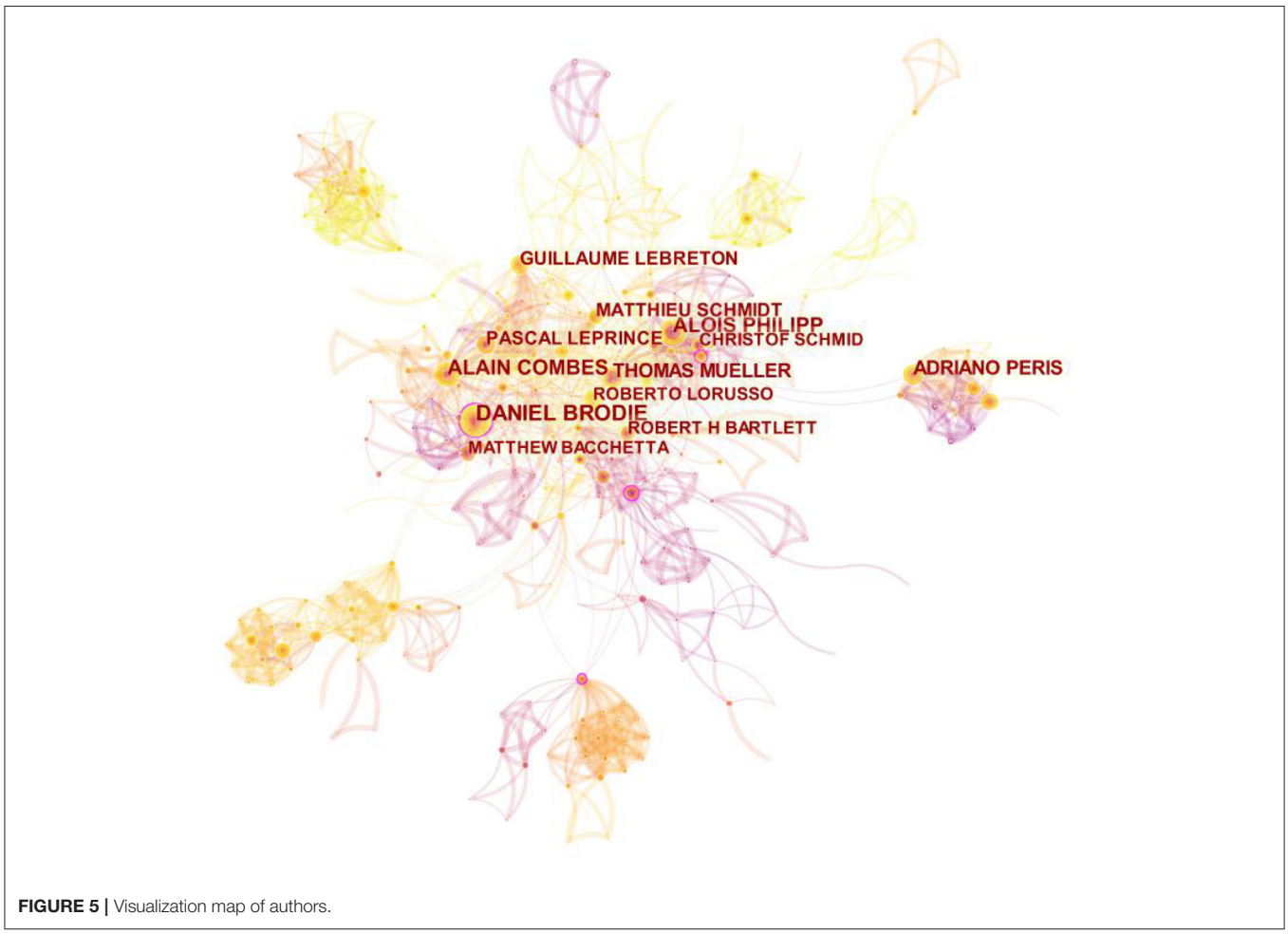

FIGURE 5 | Visualization map of authors.

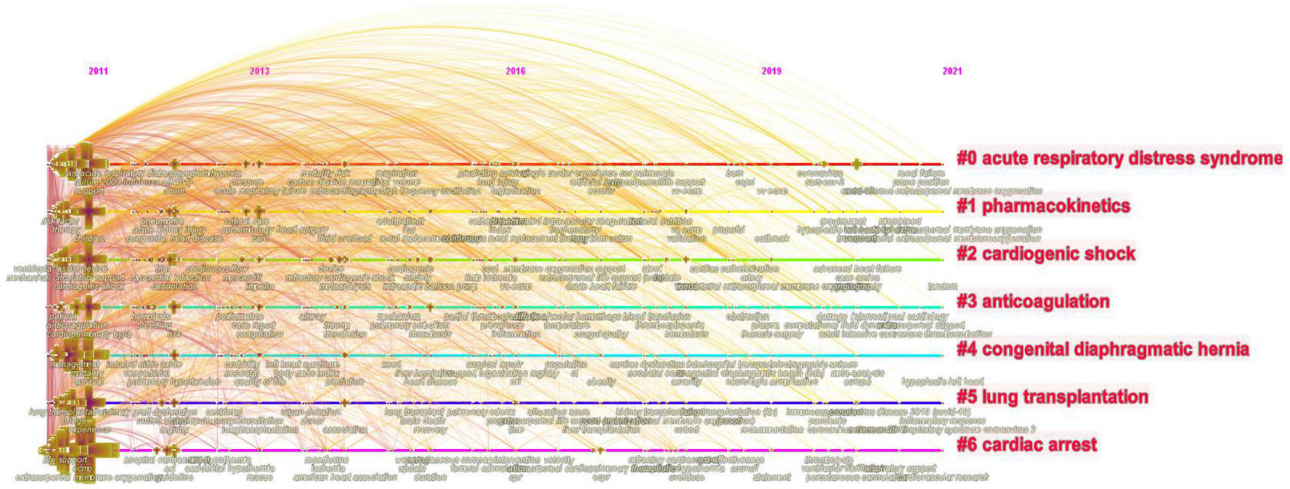

FIGURE 6 | Timeline view.

The University of Maryland (Univ Maryland) and Children's Hospital of Philadelphia (Childrens Hosp Philadelphia), while the cooperation between different organizations and institutions is less. As such, the cooperation between different institutions needs to be strengthened. The aforementioned results also reflect that researchers have a weak sense of cooperation between different institutions, and further research on ECMO needs to be further explored.

Research Hotspots Change Greatly Over Time

According to the timeline view (**Figure 6**) and burst test of keywords (**Figure 7**), combined with the number of chronological documents, the research on ECMO can be roughly divided into three stages.

The first phase from 2011 to 2013 was the initial exploration of ECMO, and researchers mostly attached attentions on the initial exploration of ECMO's treatment of children suffering from severe cardiopulmonary diseases and patients with influenza A (H1N1) (15–19). At the beginning of the first phase, many scholars found that ECMO was irreplaceable in the treatment of severe respiratory failure in children with severe illnesses, especially newborns and infants (20, 21). However, with the outbreak of H1N1 in 2013, ECMO has become the focus of research, owing to the high fatality rate and the numerous complications such as explosive acute lung injury (ALI) and acute respiratory distress syndrome (9ARDS) (22). ECMO has become a significant factor in reducing patient mortality (23, 24).

In the second phase from 2014 to 2018, ECMO studies exhibited a trend of diversification. ECMO was mainly applied to the treatment of lung transplantation, congenital diaphragmatic hernia and other diseases. For example, Hoetzenecker's (25) team studied the therapeutic effects of ECMO on patients after lung transplantation, while McHoney's (26) team developed the application of ECMO in the treatment of congenital diaphragmatic hernia. At the same time, scholars began to pay attention to various complications that occurred during the application of ECMO (27). The incidence of bleeding and thrombosis as complications is considerably high, and continuous anticoagulation increases the risk of bleeding in patients (28). Some studies have revealed that the incidence of bleeding in adults treated with ECMO is 27–60%. Once severe bleeding events such as intracranial hemorrhage and pulmonary hemorrhage occur, death rate also increases (29). Such complications have significant negative impacts on the quality of patients' life. Determining how to reduce bleeding and prevent the formation of thrombosis has become the top priority in ECMO support therapy (30, 31).

In the third phase from 2019 to 2021, there was an explosion on ECMO, mainly due to the emergence of COVID-19 in late 2019, and the resulting pandemic in 2020. Many researchers have applied previous ECMO experience in treating other diseases to the treatment of COVID-19 patients. As a new life support technology, ECMO not only saved the lives of many patients with COVID-19, but also further improved the success rate of treatment and reduced the incidence of complications. Numerous studies (17, 32, 33) have proved that ECMO is a significant factor in stabilizing and treating survival rates in critically ill COVID-19 patients. Hence, most of the studies in the third phase focused on the exploration and experience of ECMO in the treatment of COVID-19 patients.

Research Trend and Hotspot Thinking

Understanding the development trend and future trend of a discipline can help us quickly and effectively obtain the latest research hot spots and innovations of relevant disciplines, thus further promoting the efficient development of the discipline. From the salient words and related literatures in recent years, it was obvious that the research focus in this field is single diagnosis and treatment of severe diseases, focusing on the treatment of complications, and gradually deepens into the

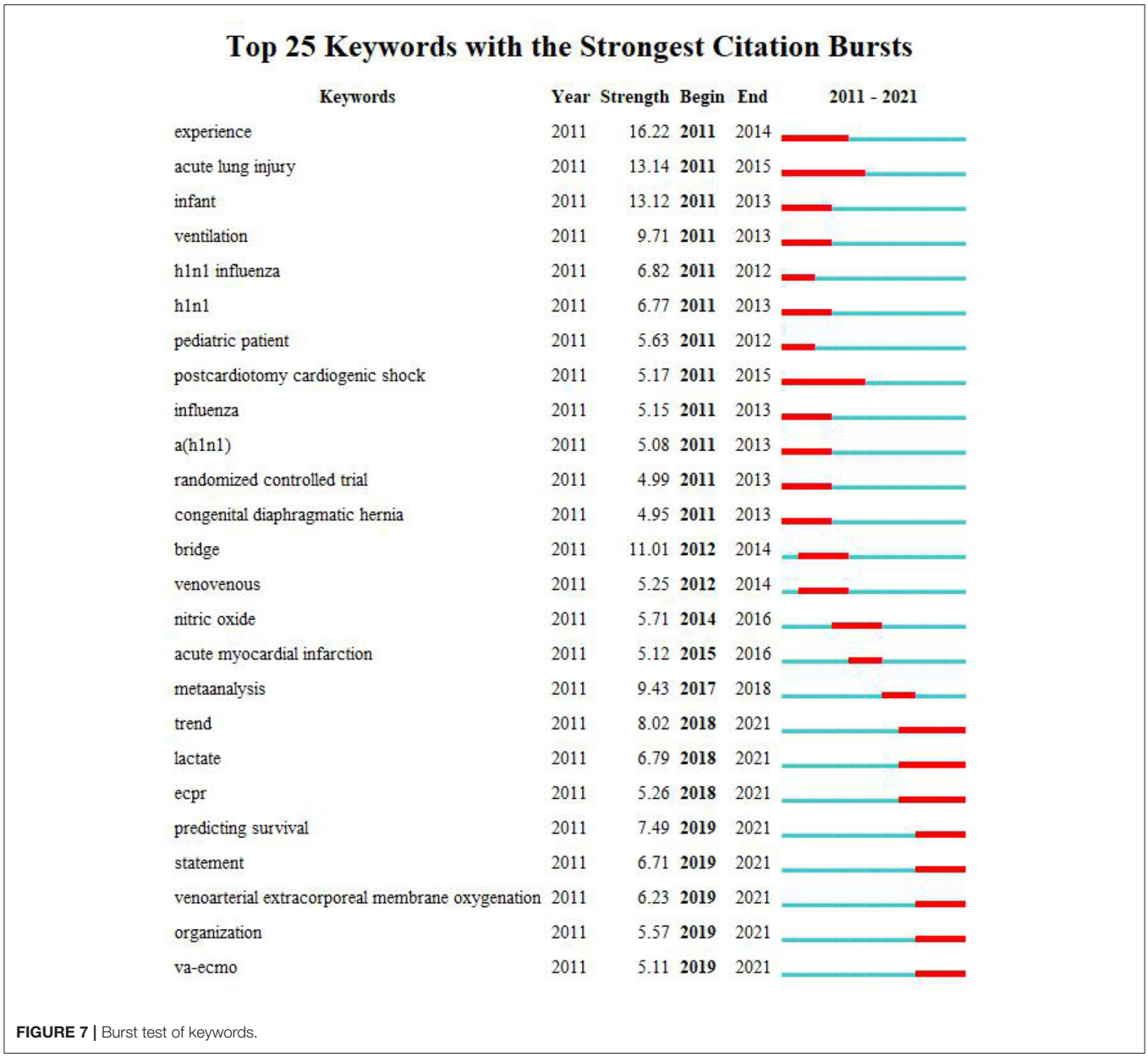

FIGURE 7 | Burst test of keywords.

treatment of multiple diseases. ECMO has been widely used for the treatment of cardiopulmonary diseases that were intractable with conventional treatment for many years. On the other hand, ECMO has played a crucial role in treating severe patients. However, a number of studies (30, 34) have demonstrated that ECMO is accompanied with high complications when treating both mechanically ventilated patients and patients in stable stage. The prevention, diagnosis and treatment of complications are always our focus and difficulty, so we should continue to explore these research hotspots in the future. What's more, there is no unified standard for the timing of ECMO use. For example, Diddle et al. (35) proposed that early use of ECMO before severe arrhythmia, heart failure and other abnormal symptoms in patients with acute myocarditis could improve the prognosis. However, some studies have also suggested that the application of ECMO in patients with organ failure such as low pH, high lactic acid, abnormal liver function, and renal dysfunction requiring renal replacement therapy will lead to the reduce of survival rate (36, 37). According to the current evidence-based medicine, the optimal application time cannot be determined. The precision of ECMO is also the direction of future research.

Most importantly, although the application and development of ECMO have been promoted by the H7N9 avian influenza in 2013 and the COVID-19 epidemic in 2020, the treatment cost of ECMO still remains high, the technology remains complex, and the treatment varies widely among individuals. Further, ECMO exists high risk, and its scope is limited,

with some hospitals encountering difficulties in applying such technology. Therefore, how to reduce the cost and improve the portability and mobility will also become the research hotspots and development trends of ECMO. A high-level ECMO team is critical for the improvement of patient's benefit rate. Future research should also pay more attention on the training and establishment of ECMO specialist teams. In the present study, only a single database, namely WOSCC, was retrieved, and other databases were not included. There are several limitations in current ECMO research, and thus, the retrieval scope should be expanded to conduct in-depth research.

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.

AUTHOR CONTRIBUTIONS

HW designed this study and collected data. SD performed the search. SD and XF rechecked data. HW and SD performed analysis. YL and BY critically revised the work. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Venoarterial Extracorporeal Membrane Oxygenation Support for Caowu-Induced Cardiac Arrest

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Introduction: Caowu, the main root of the *Aconitum* plant, is widely used in China. Aconitine is the main toxic component of *Aconitum,* which can cause a variety of malignant arrhythmias and lead to death. Four patients who developed malignant arrhythmia after drinking medicinal wine containing Caowu were reported in this study. Cardiac arrest occurred soon after symptom onset. All patients received venoarterial extracorporeal membrane oxygenation (VA-ECMO) support after conservative medical treatment had failed. Patients who were directly transferred to our hospital received VA-ECMO support earlier than patients who were first treated at a local hospital. One patient received hemoperfusion in the emergency room before VA-ECMO support; the other three patients began hemoperfusion after VA-ECMO treatment. Surviving patients who received VA-ECMO earlier after symptom onset showed no obvious neurological complications. The patient who received a longer cardiopulmonary resuscitation time but received hemoperfusion before VA-ECMO had mild neurological complications. The mortality rate was 25% (1 of 4 patients). Two patients had thrombotic complications in venous vessels.

Conclusions: Cardiogenic shock due to refractory ventricular tachycardia caused by aconitine is lethal. Conservative supportive treatment did not provide a short-term antiarrhythmic effect and the cardiogenic shock was not well controlled. VA-ECMO treatment combined with hemoperfusion is promising temporary support to successfully treat aconitine-induced cardiogenic shock caused by refractory ventricular tachycardia.

Keywords: VA-ECMO, aconitine, heart arrest, malignant arrhythmias, Caowu

INTRODUCTION

Aconitum is a widely used Chinese herbal medicine. *Caowu* is the main root of the *Aconitum* plant and contains aconitine, a toxic component. Such herbs are either used as medicine or added to food or wine and are popular in China. However, the aconitine therapeutic dose is close to the poisonous or lethal dose. Thus, the main adverse effects are aconitine-induced ventricular tachyarrhythmia and heart arrest, which are also the leading causes of death (1). Patients with Caowu poisoning often present with a stubborn arrhythmia with poor response to conventional treatment, including many

antiarrhythmic drugs, defibrillation, and cardioversion. Malignant arrhythmias occur repeatedly with unstable hemodynamics, which are difficult to control with conventional treatment.

Extracorporeal membrane oxygenation (ECMO) or extracorporeal life support to manage patients with drug-induced cardiogenic shock (DCS) have been increasingly reported (2, 3). However, there are no reports on ECMO treatment of patients with Caowu poisoning. Even reports of experiences of ECMO support of patients poisoned by Chinese herbal medicine are limited. However, patients can rapidly improve if the herbal medicine can be quickly cleared or the patients are provided temporary support to allow time for the elimination of the toxic substances. Thus, temporary life support for such patients is critical.

The two types of ECMO, venovenous ECMO (VV-ECMO) and venoarterial ECMOextracorporeal membrane oxygenation (VA-ECMO), were initially developed in the 1950s (4). VV-ECMO mainly provides adequate oxygenation to support respiratory failure, while VA-ECMO can provide both circulation and oxygenation support but is mainly used for circulation failure. VA-ECMO is increasingly used as an effective treatment for refractory cardiogenic shock, a bridge to heart transplantation, and myocardial or durable mechanical circulatory dysfunction (5). Cardiac dysfunction due to drug poisoning is usually temporary and reversible. Once the drug is cleared, the function of the heart would recover. VA-ECMO is the temporary life support which can provide mechanical support for circulation to gain time for its recovery caused by drug poisoning. To our knowledge, this is the first report of the use of ECMO to support circulation in cases of Caowu poisoning. We share our experiences about the treatment of such patients and also suggest that VA-ECMO treatment combined with hemoperfusion might be effective approaches to save the lives of these patients.

CASE DESCRIPTIONS

Four patients aged from 46 to 55 years old experienced vomiting and numbness after drinking a medicinal liquor containing Caowu. All patients were male and healthy without diabetes, hypertension, coronary heart disease, or genetic disease. Two patients were sent to the local hospital, while two patients were sent to our hospital after symptom onset. When they arrived at the emergency room, they were conscious without obvious abnormalities in physical examination. Their lungs sounded clear, no wheezing and moist rales. Cardiac auscultation showed no obvious positive signs. No obvious tenderness or rebound pain were observed in the abdomen. The patients underwent immediate gastric lavage via nasogastric tubes. While in the emergency room, three patients began to lose consciousness; the other patient also deteriorated, with chest tightness and syncope. All four patients had ventricular arrhythmia and cardiac arrest at the onset of new symptoms. Conventional cardiopulmonary resuscitation was performed immediately. The patients also received mechanical ventilation and antiarrhythmic drugs, including lidocaine and amiodarone, which were administered intravenously after intravenous loading. Calcium gluconate and magnesium sulfate were administered to maintain the electrolyte balance, as well as an equilibrium solution and normal saline to ensure fluid resuscitation to correct cardiogenic shock with the use of norepinephrine at the same time. Electrical defibrillation was performed repeatedly, nevertheless, the cardiogenic shock of the patients did not improve even with high-dose of norepinephrine (>1ug/kg/min) administration. Gastric lavage was continued and cardiopulmonary resuscitation was performed. The sinus rhythm and circulation could not be maintained despite the prolonged cardiopulmonary resuscitation. Due to the lack of circulation improvement, the two patients in our hospital received VA-ECMO support. The local hospital where the other two patients were treated had no such device. Then our emergency response team traveled to the local hospital with our device and performed VA-ECMO for these two patients. The patients were then transferred to our hospital for further treatment. Patient 4 received hemoperfusion before VA-ECMO while the other three patients underwent hemoperfusion after VA-ECMO initiation. The hemoperfusion was performed 2 h each time, twice a day using the perfusion device—HA330-IIproduced by Jafron Biomedical Co., Ltd., China. All the patients still had ventricular arrhythmia repeatedly after receiving the ECMO support. However, when ventricular arrhythmia occurred, we did not perform the CPR or electrical defibrillation for the patients any more. Lidocaine and amiodarone were continued together with the support of the VA-ECMO and hemoperfusion to improve arrhythmia and circulation. The doses of norepinephrine gradually decreased with the improvement of circulation of the patients. Sinus rhythm became stable within 3–4 h after ECMO support, followed by sporadic ventricular premature. The heart function was monitored by bedside ultrasound, and the ECMO flow was adjusted to avoid left ventricular expansion. Unfractionated heparin maintained activated coagulation time around 180 s. The clinical characteristics and treatment information of the four patients are shown in **Table 1**. This study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Jinhua Hospital, Zhejiang University School of Medicine.

RESULTS

The mean age of the four patients was 49.8 years. All four patients were male and received repeated traditional cardiopulmonary resuscitation, antiarrhythmic drugs including lidocaine (load capacity: 100 mg, maintained at 0.03 mg/kg after two repetitions), amiodarone (load capacity: 300 mg, maintained at 1 mg/min), gastric lavage, and fluid resuscitation. Noradrenaline (1–2 ug/kg/min) was used to maintain circulation but without significant improvement. The time elapsed from drinking the medicinal liquor to symptom onset ranged from 3 to 8 h. Patients 1 and 3 were first transported to our hospital for treatment. Patient 1 did not survive even when cardiac arrest occurred in the hospital and with VA-ECMO support. Patients

TABLE 1 | The clinical characteristics of the four patients.

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Male	Male	Male	Male
Age (years)	46	55	50	48
Symptoms	Vomiting, numbness, consciousness disorder	Vomiting, numbness, consciousness disorder	Vomiting, numbness, chest tightness, syncope	Vomiting, numbness, consciousness disorder
Time from drinking the medicinal liquor to symptom onset (h)	5.5	4.5	8	3
First treated place	Our hospital	Local hospital	Our hospital	Local hospital
Time from CPR to ECMO support (min)	45	80	50	90
Lactate (mmol/L)	9.9	5.5	4.6	8
PH	7.21	7.29	7.32	7.31
BE (mmol/L)	−8.3	−8.4	−9.2	−7.1
Limb ischemia complications	No	No	No	No
Bloodstream infection	No	No	No	No
Bleeding complications	No	No	No	No
Thrombotic complications	No	Yes	Yes	No
Time of norepinephrine use (h)	19	58	65	78
ECMO running time (h)	19	68	64	79
Hemoperfusion time (days)	<1	3	2	3
Time of mechanical ventilation (days)	<1	5	5	6
Left ventricular overload	No	No	No	No
NHISS scores on discharge	Die	4	0	2
Outcome	Die	Discharge	Discharge	Discharge

ECMO, Extracorporeal Membrane Oxygenation; PH, Potential of Hydrogen; BE, Base Excess; NHISS, National Herb Study Society.

2 and 4 did not receive timely VA-ECMO because of a lack of equipment in the local hospital, and Patient 4 had a longer duration of cardiopulmonary resuscitation; however, his neurological complications (speech and sensation disorders) were milder compared with Patient 2 (dyspraxia, speech, and sensation disorders). Patient 3 survived without any obvious neurological complications. Two patients developed thrombotic complications. With the improved circulation, we removed ECMO when norepinephrine was discontinued or at low doses. Due to the poorer oxygenation (improved by conducting liquid management), the ECMO of Patient 2 was removed 10 h after the norepinephrine was discontinued. The VA-ECMO support times ranged from 64 to 79 h. The minimum follow-up time was more than half a year. Two patients received antithrombotic therapy for 3 months after discharge, and no further complications occurred. Neurological complications also improved in Patient 2 and Patient 4 (their NHISS scores were 3 and 1 after 3-month follow-up, respectively).

DISCUSSION

We first retrospectively reported the patients who developed malignant arrhythmia after drinking medicinal wine containing Caowu. Aconitum combined with alcohol will lead to more complex pathophysiology. We presented our experiences for rescuing patients with cardiogenic shock caused by drinking medicinal wine containing Caowu to help better manage such critical situation.

Due to the recoverability of heart rhythm in such patients, temporary life support for the patients with cardiogenic shock caused by toxicity is necessary. The methods for providing mechanical circulatory support for cardiogenic shock caused by drug poisoning include intra-aortic balloon counterpulsation (IABP), cardiopulmonary bypass, and ECMO. Among these, IABP (6) is the most commonly used; however, the limitation of this method is the requirement that the patient retain some heart function and an arterial systolic pressure above 40 mmHg. Moreover, IABP cannot supply oxygen. While cardiopulmonary bypass (7) can provide complete circulatory and respiratory support, it requires opening the chest cavity, a median incision, a venous cannula into the right atrium, and an arterial cannula into the ascending aorta, which make it difficult to provide quick and effective support for emergency conditions. VA-ECMO can provide complete cardiopulmonary support and is also convenient to perform, with fewer requirements for implementation (8). The use of VA-ECMO to support circulatory collapse caused by poisoning is increasingly reported. The first use of VA-ECMO to treat quinidine-induced poisoning was reported in 1997 (9). Lindsay et al. (3) systematically reviewed the treatment of DCS by VA-ECMO. A total of 104 patients were included, with a survival rate of 52.9%. VA-ECMO improved mean arterial pressure, systolic blood pressure, and diastolic blood pressure. The related metabolic

indices and oxygenation were also significantly improved, thus demonstrating the significant advantages of VA-ECMO in the treatment of drug-induced cardiogenic shock. This study was the largest study of VA-ECMO to support patients with DCS.

The effectiveness and importance of Chinese herbal medicines have gradually been recognized. With the development of modern science and technology, Chinese herbal medicine has become more widely used worldwide. Caowu is a component of the *Aconitum* plant with many medicinal properties. A famous traditional Chinese medicine, Yunnan Baiyao, which is very popular in clinical diseases, contains Caowu (10). Caowu is also detoxified by the zygote (Terminalia chebula Retz) detox, and the Zhicao (Grass Aconitum) when it is prepared as part of NaRu-3 pills as a treatment for rheumatoid arthritis (11). There are many ways to process Caowu before developing it into medicine (11, 12). Due to the medicinal value of these Chinese herbal medicines since ancient times, Chinese folk remedies often soaked Chinese herbal medicines in wine, or added some herbal when cooking food. Poisoning incidents are also frequently reported (11, 13).

Aconitine is the most significant toxic component of *Aconitum* plants. It mainly acts on the heart and nervous system, causing a variety of arrhythmias, which may lead to death. The main mechanism of ethanol-induced toxicity is the inhibition of the central nervous system. However, the toxic effect of the combined action of aconitine and ethanol on the myocardium becomes even more complex. Studies on the mechanism of Caowu poisoning and Caowu combined with alcohol poisoning are increasing (14, 15); however, the mechanism requires further research.

Owing to its convenience and effectiveness, VA-ECMO has been increasingly used in patients with unstable circulation caused by various heart diseases. The value of VA-ECMO for cardiopulmonary resuscitation has also become increasingly prominent. However, acute poisoning is not a common reason for the use of VA-ECMO. Moreover, the use of VA-ECMO as a supportive treatment for Caowu-induced cardiac arrest has not been reported. There remains no effective detoxification therapy for Chinese herbal medicines such as Caowu. However, while ventricular arrhythmia in such patients may be stubborn, it is highly recoverable and may return to normal immediately after the drug is cleared. The essential treatment for such patients is timely life support to provide time for drug metabolism or to accelerate the drug clearance using methods such as the intermittent use of hemoperfusion. VA-ECMO provides sufficient circulatory support to provide more stable circulation. Once the ventricular arrhythmia stops, the patient's heart rhythm and circulation stabilize. Among the surviving patients in the present series, two developed neurological complications and two developed deep vein thrombosis. No left ventricular decompression was required. No severe bleeding events occurred during the VA-ECMO treatment. Nervous system complications and thrombotic events might be related to repeated refractory arrhythmia and long-duration cardiopulmonary resuscitation. One possible explanation for the death of Patient 1 might be an overdose of the medicinal liquor containing Caowu. As the patient showed no significant improvement, his family members decided to refuse further treatment. Patient 4 recovered with mild nervous system complications might be due to the earlier use of hemoperfusion, later combined with VA-ECMO support. The period of time between VA-ECMO and cardiopulmonary resuscitation in the patient in our study was longer than that recommended by the Extracorporeal Life Support Organization for patients with cardiac arrest due to various cardiac diseases (16). Part of the reason is that these patients can recover their heart rate after receiving traditional cardiopulmonary resuscitation, but sinus rhythm cannot be maintained. The potential benefits of the earlier use of VA-ECMO combined with hemoperfusion require additional clinical evidence.

In conclusion, the aconitine contained in Caowu can cause fatal arrhythmia and cardiac arrest. Effective cardiopulmonary resuscitation and VA-ECMO support combined with hemoperfusion could provide sufficient time for patients to recover. This is the first report on the effectiveness of VA-ECMO as a treatment in such emergency conditions. Our findings demonstrated its effectiveness, especially when combined with hemoperfusion. Nevertheless, when to perform VA-ECMO support would more benefit such patients requires further study.

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 the Affiliated Jinhua Hospital, Zhejiang University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LW, LC, and KC: study design. LC and BR: data collected. LC and HW: manuscript writing. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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The Relative Early Decrease in Platelet Count Is Associated With Mortality in Post-cardiotomy Patients Undergoing Venoarterial Extracorporeal Membrane Oxygenation

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Background: The relationship between the magnitude of platelet count decrease and mortality in post-cardiotomy cardiogenic shock (PCS) patients undergoing venoarterial extracorporeal membrane oxygenation (VA-ECMO) has not been well-reported. This study was designed to evaluate the association between the relative decrease in platelet count (RelΔplatelet) at day 1 from VA-ECMO initiation and in-hospital mortality in PCS patients.

Methods: Patients ($n = 178$) who received VA-ECMO for refractory PCS between January 2016 and December 2018 at the Beijing Anzhen Hospital were reviewed retrospectively. Multivariable logistic regression analyses were performed to assess the association between RelΔplatelet and in-hospital mortality.

Results: One hundred and sixteen patients (65%) were weaned from VA-ECMO, and 84 patients (47%) survived to hospital discharge. The median [interquartile range (IQR)] time on VA-ECMO support was 5 (3–6) days. The median (IQR) RelΔ platelet was 41% (26–59%). Patients with a RelΔ platelet $\geq$ 50% had an increased mortality compared to those with a RelΔ platelet $<$ 50% (57 vs. 37%; $p < 0.001$). A large RelΔplatelet ($\geq$50%) was independently associated with in-hospital mortality after controlling for potential confounders (OR 8.93; 95% CI 4.22–18.89; $p < 0.001$). The area under the receiver operating characteristic curve for RelΔ platelet was 0.78 (95% CI, 0.71–0.85), which was better than that of platelet count at day 1 (0.69; 95% CI, 0.61–0.77).

Conclusions: In patients receiving VA-ECMO for post-cardiotomy cardiogenic shock, a large relative decrease in platelet count in the first day after ECMO initiation is independently associated with an increased in-hospital mortality.

Keywords: post-cardiotomy cardiogenic shock, venoarterial extracorporeal membrane oxygenation, platelet count, mortality, decrease

INTRODUCTION

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) has increasingly used as a rescue strategy to provide temporary circulatory and respiratory support allowing cardiac function recovery or bridging to additional therapeutic alternatives in patients with refractory post-cardiotomy cardiogenic shock (PCS) (1, 2). Despite major innovations in ECMO support over the last few decades, this rescue therapy is still marred by high rates of complications and mortality (3, 4). Particularly, patients requiring VA-ECMO are at increased risk of developing thrombopenia (5). Platelet activation, inflammatory and coagulative cascade activation, and consumption by the extracorporeal circuit play a major role in this context (6–8). Moreover, the use of unfractionated heparin during VA-ECMO may cause thrombocytopenia, which is an immune-mediated hypercoagulable disorder (9). Thrombocytopenia has been associated with increased mortality in patients undergoing VA-ECMO after cardiac surgery and has been incorporated in newer prognostic scoring systems (10). Previous studies investigating the prognostic significance of thrombocytopenia have focused on absolute platelet counts (11). However, limited data exist on the magnitude of platelet count decrease in PCS patients who are supported with VA-ECMO. In addition, the association between the magnitude of platelet count decrease and mortality in these patients has not been well-reported.

The primary objective of this single-center retrospective study was to evaluate whether the magnitude of platelet count decrease in the first day of ECMO initiation was associated with in-hospital mortality after controlling for potential confounders. Other clinical outcomes were also evaluated.

METHODS

Patients

We retrospectively evaluated consecutive patients who received VA-ECMO from January 2016 and December 2018 at the Beijing Anzhen Hospital. Patients who received VA-ECMO for refractory PCS after cardiac surgery were included. The clinical criteria for PCS included the following (12): left atrial pressure >15 mmHg; central venous pressure >12 mmHg; metabolic acidosis (i.e., pH < 7.3 with serum lactate >3.0 mmol/L); end-organ hypoperfusion (urine output <30 mL/h); cardiac index <2.2 L/min/m^2; and systolic blood pressure <80 mmHg despite adequate filling volumes, use of multiple adrenergic agents (epinephrine > 0.1 μg/kg/min or dobutamine > 10 μg/kg/min, norepinephrine > 0.1 μg/kg/min), or an intra-aortic balloon pump (IABP). Exclusion criteria for patient selection from our institutional ECMO database were an age <18 years, venovenous ECMO support for acute respiratory failure, ECMO initiation for non-PCS (e.g., fulminant myocarditis, myocardial infarction-associated cardiogenic shock), and ECMO initiation before cardiac surgery. The study was approved by the institutional ethics committee/review board of the Beijing Anzhen Hospital (2021020X), and the requirement for informed patient consent was waived in view of the retrospective nature of the study.

ECMO Implantation and Management

The details regarding VA-ECMO initiation and management have been described previously (13). Briefly, all procedures were performed by trained ECMO team members. VA-ECMO support was initiated *via* peripheral cannulation through the femoral route with the semi-open method, and an additional 6 Fr catheter was systematically inserted distally into the femoral artery to prevent severe leg ischemia. ECMO blood flow was adjusted on based on clinical assessments (e.g., mixed venous oxygen saturation, evidence of hypoperfusion, resolution of hyperlactatemia, and normalization of mean arterial pressure). Intravenous unfractionated heparin was given to maintain an activated clotting time of 180–210 s, or an activated partial thromboplastin time of 1.5–2 times normal. ECMO-related complications were carefully monitored. ECMO weaning was performed in patients who fulfilled our published institutional weaning criteria and passed an ECMO weaning trial consisting in decreasing and clamping ECMO flow (14, 15). In general, the patient should have a pulsatile arterial waveform for at least 24 h; be hemodynamically stable, with baseline mean arterial pressure >60 mmHg with no or low doses of catecholamines; should have left ventricular ejection fraction (LVEF) of 35%, and an aortic velocity time integral (VTI) of ≥12 cm; and have recovered from major metabolic disturbances.

Data Collection and Outcome Variables

The following information was recorded retrospectively: age; sex; weight; comorbid conditions; primary diagnosis; operative parameters; IABP use; ECMO peak flow; pre-ECMO left ventricular ejection fraction (LVEF); pre-ECMO cardiac arrest; platelet count before ECMO initiation; lowest platelet count at day 1 from ECMO initiation; peak serum lactate at day 1. Magnitude of platelet count decline was defined as the relative decrease in platelet count (RelΔ platelet), which was calculated from the following formula: RelΔ platelet = (platelet count at day 1- pre-ECMO platelet count)/(pre-ECMO platelet count).

The primary outcome was in-hospital mortality, defined as death from any cause occurring in patients who were treated by post-cardiotomy VA-ECMO. Secondary outcomes included length of intensive care unit (ICU) stay, length of hospital stay, ECMO duration, survival to ECMO weaning, continuous renal replacement therapy (CRRT), bleeding need thoracotomy, leg ischemia requiring fasciotomy, and major neurological complications (brain death, ischemic stroke, hemorrhagic stroke, and anoxic encephalopathy). Weaning was considered unsuccessful if ECMO re-cannulation was required within 2 days of decannulation.

Statistical Analysis

All the analyses were performed with STATA/SE 12.0 (StataCorp, College Station, TX, USA) and SPSS 25.0 (IBM Corp, Armonk, NY, USA). The patients were grouped in two groups according to RelΔ platelet (<50, ≥50%; the optimal RelΔ platelet cut-off value for predicting mortality was 49.5%). The characteristics of patients were reported as proportions for categorical variables and as median [interquartile range (IQR)] for continuous variables. Categorical variables were compared with chi-square

or Fisher's exact-tests, and continuous variables were compared with the Mann–Whitney *U*-test. We plotted the in-hospital mortality according to intervals of RelΔ platelet to evaluate the nature of the relationship between the two variables. The variables affecting the in-hospital mortality that were significant ($P < 0.2$) in univariable analysis were included in multivariable logistic regression with backward stepwise analysis. Discriminatory performance of RelΔ platelet vs. lowest platelet count at day 1 were compared using the area under the receiver operating characteristics curve (AUROC). Short-term survival was modeled using the Kaplan-Meier method, and inter-group comparisons were performed with the log-rank test. *P*-values < 0.05 were considered significant.

RESULTS

Populations

Two hundred and ninety-two patients received ECMO treatment over a 3-year period. Among those patients, 114 patients were excluded because of an age of <18 years ($n = 20$), acute respiratory failure treated with venovenous ECMO ($n = 5$), non-PCS supported with VA-ECMO ($n = 40$), ECMO initiation before cardiac surgery ($n = 43$), or unavailable medical records ($n = 6$). Finally, 178 PCS patients who were treated by VA-ECMO were included in analysis (**Figure 1**). Clinical characteristics of the patients according to RelΔ platelet are presented in the **Table 1**. The median (IQR) age of patients was 60 (52–66) years and 138 were male (78%). Eighty-seven patients (49%) were diagnosed with coronary heart disease, and 9 (5%) patients needed heart transplantation. Sixty-eight patients (38%) were not successfully weaned from cardiopulmonary bypass (CPB) due to PCS requiring transition to ECMO. One hundred and fifteen patients (65%) received additional IABP therapy, and median (IQR) pre-ECMO LVEF was 24% (17–30%). Fifty-four patients (30%) suffered from cardiac arrest before VA-ECMO implantation. The median (IQR) platelet count at day 1 was 61 (40–88) $\times$ 10^9/L, and the median (IQR) serum lactate at day 1 was 13.0 (8.7–19.0) mmol/L. The median (IQR) RelΔ platelet was 41% (26–59%). There was no significant difference in clinical characteristics between patients with a RelΔ platelet $\geq$ 50% and patients with a RelΔ platelet $<$ 50%, except for a lower platelet count in patients with a RelΔ platelet $\geq$ 50%.

Patient Outcomes

The hospital outcomes for all the study patients are listed in **Table 2**. One hundred and sixteen patients (65%) were weaned from VA-ECMO, and 84 patients (47%) survived to hospital discharge. The median (IQR) time on VA-ECMO support was 5 (3–6) days. The median (IQR) length of ICU stay and hospital stay duration were 8 (5–12) and 19 (12–26) days, respectively. Ninety-five (53%) patients required CRRT for renal failure. Twenty-nine (16%) patients underwent repeat thoracotomy for bleeding, and repeat thoracotomy was significantly more frequent in patients with a RelΔ platelet $\geq$ 50% as compared to patients with a RelΔ platelet $<$ 50% (17 vs. 12%; $p = 0.024$). Seven patients (4%) required fasciotomy due to severe limb ischemia. Major neurologic complications were found in 31 (17%) of the patients and occurred more frequently in patients with a RelΔ platelet $\geq$ 50% as compared to patients with a RelΔ platelet $<$ 50% (19 vs. 12%; $p = 0.007$).

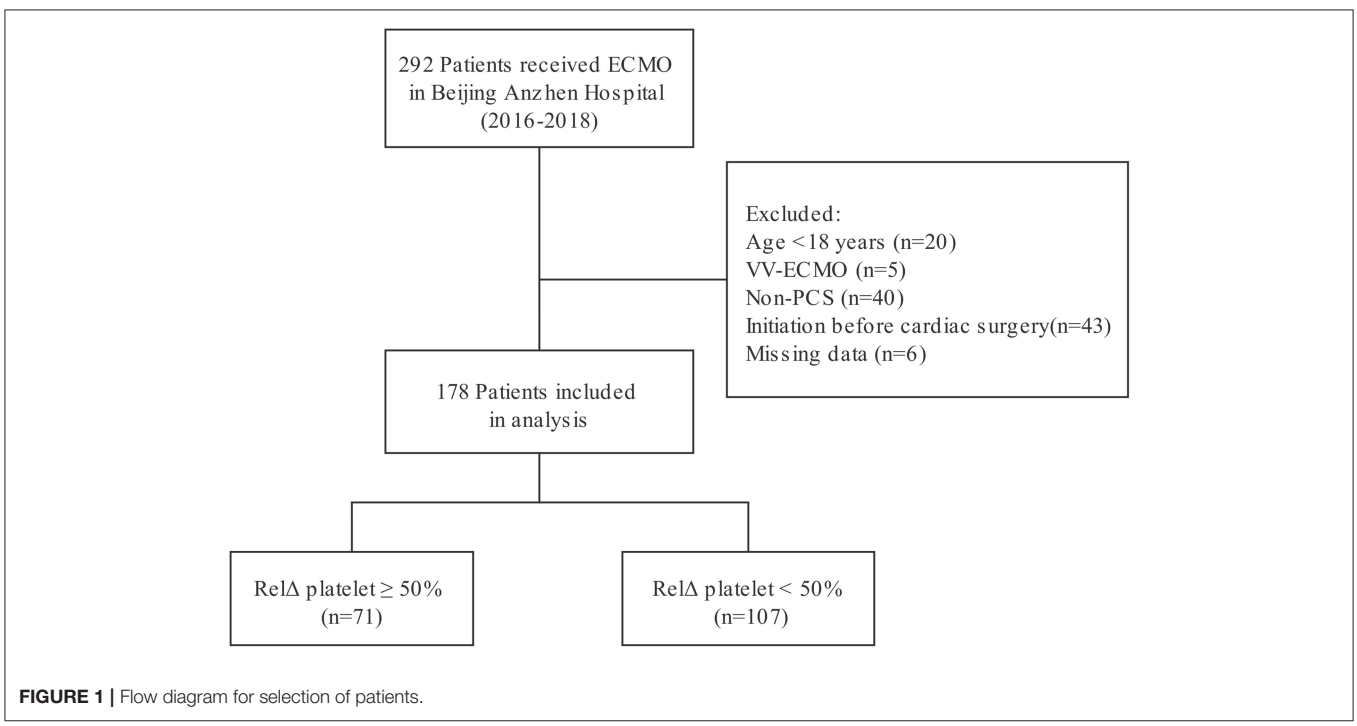

FIGURE 1 | Flow diagram for selection of patients.

TABLE 1 | Clinical characteristics of the patients.

Characteristic	Overall ($n = 178$)	RelΔ platelet ≥ 50% ($n = 71$)	RelΔ platelet < 50% ($n = 107$)	*P*-value
Age, years	60 (52–66)	61 (54–67)	60 (49–66)	0.330
Male	138 (78)	57 (80)	81 (76)	0.473
Weight, kg	70 (60–78)	70 (60–76)	70 (60–78)	0.644
Comorbid conditions				
Hypertension	99 (56)	41 (58)	58 (54)	0.642
Diabetes	41 (23)	16 (23)	25 (23)	0.898
Smoking	74 (42)	30 (42)	44 (41)	0.881
Recent MI	28 (16)	12 (17)	16 (15)	0.727
Stroke	6 (3)	2 (3)	4 (4)	0.736
Arrhythmia	18 (10)	10 (14)	8 (7)	0.152
Diagnosis				0.805
Coronary heart disease	87 (49)	38 (54)	49 (46)	
Valvular heart disease	36 (20)	13 (18)	23 (21)	
Aortic disease	17 (10)	7 (11)	10 (9)	
Coronary and valvular heart disease	22 (12)	6 (8)	16 (15)	
Heart transplantation	9 (5)	4 (6)	5 (5)	
Other	7 (4)	3 (4)	4 (4)	
Operative parameters				
Redo cardiac surgery	26 (15)	8 (11)	18 (17)	0.304
Emergency operation	17 (10)	7 (10)	10 (9)	0.909
Operative time, min	465 (300–600)	510 (300–665)	450 (300–555)	0.108
CPB time, min	151 (0–224)	159 (0–222)	137 (0–234)	0.882
Cross clamp time, min	55 (0–111)	33 (0–118)	58 (0–109)	0.715
Unsuccessful weaning off CPB	68 (38)	27 (38)	41 (38)	0.969
IABP use	115 (65)	49 (69)	66 (62)	0.317
ECMO peak flow, L/min	3.9 (3.4–4.0)	3.8 (3.5–4.0)	3.7 (3.4–3.9)	0.442
Pre-ECMO LVEF, %	24 (17–30)	24 (17–31)	23 (15–30)	0.911
Pre-ECMO cardiac arrest	54 (30)	23 (32)	31 (29)	0.627
Platelet count at day 1, $\times 10^9$/L*	61 (40–88)	45 (26–57)	72 (56–110)	<0.001
Serum lactate at day 1, mmol/L*	13.0 (8.7–19.0)	14.2 (9.7–19.6)	11.6 (8.1–19.0)	0.186

Data are presented as medians (25th−75th percentile) or n (%).

MI, myocardial infraction; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; LVEF, left ventricular ejection fraction; RelΔ platelet, relative decrease in platelet count.

**Worse value within 24 h after ECMO initiation.*

RelΔ Platelet and In-Hospital Mortality

The overall in-hospital mortality was 53%. A higher RelΔ platelet was associated with a increased mortality, and only 3% of the patients had a RelΔ platelet > 80% (**Figure 2**). Patients with a RelΔ platelet ≥ 50% had a significantly increased mortality compared to patients with a RelΔ platelet < 50% (57 vs. 37%; $p < 0.001$ by log-rank-test; **Figure 3**). In multivariable logistic regression analyses, with adjustment for sex and serum lactate, RelΔ platelet ≥ 50% was independently associated with in-hospital mortality (OR 8.93; 95% CI 4.22–18.89; $p < 0.001$; **Table 3**). The AUROC for RelΔ platelet was 0.78 (95% CI, 0.71–0.85; **Figure 4**), which was better than that of platelet count (0.69; 95% CI, 0.61–0.77).

DISCUSSION

In this cohort study of 178 patients who received VA-ECMO for PCS, we found that RelΔ platelet in the first day after ECMO initiation is independently associated with an increased in-hospital mortality, independent of sex and peak serum lactate at day 1. In addition, RelΔ platelet exhibited good performance as compared to absolute platelet count at day 1.

Despite increasing improvement in VA-ECMO technology and knowledge, thrombocytopenia is common in patients undergoing VA-ECMO, among whom more than 20% have platelet counts lower than 150×10^9/L at some points during VA-ECMO (8). The initiation of ECMO is associated with an immediate and complex inflammatory reaction, similar to

TABLE 2 | Outcomes.

Outcome variables	Overall (n = 178)	RelΔ platelet ≥ 50% (n = 71)	RelΔ platelet < 50% (n = 107)	*P*-value
In-hospital mortality	94 (53)	57 (80)	37 (35)	<0.001
ECMO duration, days	5 (3–6)	5 (3–6)	5 (3–6)	0.395
Hospital stay, days	19 (12–26)	17 (11–25)	20 (14–27)	0.191
ICU stay, days	8 (5–12)	8 (5–13)	9 (6–12)	0.373
Successful weaning off ECMO	116 (65)	33 (46)	83 (78)	<0.001
CRRT	95 (53)	46 (65)	49 (46)	0.013
Bleeding need thoracotomy	29 (16)	17 (24)	12 (11)	0.024
Limb ischemia required fasciotomy	7 (4)	4 (6)	3 (3)	0.577
Major neurological complications	31 (17)	19 (6)	12 (22)	0.007
Brain death	6 (3)	6 (0)	0 (5)	0.008
Ischemic stroke	13 (7)	6 (4)	7 (8)	0.632
Hemorrhagic Stroke	6 (3)	3 (0)	3 (5)	0.607
Anoxic encephalopathy	6 (3)	4 (2)	2 (4)	0.348

Data are presented as medians (25th–75th percentile) or n (%).
ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; CRRT, continuous renal replacement therapy; RelΔ platelet, relative decrease in platelet count.

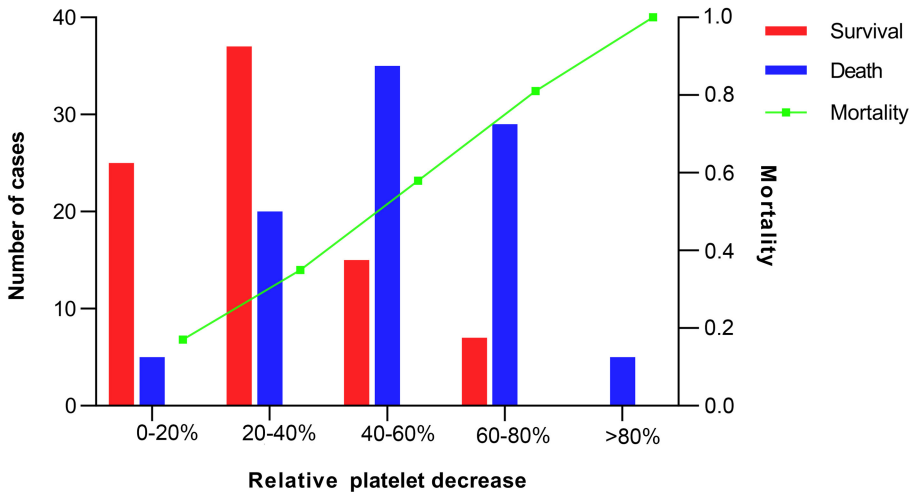

FIGURE 2 | Number of cases and mortality according to intervals of relative decrease in platelet count.

that seen in systemic inflammatory response syndrome (16). Moreover, the contact of blood with the surfaces of the extracorporeal circuit causes platelets activation and release of coagulation factors, an activation of the complement system. Thrombocytopenia might occur following cardiac surgery and ECMO due to extensive cross-talk between inflammation and coagulation, bleeding, consumption by the extracorporeal circuit, and oxidizing stress caused by high oxygen tension (17). It had been demonstrated that thrombocytopenia was related to longer ICU stays, a higher incidence of bleeding events, and higher mortality in ICU patients (18). However, there is a paucity of data on patients receiving VA-ECMO for PCS. In a recent retrospective study including 300 patients with left ventricular dysfunction after cardiac surgery (11), moderate (<100–50 $\times$ 10^9/L), severe (49–20 $\times$ 10^9/L), and very severe (<20 $\times$ 10^9/L) were independently associated with 90-day mortality. In addition, the authors found that platelet count had a biphasic temporal pattern with an initial decrease until day 4–5 after the initiation of VA-ECMO.

Thrombocytopenia and a decrease in platelet count may reflect the same pathophysiologic disturbances, including disseminated intravascular coagulation, macrophage activation, sepsis, drug-induced toxicity, and unidentified factors (18). Although most studies of the prognostic impact of platelet counts focused on outcomes in pre-specified groups according to the severity of thrombocytopenia, changes in platelet counts may carry greater prognostic significance than absolute counts in several critical conditions (19). However, few studies evaluated

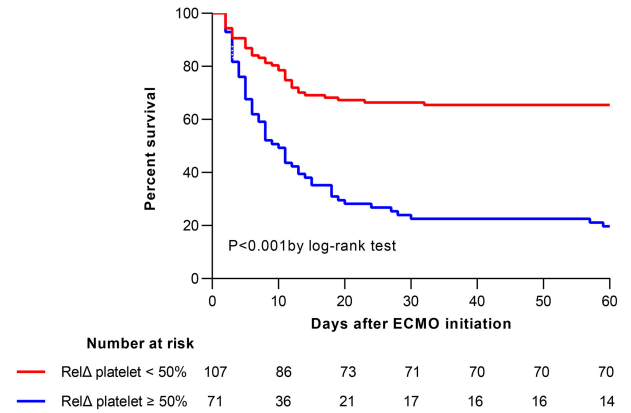

FIGURE 3 | Kaplan-Meier estimates of cumulative probabilities of 60-day survival for patients according to RelΔ platelet ≥50 or <50%. ECMO, extracorporeal membrane oxygenation; RelΔ platelet, relative decrease in platelet count.

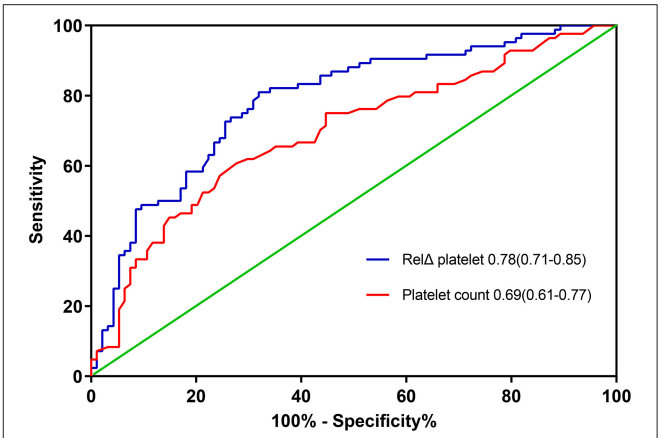

FIGURE 4 | The areas under the receiver operating characteristic curves for predicting in-hospital death. RelΔ platelet, relative decrease in platelet count.

TABLE 3 | Logistic regression analyses for in-hospital mortality.

	Univariable analysis		Multivariable analysis	
Parameter	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
Age (+10 years)	1.43 (1.10–1.86)	0.008		
Female	2.20 (1.05–4.62)	0.037	3.42 (1.46–8.01)	0.005
Diabetes	1.76 (0.86–3.61)	0.123		
Heart transplantation	0.24 (0.05–1.19)	0.080		
Redo cardiac surgery	0.51 (0.22–1.19)	0.117		
Serum lactate	1.07 (1.01–1.12)	0.016	1.07 (1.01–1.13)	0.016
RelΔplatelet (+10%)	1.82 (1.50–2.22)	<0.001		
RelΔplatelet ≥ 50%	7.70 (3.80–15.63)	<0.001	8.93 (4.22–18.89)	<0.001

Variables with P < 0.2 by univariate analysis were subjected to multivariate analysis. The multivariate logistic regression analysis was set with entry and removal P-values of 0.05 and 0.1, respectively. RelΔ platelet, relative decrease in platelet count.

the potential prognostic significance of declining platelet counts in patients supported with VA-ECMO after cardiac surgery. In our study, RelΔ platelet or a large RelΔ platelet (≥50%) in the first day after ECMO initiation is independently associated with in-hospital mortality, independent of sex and peak serum lactate at day 1. Importantly, RelΔ platelet had better discrimination than platelet count at day 1 in our cohort. As expected, severe bleeding events was more common in patients with a large RelΔ platelet ≥ 50%. Our study confirmed that the early decrease in platelet count had better prognostic significance than absolute counts in patients receiving VA-ECMO for PCS.

Platelet count has been incorporated in several prognostic scoring systems (10, 20). In the REMEMBER score, lowest platelet count $<100 \times 10^9$/L was associated with in-hospital mortality. Nevertheless, absolute platelet count cannot reflect changes in clinical status in patients whose platelet counts decrease but remained within the normal range. This might account for our findings that RelΔ platelet had better prognostic significance than platelet count. Thus, RelΔ platelet might help improve discrimination of new prognostic scoring systems for patients supported with VA-ECMO for PCS. Furthermore, RelΔ platelet at day 1 can be easily computed in real-time at the bedside and may afford clinicians the opportunity to evaluate the severity of illness before the development of other end-organ dysfunction, which may prompt earlier intervention, or a change in management strategy.

Our study has several limitations. First, it was a single-center, retrospective study which may limit the generalizability of our results. Second, bleeding and platelet transfusion would result in changes in platelet count. These factors might have affected the effect of RelΔ platelet on mortality.

Third, because left ventricular assist devices were not registered in China, no patients underwent ventricular assist device after VA-ECMO. The usefulness of VA-ECMO for PCS patients might have therefore been underestimated. Fourth, variables regarding platelet function, including platelet aggregation and activation of platelet, were not available. Finally, additional potential confounders undoubtedly exist, but it is unlikely the large magnitude of effect of RelΔ platelet has on mortality can all be explained by a yet undetermined variable. In the present study, we performed adjusted analyses to control for confounders in the evaluation of patients' outcomes.

CONCLUSIONS

In patients receiving VA-ECMO for post-cardiotomy cardiogenic shock, a large relative decrease in platelet count in the first day after ECMO initiation is independently associated with an increased in-hospital mortality, independent of sex and peak serum lactate at day 1. Our study suggests that clinicians should monitor RelΔ platelet frequently and might identify high-risk patients early. Prospective studies are needed to externally validate the prognostic significance of RelΔ platelet

in other populations of patients who received VA-ECMO for PCS.

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 Institutional Ethics Committee/Review Board of the Beijing Anzhen Hospital. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

LW and XH: conception and design. LW, JS, CS, and MJ: analysis and interpretation. JS and LW: drafting of the manuscript. HW and XH: revision of the manuscript. All authors read and approved the final version.

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BRIEF RESEARCH REPORT
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Extracorporeal Membrane Oxygenation for COVID-19: Case Report of Nine Patients

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Covid-19, Coronavirus disease 2019; ARDS, Acute respiratory distress syndrome; ECMO, Extracorporeal Membrane Oxygenation; WHO, World Health Organization; ICUs, Intensive care units. Acute respiratory distress syndrome (ARDS) is a fatal comorbidity of critically ill patients with COVID-19, who often end up on respiratory support. However, the safety and effectiveness of Extracorporeal Membrane Oxygenation (ECMO) in the treatment of COVID-19 remains to be elucidated at present. Here, we report on nine patients who received ECMO due to severe SARS-CoV-2 infection in Wuhan, China. Our initial experiences suggest that carefully selecting patients, as well as management by a well-trained team, are critical to implementing ECMO in patients with COVID-19. More randomized controlled trials with larger sample sizes are needed to evaluate the usefulness of ECMO in patients with COVID-19.

Keywords: COVID-19, acute respiratory distress syndrome, extracorporeal membrane oxygenation, extracorporeal life support (ECLS), respiratory failure

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INTRODUCTION

The spread of the COVID-19 is associated with a larger number of patients requiring intensive care, based on the initial studies (1). Acute respiratory distress syndrome (ARDS) is a fatal comorbidity of critically ill patients with COVID-19, who often end up on respiratory support. Patients who experience persistent refractory hypoxemia despite mechanical ventilation maybe benefit from Extracorporeal Membrane Oxygenation (ECMO), which was recommended by the World Health Organization (WHO) interim guidelines (2). However, the safety and effectiveness of ECMO in the treatment of COVID-19 remains to be elucidated at present, as studies report mixed results regarding the benefit of ECMO treatment (3, 4). Moreover, knowing the pathogenicity of SARS-CoV-2 in the early stage of the pandemic would be useful for tracing its evolution. Here, we report on nine patients who received ECMO due to severe SARS-CoV-2 infection in the city of Wuhan, China.

MATERIALS AND METHODS

This study recruited patients with confirmed COVID-19 who received ECMO from 11 designated intensive care units (ICUs) in Wuhan. The detailed information of each patient before and

after ECMO implementation was collected by physicians using a standard data form, including demographic data, medical history, underlying medical conditions, signs and symptoms, laboratory and radiological findings, and the treatment the patients received. ARDS was defined according to the Berlin definition (5). This study was approved by the Shanghai East Hospital Ethics Committee and carried out in accordance with the Declaration of Helsinki.

RESULTS

Between February 2 and March 20, 2020, a total of 354 COVID-19 patients from 11 ICUs in Wuhan were retrospectively evaluated. Among these patients, there were nine cases from six different ICUs who received ECMO treatment due to ARDS, with all of them starting ECMO implementation in the ICU rather than transferring from other departments. The medical team charged with their care was brought in from different areas of China to support the local hospital. The detailed baseline clinical characteristics of those patients are shown in **Table 1**. The median (min to max) age was 58 (47–68) years and 6 (66.7%) patients were men. Five patients had underlying medical conditions, including diabetes, hypertension, and coronary artery disease. The primary reason for ECMO implementation was ARDS in all nine cases (**Figure 1**). Before ECMO implementation, the median (min to max) duration of mechanical ventilation before implementation of ECMO was 48 (11–345) h. A prone position was used for six (66.7%) patients.

TABLE 1 | Characteristics and severity of ARDS and outcome of COVID-19 patients received ECMO*.

	All % or median (min–max)	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age (years)	58 (47-68)	68	47	58	60	62	55	66	55	56
Sex	66.7% Male	M	M	F	F	M	M	M	F	M
Comorbidities										
Hypertension	33.3%	Yes	No	Yes	No	Yes	No	No	No	No
Diabetes	33.3%	No	Yes	Yes	No	No	No	No	No	Yes
Coronary artery disease	11.1%	Yes	No	No	No	No	No	No	No	No
BMI	20.8 (24.0–27.0)	23.7	23.1	26.0	24.0	27.0	20.8	26.4	24.8	23.0
From illness onset to Mechanical ventilation, days	24 (11-46)	16	25	38	30	24	21	21	11	46
From illness onset to ECMO, days	31 (13–49)	31	35	40	31	31	22	22	13	49
From Mechanical ventilation to ECMO, hours	48 (11–345)	345	239	47	11	194	47	29	48	54
Prone positioning	66.7%	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Renal replacement therapy	44.4%	No	No	Yes	Yes	Yes	No	Yes	No	No
24 h Before Commencement of ECMO										
Lowest PaO_2/FIO_2 ratio	92 (41–156)	114	45	92	45	122	41	116	42	156
Highest FIO_2	85 (70–100)	81%	100%	85%	100%	70%	100%	80%	100%	75%
Highest PEEP, cm H_2O	10 (7–15)	12	10	7	14	7	15	10	10	8
Highest peak airway pressure, cm H_2O	38 (27–45)	35	38	N/A	45	27	35	45	40	40
Lowest pH	7.35 (7.21–7.42)	7.33	7.24	7.34	7.41	7.37	7.40	7.21	7.42	7.35
Highest $PaCO_2$, mm Hg	72.0 (41.2–102.0)	73.4	102.0	60.3	55.1	78.8	44.3	72.0	41.2	79.3
Highest tidal volume, mL/kg	6.4 (4.7–7.5)	4.7	6.4	7.5	5.8	N/A	7.5	5.4	6.1	6.9
SOFA score	8 (6–12)	10	12	8	6	7	8	8	6	7
ECMO parameters										
Model	100% V-V	V-V	V-V to V-V-A	V-V	V-V	V-V	V-V	V-V	V-V	V-V
Circuit blood flow at 4 h, L/min	4.0 (3.0–5.6)	4.6	5.6	3.5	4.3	4.0	N/A	3.5	3.0	3.0
Outcome										
Hemorrhage	55.6%	No	Yes	Yes	Yes	Yes	No	Yes	No	No
Duration of Mechanical ventilation, hours	290 (79–871)	500	290	871	158	644	79	583	231	241
Duration of ECMO, hours	147 (32–450)	155	51	378	147	450	32	255	133	144
Withdraw Mechanical ventilation	11.1%	No	No	No	No	No	No	No	Yes	No
Withdraw ECMO	44.4%	No	No	Yes	No	No	No	Yes	Yes	Yes
Duration of ICU stay, days	24 (8–45)	8	19	45	24	30	13	26	37	13
Duration of hospital stay, days	26 (8–58)	8	20	58	28	40	13	26	45	22
Survival	33.3%	No	No	No	No	No	No	Yes	Yes	No

Case 7 was discharged and case 8 was still in hospital after mechanical ventilation as of April 15, 2020.

ECMO, Extracorporeal Membrane Oxygenation; SOFA score, Sepsis-related Organ Failure Assessment (SOFA) score; V-V, veno-venous; V-A, veno-arterial; V-V-A, veno-arterial-venous.

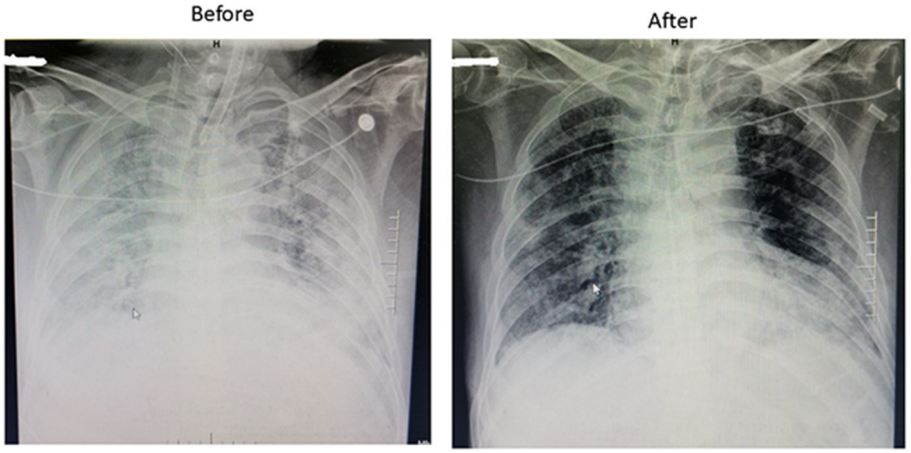

FIGURE 1 | Representative chest X-ray of COVID-19 patients before and after ECMO treatment.

The median (min to max) highest recorded FIO_2, positive end-expiratory pressure, tidal volume (per kg body weight), and peak airway pressure before ECMO commencement were 85% (70–100%), 10 (7–15) cmH_2O, 6.4 (4.7–7.5) mL/kg, and 38 (27–45) cm H_2O, respectively. The Median (min–max) SOFA score in the 24 h before ECMO implementation was 8 (6–12).

The veno-venous model of ECMO was used in all patients, though one patient was later changed to a veno-arterial-venous model due to unstable cardiac output. The median (min to max) duration of ECMO support was 147 (32–450) h and the median (min to max) circuit blood flow at 4 h was 4.0 (3.0–5.6) L/min.

Hemorrhagic complications occurred in five patients (55.6%) during ECMO therapy. Of the nine patients, 5 (55.6%) died while receiving ECMO, and 4 (44.4%) were weaned from ECMO. After ECMO withdrawal, two patients died, one patient was discharged, and one patient was withdrawn from mechanical ventilation but remained in hospital as of May 15, 2020.

DISCUSSION

To the best of our knowledge, studies that reported the clinical characteristics, technical details, and outcomes in COVID-19 patients who received ECMO in China were limited. As the respiratory system is the primary target of the virus, which causes ARDS in a substantial proportion of ICU patients, the requirement of respiratory supports like ECMO is expected. However, the usefulness of ECMO, which was associated with reduced mortality in patients with MERS-CoV infection (6), remains debatable in terms of its safety and effectiveness in COVID-19 patients according to initial studies (7). In a study conducted by Yang et al. (8) five (83%) of six patients with COVID-19 receiving ECMO died in the city of Wuhan, China. A recent study reported that the 90-days mortality was 54% in patients who received ECMO treatment due to COVID-19. Our study found seven in nine patients had died and one patient remained in hospital (9). The mortality is higher than those with MERS or H1N1 infection (3, 6) and those with COVID-19 outside of Wuhan (9). This might be due to several reasons. First, the patients in the current study were older than those with MERS or H1N1 infections, and more patients had underlying medical conditions. Second, the ECMO specialists were from different centers elsewhere in China and therefore different standards and criteria might be adopted during the implementation of ECMO. Third, it is likely that related equipment was in shortage, given the heavy burden COVID-19 presented during the outbreak in the city of Wuhan. Fourth, the potential harm of ECOM itself in the treatment of COVID-19 cannot be excluded based on our and previous studies (10). Therefore, our initial experiences suggested that carefully selecting patients who might benefit from ECMO, as well as management by a well-trained team with relevant equipment, were critical to implementing ECMO in patients with COVID-19. More randomized controlled trials with larger sample sizes are needed to evaluate the usefulness of ECMO in patients with COVID-19.

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 Shanghai East Ethics Committee. The Ethics Committee waived the requirement of written informed consent for participation. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

FW conceived, designed the study, analyzed the data, and wrote the paper. JH, XZ, ZL, LR, NW, SW, CQ, WGa, and WGu contributed to data acquisition and analysis. QL and

ZL interpreted the data and gave their expert insight to this study. All authors contributed to the article and approved the submitted version.

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Impact of Cumulative Fluid Balance During Continuous Renal Replacement Therapy on Mortality in Patients With Septic Acute Kidney Injury: A Retrospective Cohort Study

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Background: The clinicians often use continuous renal replacement therapy (CRRT) for the fluid management of patients with septic acute kidney injury (AKI). However, there is limited knowledge of the effects of changes in fluid balance (FB) on CRRT and its association with outcomes in patients with septic AKI.

Objective: This study aimed to determine the association of cumulative FB (CFB) during treatment with 28-day all-cause mortality in the patients with septic AKI who require CRRT.

Methods: This retrospective observational study examined patients who received CRRT due to septic AKI in a mixed intensive care unit (ICU) of a tertiary teaching hospital between January 2015 and December 2018. The patients were divided into three groups—negative FB, even FB, and positive FB—based on the CFB during CRRT. The primary outcome was 28-day all-cause mortality.

Results: We examined 227 eligible patients and the mean age was 62.4 ± 18.3 years. The even FB group had a significantly lower 28-day mortality (43.0%, $p = 0.007$) than the positive FB group (72.7%) and the negative FB group (54.8%). The unadjusted and adjusted Cox regression models indicated that the positive FB group had an increased risk for 28-day all-cause mortality relative to the even FB group. A restricted cubic splines model indicated a J-shaped association between the CFB and 28-day all-cause mortality in the unadjusted model.

Conclusion: Among the critically ill patients with septic AKI who require CRRT, those with positive FB had a higher mortality rate than those with even FB.

Keywords: sepsis, acute kidney injury, continuous renal replacement therapy, fluid balance, mortality

INTRODUCTION

Sepsis is the leading cause of acute kidney injury (AKI) in intensive care units (ICUs). A septic AKI is increasingly recognized as a common and serious problem in critically ill patients, particularly in the ICU, and septic AKI occurs in about 50% of the critically ill patients with sepsis (1, 2). The previous studies reported that the mortality of ICU patients with septic AKI was 30–45% (1, 3–5), and the mortality rate for those who required renal replacement therapy (RRT) was 56–70% (6–8).

The mortality of patients with septic AKI is associated with several factors, such as AKI severity, multiple organ failure, and fluid accumulation (9, 10). Effective fluid resuscitation is crucial for the stabilization of sepsis-induced tissue hypoperfusion or septic shock (11). However, over time the initial benefit of fluid therapy can lead to fluid accumulation and tissue edema, and this can exacerbate organ dysfunction (12). Several observational studies found an association between the positive fluid balance (FB) and poor outcomes in critically ill patients with septic AKI (9, 13–15). Optimizing fluid status is essential for patients with excess fluid accumulation but is difficult to achieve when the patients develop AKI.

The clinicians often use continuous renal replacement therapy (CRRT) for fluid management of the patients with severe AKI (16, 17), although determining the appropriate fluid volume in those patients during CRRT is challenging. Some studies demonstrated that a positive FB after CRRT initiation was associated with an unfavorable outcome (18–20), but others reported that active fluid withdrawal using RRT in critically ill patients was associated with poorer survival than standard care (21). Compared with the patients with non-septic AKI, the patients with septic AKI and septic shock may have different responses to the RRT due to differences in pathophysiology (22). However, there is limited knowledge about the effects of changes in the FB on CRRT and its association with outcomes in patients with septic AKI.

This study aimed to examine the association between cumulative FB (CFB) during treatment with CRRT and 28-day all-cause mortality in critically ill patients with septic AKI. Considering that an even FB is more similar to the normal physiological state, we used a group of patients with even FB as a comparator. We hypothesized that a positive or negative FB is associated with the increased 28-day all-cause mortality.

METHODS

Study Population

This retrospective study was conducted in a 30-bed medical-surgical ICU of a tertiary teaching hospital in Beijing, China (Beijing Friendship Hospital, Capital Medical University). A retrospective review of the medical records of patients admitted to this ICU from January 2015 to December 2018 was performed. The patients included were those admitted to the ICU with septic AKI and undergoing CRRT. Septic AKI was defined as the simultaneous presence of sepsis and AKI. The patients with the following characteristics were excluded: pre-existing chronic kidney disease (estimated glomerular filtration rate [GFR] < 20 ml/min/1.73 m^2 for at least 1 year); ICU stay of less than 48 h; and missing data on the fluid status and body weight. Data were collected only from the first ICU admission if a patient underwent multiple ICU admissions that required CRRT during the study period. This study was approved by the Bioethics Committee of Beijing Friendship Hospital, Capital Medical University (2020-P2-210-01).

Definitions

The definition of AKI was based on the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI. Thus, AKI was defined by the presence of at least one of the following three criteria: an increase in the serum creatinine (sCr) level to at least 0.3 mg/dl (26.5 μmol/L) within 48 h; an increase in the sCR level to at least 1.5 times the baseline level that was known or was presumed to have occurred within the previous 7 days; or urine volume below 0.5 ml/kg/h for 6 h (23). The diagnostic criteria for sepsis and septic shock were in accordance with the 2016 International Sepsis Definitions (24). The baseline eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (25). This eGFR calculation used the sCr value closest to the date of hospitalization, but not more than 1 year prior to the hospitalization, or the lowest sCr value documented during the current hospitalization if no other value was available. Chronic kidney disease (CKD) was defined as the eGFR below 60 ml/min/1.73 m^2.

Determination of CFB

For each patient, the CFB was expressed as a percentage (%) and calculated using the following equation.

$$\text{Weight–adjusted CFB (\%)} = \frac{\left(\textit{Cumulative daily fluid input} - \textit{output}\right)\ \textit{in liters} \times 100}{\textit{ICU admission weight}\ (\textit{kg})}$$

The CFB was assessed at 48 and 72 h after initiation of CRRT. A negative FB was defined as a weight-adjusted CFB less than 0%, an even FB as a weight-adjusted CFB of 0% to less than 5%, and a positive FB as a weight-adjusted CFB of 5% or more (26). In addition, we collected data on input and output from the hospital admission to CRRT initiation to calculate the CFB and weight-adjusted CFB at the initiation of CRRT.

Clinical Outcomes

The primary outcome was all-cause mortality at 28 days after CRRT initiation. The secondary outcomes were all-cause mortality at 60 days, length of stay in the ICU, mechanical ventilation-free days, and vasopressor-free days within 28 days from the CRRT initiation.

Data Collection

At baseline, the following characteristics of the enrolled patients were recorded at the time of CRRT initiation: demographic data (age, sex, body weight, and body mass index [BMI]); clinical data (admission type, comorbidities, septic shock, the CFB before CRRT initiation, and indication for CRRT); infection data (site of

infection and infection category); laboratory data (white blood cells, hemoglobin, platelets, eGFR, sCr, albumin, and lactate). For assessment of disease severity, the Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were determined at the time of CRRT initiation. The organ support measures at the time of CRRT initiation, such as the need for mechanical ventilation and vasopressor support, were recorded.

Statistical Analysis

For comparisons, the patients were stratified into three groups based on 48 h weight-adjusted CFB: positive FB, negative FB, and even FB. The baseline values of the continuous variables were reported as means and SDs or medians and interquartile ranges (IQR) for normally and non-normally distributed variables, respectively. The categorical variables were presented as numbers and percentages. The categorical variables were compared using the chi-squared test and continuous variables using a one-way ANOVA and the Kruskal–Wallis test.

Survival analysis was performed using a Kaplan–Meier method and the log-rank test. The multivariable Cox regression models were used to examine the association of 28-day mortality with CFB. The Cox regression was first adjusted for demographic data (age, sex, and BMI; Model 1) and then additionally adjusted for severity of illness (SOFA score and APACHE II score; Model 2). The clinical variables with p values below 0.03 in the univariate analysis and previous variables were entered into the final model (Model 3). If two variables were strongly correlated, only one of these variables was retained and added to the multivariable model. The weight-adjusted CFB was also treated as a continuous variable in a Cox regression model that was used to calculate the unadjusted and adjusted hazard ratio (*HR*s); these HRs were plotted using restricted cubic spline models to assess the potential nonlinear associations between the CFB and 28-day mortality.

A subgroup analysis was performed to examine primary outcomes in the patients with fluid overload before CRRT initiation and patients with septic shock. To explore the robustness of the results, three sensitivity analyses were performed. First, the multivariable logistic regression models were constructed to calculate the unadjusted and adjusted odds ratios (*OR*s) to test the robustness of the findings from the Cox models. Second, to account for potential survivorship bias, the

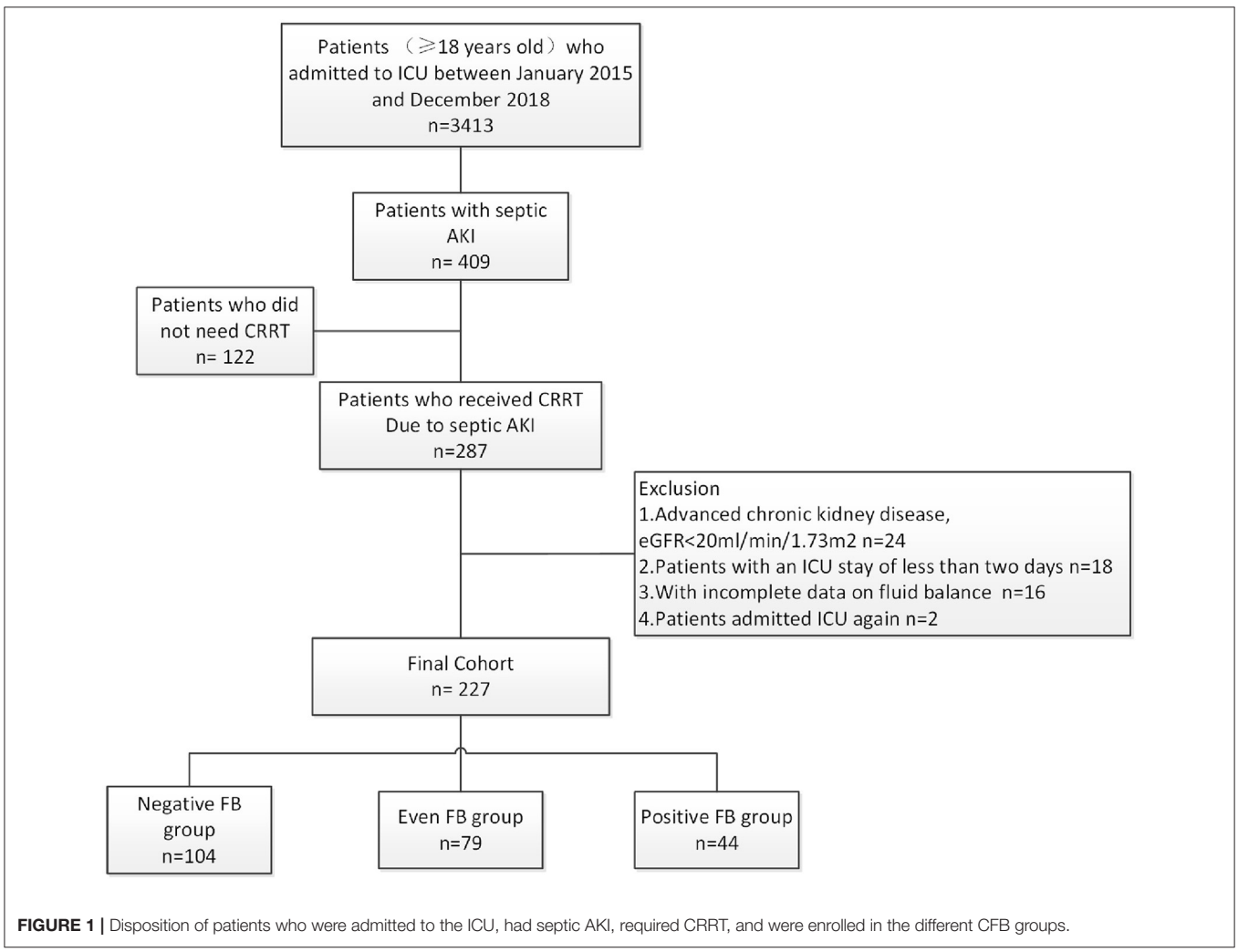

FIGURE 1 | Disposition of patients who were admitted to the ICU, had septic AKI, required CRRT, and were enrolled in the different CFB groups.

TABLE 1 | Characteristics of patients at baseline (CRRT initiation) who had different CFB status.

Characteristic	All $n = 227$	Negative FB ($n = 104$)	Even FB ($n = 79$)	Positive FB ($n = 44$)	*p* value
Age (years)	62.4 ± 18.3	61.7 ± 19.7	62.2 ± 18.2	64.1 ± 15.1	0.76
Male sex, *n* (%)	146 (64.3)	52 (50.0)	61 (77.2)	33 (75.0)	0.001
Weight (kg)	67.4 ±14.6	65.7 ±14.0	69.7 ± 17.1	67.4 ± 9.9	0.19
BMI (kg/m^2)	24.2 ± 5.1	23.7 ± 4.2	24.1 ± 5.1	23.5 ± 3.1	0.76
Pre-admission renal function					
*Baseline Cr	86.0 [66.5, 153.0]	89.5 [67.5, 162.0]	86.9 [65.7, 190.0]	80.0 [63.0, 105.0]	0.26
*Baseline eGFR, mL/min/1.73 m^2	92.6 [46.0, 123.5]	82.6 [34.9, 123.9]	92.1 [39.1, 123.1]	101.4 [74.7, 122.9]	0.14
Comorbid condition, *n* (%)					
Hypertension	111 (48.9)	57 (54.8)	32 (40.5)	22 (50.0)	0.16
Diabetes	56 (24.7)	26 (25.0)	24 (30.4)	6 (13.6)	0.12
Cardiac disease	73 (32.2)	38 (36.5)	21 (26.6)	14 (31.8)	0.36
Chronic liver disease	27 (11.9)	13 (12.5)	12 (15.2)	2 (4.5)	0.21
Chronic kidney disease	55 (24.2)	29 (27.9)	21 (26.1)	5 (4.5)	0.009
Surgery admission, *n* (%)	80 (35.2)	33 (31.7)	28 (35.4)	19 (34.2)	0.41
Septic shock, *n* (%)	172 (75.8)	70 (67.3)	59 (74.7)	43 (97.7)	<0.001
Hospital-acquired infection, *n* (%)	100 (44.1)	31 (29.8)	47 (59.5)	22 (50.0)	<0.001
Site of infection, *n* (%)					<0.001
Respiratory	136 (59.9)	77 (74.0)	47 (59.5)	12 (27.3)	
Intra-abdominal	66 (29.1)	19 (18.3)	25 (31.6)	22 (50.0)	
Urinary	6 (2.6)	2 (1.9)	0 (0.0)	4 (9.1)	
Blood	9 (4.0)	2 (1.9)	3 (3.8)	4 (9.1)	
Other	10 (4.4)	4 (3.8)	4 (5.1)	2 (4.5)	
Indications for CRRT, *n* (%)					
worsening azotemia	62 (27.3)	26 (25.0)	25 (31.6)	11 (25.0)	0.56
Oligouria or anuria	148 (65.2)	53 (67.1)	61 (58.7)	34 (77.3)	0.08
Fluid overload	59 (26.0)	31 (29.8)	15 (19.0)	13 (29.5)	0.21
Electrolyte imbalance	39 (17.2)	16 (15.4)	19 (24.1)	4 (9.1)	0.08
Acid base imbalance	51 (22.5)	21 (20.2)	19 (24.1)	11 (25)	0.75
Before CRRT initiation					
Invasive mechanical ventilation, *n* (%)	149 (65.6)	67 (64.4)	49 (62.0)	33 (75.0)	0.33
Vasopressor support, *n* (%)	138 (60.8)	61 (58.7)	43 (54.4)	34 (77.3)	0.038
APACHE II score	23.6 ± 7.0	21.8 ± 5.9	24.7 ± 7.9	26.5 ± 7.0	<0.001
SOFA score	10.5 ± 3.8	10.3 ± 3.7	10.5 ± 4.2	11.3 ± 3.3	0.34
Laboratory before CRRT					
White blood cells (×10^9/L)	12.6 ± 7.6	12.4 ± 6.2	12.8 ± 6.6	12.7 ± 11.6	0.94
Platelets (×10^9/L)	94 [48,171]	126.2 ± 98.8	110.6 ± 84.4	77 [45,179]	0.72
Hemoglobin (g/L)	93.7 ± 26.3	87.2 ± 22.7	95.3 ± 26.1	106.1 ± 30.1	<0.001
Albumin (g/L)	25.7 ± 4.7	26.8 ± 3.8	26.0 ± 5.2	22.1 ± 4.2	<0.001
**eGFR, mL/min/1.73m^2	20.4 [12.7, 35.2]	18.8 [10.1, 33.9]	21.2 [12.9, 42.1]	22.7 [15.9, 32.2]	0.31
Creatinine (μmmol/L)	246.6 [155.6, 394.0]	243.8 [170.1, 420.8]	264.0 [146.5, 409.4]	241.9 [179.3, 348.7]	0.71
Lactate (mmol/L)	2.2 [1.4, 5.2]	2.0 [1.1, 4.5]	1.9 [1.5, 4.2]	3.5 [1.9, 10.2]	<0.001
CFB before CRRT (ml)	3,980 [1,910, 8,379]	3,823 [1,360, 7,001]	3,688 [1,845, 7,763]	8,294 [3,864, 11,930]	0.001
Weight-adjusted CFB (%) before CRRT	5.9 [2.7, 12.8]	5.2 [2.4, 10.2]	5.7 [2.8, 12.3]	12.6 [5.3, 16.3]	0.004
Duration of treatment					
Cumulative fluid balance, mL					
48h	204 [−1,400–2,203]	−1,550 [−2,802, −680]	1,197 [488, 1,491]	5,562 [3,798, 7,089]	<0.001
72h	367 [−2,029–2,559]	−2,043 [−3,480, −1,154]	1,679 [588, 2,332]	6,607 [5,178, 8,613]	<0.001
Weight–adjusted CFB (%)					
48h	0.2 [−2.0–2.9]	−2.2 [−4.2, −1.0]	1.7 [0.8, 2.5]	7.3 [6.1, 10.6]	<0.001
72h	0.6 [−2.8–4.3]	−3.0 [−5.2, −1.7]	2.5 [0.7, 3.5]	9.3 [7.3, 10.9]	<0.001

**Based on SCr before hospitalization. **Based on SCr at CRRT initiation. FB, fluid balance; CFB, cumulative fluid balance; BMI, Body Mass Index; eGFR, estimated glomerular filtration rate; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, continuous renal replacement therapy. Here and below, continuous variables are expressed as mean ± SD or median [Q1, Q3] and nominal variables as n (%).*

TABLE 2 | Characteristics of patients at baseline (CRRT initiation) who were survivors and non-survivors at day-28.

Characteristic	All ($n = 227$)	Survivors ($n = 104$)	Non-survivors ($n = 123$)	*p* value
Age (years)	62.4 ± 18.3	60.4 ± 16.9	64.0 ± 19.2	0.14
Male sex, *n* (%)	146 (64.3)	78 (75.0)	68 (55.3)	0.002
Weight (kg)	67.4 ± 14.6	70.5 ± 16.4	64.8 ± 12.2	0.003
BMI (kg/m^2)	24.2 ± 5.1	24.5 ± 5.2	23.2 ± 3.4	0.022
Pre-admission renal function				
*Baseline Cr	86.0 [66.5, 153.0]	91.0 [72.7, 246.3]	83.2 [63.0, 109.4]	0.002
*Baseline eGFR, mL/min/1.73 m^2	92.6 [46.0, 123.5]	80.2 [29.9, 119.8]	98.1 [73.1, 131.4]	0.002
Comorbid condition, *n* (%)				
Hypertension	111 (48.9)	56 (53.8)	55 (44.7)	0.19
Diabetes	56 (24.7)	25 (24.0)	31 (25.2)	0.88
Cardiac disease	73 (32.2)	35 (33.7)	38 (30.9)	0.67
Chronic liver disease	27 (11.9)	9 (8.7)	18 (14.6)	0.22
Chronic kidney disease	55 (24.2)	33 (31.7)	22 (17.9)	0.019
Surgery admission, *n* (%)	80 (35.2)	38 (36.5)	42 (34.1)	0.78
Septic shock, *n* (%)	172 (75.8)	65 (62.5)	107 (87.0)	<0.001
Hospital-acquired infection, *n* (%)	100 (44.1)	36 (34.6)	64 (52)	0.011
Site of infection, *n* (%)				0.31
Respiratory	136 (59.9)	56 (53.8)	80 (65.0)	
Intra-abdominal	66 (29.1)	37 (35.6)	29 (23.6)	
Urinary	6 (2.6)	2 (1.9)	4 (3.3)	
Blood	9 (4.0)	5 (4.8)	4 (3.3)	
Other	10 (4.4)	4 (3.8)	6 (4.9)	
Before CRRT initiation				
Invasive Mechanical ventilation, *n* (%)	149 (65.6)	67 (64.4)	82 (66.7)	0.78
Vasopressor support, *n* (%)	138 (60.8)	54 (51.9)	84 (68.3)	0.014
APACHE II score	23.6 ± 7.0	22.7 ± 6.6	24.7 ± 7.2	0.034
SOFA score	10.5 ± 3.8	9.5 ± 4.0	11.4 ± 3.4	<0.001
Laboratory before CRRT				
White blood cells (×10^9/L)	12.6 ±7.6	12.2 ± 6.4	12.9 ± 8.5	0.50
Platelets (×10^9/L)	94 [48, 171]	113.5 [55.5, 184]	77.0 [41.0, 151.0]	0.014
Hemoglobin (g/L)	93.7 ± 26.3	96.7 ± 29.3	91.1 ± 23.3	0.11
Albumin (g/L)	25.7 ± 4.7	26.1 ± 4.8	25.2 ±4.8	0.19
**eGFR mL/min/1.73 m^2	20.4 [12.7, 35.2]	17.4 [12.0, 26.7]	25.2 [14.6, 42.1]	0.002
Creatinine (μmmol/L)	246.6 [155.6, 394.0]	296.4 [216.6, 435.8]	222.0 [133.1, 334.1]	0.001
Lactate (mmol/L)	2.2 [1.4, 5.2]	1.7 [1.3, 3.6]	2.7 [1.7, 6.2]	<0.001
CFB before CRRT (ml)	3,980 [1,910, 8,379]	4,016 [1,928, 7,808]	3,940 [1,410, 8,399]	0.73
Weight-adjusted CFB (%) before CRRT	5.9 [2.7, 12.8]	5.6 [2.8, 10.5]	6.7 [2.4, 14.3]	0.36
Duration of treatment				
Cumulative fluid balance, ml				
48h	204 [−1,400–2,203]	204 [−1,505–1,491]	379 [−1,394–3,274]	0.36
72h	367 [−2,029–2,559]	339 [−2,055–2,049]	403 [−2,029–3,811]	0.12
Weight-adjusted CFB				
48h	0.2 [−2.0–2.9]	0.2 [−2.0–2.5]	0.5 [−2.0–5.1]	0.36
72h	0.6 [−2.8–4.3]	0.4 [−3.0–3.4]	0.8 [−2.7–6.1]	0.42

**Based on SCr before hospitalization. **Based on SCr at CRRT initiation.*

effect of CFB on 28-day mortality in a subgroup of patients who survived at least 3 days after CRRT initiation was examined. Third, to reduce the effect of selection bias and potential confounding, a propensity score representing the probability that a patient would be in a fluid balance group was developed based on the following variables: age, sex, BMI, SOFA score, APACHE II score, septic shock, CKD, hospital-acquired infection, lactate, eGFR, and weight-adjusted CFB before CRRT. This score was

TABLE 3 | Primary and secondary outcome.

Outcome	All $n = 227$	Negative FB ($n = 104$)	Even FB ($n = 79$)	Positive FB ($n = 44$)	*p* value
Primary					
Death at 28 days, *n* (%)	123 (54.2)	57 (54.8)	34 (43.0)	32 (72.7)	0.007
Secondary					
Death at 60 days	144 (63.4)	66 (63.5)	45 (57.0)	33 (75.0)	0.13
RRT among survivors, *n*/total (%)	37/104 (35.6)	16/49 (34.0)	16/45 (35.6)	5/12 (41.7)	0.89
MV-free days in survivors	19 [11, 24]	20 [11, 26]	18 [12, 24]	13 [8, 21]	0.16
Vasopressor-free days	24 [14, 27]	25 [23, 28]	20 [0, 26]	24 [19, 27]	0.89
Length of ICU stay					
Survivors	22 [13.5, 44]	21 [15, 34]	26 [13, 48]	20 [11, 35]	0.31
Non-survivors	8 [3, 15]	8 [4, 15]	8 [3, 16.5]	8 [2, 14.75]	0.70

MV, mechanical ventilation; ICU, Intensive Care Unit; RRT, Renal Replacement Therapy.

calculated using logistic regression and additionally adjusted in the Cox regression model. Another propensity score was calculated using the baseline variables that differed significantly among the three groups and adjusted in the Cox regression.

Data were analyzed using IBM SPSS software version 19.0 (IBM, NY, USA), R version 4.0.1 (Austria), and STATA version 14.1 (Stata Corp LLC, TX, USA). A two-sided *p*-value below 0.05 was considered significant.

RESULTS

The Baseline Characteristics

During the 4-year study period, 3,413 critically ill adult patients were admitted to the ICU, and 287 patients developed severe septic AKI that required CRRT (**Figure 1**). After the exclusion of patients based on pre-defined criteria, we included 227 patients in this study.

We recorded the demographic, clinical, and laboratory characteristics of all the patients with stratification by CFB at baseline (**Table 1**). Overall, most of the patients were male (64.3%) and the mean age was 62.4 ± 18.3 years. There were 104 patients (45.8%) in the negative FB group, 79 (34.8%) in the even FB group, and 44 (19.3%) in the positive FB group. The history of CKD was more prevalent in the negative and even FB groups. The positive FB group had a higher APACHE-II score, a higher prevalence of receiving vasopressor support and septic shock, a lower level of albumin, and a higher level of lactate. The CFB at the initiation of CRRT was significantly higher in the positive FB group. The negative FB group had a lower level of hemoglobin and smaller proportions of men and patients with hospital-required infections. The most common indications for CRRT were oliguria and anuria, followed by worsening azotemia and fluid overload. There were no significant differences among the three groups.

We assessed the CFB at 48 and 72 h after initiation of CRRT. At these two times, the positive FB group had median FBs of 5,562 and 6,607 ml, and the negative FB group had median FBs of −1,550 and −2,043 ml.

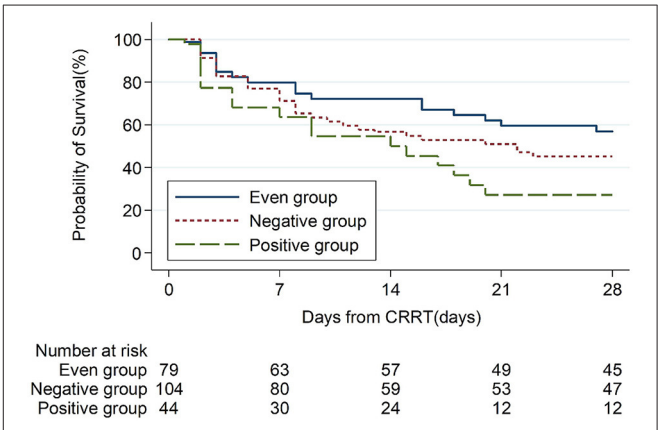

FIGURE 2 | Kaplan Meier analysis of overall survival from baseline (CRRT initiation, day-0) to day-28 in patients with different CFB status.

FB in Survivors and Non-survivors

Among all the 227 patients, 123 patients (54.2%) died within 28 days after CRRT initiation (**Table 2**). The CFB at 48 h was 204 ml (range: −1,505, 1,491) in the survivors and 379 ml (range: −1,394, 3,274) in the non-survivors. The non-survivors also had a higher CFB at 72 h after CRRT initiation, but this difference was not statistically significant.

Primary and Secondary Outcomes

The 28-day mortality was significantly lower in the even FB group (43.0%, $p = 0.007$, **Table 3**) than in the positive FB group (72.7%) and the negative FB group (54.8%). A Kaplan–Meier analysis and the log-rank test (**Figure 2**) indicated significantly longer survival in the even FB group than in the positive FB group, but no significant difference between the even FB and negative FB groups.

We initially used the univariate Cox models to identify the factors associated with all-cause mortality. Relative to the even FB group, the positive FB group (but not the negative FB group) had an increased adjusted *HR* for mortality in all the

TABLE 4 | Univariate and multivariate Cox model analysis of factors associated with all-cause mortality at day-28 based on CFB status at 48 h.

Variables	Unit	Univariate model		Multivariate model					
		95%CI	*p* value	Model 1		Model 2		Model 3	
				95%CI	*p* value	95%CI	*p* value	95%CI	*p* value
CFB group	Even FB	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
	Positive FB	2.26 (1.39–3.67)	0.001	2.44 (1.49–3.97)	<0.001	2.09 (1.27–3.43)	0.004	2.30 (1.27–4.17)	0.006
	Negative FB	1.43 (0.93–2.18)	0.10	1.22 (0.78–1.91)	0.38	1.23 (0.77–1.95)	0.39	1.46 (0.88–2.44)	0.15
Age	per 1 year older	1.00 (0.99–1.01)	0.54	1.01 (0.99–1.02)	0.35	1.01 (0.99–1.02)	0.17	1.01 (1.00–1.02)	0.29
Male	vs. Female	0.58 (0.41–0.83)	0.003	0.60 (0.41–0.87)	0.007	0.59 (0.40–0.87)	0.008	0.50 (0.33–0.77)	0.002
BMI	per 1 kg/m^2	0.95 (0.92–0.99)	0.026	0.95 (0.91–0.99)	0.026	0.95 (0.91–0.99)	0.034	0.97 (0.92–1.02)	0.17
APACHE II score	per 1 pt. increase	1.03 (1.00–1.05)	0.031			1.01 (0.98–1.04)	0.51	1.01 (0.98–1.04)	0.62
SOFA score	per 1 pt. increase	1.10 (1.05–1.16)	<0.001			1.10 (1.04–1.16)	0.002	1.10 (1.03–1.18)	0.003
Septic shock	vs. No	2.71 (1.60–4.59)	<0.001					0.89 (0.57–1.38)	0.59
Chronic kidney disease	vs. No	0.58 (0.37–0.92)	0.022					1.26 (0.73–2.17)	0.41
Hospital–acquired infection	vs. Community–acquired infection	1.50 (1.05–2.14)	0.025					1.53 (0.97–2.43)	0.07
eGFR	per 1ml/min/1.73 m^2 increase	1.01 (1.00–1.02)	0.009					1.01 (1.00–1.02)	0.017
Lactate	per 1 mmol/l increase	1.06 (1.02–1.10)	0.001					1.02 (0.98–1.07)	0.34
Weight–adjusted CFB (%) before CRRT	per 1% increase	1.02 (1.00–1.04)	0.024					0.99 (0.97–1.01)	0.42

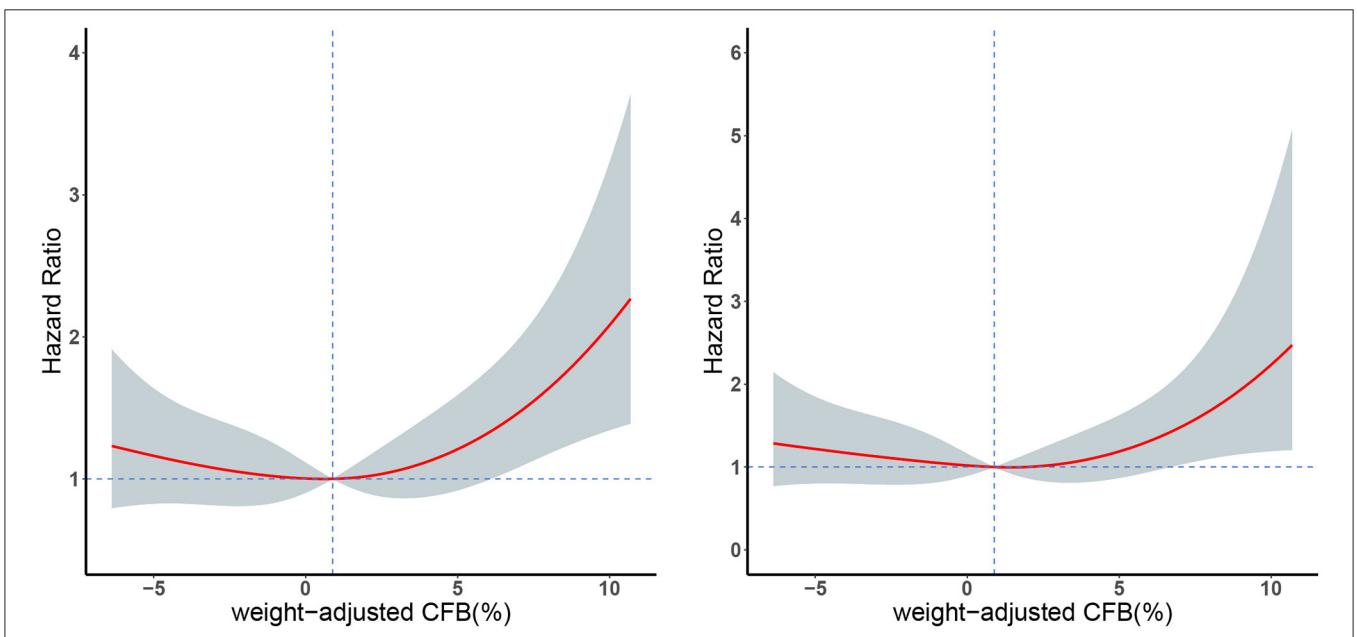

FIGURE 3 | Restricted cubic spline plots of 28-day mortality in patients with different weight-adjusted CFB in an unadjusted Cox model analysis (left) and an adjusted Cox model analysis (right). Red line: hazard ratio, shaded area: 95% CI.

Cox regression models (**Table 4**). In addition, the multivariate Cox model indicated that the 28-day mortality was significantly associated with the female gender, higher SOFA score, and higher eGFR (**Table 4**). We then used a restricted cubic spline procedure to examine the relationship of the *HR* for 28-day all-cause mortality with CFB, which was treated as a continuous variable

TABLE 5 | The cause of death.

Death of cause	All $n = 123$	Negative FB ($n = 57$)	Even FB ($n = 34$)	Positive FB ($n = 32$)	*p* value
Cardiovascular—no. (%)					
Septic shock	41 (33.3)	18 (31.6)	8 (23.5)	15 (46.9)	0.12
Refractory cardiogenic shock	20 (16.3)	12 (21.1)	5 (14.7)	3 (9.4)	0.33
Hypovolemia (bleeding)	15 (12.2)	8 (14.0)	4 (11.8)	3 (9.4)	0.81
Respiratory—no. (%)					
Refractory hypoxia due to ARDS	14 (11.4)	9 (15.8)	2 (5.9)	3 (9.4)	0.33
Pulmonary hemorrhage	5 (4.1)	2 (5.9)	2 (3.5)	1 (3.1)	0.82
Neurological—no. (%)					
Intracranial hemorrhage	2 (1.6)	0 (0.0)	2 (5.9)	0 (0.0)	0.07
Hypoxic encephalopathy	1 (0.8)	0 (0.0)	1 (2.9)	0 (0.0)	0.27
Brain death	4 (3.2)	0 (0.0)	2 (5.9)	2 (6.3)	0.17
Metabolic—no. (%)					
Liver failure	8 (6.5)	2 (3.5)	5 (14.7)	1 (3.1)	0.07
Abandonment of treatment—no. (%)	13 (10.6)	6 (10.5)	3 (8.8)	4 (12.5)	0.89

TABLE 6 | Univariate and multivariate logistic model analysis of factors associated with all-cause mortality at day-28 based on CFB status at 48h.

Variable	Unit	Univariate model		Multivariate model	
		OR (95%CI)	*P*-value	aOR (95%CI)	*P*-value
CFB group	Even FB	1 (reference)			
	Positive FB	3.53 (1.59–7.85)	0.002	3.68 (1.34–10.13)	0.012
	Negative FB	1.61 (0.89–2.89)	0.12	1.80 (0.84–3.89)	0.16
Age	per 1 year older	1.01 (0.99–1.03)	0.14	1.02 (0.99–1.04)	0.06
Male	vs. Female	0.41 (0.23–0.73)	0.002	0.25 (0.20–0.53)	<0.001
BMI	per 1 kg/m^2	0.93 (0.87–0.99)	0.024	0.93 (0.86–1.02)	0.11
APACHE II score	per 1 pt. increase	1.04 (1.00–1.08)	0.036	1.03 (0.97–1.09)	0.29
SOFA score	per 1 pt. increase	1.15 (1.07–1.24)	<0.001	1.15 (1.04–1.27)	0.008
Septic shock	vs. No	4.01 (2.08–7.75)	<0.001	2.64 (1.20–5.80)	0.016
Chronic kidney disease	vs. No	0.47 (0.25–0.87)	0.016	1.11 (0.51–2.42)	0.80
Hospital-acquired infection	vs. Community–acquired infection	2.05 (1.20–3.51)	0.009	2.40 (1.18–4.89)	0.016
eGFR	per 1 ml/min/1.73 m^2 increase	1.01 (1.00–1.03)	0.057	1.01 (0.99–1.03)	0.18
Lactate	per 1 mmol/l increase	1.13 (1.04–1.21)	0.002	1.09 (0.99–1.20)	0.09
Weight-adjusted CFB (%) before CRRT	per 1% increase	1.01 (0.99–1.04)	0.29	0.97 (0.94–1.00)	0.051

(**Figure 3**). There was a marginal J-shaped association between the CFB and 28-day all-cause mortality in the unadjusted model (p for non-linearity = 0.0435), but this relationship was not significant in the adjusted model (p for non-linearity = 0.1165).

In addition, the three groups had no significant differences in all the four secondary outcome measures—RRT dependence in survivors, vasopressor-free days, mechanical ventilation-free days, and length of ICU stay (**Table 3**).

Additionally, we collected detailed data on the cause of death (**Table 5**). Septic shock was the most common cause of death, followed by refractory cardiogenic shock.

Sensitivity Analysis

A logistic regression, with even FB as the comparator, indicated that positive FB was associated with the 28-day mortality (a*OR*: 3.68, 95% *CI*, 1.34–10.13; **Table 6**). This finding confirmed the robustness of our results.

To account for the potential survivorship bias, we used the univariate and multivariate Cox models to analyze the 207 patients who survived beyond 72 h to assess the effect of FB on the 28-day mortality (**Table 7**). Similar to the above results, the positive FB group had greater 28-day mortality than the even FB group, but there was no significant difference between the even FB and negative FB groups.

Furthermore, the positive FB group still had a higher risk of death at 28 days when we used the propensity score as a covariate in the two other sensitivity analyses (**Tables 8**, **9**).

Subgroup Analysis

We performed a subgroup analysis using the univariate and multivariate Cox models to assess the association of CFB with

TABLE 7 | Univariate and multivariate Cox model analysis of factors associated with all-cause mortality at day-28 based on CFB status at 72 h.

Variable	Unit	Univariate model		Multivariate model	
		HR (95%CI)	*P*–value	aHR (95%CI)	*P*–value
CFB group	Even FB	1 (reference)			
	Positive FB	2.81 (1.67–4.73)	<0.001	2.11 (1.17–3.83)	0.014
	Negative FB	1.37 (0.87–2.17)	0.18	0.99 (0.61–1.62)	0.97
Age	per 1 year older	1.09 (0.99–1.01)	0.60	1.01 (1.00–1.03)	0.03
Male	vs. Female	0.51 (0.35–0.75)	0.001	0.44 (0.29–0.68)	<0.001
BMI	per 1 kg/m^2	0.95 (0.91–0.99)	0.021	0.96 (0.90–1.01)	0.13
APACHE II score	per 1 pt. increase	1.02 (0.99–1.05)	0.13	0.99 (0.96–1.03)	0.58
SOFA score	per 1 pt. increase	1.10 (1.05–1.16)	<0.001	1.13 (1.05–1.21)	0.001
Septic shock	vs. No	2.84 (1.60–5.07)	<0.001	1.52 (0.78–2.94)	0.22
eGFR	per 1 ml/min/1.73 m^2 increase	1.01 (1.00–1.02)	0.013	1.01 (1.00–1.02)	0.024
Lactate	per 1 mmol/l increase	1.06 (1.02–1.10)	0.007	1.03 (0.98–1.08)	0.22
Weight-adjusted CFB (%) before CRRT	per 1% increase	1.03 (1.01–1.04)	0.006	1.01 (0.98–1.03)	0.82

TABLE 8 | Univariate and multivariate Cox model analysis of factors associated with all-cause mortality at day-28–propensity score Model 1.

Variable	Unit	Univariate model		Multivariate model	
		HR (95%CI)	*P*–value	aHR (95%CI)	*P*–value
CFB group	Even FB	1 (reference)			
	Positive FB	2.26 (1.39–3.67)	0.001	1.77 (1.04–3.00)	0.034
	Negative FB	1.43 (0.93–2.18)	0.10	1.33 (0.86–2.05)	0.20
Propensity score	per 1 pt	0.12 (0.03–0.50)	0.003	0.20 (0.04–0,87)	0.033

28-day mortality in the patients who had septic shock (**Table 10**). The univariate analysis showed that the positive FB and negative FB groups had higher mortality rates than the even FB group, but only the positive FB group had a greater mortality rate in the multivariate analysis. We conducted another subgroup analysis in the patients with fluid overload at CRRT initiation, in which the fluid overload was defined as a weight-adjusted CFB (from hospital admission to CRRT initiation) more than 5%. In line with the previous results, the positive FB group had a significantly higher mortality rate than the even FB group (**Table 11**).

DISCUSSION

Key Findings

We assessed the prognostic value of early CFB after CRRT initiation in a homogeneous population of patients with septic AKI. The results indicated that the patients with positive FB had a higher risk of 28-day mortality than the patients with even FB, but the patients with negative FB and even FB had similar risks of 28-day mortality. Furthermore, the survivors in the positive FB, even FB, and negative FB groups had no significant differences in the RRT dependence, mechanical ventilation-free days, vasopressor-free days, or length of ICU stay.

Comparisons With the Previous Studies

One of the main concerns in the treatment of patients with AKI undergoing CRRT is providing precise control of FB (27, 28). Hyung et al. reported that the CFB at 24 and 72 h after the initiation of CRRT were significantly higher in the 28-day non-survivors than survivors (19); however, we found no significant difference in CFB between the survivor and non-survivor groups. One possible reason for our disparate results is that we included the patients who had simultaneous sepsis and AKI, and fluid resuscitation was a major step in the management of these patients. The previous studies of patients with AKI reported that a positive FB after CRRT initiation increased the risk of adverse outcomes (18, 20). A secondary analysis of the Randomized Evaluation of Normal versus Augmented Level (RENAL) trial clearly showed that the presence of a mean daily positive FB after RRT initiation, even within the first 48 h of RRT, was independently associated with the higher mortality in the critically ill patients with severe AKI (18). A prospective cohort study that assessed the association of FB in the 7 days after RRT initiation reported similar results (20). The findings of our study are consistent with these previous studies, in that a positive FB is associated with an increased risk of death in the patients with septic AKI undergoing CRRT. A difference in our study is that we used an even FB group (rather than the negative FB group) as a comparator. Additionally, the prior studies measured volume status as mean daily FB after CRRT initiation, whereas we used CFB during the first 48 and 72 h after onset of CRRT. Despite this methodologic difference, we found similar associations between the positive FB and unfavorable outcomes. Thus, the determination of appropriate

TABLE 9 | Univariate and multivariate Cox model analysis of factors associated with all-cause mortality at day-28–propensity score Model 2.

Variable	Unit	Univariate model		Multivariate model	
		HR (95%CI)	*P*-value	aHR (95%CI)	*P*-value
CFB group	Even FB	1 (reference)			
	Positive FB	2.26 (1.39–3.67)	0.001	1.89 (1.07–3.33)	0.027
	Negative FB	1.43 (0.93–2.18)	0.10	1.37 (0.89–2.11)	0.16
Propensity score	per 1 pt	0.31 (0.10–0.94)	0.039	0.57 (0.16–2.01)	0.38

TABLE 10 | Univariate and multivariate Cox model analysis of factors associated with all-cause mortality at day-28 in patients with septic shock based on CFB status at 48 h.

Variable	Unit	Univariate model		Multivariate model	
		HR (95%CI)	*P*-value	aHR (95%CI)	*P*–value
CFB group	Even FB	1 (reference)			
	Positive FB	2.01 (1.26–3.49)	0.004	2.30 (1.24–4.29)	0.009
	Negative FB	1.74 (1.09–2.78)	0.021	1.46 (0.83–2.56)	0.19
Age	per 1 year older	1.01 (0.99–1.02)	0.39	1.01 (0.99–1.02)	0.20
Male	vs. Female	0.55 (0.38–0.81)	0.002	0.52 (0.33–0.82)	0.005
BMI	per 1 kg/m^2	0.97 (0.93–1.01)	0.16	0.98 (0.93–1.04)	0.53
APACHE II score	per 1 pt. increase	1.01 (0.98–1.04)	0.47	1.00 (0.96–1.03)	0.78
SOFA score	per 1 pt. increase	1.07 (1.01–1.12)	0.017	1.08 (1.01–1.16)	0.022
Hospital-acquired infection	vs. Community–acquired infection	1.28 (0.88–1.87)	0.20	1.40 (0.84–2.34)	0.20
eGFR	per 1ml/min/1.73m^2 increase	1.01 (1.00–1.02)	0.16	1.01 (0.99–1.02)	0.07
Lactate	per 1mmol/l increase	1.05 (1.01–1.10)	0.018	1.02 (0.97–1.07)	0.46
Weight-adjusted CFB (%) before CRRT	per 1% increase	1.02 (1.00–1.13)	0.09	1.00 (0.97–1.02)	0.78

fluid management during the RRT is an important topic for future clinical trials.

A recent large retrospective study by Balakumar et al. (26) demonstrated that positive FB and negative FB before RRT initiation were both associated with higher mortality relative to even FB. Furthermore, the present study found that the 28-day mortality in the negative FB group was higher than in the even FB group; however, our univariate and multivariate Cox analysis indicated that negative FB did not significantly increase the risk of all-cause mortality at day-28 relative to even FB. One possible interpretation of these results is that fluid removal using the RRT may provide benefits to some patients because we calculated CFB during the first 48 h after the CRRT initiation. In contrast, Balakumar et al. (26) calculated CFB before RRT initiation. Moreover, we found a marginal J-shaped relationship (rather than a linear relationship) between the 48 h CFB and 28-day mortality in an unadjusted model, although this relationship was not significant in the adjusted model. It is likely that our finding of a negative effect of FB during RRT differed from some previous studies (29, 30) because of differences in the characteristics of patients. In our study, 60% of the patients received vasopressor support at CRRT initiation and 80% experienced septic shock during their ICU stays. The safe achievement of a negative FB during the late phases of septic shock is considered an effective strategy of fluid management (31), and active fluid removal using RRT may cause hemodynamic instability and lead to a worse outcome. Our results may suggest that achieving a negative FB rapidly after CRRT initiation is potentially harmful in patients with septic AKI. Thus, further research is needed to elucidate the benefits and harms associated with the negative FB in these patients.

Our study also evaluated the relationships of CFB and renal recovery in critically ill adults with septic AKI. We found that negative FB and positive FB after CRRT initiation were unrelated to the renal recovery, consistent with the prior studies (20, 26). Our study, thus, confirmed the recent findings that a substantial percentage of RRT-requiring AKI survivors remain dependent on the RRT even after the acute phase of their illness has resolved (20, 32, 33). This serves as a reminder of the need for the measures that protect and restore kidney functions during and after an episode of AKI that necessitates RRT.

Strengths and Limitations

To our knowledge, this is the first study to use an even FB group as a comparator to evaluate the association of CFB status during the CRRT and mortality in patients with septic AKI. Nonetheless, there were several limitations in the current study. First, our study was retrospective, conducted in a single center, and the sample size was relatively small. Thus, the selection bias was possible and we were unable to make causal inferences regarding the FB and outcomes. However, we used propensity

TABLE 11 | Univariate and multivariate Cox model analysis of factors associated with all-cause mortality at day-28 in patients with fluid overload based on CFB status at 48 h.

Variable	Unit	Univariate model		Multivariate model	
		HR (95%CI)	*P*–value	aHR (95%CI)	*P*–value
CFB group	Even FB	1 (reference)			
	Positive FB	2.67 (1.41–5.08)	0.003	2.33 (1.19–4.55)	0.013
	Negative FB	1.81 (0.99–3.31)	0.054	1.15 (0.58–2.27)	0.69
Age	per 1 year older	1.00 (0.99–1.02)	0.90	1.01 (0.99–1.02)	0.48
Male	vs. Female	0.50 (0.31–0.81)	0.005	0.45 (0.26–0.77)	0.004
APACHE II score	per 1 pt. increase	1.03 (0.99–1.06)	0.07	1.01 (0.98–1.05)	0.50
SOFA score	per 1 pt. increase	1.08 (1.02–1.15)	0.009	1.08 (1.00–1.17)	0.042
Septic shock	vs. No	2.71 (1.09–6.73)	0.032	1.41 (0.54–3.70)	0.49
Lactate	per 1mmol/l increase	1.09 (1.04–1.15)	0.001	1.08 (1.02–1.14)	0.007

scores in the sensitivity analysis to reduce the effects of outcome-selection bias. Second, our choice of measuring CFB at 48 h after initiation of CRRT was somewhat arbitrary. Nevertheless, the timing of this assessment varies among the studies, and there is no consensus on the optimal time for this measurement. In addition, our sensitivity analysis of the patients who survived at least 3 days after CRRT initiation produced similar results. Third, although we adjusted for confounding using robust multivariable regression analysis, residual confounding by unknown factors is possible.

CONCLUSION

Our study of critically ill patients with septic AKI indicated that the patients with positive FB after CRRT initiation had an increased risk of 28-day mortality relative to the patients with even FB. Although not statistically significant, we noted a trend toward higher mortality in the patients with negative FB compared with those with even FB, a topic that might warrant further investigation.

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 Bioethics Committee of Beijing Friendship Hospital, Capital Medical University. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

JL and MD designed the study. JL and HZ conducted the statistical analysis, interpreted the results, and critically revised the manuscript. JB, DZ, ZQ, and SL made a substantial contribution to the acquisition of the data. LD conducted the revision for the manuscript. All authors contributed to the manuscript, approved the final version to be considered for publication, and read and approved the final manuscript.

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Application of Near-Infrared Spectroscopy to Monitor Perfusion During Extracorporeal Membrane Oxygenation After Pediatric Heart Surgery

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Objective: Venoarterial extracorporeal membrane oxygenation is an effective mechanical circulatory support that is used to rescue critically ill patients after congenital heart surgery. As there was still no recommended guideline for monitoring parameters during extracorporeal membrane oxygenation (ECMO), this study aimed to investigate the role of near-infrared spectroscopy (NIRS) in the early period of venoarterial (VA)-ECMO.

Method: This study enrolled patients with NIRS monitoring during ECMO after pediatric cardiac surgery at Shanghai Children's Medical Center (2018–2020). The information obtained from the retrospective, the observational dataset included the demographic information, diagnoses, baseline characteristics, procedural details, ECMO data, monitoring data, in-hospital mortality, and complications of the patients.

Results: The overall mortality rate was 43.6%. Lactate was significantly higher in non-survivors compared to survivors at 12 h (11.25 ± 7.26 vs. 6.96 ± 5.95 mmol/l, $p = 0.022$) and 48 h [2.2 (0.7, 20) vs. 1.4 (0.7, 5.8) mmol/l, $p = 0.008$] after initiation of ECMO. The cranial regional oxygen saturation ($CrSO_2$) was significantly higher in survivors compared to non-survivors at 24 h (62.5 ± 14.61 vs. 52.05 ± 13.98%, $p = 0.028$), 36 h (64.04 ± 14.12 vs. 51.27 ± 15.65%, $p = 0.005$), and 48 h (65.32 ± 11.51 vs. 55.00 ± 14.18%, $p = 0.008$). Multivariate logistics regression analysis of the hemodynamic and laboratory parameters revealed that the $CrSO_2$ at 36 h (OR = 0.945, $p = 0.049$) and 48 h (OR = 0.919, $p = 0.032$) was related to mortality. The use of continuous renal replacement therapy (OR = 14.940, $p = 0.039$) was also related to mortality. The optimal cutoff values for $CrSO_2$ for predicting mortality after weaning off ECMO at 36 and 48 h were 57% (sensitivity: 61.5%, specificity: 80%) and 56% (sensitivity: 76.9%, specificity: 70%), respectively. The risk of mortality was higher among patients with a $CrSO_2$(36h)< 57% ($p = 0.028$) by Kaplan-Meier analysis.

Conclusion: Near-infrared spectroscopy may be a useful tool for monitoring the hemodynamic stability during the early period of ECMO, while $CrSO_2$ can predict the in-hospital mortality after ECMO.

Keywords: ECMO perfusion, NIRS, pediatric, heart surgery, mortality

INTRODUCTION

Extracorporeal membrane oxygenation is an effective method for the management of refractory cardiogenic shock (1). It is a life-saving procedure in the event of failure of other conventional therapies. Recent advancements in technology have expanded its applications to more complex diseases, including congenital heart disease (CHD) in children. Extracorporeal membrane oxygenation (ECMO) has been used in increasingly complicated cases of pediatric CHD during the early postoperative risk stage after open heart surgery in recent years. It was reported that up to 2–5% of all children undergoing cardiac surgery require mechanical cardiac support with ECMO during the postoperative period (2). Unlike adults, the body weight and blood volume vary over a wide range in children. Therefore, the clinical management of ECMO presents a huge challenge in children.

A variety of hemodynamic monitoring methods, including the pulse contour cardiac output and other invasive monitoring modalities, cannot be applied during the period of ECMO assistance. In 1977, Jobsis first used near-infrared spectroscopy (NIRS) for monitoring cerebral oxygen levels (3). The recent technological advancement in optical instruments and improvement in light propagation in tissues has facilitated the use of multisite NIRS technology for noninvasive and continuous monitoring of oxygen saturation in the brain and body tissue in clinical practice to facilitate real-time monitoring of blood and oxygen supply to the organs (4–6). Traditional monitoring parameters, such as blood pressure, cannot adequately reflect the oxygenation state of the brain and abdominal microcirculation, especially for the non-pulsatile blood flow generated by ECMO. The abnormalities in systemic oxygen balance can be detected through the monitoring of systemic venous oxygen saturation (SvO_2), lactic acid, and noninvasive multisite NIRS (7). But the blood gas tests require frequent blood sampling which would cause anemia and cannot realize the real time. Thus, this study aimed to study the noninvasive monitoring parameters during ECMO after pediatric heart surgery related to organ perfusion and mortality and explore the clinical significance of multi-channel NIRS monitoring during the period of ECMO assistance.

MATERIALS AND METHODS

Study Population

This retrospective study included children who underwent cardiac surgery between January 1, 2018, and December 31, 2020, and was approved by the medical ethics committee of Shanghai Children's Medical Center, School of Medicine, Shanghai Jiaotong University. The cerebral and abdominal oxygenation monitoring data were available for 56 of 124 patients who underwent venoarterial (V-A) ECMO. One patient was found with congenital hypertrophic cardiomyopathy with NIRS monitoring and was excluded. Therefore, a final total of 55 cases were included in this study. The participants were under 18 years of age. Any death occurring before hospital discharge was designated as death after weaning off ECMO. Congenital heart surgery was defined as any surgical procedure for a cardiac defect with or without cardiopulmonary bypass (CPB). ECMO was implemented immediately after surgery in the operating room, after cardiopulmonary resuscitation in the cardiac intensive care unit (CICU), or selectively due to circulatory instability in the CICU.

Data Collection

The information obtained from the retrospective, observational dataset included the demographic information, diagnoses, baseline characteristics, procedural details, ECMO data, monitoring data, in-hospital mortality, and complications of patients. The CICU monitoring indices included blood pressure, central venous pressure (CVP), blood gas, and lactic acid.

Near-infrared spectroscopy monitoring (INVOS5100C, Covidien, USA) was conducted by affixing the head electrode approximately 1 cm above the eyebrow arch on the left or right side to measure the cranial regional oxygen saturation ($CrSO_2$). The abdominal electrode was generally attached above or below the umbilicus to obtain the mesenteric regional oxygen saturation ($MrSO_2$). The electrodes are used according to body weight, that is, <5, 5–40, and ≥ 40 kg.

ECMO Management

Extracorporeal membrane oxygenation was implanted by a central cannulation way, and a left atrium drainage tube was placed in patients with insufficient intracardial shunting. Arterial blood pressure was maintained within the normal range of mean arterial pressure for different age groups. The pump inlet pressure exceeded -20 mmHg, and the outlet pressure was within 200 mmHg. The activated partial thromboplastin time (APTT), activated clotting time (ACT), and anti-Xa were monitored for anticoagulation. The target ACT value was 140–180 s, and the standard APTT and anti-Xa values were 40–80 s and 0.3–0.8 IU/ml, respectively. The ventilator was set to the pressure-regulated volume control mode with a positive end-expiratory pressure of 10 mmHg, tidal volume of 6–8 ml/kg, and respiratory rate of 10–12 bpm. Enteral nutrition was supplied to patients without obvious contraindications such as gastrointestinal bleeding, storage, or $MrSO_2$ $<35\%$. Diuretics were administered as soon as the ECMO flow was stabilized to prevent fluid overload.

Statistical Analysis

All data were analyzed using SPSS 22.0 (IBM, Armonk, NY, USA). Data with normal distribution were presented as the mean ± SD. Abnormally distributed values were presented as the median and range (minim, max). The medians of the two groups were compared using the Mann-Whitney U test. Categorical data were represented as frequencies and percentages and were evaluated using the chi-squared test. Multivariable logistics regression models explored meaningful variables to predict mortality. The receiver operating characteristic (ROC) was used to determine the cut-off value of the monitoring index to distinguish between survivors and non-survivors. Kaplan-Meier analysis was used to analyze the survival between different subgroups according to the $CrSO_2$. $P < 0.05$ was considered statistically significant.

TABLE 1 | Diagnosis of patients with extracorporeal membrane oxygenation (ECMO).

Diagnosis	Number
Transposition of great arteries	10
Aortic valve stenosis	7
Pulmonary atresia	6
Double outlet right ventricle	6
Ventricular septum defect	5
Interruption of the aortic arch	3
Ebstein's malformation	3
Mitral stenosis	3
Patent ductus arteriosus	3
Coarctation of the aorta	3
Anomalous left coronary artery from the pulmonary artery	2
Tetralogy of Fallot	1
Single ventricle	1
Total anomalous of pulmonary venous connection	1
Complete atrioventricular canal	1

RESULTS

Among the 55 patients, there were 16 types of CHD (**Table 1**). The first three types were transposition of the great arteries (TGA) ($n = 10$, 18.1%), pulmonary atresia (PA) ($n = 6$, 10.9%), and double outlet right ventricle ($n = 6$, 10.9%). Although there were some simple cases of CHD, such as ventricular septum defect, most of these patients had heart dysfunction or extracardiac problems before the procedure. Palliative surgery was performed in 22% of patients, including three patients with Ebstein's malformation, two patients with TGA, two with Tetralogy of Fallot, one with PA with intact ventricular septal, one with PA with VSD, and one patient with a single ventricle.

Twenty-four patients died and the overall mortality was 43.6%. The causes of the death included heart failure ($n = 7$), multiple organ dysfunction ($n = 6$), residual anatomy ($n = 5$), pulmonary hypertension ($n = 3$), brain death ($n = 2$), and sepsis ($n = 1$).

No significant differences were observed between the age, sex, CPB time, and aortic cross-clamp (ACC) time of the survivors and non-survivors (**Table 2**). Significant differences were not observed in the number of patients who underwent different ECMO protocols, i.e., after cardiopulmonary resuscitation (ECPR) ($p = 0.214$) or in the operating room (OR) ($p = 0.595$). There was no significant difference in proportion between cyanotic CHD and non-cyanotic CHD ($p = 0.551$). The ECMO flow was higher among the neonatal non-survivors than that in the survivors (156.73 ± 8.71 vs. 124.48 ± 10.10 ml/kg/min, $p = 0.001$). But there is no significant difference between the neonates and infants in the $CrSO_2$ (68.23 ± 11.40 vs. 64.93 ± 8.96%, $p = 0.402$). There were more

TABLE 2 | Comparison of the clinical characteristics between survivors and non-survivors.

	Total ($N = 55$)	Survivors ($N = 31$)	Non-survivors ($N = 24$)	P
Age (months)	3 (0.03, 189.5)	3 (0.03, 189.5)	2.72 (0.17, 171.33)	
Sex (Female/Male)	21/34	11/20	10/14	0.640
CPB (min)	202.14 ± 135.55	199.86 ± 131.08	205.14 ± 144.28	0.892
ACC (min)	90.96 ± 60.11	80.37 ± 51.58	106.00 ± 69.17	0.157
ECPR	18	8	10	0.214
OR	23	12	11	0.595
Cyanotic/non-cyanotic	30/25	18/13	12/12	0.551
CRRT	8	1	7	0.007*
ECMO duration (h)	112.20 ± 73.44	91.74 ± 40.12	138.64 ± 96.27	0.033*
ECMO flow (ml/kg/min)				
Neonates ($n = 10$)	140.61 ± 19.18	124.48 ± 10.10	156.73 ± 8.71	0.001*
Infants /children (45)	113.34 ± 28.15	112.91 ± 25.75	109.20 ± 31.75	0.668
TΔp (h)	45.99 ± 35.90	38.18 ± 28.95	59.44 ± 43.10	0.044*

*CPB, cardiopulmonary bypass; ACC, arterial cross-clamp; ECPR, cardiopulmonary resuscitation; OR, operating room; CRRT, continuous renal replacement therapies; TΔp, time to achieve pulse pressure 10 mmHg. *p < 0.05.*

patients who received continuous renal replacement therapies (CRRT) ($p = 0.007$). The duration of ECMO was longer in the non-survivor group ($p = 0.033$). The time required to achieve pulse pressure >10 mmHg was shorter in the survivor group than that in the non-survivor group (38.18 ± 28.95 vs. 59.44 ± 43.10 h, $p = 0.044$).

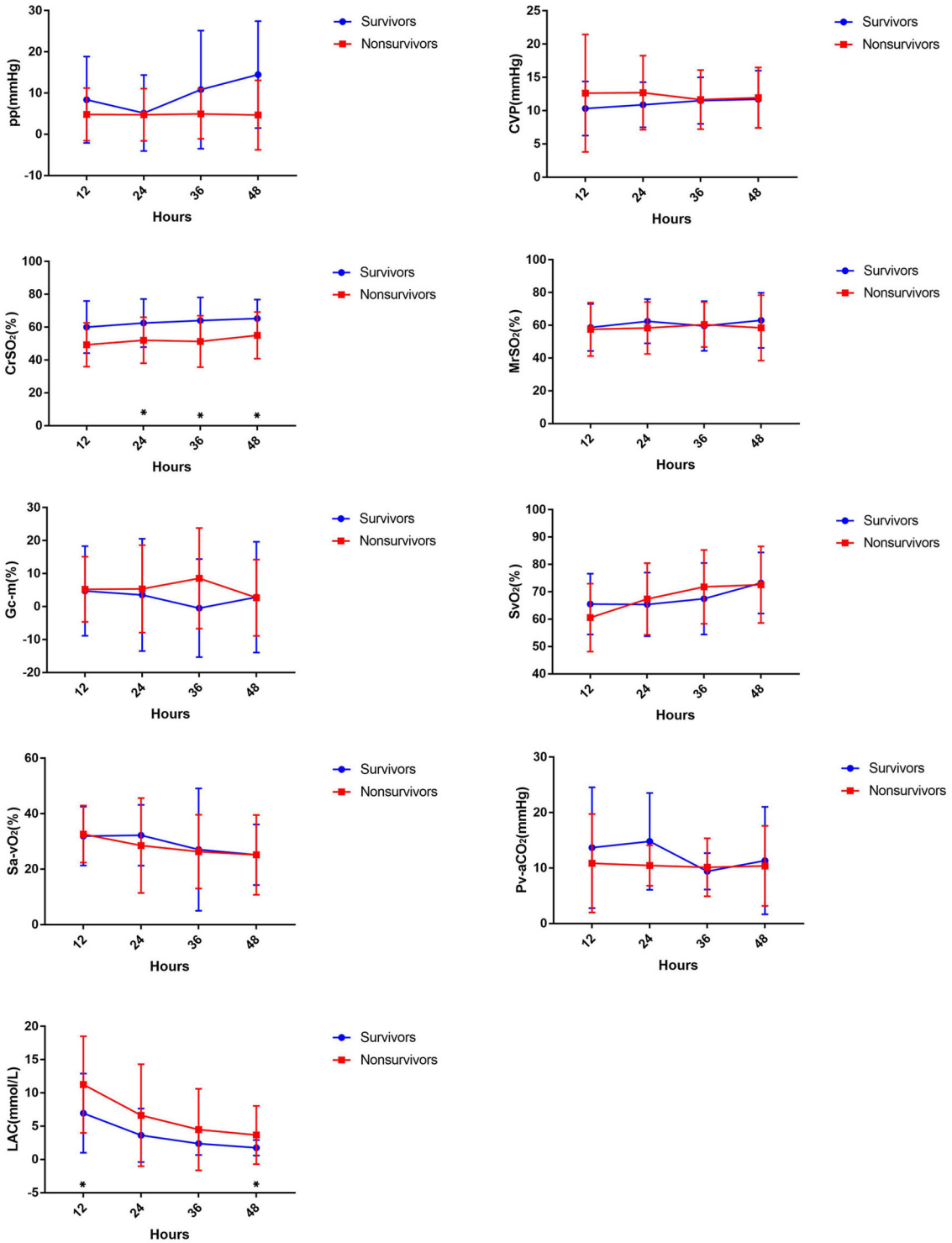

FIGURE 1 | Comparing hemodynamic parameters in the first 48 h between survivors and non-survivors during ECMO.

TABLE 3 | Comparison between the monitoring parameters of survivors and non-survivors.

	Total ($N = 55$)	Survivors ($N = 31$)	Non-survivors ($N = 24$)	*P*-value
ECMO-12 h				
mABP (mmHg)	58.56 ± 15.59	59.00 ± 12.26	58.00 ± 19.34	0.816
CVP (mmHg)	11.38 ± 6.72	10.32 ± 4.06	12.63 ± 8.82	0.221
CrSO2 (%)	54.68 ± 15.38	60.07 ± 15.87	49.29 ± 13.31	0.062
MrSO2 (%)	58.11 ± 15.09	58.71 ± 14.34	57.50 ± 16.32	0.836
Gc-m (%)	5.93 (−18, 30)	5.51 (−18,30)	6 (−8.8,27)	0.927
SvO2 (%)	63.34 ± 11.71	65.51 ± 1.10	60.58 ± 12.40	0.306
Sa-vO2 (%)	32.24 ± 10.25	31.94 ± 10.61	32.63 ± 10.28	0.870
Pv-aCO2 (%)	12.44 ± 9.95	13.68 ± 10.89	10.87 ± 8.88	0.496
Lac (mmol/l)	8.74 ± 6.80	6.96 ± 5.95	11.25 ± 7.26	0.022*
ECMO-24 h				
mABP (mmHg)	59.98 ± 16.74	62.00 ± 14.99	57.38 ± 18.76	0.314
CVP (mmHg)	11.68 ± 4.52	10.88 ± 3.40	12.70 ± 5.55	0.152
CrSO2 (%)	57.41 ± 15.07	62.5 ± 14.61	52.05 ± 13.98	0.028*
MrSO2 (%)	60.49 ± 14.59	62.47 ± 13.46	58.39 ± 15.81	0.402
Gc-m (%)	2 (−0.26, 41)	−2 (−14, 41)	6 (−26, 24)	0.499
SvO2 (%)	66.16 ± 15.06	65.40 ± 11.61	67.37 ± 13.09	0.639
Sa-vO2 (%)	30.79 ± 13.57	32.23 ± 10.96	28.52 ± 17.11	0.432
Pv-aCO2 (%)	13.13 ± 7.44	14.46 ± 3.66	10.46 ± 3.66	0.047
Lac (mmol/l)	2.8 (0.8, 28)	2.3 (0.8, 19)	3.4 (0.9, 28)	0.107
ECMO-36 h				
mABP (mmHg)	63.17 ± 15.76	64.25 ± 14.62	61.26 ± 16.97	0.449
CVP (mmHg)	11.57 ± 3.90	11.51 ± 3.51	11.65 ± 4.44	0.897
CrSO2 (%)	58.06 ± 16.04	64.04 ± 14.12	51.27 ± 15.65	0.005*
MrSO2 (%)	60.00 ± 14.32	59.60 ± 15.11	60.48 ± 13.69	0.839
Gc-m (%)	67.6 (33, 95.4)	−3.1 (−22.2, 30.4)	8.25 (−20.2, 44.3)	0.097
SvO2 (%)	69.45 ± 13.28	67.48 ± 13.05	71.81 ± 13.49	0.288
Sa-vO2 (%)	26.72 ± 18.40	27.06 ± 22.04	26.32 ± 13.31	0.896
Pv-aCO2 (%)	9.74 ± 4.23	9.42 ± 3.27	10.13 ± 5.22	0.584
Lac (mmol/l)	3.28 ± 4.28	2.38 ± 1.71	4.49 ± 6.13	0.122
ECMO-48 h				
mABP (mmHg)	63.81 ± 12.32	66.07 ± 12.25	60.73 ± 12.01	0.124
CVP (mmHg)	11.82 ± 4.36	11.71 ± 4.30	11.95 ± 4.54	0.8445
CrSO2 (%)	60.61 ± 13.68	65.32 ± 11.51	55.00 ± 14.18	0.009*
MrSO2 (%)	61.00 ± 18.23	63.04 ± 16.84	58.45 ± 19.97	0.407
Gc-m (%)	6 (−25, 29)	2 (−25, 29)	6 (−19, 19)	0.987
SvO2 (%)	72.94 ± 12.28	73.20 ± 11.15	72.59 ± 13.99	0.871
Sa-vO2 (%)	25.18 ± 12.34	25.20 ± 10.92	25.15 ± 14.37	0.99
Pv-aCO2 (%)	10.94 ± 8.65	11.35 ± 9.68	10.39 ± 7.21	0.720
Lac (mmol/l)	1.7 (0.7, 20)	1.4 (0.7, 5.8)	2.2 (0.7, 20)	0.008*

*mABP, mean arterial blood pressure; CVP, central venous pressure; $CrSO_2$, cranial regional oxygen saturation; $MrSO_2$, mesenteric regional oxygen saturation; Gc-m, gap of $CrSO_2$ and $MrSO_2$(calculated by $CrSO_2$ minus $MrSO_2$); SvO_2, mixed venous saturation; Sa-vO_2, arteriovenous difference of partial pressure of oxygen; Pv-aCO_2, venoarterial difference of partial pressure of carbon dioxide. *$p < 0.05$.*

The changes in monitoring indicators during ECMO are shown in **Figure 1**. Lactate levels were significantly higher in non-survivors compared to the survivors at 12 h (11.25 ± 7.26 vs. 6.96 ± 5.95 mmol/l, $p = 0.022$) and 48 h [2.2 (0.7, 20) vs. 1.4 (0.7, 5.8) mmol/l, $p = 0.008$]. The $CrSO_2$ was significantly higher in survivors compared to non-survivors at 24 h (62.5 ± 14.61 vs. 52.05 ± 13.98%, $p = 0.028$), 36 h (64.04 ± 14.12 vs. 51.27 ± 15.65%, $p = 0.005$), and 48 h (65.32 ± 11.51 vs. 55.00 ± 14.18%, $p = 0.008$) (**Figure 1** and **Table 3**).

Multivariate logistics regression analysis for the hemodynamic and laboratory parameters revealed that the $CrSO_2$ at 36 h (OR = 0.945, $p = 0.049$) and 48 h (OR = 0.919, $p = 0.032$) was related to mortality. Besides, CRRT (OR = 14.940, $p = 0.039$) was also related to mortality (**Table 4**).

TABLE 4 | Multivariate logistics regression analysis of the hemodynamic monitoring indices during ECMO and their association with mortality.

	OR	95%	*P*
ECMO 12 h			
$CrSO_2$ (%)	0.885	0.778–1.007	0.064
Lac (mmol/l)	0.969	0.763–1.230	0.795
CRRT	20.278	0.709–579.616	0.079
TΔp (h)	1.051	0.998–1.106	0.060
ECMO 24 h			
$CrSO_2$ (%)	0.950	0.887–1.017	0.138
Lac (mmol/l)	1.068	0.850–1.341	0.572
CRRT	8.879	0.606–130.038	0.111
TΔp (h)	1.023	0.997–1.049	0.081
ECMO 36 h			
$CrSO_2$ (%)	0.945	0.893–0.999	0.049*
Lac (mmol/l)	0.99	0.760–1.290	0.941
CRRT	10.687	0.890–128.329	0.062
TΔp (h)	1.016	0.994–1.038	0.149
ECMO 48 h			
$CrSO_2$ (%)	0.919	0.850–0.993	0.032*
Lac (mmol/l)	1.056	0.564–1.977	0.864
CRRT	14.940	1.148–194.460	0.039*
TΔp (h)	1.011	0.990–1.034	0.302

*$CrSO_2$, cranial regional oxygen saturation; CRRT, continuous renal replacement therapies; TΔp, time to achieve pulse pressure 10 mmHg. *p < 0.05.*

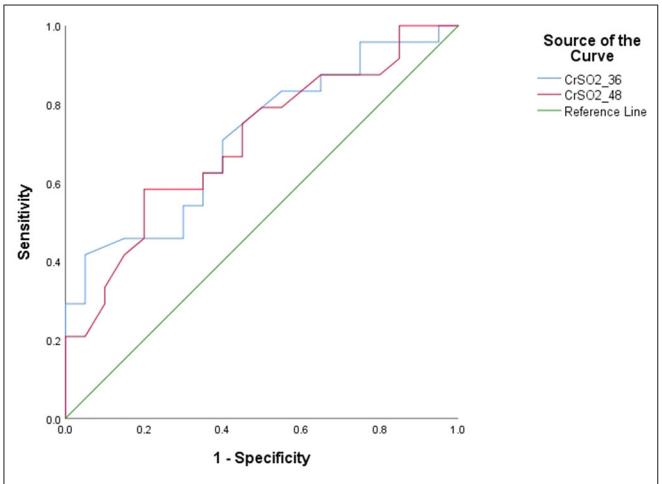

FIGURE 2 | Receiver operating characteristic curves (ROC) of CrSO2 (36 h) and CrSO2 (48 h) between survivors and non-survivors.

The area under the ROC curve was 0.769 ($p = 0.03$) for $CrSO_2$ at 36 h and 0.758 ($p = 0.038$) at 48 h (**Figure 2**). The optimal cutoff value for $CrSO_2$ for the prediction of mortality after weaning off ECMO was 57% at 36 h (sensitivity: 61.5%, specificity: 80%) and 56% at 48 h (sensitivity: 76.9%, specificity: 70%) (**Table 5**).

The risk of mortality was higher among patients with a $CrSO_2$(36h)< 57% ($p = 0.028$) by Kaplan-Meier analysis. However, there was no difference in the mortality with $CrSO_2$ (48 h) <56% ($p = 0.103$) (**Figure 3**).

DISCUSSION

Recent technological advancements have led to dramatic improvements in the prognosis of patients undergoing treatment with ECMO. In children, the assessment of organ perfusion using flow alone is limited due to differences in body weight and vascular volume. Therefore, enhanced tissue perfusion monitoring is essential during ECMO. However, no guidelines exist for the monitoring parameters for VA-ECMO.

Lactate, a routine ECMO monitoring indicator, was found to be associated with prognosis in this study. Park et al. (8) have reported that the appropriate cut-off values for predicting mortality were 7.05 mmol/L at 6 h, 4.95 mmol/L at 12 h, and 4.15 mmol/L at 24 h. Kim et al. (9) revealed that survivors had mean lactate levels of 3.85 mmol/L after the first day (vs. 10.69 mmol/L among non-survivors) and that the optimal cutoff value was 4.66 mmol/L (sensitivity: 75%, specificity: 75%). Our study also found a significant difference in the blood lactate level between survivors and non-survivors. In our study, lactate levels were significantly higher in non-survivors compared to survivors at 12 h (11.25 ± 7.26 vs. 6.96 ± 5.95 mmol/l, $p = 0.022$) and 48 h [2.2 (0.7, 20) vs. 1.4 (0.7, 5.8) mmol/l, $p = 0.008$], but no significant difference was observed on multivariate logistic regression, which meant that lactate was not a predictor of mortality.

There were no significant differences between the survival and non-survival groups in other routine monitoring measures, such as SvO_2, Sa-vO_2, and Pv-aCO_2, which can be used to assess circulation state and discriminate shock. A study that investigated infants with CHD postoperatively showed that the sensitivity and specificity of Pv-$aCO_2 \geq 12.3$ mmHg in predicting oxygen supply/oxygen consumption ≤ 2 were 78.6 and 82.1%, respectively (10).

The area under the ROC curve was 0.769 ($p = 0.03$) for $CrSO_2$ at 36 h and 0.758 ($p = 0.038$) at 48 h. The optimal cutoff values for $CrSO_2$ for the prediction of mortality after weaning off ECMO was 57% at 36 h (sensitivity: 61.5%, specificity: 80%) and 56% at 48 h (sensitivity: 76.9%, specificity: 70%). Similarly, Tsou et al. (11) showed that any regional oxygen saturation index (rSO_2) levels $\leq$ 50% were associated with unfavorable outcomes at hospital discharge [multivariable-adjusted odds ratio (OR), 2.82 (95% CI: 1.10–7.25)]. Kim et al. also showed the optimal cutoff values for right-sided and left-sided $CrSO_2$ for predicting mortality were 58% (sensitivity: 78.7%, specificity: 83.3%) and 57% (sensitivity: 80.0%, specificity: 70.8%), respectively (9).

Previous studies have found that the differences in cerebral and abdominal oxygen possess a certain clinical significance in assessing perfusion (12–14). Generally speaking, abdominal oxygen varied in a wide range and decreased when cardiac output was reduced. Therefore, the larger the difference between cerebral and abdominal oxygen is, the poorer the prognosis is. We compared the $MrSO_2$ between the survival and non-survival groups. However, there was no significant difference in the $MrSO_2$ or the gap between $CrSO_2$ and $MrSO_2$. This may be

TABLE 5 | Cut-off of $CrSO_2$ for the prediction of mortality.

	Area under the curve	*P*-value	Cutoff (%)	Sensitivity (%)	Specificity (%)
$CrSO_2$ (36 h)	0.769	0.030	57	61.5	80
$CrSO_2$ (48 h)	0.758	0.038	56	76.9	70

$CrSO_2$, cranial regional oxygen saturation.

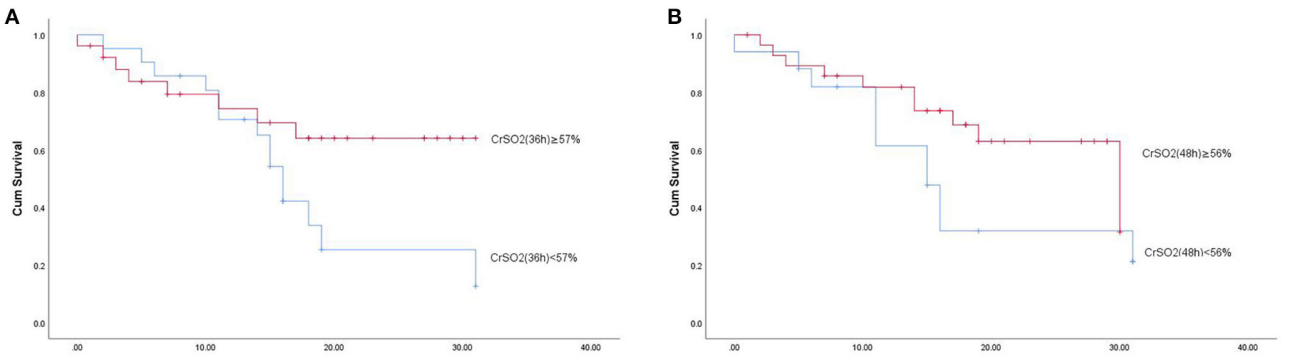

FIGURE 3 | Kaplan-Meier analysis according to CrSO2 (36 h) and CrSO2 (48 h) between survivors and non-survivors.

related to the variation in abdominal oxygen in children, which is susceptible to the influence of abdominal bloating, peritoneal dialysis, and urine retention.

Similarly, our study showed that CRRT (OR = 14.940, $p = 0.039$) was related to mortality, as reported by some previous studies (15–18). Acute kidney injury (AKI) was a common occurrence in patients receiving ECMO after congenital heart surgery, and some studies have demonstrated an association between AKI and mortality (15, 16). Pilar et al. (17) found that the use of CRRT during ECMO was associated with higher mortality (OR: 6.12, $p = 0.06$). A systematic review conducted by Chen et al. (18) also showed higher mortality (OR: 5.89, $p < 0.0001$) and longer ECMO duration in patients requiring CRRT while on ECMO support. However, the drawback of the study was that kidney regional saturation was not monitored by NIRS due to the difficulty of the electrode adhesion to the costovertebral angle for children implanted ECMO in a central cannulation way.

Our study has some other limitations. First, statistical bias was inevitable owing to the retrospective design of the study. Further study should be applied in a proper prospective randomized way. Second, the changes in brain oxygen caused by brain injury were not excluded using computed tomography or magnetic resonance imaging. Finally, the study focused more on monitoring during ECMO and failed to analyze the data before and after ECMO initiation.

In conclusion, cerebral oxygen monitoring has important clinical significance as a non-invasive real-time monitoring technique for assessing perfusion and prognosis. Therefore, NIRS may be instrumental for monitoring the hemodynamic stability during the early period of ECMO, and cranial regional oxygen saturation ($CrSO_2$) could predict hospital mortality after weaning patients off ECMO. However, more studies should be performed to validate the clinical significance of NIRS in children with ECMO after cardiac surgery.

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.

AUTHOR CONTRIBUTIONS

MZ and XC: statistics and drafting of the article. YY and YS: data collection. LZ and XG: data interpretation. ZX and HZ: concept and design. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Bronchoscopy-Guided Intervention Therapy With Extracorporeal Membrane Oxygenation Support for Relapsing Polychondritis With Severe Tracheobronchomalacia: A Case Report and Literature Review

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Relapsing polychondritis is an immune disorder of unknown etiology involving multiple systems that is characterized by persistent inflammation and destruction of cartilage, including the ears, nose, costal, joint, and airways. Airway involvement caused by relapsing polychondritis is common, and tracheobronchomalacia is the most serious complication, which is life-threatening. Currently, the exact mechanism of relapsing polychondritis with tracheobronchomalacia is unknown. Although glucocorticoids and immunosuppressive agents are administered, failures often occur. Currently, bronchoscopy-guided intervention therapy used in tracheobronchomalacia caused by chronic obstructive pulmonary disease or other etiology has gradually increased, but bronchoscopy-guided intervention therapy with extracorporeal membrane oxygenation assist used in tracheobronchomalacia caused by relapsing polychondritis has not been reported. Here, we report a case of relapsing polychondritis with severe tracheobronchomalacia. Although drug therapy was provided and airway stent implantation was performed, the tracheal stenosis was further aggravated. Because conventional anesthesia and mechanical ventilation cannot meet the needs of bronchoscopy-guided intervention therapy or guarantee sufficient safety. The intervention treatment was performed with the support of extracorporeal membrane oxygenation, which was successfully completed without obvious complications. The symptoms were significantly improved, and the patient was discharged uneventfully.

Keywords: extracorporeal membrane oxygenation, relapsing polychondritis, tracheobronchomalacia, severe airway stenosis, bronchoscopy, interventional therapy

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INTRODUCTION

Relapsing polychondritis (RP) is a rare immune disorder involving multiple systems, in which the cartilage is the main target organ. The literature shows that at least 50% of RP cases involve the airway cartilage, among which tracheobronchomalacia (TBM) is the most serious complication (1). Currently, the mechanism of TBM caused by RP remains unclear; there is a lack of effective therapeutic drugs and the prognosis is extremely poor. Although glucocorticoids and immunosuppressants are often empirically recommended as first-line treatments, their clinical efficacy is often unsatisfactory. Despite the gradual increase in reports of new technologies such as stents and tracheobronchoplasty applied to TBM caused by chronic obstructive pulmonary disease (COPD) or other etiologies (2, 3), bronchoscopy-guided interventional therapy with extracorporeal membrane oxygenation (ECMO) support used in TBM caused by RP has not been reported. Here, we report a case of RP with severe TBM. Although glucocorticoids were administered according to the guidelines, the condition continued to worsen. Subsequently, the patient's symptoms and lung function significantly improved after the airway stent was implanted. However, as the disease progressed, severe stenosis appeared again from the subglottis to the upper segment of the tracheal stent. As conventional anesthesia and mechanical ventilation could not guarantee the safety of the operation, bronchoscopy-guided intervention was performed under the support of venous-venous (VV)-ECMO and was successful. After the treatment, the spirometry test showed improvement, and symptoms such as cough, shortness of breath, and hypoxia were significantly relieved.

CASE PRESENTATION

The patient was a 60-year-old worker with repeated cough and dyspnea for ∼10 years. The patient had a smoking history of 20 pack-years for 30 years and had chronic obstructive pulmonary disease and pulmonary bullae. Usually, these symptoms can be controlled using bronchodilators and inhaled corticosteroids; however, the dyspnea, cough, and sputum expectoration of the patient gradually worsened. The patient was admitted to our hospital for the first time due to sudden shortness of breath 1.5 years ago. Physical examination showed that the patient was thin, had clubbing digits, a slightly collapsed bridge of the nose, and had stunted auricles (**Figures 1A–C**). The chest was in a typical barrel shape, the intercostal space was widened, the breath sounds were lower, and wet rales can be heard in both lower lungs. Chest computed tomography (CT) showed reduced tracheal lumen, thickened tracheal wall, emphysema, and bilateral lung infections (**Figures 2A–C**). Pulmonary function tests revealed severe mixed ventilatory dysfunction, which was mainly obstructive, with a slight decrease in diffusion function (**Figure 2H**). Blood gas analysis suggested type 2 respiratory failure. Routine blood tests showed that white blood cells, neutrophils, and C-reactive protein were significantly elevated, suggesting an infection in the lungs. Although low-flow oxygen (2 L/min), antibiotics, glucocorticoids, and bronchodilators were administered, the patient's symptoms were not significantly relieved. A chest CT scan including the inspiratory and expiratory phases showed that the lumen of the trachea and main bronchus severely collapsed at the end of expiration compared with inspiration (**Figures 2D–G**). Subsequently, bronchoscopy showed that the mucosa of the trachea and main bronchi were severely hyperemic and swollen, and the cartilage had disappeared (**Figures 3A–G**). Although the lumen was normal during inhalation, the tracheal membrane protruded into the lumen during exhalation, resulting in the complete collapse of the lumen, and inability to eliminate secretions; these changes were not seen in the distal airway. A diagnosis of RP with TBM was highly suspected. Subsequently, a biopsy of the patient's auricular cartilage was performed. Pathology reports showed multiple necrotic chondrocytes accompanied by inflammatory cell infiltration (**Figure 1D**). Finally, the diagnosis was clear and consistent with our hypothesis. Subsequently, three nickel–titanium alloy coated memory stents were implanted in the trachea and bilateral main bronchus under local anesthesia (**Figures 2I–K**). Pulmonary function tests revealed moderate mixed ventilatory dysfunction, which was mainly obstructive, with a slight decrease in diffusion function (**Figure 2L**). Prednisone (1 mg/kg) was continued, and the patient was discharged. The patient was readmitted to our hospital for worsening dyspnea 1 year ago. Chest CT showed an unobstructed trachea and bilateral main bronchus, the stent was well-fixed, and the subglottis and upper part of the stent were slightly narrowed (**Figures 2M–Q**). Bronchoscopy showed that the lumen of the subglottis to the upper segment of the tracheal stent was narrow, the mucosa was severely swollen, cartilage had disappeared, and granulation hyperplasia was present (**Figures 3H–L**). The narrow lesion was significantly

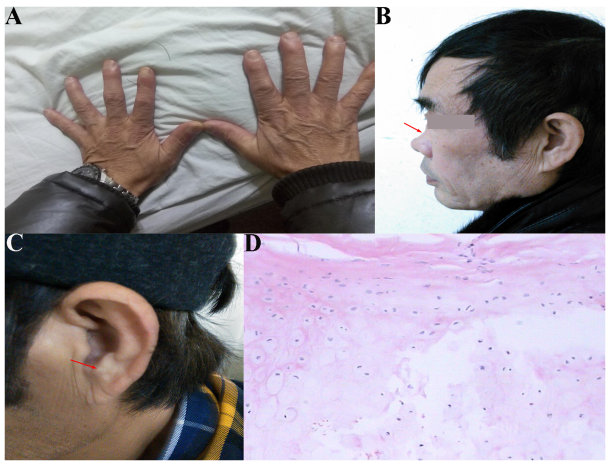

FIGURE 1 | (A) Clubbing digits; **(B)** collapsed of the bridge of the nose (red arrow); **(C)** stunted auricles (red arrow); **(D)** pathology showed multiple necrosis of ear chondrocytes accompanied by inflammatory cell infiltration.

Abbreviations: CT, computed tomography; ECMO, extracorporeal membrane oxygenation; RP, relapsing polychondritis; TBM, tracheobronchomalacia; ACT, activated clotting time.

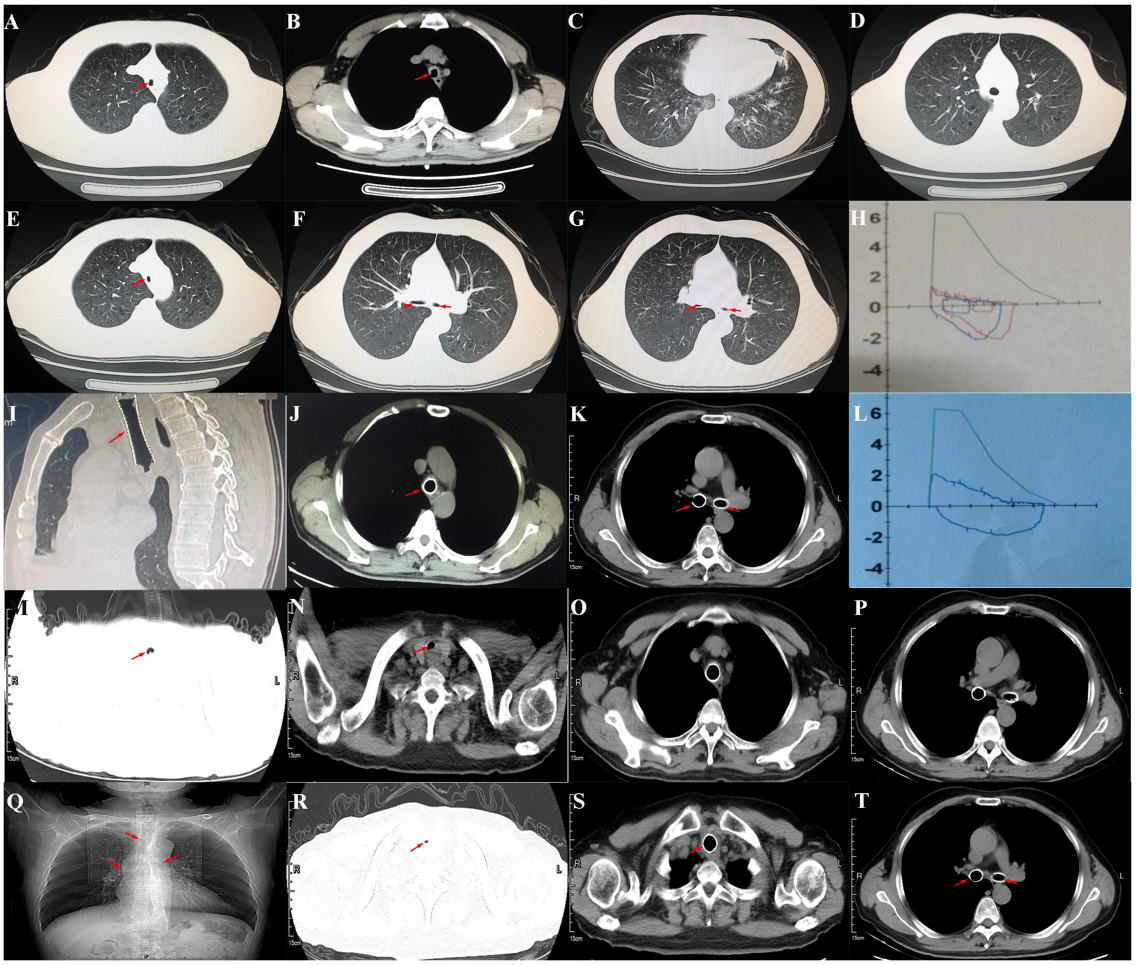

FIGURE 2 | (A) Chest CT showed reduced tracheal lumen (red arrow); **(B)** thickened tracheal wall (red arrow); **(C)** emphysema and bilateral lung infections; **(D)** the lumen of trachea during the inspiratory phase (red arrow); **(E)** the lumen of trachea during the expiratory phase (red arrow); **(F)** the lumen of both mainstem bronchus during the inspiratory phase; **(G)** the lumen of both mainstem bronchus during the expiratory phase; **(H)** pulmonary function tests revealed severe mixed ventilatory dysfunction, which was mainly obstructive; **(I–K)** after the covered nickel-titanium memory alloy stent was implanted, the lumen was unobstructed (red arrow); **(L)** pulmonary function tests revealed moderately mixed ventilatory dysfunction, which was mainly obstructive; **(M,N)** chest CT showed that the lumen of subglottis to the upper of the stent was slightly narrowed (red arrow); **(O,P)** the stents were well fixed; **(R)** chest CT showed that the lumen of subglottis to the upper of the stent was severely narrowed; **(Q,S,T)** the stents were well fixed (red arrow).

improved after bronchoscopy-guided argon plasma coagulation, and CO_2 cryoablation was performed, which significantly relieved the patient's symptoms (**Figures 3M–P**). The patient was administered prednisone (1 mg/kg). Six months ago, the patient was readmitted to our hospital because of sudden dyspnea. Emergency chest CT and bronchoscopy showed granulation hyperplasia and scar tissue in the lumen of the subglottis to the upper segment of the tracheal stent, hyperemia and swelling of the mucosa, and a large amount of thick sputum blockage in the lumen, resulting in severe narrowing of the lumen (**Figures 2R**, **3Q**). To avoid the risk of major airway bleeding and asphyxia during bronchoscopy under conventional ventilation, we decided to perform bronchoscopy-guided interventional therapy with VV-ECMO using a heparin-coated membrane lung.

We first percutaneously inserted a 22-Fr cannula into the left femoral vein and a 16-Fr venous cannula into the right internal jugular vein of the patient. The direction of the pipe connection was as follows: left femoral vein→centrifugal pump→membrane lung→right internal jugular vein. The circulatory system was pre-filled with Wanwen 1,500 mL and continuously infused with heparin during ECMO. The mean arterial pressure, SpO_2, hematocrit, and activated clotting time (ACT) during transfusion were monitored. The ECMO speed was 3,500 rpm, the blood flow velocity was 3 L/min, the average arterial pressure was maintained at 90 ± 10 mmHg, and ACT was maintained at 250 s (4). We performed bronchoscopy interventional therapy under general anesthesia with oxygen supply guaranteed by ECMO. For the intervention, we first used a CO_2 cryotherapy instrument to remove the local granulation tissue during the operation and then

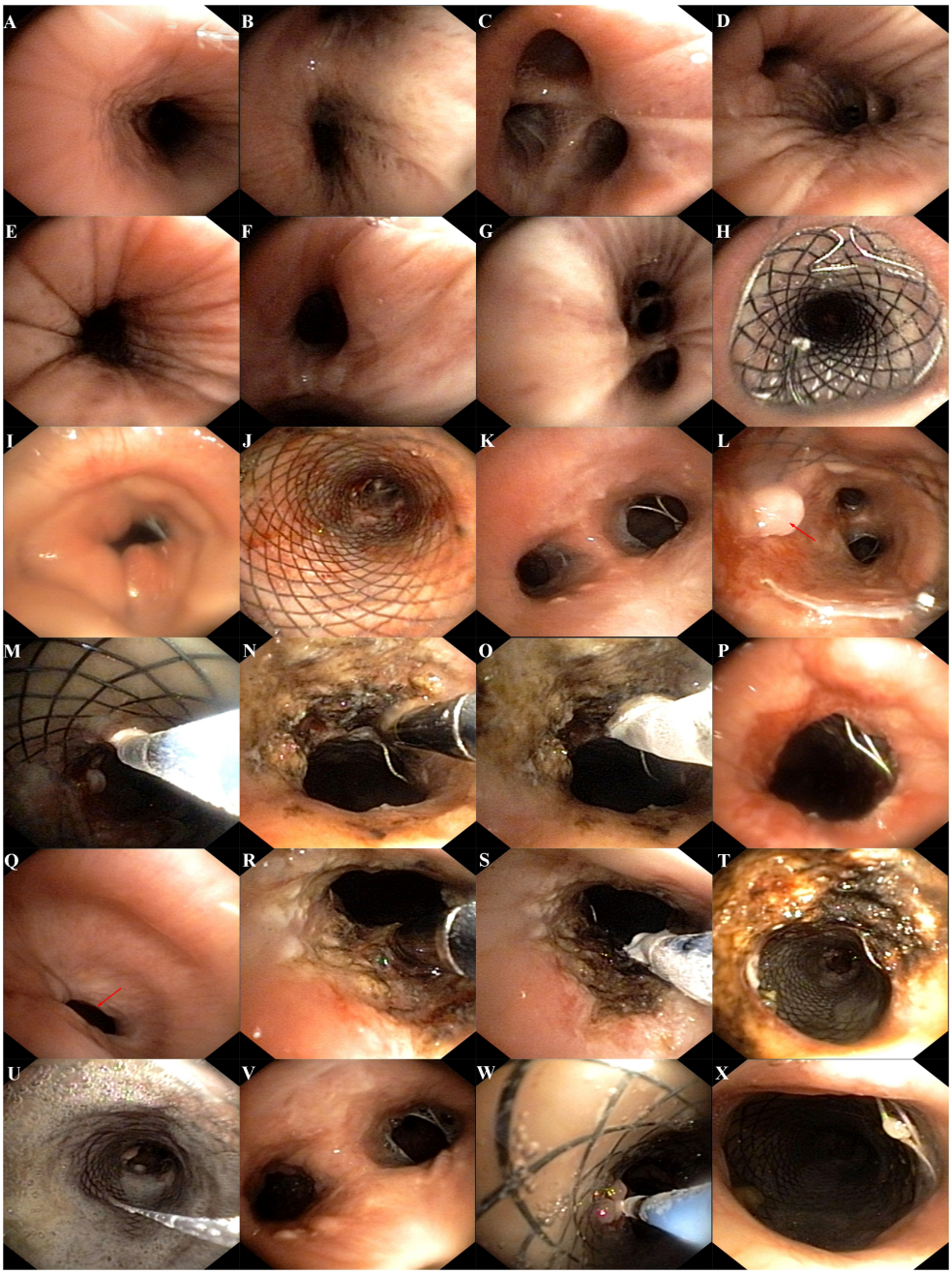

FIGURE 3 | (A–G) Bronchoscopy showed that the mucosa of trachea and main bonchus were severely hyperemic and swollen, cartilage was disappeared, and the lumen was stenosis; **(H,J)** the stents were well fixed; **(I)** bronchoscopy showed that the lumen of subglottis to the upper of the stent was severe narrowed and accompanied by scar tissue; **(K,L)** bronchoscopy showed that the mucosa was severe swollen, cartilage was disappeared, and granulation hyperplasia can be found (red arrow); **(M)** CO_2 cryotherapy of granulation tissue; **(N)** argon plasma coagulation was performed; **(O)** CO_2 cryoablation was performed; **(P)** the airway lumen is obviously enlarged after therapy; **(Q)** bronchoscopy showed that the lumen of subglottis to the upper of the stent was severe narrowed and accompanied by scar tissue (red arrow); **(R,S)** bronchoscopy-guided argon plasma coagulation and CO_2 cryoablation were performed; **(T)** the airway lumen is obviously enlarged after therapy; **(U,V)** granulation and a large amount of thick sputum blockage in the lumen; **(W)** CO_2 cryotherapy of granulation tissue; **(X)** the airway lumen is further enlarged after therapy with ECMO assist.

a needle-shaped high-frequency electrosurgical knife to make a radial cut on the narrow opening (**Figure 3R**). Subsequently, balloon dilations were performed three times at the lesion. Finally, CO_2 cryoablation was performed (**Figure 3S**). The total treatment time was 1 h, the intraoperative bleeding volume was ∼50 mL, and the SPO_2 was maintained at 90–95%; the rest of the

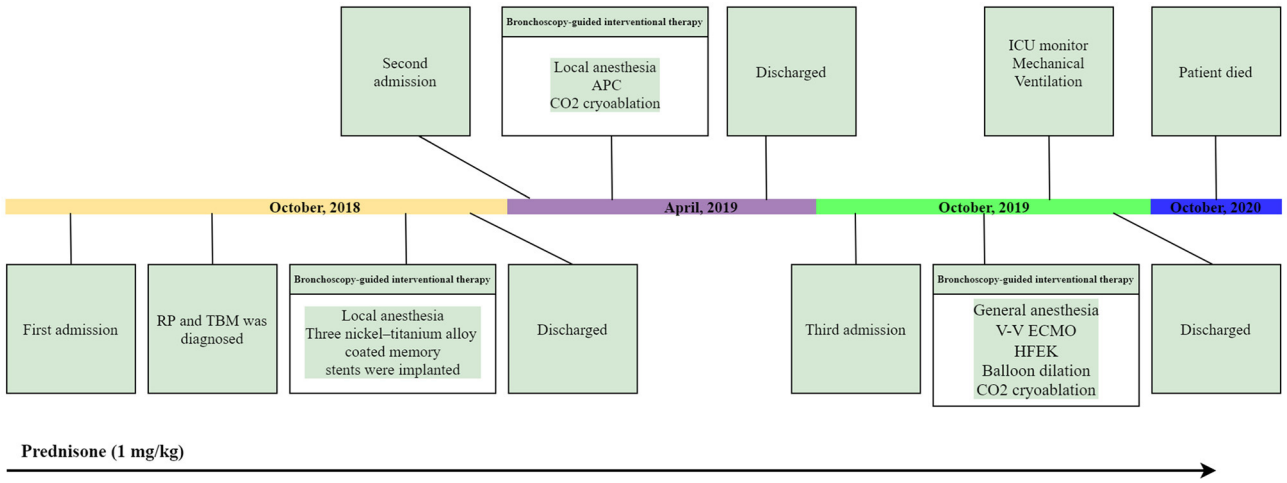

FIGURE 4 | Clinical history of the patient. APC, argon plasma coagulation; HFEK, high-frequency electrosurgical knife.

vital signs were stable. After the operation, the patient's tracheal stenosis significantly improved, and the bronchoscope was able to enter the distal airway smoothly, enabling the aspiration of large amounts of viscous secretions; the airway stent was in a good position and no serious complications, such as rupture were observed (**Figures 3T–X**, **2S,T**). After the operation, the patient was transferred to the ICU for monitoring. After 12 h, ECMO support was stopped, and the patient was implanted with a laryngeal mask and switched to a mechanical ventilator for oxygenation. On the second day after surgery, we removed the laryngeal mask and switched to non-invasive ventilator-assisted ventilation. On the fourth day, the patient was discharged from the hospital. However, the patient eventually died due to sudden respiratory failure during half year follow-up. Clinical history of the patient can be seen in **Figure 4**.

DISCUSSION

RP is an immune disorder with an unknown etiology and multiple-system involvement. The literature shows that the disease mainly affects the cartilage tissues of the body, of which ear chondritis is the most common sign, usually manifesting as congestion, pain, swelling of the auricle cartilage and skin, and loss of normal auricle shape (5). The second is rhinochondritis, which often manifests as nasal congestion, pain, and even "saddle nose" deformity, but it rarely manifests as epistaxis (6). Moreover, the involvement of organs such as the heart, eyeballs, joints, skin, and nervous system are also common (7). RP usually occurs between 40 and 60 years of age, and fever, fatigue, weight loss, or skin rash may be the first symptoms (8). At least 50% of cases in the late stage of RP involve the airway, and both the upper and lower airway cartilage can be affected (9). Involvement of the larynx can cause stenosis of the glottis, manifested by hoarseness, wheezing, or tenderness in the front of the neck. The symptoms of tracheal and main bronchus involvement are often insidious, mainly manifested as TBM, which is a dynamic airway collapse and is a severe complication of RP (9); dry cough, dyspnea, and wheezing are the main symptoms. Because of disease progression and lack of effective treatments, it is obviously associated with a higher mortality rate.

The diagnosis of RP with TBM is often misdiagnosed as asthma (10). Once patients with RP have persistent cough, shortness of breath, and dyspnea, the possibility of TBM needs to be considered first. The gold standard for diagnosis is bronchoscopy, and the diagnostic criterion of TBM is reduction of the cross-sectional area of the trachea or bronchus lumen by at least 50% at the end of expiration or coughing compared with the inspiratory phase (2, 3). Considering that bronchoscopy is an invasive examination, chest CT has recently been recommended as an alternative method, and it has good sensitivity and specificity (11). Chest CT examination requires a biphasic CT scan, including the inspiratory and expiratory phases, and the diagnostic criteria are consistent with bronchoscopy (12). Spirometry also plays an important role in the diagnosis of TBM. The flow volume curve is characterized by a decrease in the flow rate from the peak flow to an inflection point with a peak flow rate $<$50%. The inflection point occurs within the first 25% of the expired vital capacity. The inspiratory limb of the curve showing no evidence of obstruction was observed in almost all patients (13). Spirometry in patients with TBM may reveal obstructive ventilatory impairment but does not correlate with the severity of airway narrowing (14). Besides, studies have shown that PET-CT also has a better effect in diagnosing TBM (15); however, the cost is too high, which is not conducive to general screening of the disease.

Currently, glucocorticoids and methotrexate are the most important drugs for the treatment of RP, and long-term use can prevent further deterioration of TBM. Nevertheless, there are still many reports on treatment failure. Non-invasive ventilators can provide continuous positive airway pressure, help maintain airway patency, and have a certain effect on patients with

TABLE 1 | The reported literature of ECMO used in RP with TBM.

ECMO treatment of RP involving the airway									
Num.	**Age**	**Gender**	**Main symptoms**	**Primary diagnosis**	**Initial treatment**	**Complications**	**Later treatment**	**Follow-up**	**References**
Case 1	24	Man	Dyspnea	RP and airway severe obstruction	Montgomery T-tube	Tracheal tear; Bilateral Tension pneumothorax; Tension pneumoperitoneum	VV-ECMO + tracheotomy	Death	(25)
Case 2	39	Man	Dyspnea	RP and airway stenosis	Dumon stent	Laceration of trachea and left main stem bronchus; Acute respiratory distress; Subcutaneous emphysema	PCPS (like ECMO) + esophageal tracheobronchoplasty	Good	(26)
Case 3	41	Man	Dyspnea	RP and airway malacia	Y stent	Perforation of the tracheal membranous; Bilateral tension pneumothorax; Hemodynamic instability	VV-ECMO + tracheotomy	Good	(27)
Case 4	55	Man	Dyspnea	RP and tracheomalacia	Dumon stent	Tracheal tear; Subcutaneous emphysema	VA-ECMO + silicone Y stent	Good	(28)

ECMO, extracorporeal membrane oxygenation; RP, relapsing polychondritis; PCPS, percutaneous cardiopulmonary support.

mild TBM (2, 3). Recently, reports of airway stents, including metal stents, silicone stents, and Montgomery T-tubes, used in RP with TBM have increased gradually (16–18). Studies have shown that stents can maintain airway stability and significantly improve airway collapse and its consequent symptoms (19). However, long-term follow-ups and prognostic data are generally lacking. In addition, long-term airway stent implantation also has many complications, such as displacement, fracture, granulation hyperplasia, airway bleeding, and mucus obstruction, which may affect the efficacy and subsequent treatment (20–22). The literature shows that tracheobronchoplasty has a better effect on severe TBM caused by COPD and can significantly improve recent clinical symptoms and quality of life (19). However, this therapy often requires surgical intervention, which is more traumatic and has more complications, including post-operative death. The effect of tracheobronchoplasty on TBM caused by RP has not yet been reported. Therefore, the treatment of RP with TBM remains challenging. For RP with severe TBM with respiratory failure or cardiac insufficiency, conventional mechanical ventilation and general anesthesia often cannot guarantee the oxygen supply or safety during the operation. Hence, ECMO as an alternative for cardiopulmonary function, plays an important role in bronchoscopy-guided interventional therapy.

ECMO is also called extracorporeal life support. Its main purpose is to provide blood oxygenation, remove carbon dioxide, and ensure effective blood supply to the body; hence, by providing emergency and critically ill patients with respiratory and circulatory support, thereby playing an important role in emergency and critical care (4). The treatment modes of ECMO mainly include VV-ECMO and venous-arterial ECMO (VA-ECMO). The former is mainly used for respiratory failure and ARDS, and the latter is mainly used for cardiac surgery. In addition, VA-ECMO used in Extracorporeal Cardio-Pulmonary Resuscitation (E-CPR) can improve survival with good neurologic outcomes when initiated early in selected patients (23). Recently, ECMO has been gradually used in bronchoscopy-guided interventional therapies. For example, Natt et al. successfully performed balloon dilatation and tracheal stenting with VV-ECMO support in patients with severe tracheal occlusion after tracheal intubation, and the patient's post-operative dyspnea was significantly restored (24). With the support of ECMO, Kim et al. successfully performed bronchoscope-guided tumor resection in an 88-year-old patient with tracheal metastases of a mediastinal teratoma (25). Although reports of ECMO used in RP with TBM are rare, they have shown important clinical value [(26–29); **Table 1**]. Mitilian et al. reported a case of severe RP with TBM, who developed extensive airway tear, bilateral pneumothorax, and mediastinal emphysema after a Y-stent was placed under general anesthesia. After failure of mechanical ventilation, the patient was successfully discharged from the hospital with the help of VV-ECMO (28). Laliberte et al. reported that a patient with RP and severe TBM had tracheal perforation and subcutaneous emphysema when the Dumon silicone stent was replaced, but the airway was successfully repaired after reinserting the Y-shaped silicone stent with the assistance of VA-ECMO (29). Although ECMO provides adequate cardiopulmonary support, it also has complications such as hemorrhage, embolism, hemolysis, edema, and infection (30). Sy et al. conducted a systematic review of the complications of ∼1,496 patients in 26 studies using ECMO. The results showed that bleeding was the most common complication of ECMO, with a prevalence rate of 27%, and the overall prevalence of thromboembolic events was 8%. Among them, limb ischemia, blood vessel-related coagulation, and stroke are the most frequently reported events (31). We successfully performed a bronchoscopy-guided intervention therapy with ECMO support for advanced cancer metastasis to the central airway, and the tumor was completely removed by surgery. Although airway oozing and blood clots filled part of the bronchus after the

operation, no other complications occurred after adjusting the heparin dose and airway clearing (4). Although this patient reported in this article eventually died, the specific reasons are complicated. In addition to RP and TBM, COPD and lung bullae can also cause respiratory failure. Moreover, the irreversible progression of TBM and RP and stent-related complications can also aggravate the original symptoms and disease risks. Despite the aforementioned shortcomings of ECMO, its important role in bronchoscopy-guided interventional therapy is very obvious: first, even though the intervention and anesthesia share the airway, ECMO eliminates the interference of tracheal intubation, providing a more open and clear surgical field; second, it allows the surgeon a longer operation time and more room to perform the surgery in an orderly manner; finally, it maintains stable oxygenation and hemodynamics during surgery (4). However, hemorrhage commonly occurs during bronchoscopy-guided therapy, and systemic heparinization during ECMO is bound to further increase the risk of coagulopathy, such as major bleeding and embolism. Therefore, further research on the amount and timing of heparin should be conducted in the future to improve the safety of interventional surgery. Besides, the practices of ECMO and bronchoscopy-guided intervention therapy need adequate technical skills that can be acquired only through defined learning pathways (32). The case in this article shows that VV-ECMO can provide sufficient oxygenation and safety for bronchoscopy-guided interventional therapy for RP with TBM.

CONCLUSION

TBM is a common and serious complication of RP involving the airway. ECMO can be used as an important support tool for patients with cardiopulmonary insufficiency or severe airway stenosis when conventional general anesthesia and mechanical ventilation cannot maintain oxygenation or ensure safety during bronchoscopy-guided intervention therapy.

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

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

PZ and WY: conception and design. QX and CZ: administrative support. KC and WT: provision of study materials or patients. WY and BF: collection and assembly of data. PZ and BF: data analysis and interpretation. PZ, BF, and WY: manuscript writing. WY and WH: final approval of manuscript. All authors contributed to the article and approved the submitted version.

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Endotoxin Activity in Patients With Extracorporeal Membrane Oxygenation Life Support: An Observational Pilot Study

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Background: Extracorporeal membrane oxygenation (ECMO) life support has become an integral part of intensive care. The endotoxin activity assay (EAA) is a useful test to measure endotoxemia severity in whole blood. To date, no information is available regarding the EAA levels and their effect on clinical outcomes in critically ill patients with ECMO support.

Methods: This prospective observational pilot study enrolled adult critically ill patients with ECMO support from August 2019 to December 2020. The EAA levels were measured within 24 h (T1), and at 25–48 (T2), 49–72 (T3), and 73–96 h (T4) after ECMO initiation. This study primarily aimed to investigate the incidence of high EAA levels (≥0.6) at each time point. Subsequent exploratory analyses were conducted to compare the EAA levels of venoarterial ECMO (VA-ECMO) patients between 30-day survivors and non-survivors. *Post-hoc* analysis was performed to compare the clinical outcomes of VA-ECMO patients with elevated EAA levels at T3 (vs. T1) and those without elevated EAA levels.

Results: A total of 39 VA-ECMO patients and 15 venovenous ECMO (VV-ECMO) patients were enrolled. At T1, the incidence of high EAA level (≥0.6) was 42% in VV-ECMO patients and 9% in VA-ECMO patients ($P = 0.02$). At T2, the incidence of high EAA level was 40% in VV-ECMO patients and 5% in VA-ECMO patients ($P = 0.005$). In VA-ECMO patients, EAA levels at T3 were significantly higher in 30-day non-survivors than in survivors (median [interquartile range]: 0.49 [0.37–0.93] vs. 0.31 [0.19–0.51], median difference 0.16 [95% confidence interval [CI], 0.02–0.31]; $P = 0.024$). Moreover, VA-ECMO patients with elevated EAA levels at T3 (vs. T1) had lower 30-day survival than patients without elevated EAA levels (39 vs. 83%, $P = 0.026$) and fewer ECMO free days by day 30 (median: 3 vs. 23 days, median difference 12 days [95% CI, 0–22]; $P = 0.028$).

Conclusions: A certain proportion of patients experienced high EAA levels (≥0.6) after VV-ECMO or VA-ECMO initiation. VA-ECMO patients with an elevated EAA level at 49–72 h were associated with poor clinical outcomes.

Keywords: critical care, endotoxin, extracorporeal membrane oxygenation (ECMO), survival, infection

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) life support has become an integral part of intensive care (1), but contingent infection increases morbidity and mortality in patients receiving ECMO (2, 3). Venovenous ECMO (VV-ECMO) is primarily indicated for patients with acute respiratory distress syndrome (ARDS), which is frequently associated with pneumonia and sepsis. Venoarterial ECMO (VA-ECMO) is primarily used for supporting patients with refractory cardiogenic shock. According to our clinical experience, fever and sepsis after VA-ECMO are common. In addition to some common nosocomial infections, severe hypoperfusion can disrupt the intestinal barrier and result in bacteremia and endotoxemia (4, 5).

High endotoxin levels are associated with poor survival outcomes in critically ill patients (6). A novel immunoassay using neutrophil-dependent chemiluminescence, the endotoxin activity assay (EAA), was developed to measure endotoxin activity in whole blood (7). Previous research demonstrated that an EAA level ≥0.6 was strongly associated with the development of septic shock and mortality in critically ill patients (8). However, the incidence and effects of high endotoxin levels on clinical outcomes in critically ill patients on ECMO support remain unclear. The primary goal of this pilot study was to investigate that how many critically ill patients with VV-ECMO or VA-ECMO support would have an EAA level higher than 0.6. In addition, for these patients with VV-ECMO or VA-ECMO support, the secondary goals of this study were to investigate whether survivors and non-survivors were different in EAA levels, and to investigate whether patients with or without elevated EAA levels had different clinical outcomes within 30 days after ECMO initiation.

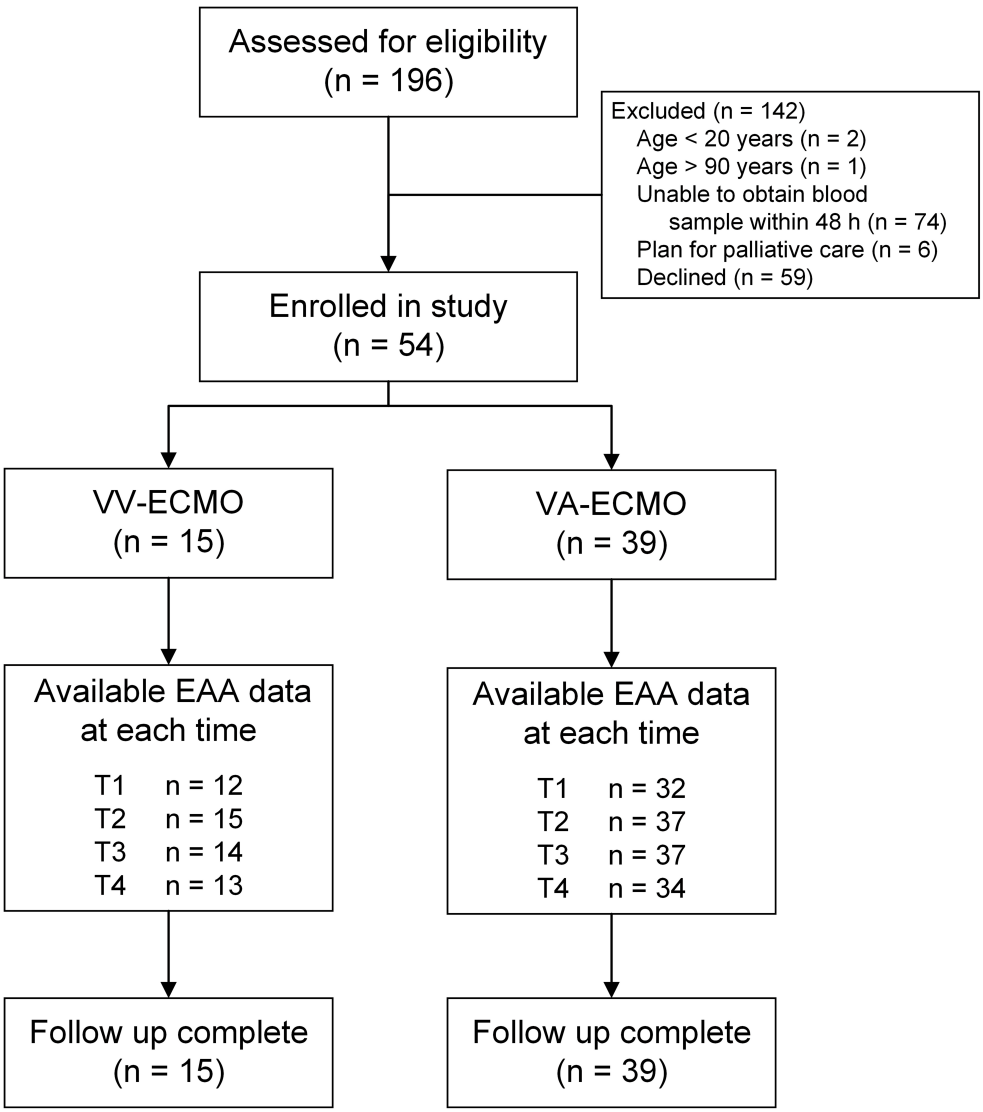

FIGURE 1 | Flow diagram. EAA, endotoxin activity assay; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VV-ECMO, venovenous extracorporeal membrane oxygenation.

MATERIALS AND METHODS

Patients

This prospective observational pilot study was approved by the Research Ethics Committee of National Taiwan University Hospital (approval number 201811061RINC), and was registered at clinicaltrials.gov (NCT03978728). This study was conducted between August 2019 and December 2020 and was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (9). Adult critically ill patients who underwent VV-ECMO or VA-ECMO were evaluated for eligibility within 24 h of ECMO initiation. Patients were excluded if they aged younger than 20 years or elder than 90 years, had do-not-resuscitate orders, underwent extracorporeal endotoxin adsorption treatment during the study period, had no blood sample obtained within 48 h of ECMO initiation, or did not speak Taiwanese natively. Informed consent was obtained from the legally authorized representatives of all participants before enrollment. A total of 196 critically ill patients receiving ECMO support were assessed for the eligibility of this study.

ECMO Components

The implementation and principal components of ECMO for all enrolled patients were as described in our previous study (10). The VA-ECMO was placed in the femoral vein (21–23 French) and artery (15–19 French), and VV-ECMO was achieved using femoral inflow (21–23 French) and jugular outflow (15–19 French). To avoid malperfusion of the distal limb, an antegrade distal perfusion catheter was used when the mean pressure of the superficial femoral artery was <50 mmHg (11). All enrolled patients received standard ECMO management and intensive care unit (ICU) care. Heparin was continuously administered to maintain an activated clotting time of 160–180 s if no active bleeding or other complications were observed. Antibiotic prophylaxis with vancomycin and ceftazidime were administered shortly after ECMO to patients without antibiotic use; the antibiotics were subsequently downgraded in accordance with institutional protocols.

Data Collection

Demographic data including age, sex, height, body weight, indications for ECMO support, Survival after VA-ECMO (SAVE) score, Respiratory ECMO Survival Prediction (RESP) score, and Acute Physiology and Chronic Health Evaluation (APACHE) II score were recorded after enrollment. Blood samples were obtained at four time points after ECMO initiation: within 24 h (T1) and at 25–48 (T2), 49–72 (T3), and 73–96 h (T4). White blood cell (WBC) counts; lactate, procalcitonin, diamine oxidase (DAO), and cystatin C levels; and EAA levels were examined. The inotropic score (IE) was calculated at the four time points as 100 × epinephrine dose (μg/kg/min) + 100 × norepinephrine dose (μg/kg/min) + dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) (12). The duration of ECMO support and survival status at 30 days were recorded.

Measurements of EAA Levels and Blood Inflammatory Biomarkers

The blood samples were collected from the peripheral arterial line. An EAA measurement was performed within 3 h after blood sample collection using the EAA Kit (Spectral Medic al Inc., Toronto, Canada) according to the manufacturer's instructions. An EAA level ≥0.6 was considered high. Biomarkers were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. Procalcitonin was measured using the Human Procalcitonin SimpleStep ELISA Kit (Abcam, Cambridge, UK). DAO was measured using the IDK DAO ELISA Kit (Immundiagnostik AG, Bensheim, Germany). Finally, cystatin C was measured using the Cystatin C (CST3) (Human) ELISA Kit (Biovision, Inc., CA, USA).

The primary goal was to obtain the EAA levels, particularly the incidence of high EAA levels (≥0.6), at each time point in patients with VV-ECMO or VA-ECMO. Exploratory

TABLE 1 | Characteristics and clinical outcomes of patients with VV-ECMO or VA-ECMO.

	VV-ECMO (*n* = 15)	**VA-ECMO (*n* = 39)**
Age (year)	64 (51–71)	63 (52–69)
Height (cm)	164 (159–168)	168 (157–174)
Weight (kg)	62.9 (57.0–75.2)	67.4 (56.3–82.3)
Sex (female/male)	6/9	7/32
APACHE II score	31 (26–40)	29 (24–36)
SAVE score	-	−8 (−10 to −2)
RESP score	0 (−3 to 4)	-
RRT, n (%)	4 (27%)	22 (56%)
ECMO indication		
E-CPR	-	16
Heart failure	-	17
Postcardiotomy	-	4
Septic shock	-	2
ARDS	15	-
EAA level		
T1 median (IQR)	0.44 (0.31–0.71)	0.33 (0.22–0.50)
T2 median (IQR)	0.50 (0.36–0.66)	0.38 (0.28–0.52)
T3 median (IQR)	0.50 (0.33–0.78)	0.40 (0.23–0.57)
T4 median (IQR)	0.49 (0.37–0.59)	0.44 (0.29–0.56)
ECMO free days[a]	0 (0–17)	14 (0–24)
ICU free days[b]	0	0 (0–2)
30-day survival, *n* (%)	11 (73%)	21 (54%)

Data are presented as medians (interquartile ranges, IQRs), numbers, and percentages as appropriate. Four study time points: within 24 h (T1) and 25–48 (T2), 49–72 (T3), and 73–96 h (T4) after ECMO initiation. APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; EAA, endotoxin activity assay; ECMO, extracorporeal membrane oxygenation; E-CPR, extracorporeal cardiopulmonary resuscitation; ICU, intensive care unit; IQR, interquartile range; RRT, renal replacement therapy; SAVE, Survival after Venoarterial ECMO; RESP, Respiratory ECMO Survival Prediction; VA-ECMO, venoarterial ECMO; VV-ECMO, venovenous ECMO.

[a] *ECMO free days were defined as days free from ECMO support, between ECMO initiation and day 30.*

[b] *ICU free days were defined as days bot in the ICU, between ECMO initiation and day 30.*

analyses were conducted to compare EAA levels between 30-day survivors and non-survivors. *Post-hoc* exploratory analysis was performed to compare the clinical outcomes between VA-ECMO patients with and without an elevated EAA level at T3 (vs. T1).

Statistical Analysis

Data were analyzed in SPSS Version 27.0 (IBM, Armonk, NY, USA). Continuous variables are reported as medians (interquartile ranges) and were compared using the Mann–Whitney *U* test; median differences (95% confidence intervals [CIs]) between groups were calculated using the Hodges–Lehmann estimator. Categorical variables are reported as numbers (percentages) and were compared using chi-square tests or Fisher's exact tests as appropriate. The Kaplan–Meier survival curve was employed to visualize the survival differences between groups, which were tested using log-rank tests. A $P < 0.05$ indicated a significant difference.

RESULTS

Patient Characteristics and EAA Levels

After eligibility assessment and informed consent, 39 VA-ECMO patients and 15 VV-ECMO patients were enrolled (**Figure 1**).

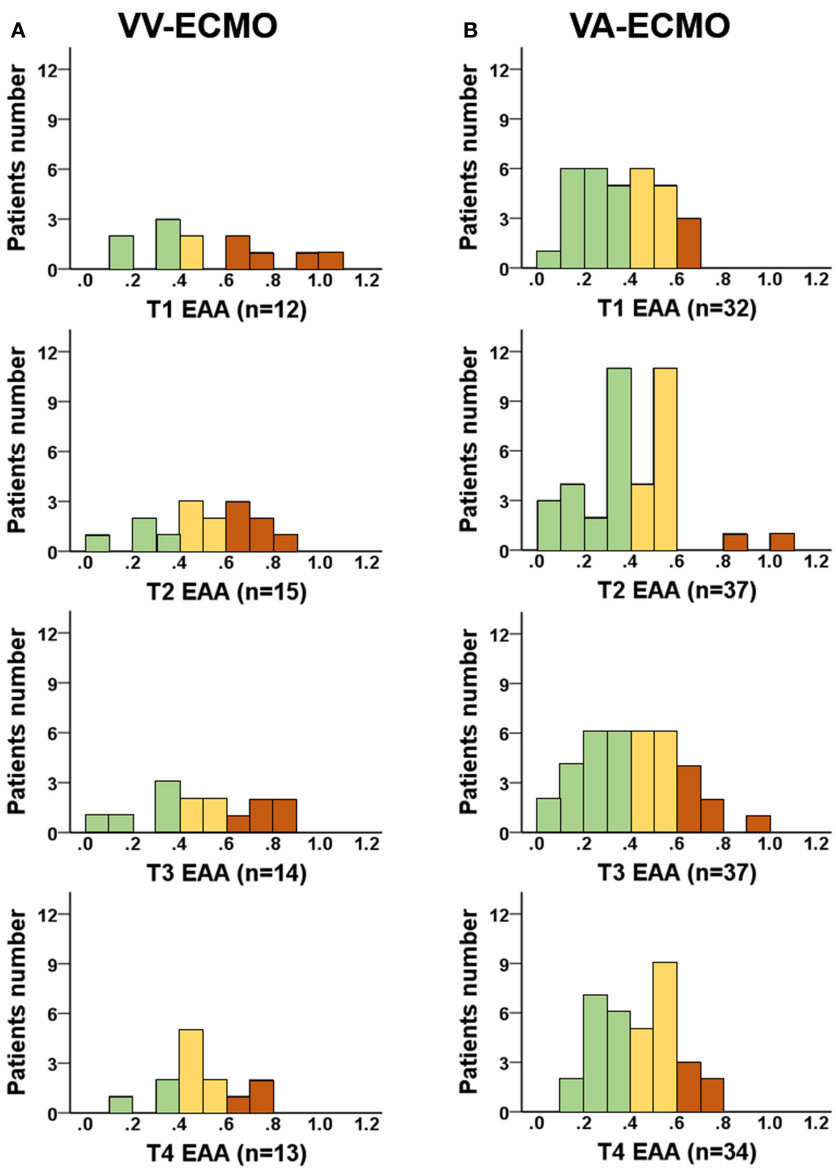

FIGURE 2 | EAA levels in VA-ECMO or VV-ECMO patients. EAA levels were measured at four time points: within 24 h (T1) and 25–48 (T2), 49–72 (T3), and 73–96 h (T4) after ECMO initiation. **(A)** EAA levels in VV-ECMO patients; **(B)** EAA levels in VA-ECMO patients. Brown column stands for high EAA level (≥0.6); yellow column stands for intermediate EAA level (0.4 to 0.6); green column stands for low EAA level (<0.4). EAA, endotoxin activity assay; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VV-ECMO, venovenous extracorporeal membrane oxygenation.

The patient characteristics, indications for ECMO, and EAA levels are summarized in **Table 1**. The 30-day survival rates were 54 and 73% in VA-ECMO and VV-ECMO patients, respectively. The EAA levels in VV-ECMO patients and VA-ECMO patients are presented in **Figure 2**. At T1, the incidence of high EAA levels (≥0.6) was 42% in VV-ECMO patients and 9% in VA-ECMO patients ($P = 0.02$). At T2, the incidence of high EAA levels was 40% in VV-ECMO patients and 5% in VA-ECMO patients ($P = 0.005$).

Clinical and Laboratory Data in 30-Day Survivors and Non-survivors

The EAA levels and clinical and laboratory data for VA-ECMO patients surviving or not surviving at 30 days are summarized in **Table 2**. Significantly higher APACHE II scores and SAVE scores at VA-ECMO initiation were found in 30-day non-survivors. In VA-ECMO patients, EAA levels at T3 were higher in 30-day non-survivors than in survivors (median [interquartile range]: 0.49 [0.37–0.93] vs. 0.31 [0.19–0.51], median difference 0.16 [95% CI, 0.02–0.31]; $P = 0.024$). Biomarker levels are presented in **Table 3**. Procalcitonin levels at T3 were higher in 30-day non-survivors than in survivors.

Post hoc Analysis: Clinical and Laboratory Data in VA-ECMO Patients With or Without Elevated EAA Levels at T3

The EAA levels and clinical and laboratory data of VA-ECMO patients with or without elevated EAA levels at T3 (vs. T1) are summarized in **Table 4**. In VA-ECMO patients, patients with an elevated EAA level at T3 (vs. T1) had lower 30-day survival (39 vs. 83%, $P = 0.026$) and fewer ECMO free days by day 30 (median [interquartile range]: 3 [0–21] vs. 23 [15–25] days, median difference 12 days [95% CI, 0–22]; $P = 0.028$) than did those without an elevated EAA level. Biomarker levels are presented in **Table 5**. The DAO levels at T1 and the WBC counts at T4 were higher in VA-ECMO patients with an elevated EAA level than in those without. The 30-day survival curves for VA-ECMO patients with or without elevated EAA levels at T3 are presented in **Figure 3**. The EAA levels in VA-ECMO patients with a proven infection within 96 h are presented in **Table 6**.

TABLE 2 | Data of 30-day survivors and non-survivors with VA-ECMO.

VA-ECMO	30-day survivors (n = 21)	30-day non-survivors (n = 18)	*P* values
Age (year)	65 (55–71)	62 (49–66)	0.367
Sex (female/male)	2/19	5/13	
APACHE II score	27 (24–32)	36 (27–39)	0.020
SAVE score	−5 (−9–−1)	−10 (−15–−7)	0.003
ECMO free days[a]	22 (17–26)	1 (0–13)	0.001
ICU free days[b]	0 (0–15)	0	0.009
T1 (within 24 h)			
EAA	0.38 (0.20–0.51)	0.29 (0.20–0.46)	0.319
WBC (k/μL)	12.2 (9.5–17.4)	12.1 (9.7–15.9)	0.988
Inotropic score	4.1 (0–20.7)	12.9 (1.9–19.4)	0.483
Lactate (mmol/L)	10.1 (3.4–13.5)	9.5 (7.7–13.1)	0.478
T2 (25–48 h)			
EAA	0.38 (0.20–0.52)	0.38 (0.33–0.52)	0.660
WBC (k/μL)	12.1 (10.6–15.3)	12.8 (8.8–15.6)	0.885
Inotropic score	4.6 (0.7–11.5)	9.2 (3.3–18.8)	0.147
Lactate (mmol/L)	2.9 (1.7–4.5)	3.1 (2.0–4.4)	0.641
T3 (49–72 h)			
EAA	0.31 (0.19–0.51)	0.49 (0.37–0.63)	0.024
WBC (k/μL)	12.3 (9.0–15.2)	10.4 (7.9–12.2)	0.128
Inotropic score	2.3 (0.0–8.1)	7.5 (1.1–13.9)	0.220
Lactate (mmol/L)	1.9 (1.4–3.0)	2.5 (1.8–5.3)	0.056
T4 (73–96 h)			
EAA	0.41 (0.29–0.52)	0.49 (0.29–0.61)	0.391
WBC (k/μL)	10.1 (8.8–13.5)	11.3 (7.9–11.9)	0.977
Inotropic score	0.9 (0–7.9)	3.2 (0–15.4)	0.427
Lactate (mmol/L)	1.8 (1.2–2.5)	2.5 (1.4–4.0)	0.126

Data are presented as medians (interquartile ranges), numbers, and percentages as appropriate. Study time points (T1–T4) represent the time after ECMO initiation. APACHE II, Acute Physiology and Chronic Health Evaluation II; EAA, endotoxin activity assay; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; SAVE, Survival after Venoarterial ECMO; VA-ECMO, venoarterial ECMO; WBC, white blood cell.

[a] *ECMO free days were defined as days free from ECMO support from ECMO initiation until day 30.*

[b] *ICU free days were defined as days bot in the ICU, between ECMO initiation and day 30.*

DISCUSSION

This study discovered that 42% of VV-ECMO patients and 9% of VA-ECMO patients had high EAA levels (≥0.6) at the initiation of ECMO support. In VA-ECMO patients, EAA levels at T3 were higher in 30-day non-survivors than in survivors. VA-ECMO patients with elevated EAA levels at T3 (vs. T1) had lower 30-day survival than those without elevated EAA levels had.

Our study demonstrated that incidence of high EAA levels (≥0.6) was higher in VV-ECMO patients than in VA-ECOM patients; this finding is compatible with a report that patients with VV-ECMO have a higher risk of infection than do those with VA-ECMO (13). It has been reported that 63% of ventilator-associated pneumonia were due to gram-negative bacteria (GNB) (14), and the GNB sepsis directly result in high endotoxin activity. However, in patients with non-GNB sepsis, severe hypoperfusion or hypoxemia could damage the intestinal barrier and results in the translocation of intestinal resident bacteria (mainly GNB) and endotoxins (5). Therefore, the translocation could secondarily result in high endotoxin toxicity in these patients with non-GNB sepsis. Moreover, current surviving sepsis guidelines suggest using VV-ECMO for patients with sepsis-induced severe ARDS when conventional mechanical ventilation fails (15). We suggest that more concerns should be raised for high endotoxin activity in VV-ECMO patients, and further investigations of the impact of high endotoxin activity on clinical outcomes are needed.

Elevated EAA levels at T3 were associated with lower 30-day survival and fewer ECMO-free days in VA-ECMO patients of this study. Several factors may contribute to subsequent elevated endotoxin activity in the whole blood of

TABLE 3 | Biomarker levels in 30-day survivors and non-survivors with VA-ECMO.

VA-ECMO	30-day survivors	30-day non-survivors	*P* values
T1 (within 24 h)			
Procalcitonin	4 (1–17)	8 (4–15)	0.442
DAO	14 (8–33)	18 (8–76)	0.419
Cystatin C	0.7 (0.4–1.0)	1.0 (0.3–1.3)	0.338
T2 (25–48 h)			
Procalcitonin	4 (1–13)	10 (4–15)	0.165
DAO	9 (5–26)	13 (5–23)	0.705
Cystatin C	0.6 (0.5–1.0)	1.0 (0.4–1.2)	0.338
T3 (49–72 h)			
Procalcitonin	3 (1–5)	8 (3–12)	0.022
DAO	5 (4–11)	6 (4–13)	0.752
Cystatin C	0.7 (0.4–1.0)	0.9 (0.5–1.2)	0.209
T4 (73–96 h)			
Procalcitonin	2 (0–7)	4 (2–8)	0.202
DAO	6 (4–9)	6 (3–12)	0.667
Cystatin C	0.6 (0.4–1.1)	1.0 (0.6–1.1)	0.131

Data are presented as medians (interquartile ranges), numbers, and percentages as appropriate. Study time points (T1–T4) represent the time after ECMO initiation. DAO, diamine oxidase; VA-ECMO, venoarterial ECMO.

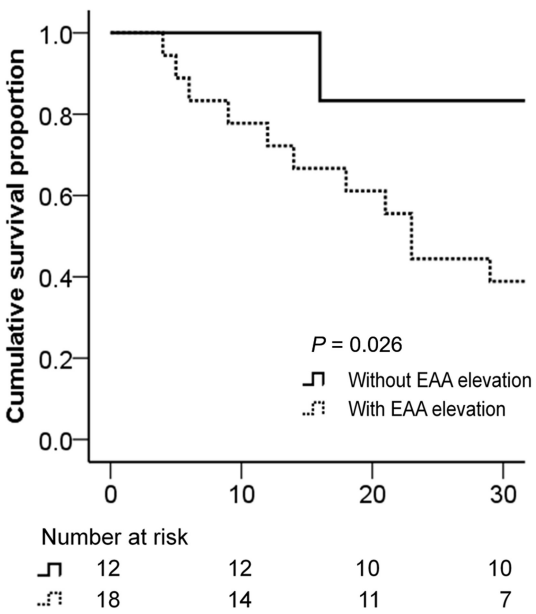

FIGURE 3 | Kaplan–Meier 30-day survival curve for VA-ECMO patients. Patients with or without elevated EAA level at T3 (vs. T1). Study time points: within 24 h (T1) and 49–72 (T3) after ECMO initiation. Result of statistical comparison using log-rank test. EAA, endotoxin activity assay; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

TABLE 4 | Data of VA-ECMO patients with or without elevated EAA levels at T3.

VA-ECMO	Δ EAA $_{T3-T1}$ < 0 (*n* = 12)	Δ EAA $_{T3-T1}$ ≥ 0 (*n* = 18)	*P*-values
Age (year)	66 (58–71)	63 (48–68)	0.439
SAVE score	−5 (−10 to −1)	−10 (−11 to −4)	0.232
APACHE II score	30 (25–37)	28 (24–36)	0.692
ECMO indication			
E-CPR	4	6	
Heart failure	7	8	
Postcardiotomy	0	3	
Septic shock	1	1	
ECMO free days[a]	23 (15–25)	3 (0–21)	0.028
ICU free days[b]	0 (0–3)	0 (0–4)	0.602
30-day survival	10 (83%)	7 (39%)	0.026
T1 Number, *n* (%)	12 (40%)	18 (60%)	
EAA	0.42 (0.24–0.51)	0.28 (0.17–0.42)	0.146
WBC (k/μL)	12.9 (10.3–15.2)	11.9 (9.1–15.9)	0.602
Inotropic score	9.9 (3.9–30.6)	3.7 (0–15.8)	0.215
Lactate (mmol/L)	9.0 (3.4–13.2)	9.2 (7.0–12.5)	0.662
T2 Number, *n* (%)	12 (41%)	17 (59%)	
EAA	0.25 (0.12–0.47)	0.46 (0.35–0.52)	0.034
WBC (k/μL)	11.3 (9.3–13.0)	12.9 (11.3–16.9)	0.087
Inotropic score	4.8 (2.4–9.1)	7.6 (0.0–22.1)	0.647
Lactate (mmol/L)	2.5 (1.7–2.9)	3.3 (1.5–5.0)	0.245
T3 Number, *n* (%)	12 (40%)	18 (60%)	
EAA	0.20 (0.11–0.30)	0.51 (0.38–0.60)	0.001
WBC (k/μL)	9.0 (7.5–12.5)	11.4 (8.9–13.2)	0.146
Inotropic score	4.9 (1.7–8.5)	5.4 (0.0–15.9)	0.723
Lactate (mmol/L)	1.8 (1.4–2.5)	2.9 (1.4–5.0)	0.180
T4 Number, *n* (%)	11 (41%)	16 (59%)	
EAA	0.32 (0.21–0.51)	0.48 (0.30–0.52)	0.195
WBC (k/μL)	8.8 (6.8–10.5)	11.5 (9.4–12.8)	0.019
Inotropic score	1.6 (0–6.7)	1.6 (0.0–13.1)	1.000
Lactate (mmol/L)	1.8 (1.2–3.1)	2.1 (1.1–3.2)	0.645

Data are presented as medians (interquartile ranges), numbers, and percentages as appropriate. Four study time points: within 24 h (T1) and 25–48 (T2), 49–72 (T3), and 73–96 h (T4) after ECMO initiation. APACHE II, Acute Physiology and Chronic Health Evaluation II; EAA, Endotoxin Activity Assay; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; SAVE, Survival after Venoarterial ECMO; VA-ECMO, venoarterial ECMO; WBC, white blood cell.

[a] *ECMO free days were defined as days free from ECMO support from ECMO initiation until day 30.*

[b] *ICU free days were defined as days bot in the ICU, between ECMO initiation and day 30.*

VA-ECMO patients. First, ICU-related nosocomial infections (e.g., ventilator-associated pneumonia and bloodstream infection) are common prior to and during ECMO support (14, 16, 17). Among the 39 VA-ECMO patients in the present study, six presented with infections prior to ECMO initiation, and nine developed infections within the first week after ECMO initiation. Most microorganisms reported within 96 h after VA-ECMO placement in this study were GNB. Second, microcirculatory dysfunction may disrupt the intestinal barrier and precipitate the translocation of resident intestinal bacteria and endotoxins (5, 18). Third, we found that DAO levels at T1 were higher in VA-ECMO patients with an elevated EAA level at T3 than in those without. This finding might be associated with intestinal barrier disruption. Moreover, several reports suggest that some *Klebsiella pneumoniae* infections originate from the gastrointestinal reservoir (19, 20), which is compatible

TABLE 5 | Biomarker levels in VA-ECMO patients with or without elevated EAA levels at T3.

VA-ECMO	Δ EAA $_{T3-T1} < 0$	Δ EAA $_{T3-T1} \geq 0$	*P* values
T1 (within 24 h)			
Procalcitonin	3 (1–16)	7 (3–16)	0.632
DAO	8 (7–21)	28 (13–76)	0.013*
Cystatin C	1 (0.6–1.2)	0.6 (0.3–1.0)	0.079
T2 (25–48 h)			
Procalcitonin	5 (2-13)	8 (2–19)	0.444
DAO	5 (4–17)	14 (6–23)	0.117
Cystatin C	1 (0.6–1.2)	0.5 (0.3–1.0)	0.080
T3 (49–72 h)			
Procalcitonin	2 (1–5)	8 (3–12)	0.065
DAO	5 (3–20)	6 (4–9)	0.851
Cystatin C	0.9 (0.5–1.3)	0.8 (0.4–1.0)	0.124
T4 (73–96 h)			
Procalcitonin	2 (1–4)	5 (2–10)	0.241
DAO	5 (4–14)	5 (4–8)	0.698
Cystatin C	0.9 (0.5–1.2)	0.7 (0.4–1.1)	0.100

*Data are presented as medians (interquartile ranges), numbers, and percentages as appropriate. DAO; diamine oxidase; EAA, endotoxin activity assay; VA-ECMO, veno-arterial ECMO. *significant difference between patients with or without elevated EAA level from T1–T3. Study time points (T1–T4) represent the time after ECMO initiation.*

TABLE 6 | EAA levels in VA-ECMO patients with a proven infection within 96 h.

No.	Type	Microorganisms	Day	EAA			
				T1	T2	T3	T4
4	Bacteremia	*Actinomyces odontolyticus*	0	0.38	0.35	0.59	0.49
10	Pneumonia	*Klebsiella pneumoniae*	1	0.47	0.57	0.47	0.52
14	Bacteremia	*Klebsiella pneumoniae*	0	-	0.57	0.76	0.61
26	Pneumonia	*Klebsiella pneumoniae*	0	0.17	0.38	0.52	0.56
31	Pneumonia	*Stenotrophomonas maltophilia*	3	0.49	0.35	0.61	0.5
37	Pneumonia	*Klebsiella pneumoniae*	0	0.26	0.52	0.9	0.59
44	Pneumonia	*Acinetobacter nosocomialis*	4	0.17	0.14	0.38	0.29
45	Pneumonia	*Klebsiella pneumoniae*	4	0.13	0.81	0.24	0.32
46	Pneumonia	*Klebsiella pneumoniae*	0	0.5	0.11	0.05	-
47	Pneumonia	*Elizabethkingia meningoseptica*	3	0.21	0.39	0.16	0.29
48	Pneumonia	*Pseudomonas aeruginosa*	4	0.4	0.35	0.4	-
51	Pneumonia	*Klebsiella pneumoniae*	0	-	0.36	0.28	0.32

Four study time points: within 24 h (T1) and 25–48 (T2), 49–72 (T3), and 73–96 h (T4) after ECMO initiation. EAA, endotoxin activity assay.

with the finding of this study that *Klebsiella pneumoniae* is the most common pathogen. Furthermore, extracorporeal endotoxin adsorption treatment has been reported to reduce EAA and inflammatory cytokine levels (21, 22). Further studies are warranted to investigate the clinical efficacy of extracorporeal endotoxin adsorption treatment in VA-ECMO patients with elevated EAA levels.

This study has several limitations. First, with limited sample size, the results of exploratory analyses require further investigation in future studies. Second, the mechanism of increased endotoxin activity may vary among patients with different indications for VA-ECMO support. Further studies are warranted to investigate such variation. Third, an aggravated systemic inflammatory response resulting from the exposure of blood to extracorporeal circulation has been recognized as an independent cause of intestinal barrier dysfunction in porcine models (23, 24). Further studies are warranted to investigate the relationship between cytokine level and endotoxin activity.

CONCLUSIONS

A certain proportion of critically ill adult patients with ECMO have an EAA level $\geq$0.6, and an elevated EAA levels at 48 h after VA-ECMO initiation was associated with lower 30-day survival. Further studies are warranted to investigate the risk factors for high endotoxin activity and the effects of high endotoxin activity on further clinical outcomes in larger patient groups. Additionally, new therapeutic strategies for high endotoxin activity are required to be investigated.

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 Research Ethics Committee of National Taiwan University Hospital. The legally authorized representatives of the patients provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

C-TL, C-HW, W-SC, and Y-CY: concept and design and drafting manuscript. C-HW, C-HL, and Y-CY: patient enrollment and data collection. T-JW, W-SC, M-JW, and Y-CY: interpretation of data. C-HW, M-JW, Y-SC, and Y-CY: critical revision of the manuscript. M-JW and Y-SC: study supervision. All authors contributed to the article and approved the submitted version.

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Effects of *ex vivo* Extracorporeal Membrane Oxygenation Circuits on Sequestration of Antimicrobial Agents

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Objectives: Our *ex vivo* study was designed to determine the sequestration of teicoplanin, tigecycline, micafungin, meropenem, polymyxin B, caspofungin, cefoperazone sulbactam, and voriconazole in extracorporeal membrane oxygenation (ECMO) circuits.

Methods: Simulated closed-loop ECMO circuits were prepared using 2 types of blood-primed ECMO. After the circulation was stabilized, the study drugs were injected into the circuit. Blood samples were collected at 2, 5, 15, 30 min, 1, 3, 6, 12, and 24 h after injection. Drug concentrations were measured by high-performance liquid chromatography-tandem mass spectrometry. Control groups were stored at 4°C after 3, 6, 12, and 24 h immersing in a water bath at 37°C to observe spontaneous drug degradation.

Results: Twenty-six samples were analyzed. The average drug recoveries from the ECMO circuits and control groups at 24 h relative to baseline were 67 and 89% for teicoplanin, 100 and 145% for tigecycline, 67 and 99% for micafungin, 45 and 75% for meropenem, 62 and 60% for polymyxin B, 83 and 85% for caspofungin, 79 and 98% for cefoperazone, 75 and 87% for sulbactam, and 60 and 101% for voriconazole, respectively. Simple linear regression showed no significant correlation between lipophilicity ($r^2 = 0.008$, $P = 0.225$) or the protein binding rate ($r^2 = 0.168$, $P = 0.479$) of drugs and the extent of drug loss in the ECMO circuits.

Conclusions: In the two ECMO circuits, meropenem and voriconazole were significantly lost, cefoperazone was slightly lost, while tigecycline and caspofungin were not lost. Drugs with high lipophilicity were lost more in the Maquet circuit than in the Sorin circuit. This study needs more *in vivo* studies with larger samples for further confirmation, and it suggests that therapeutic drug concentration monitoring should be strongly considered during ECMO.

Keywords: antimicrobial agents, extracorporeal membrane oxygenation, sequestration, *ex vivo*, intensive care unit

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a prolonged form of cardiopulmonary bypass used to support patients with life-threatening respiratory or cardiac failure (1). The ECMO circuit consists of a membrane oxygenator, a centrifugal pump, a heat exchanger and, PVC tubing.

Patients receiving ECMO require multiple medications, including sedatives, analgesics, antimicrobial agents, anticoagulants, and vasoactive agents. The pharmacokinetics of drugs administered during ECMO is complicated. As an extension of the human cardiovascular system, the presence of ECMO circuits can further increase the total circulation volume, cause increases in the apparent volume of distribution (Vd), and lead to drug sequestration, thus affecting the pharmacokinetics of various drugs (2–4). *Ex vivo* experiments (5–7) confirmed significant drug sequestration in the ECMO circuit, and the extent of loss depends upon the physicochemical properties of the drug, the types of components of the circulation circuit, and circuit duration of use (8–10). Drugs with high octanol/water partition (log P), such as propofol (log P = 4.0) (8), have high solubility in organic materials and thus exhibit a considerable loss in the ECMO circuit.

Patients requiring ECMO treatment often have severe infectious diseases, so antimicrobial treatment is particularly critical. Inadequate antimicrobial treatment is closely associated with the presence of antibiotic resistance in clinically important pathogens (11) and may result in therapeutic failure. Some studies suggest a significant drug loss of meropenem (10), voriconazole (5), and caspofungin (6) within the ECMO circuits. However, the drug loss of teicoplanin, tigecycline, polymyxin B, and cefoperazone-sulbactam in ECMO circuits has not been reported. To address this issue, we set out to determine the drug absorption of these antimicrobial agents in different types of ECMO circuits. Our research attempts to provide experimental evidence for the use of teicoplanin, tigecycline, micafungin, meropenem, polymyxin B, caspofungin, cefoperazone sulbactam, and voriconazole in future ECMO treatment.

MATERIALS AND METHODS

Ethics

This study was approved by the Medical Ethics Committee of NanFang Hospital of Southern Medical University (NFEC-2020-021). We obtained informed consent from each volunteer.

Study Design and Participants

Four healthy volunteers were recruited. After obtaining informed consent, 402 ml of blood was collected through the cubitus vein using disposable blood bags (Fresenius Kabi), of which 2 ml was used for a routine blood examination. Sorin (LivaNova, London, United Kingdom) and Maquet (Getinge AB, Hirrlingen, Germany) ECMO circuits were used to establish self-circulation and were primed with fresh whole human blood. After the circulation stabilized, the drugs were added to the circuit. Blood samples were collected at different time points, and the drug concentration was measured to observe the recovery rate of different drugs in the ECMO cycle.

Extracorporeal Membrane Oxygenation Circuits

Each circuit consisted of a membrane oxygenator, centrifugal pump, cannula, heat exchanger, and PVC tubing. The materials of each ECMO component are shown in **Supplementary Material 1**. A reservoir bag containing 30 mL of blood was used to construct a bypass to maintain the pressure of the circuit (**Figure 1**). Eight hundred milliliters of fresh whole human blood (<1 h old) was used to prime the circuit. Heparin (5,000 U) was added to the circuits to prevent clotting.

The final volumes in the Maquet circuit and Sorin circuit were 818 ± 1 mL and 525 ± 1 mL, respectively. The circuit flow rate was controlled at 4–5 L/min. Circuit temperature was maintained at 37°C. Carbon dioxide gas and sodium bicarbonate solution were added to the circuit to maintain the pH of the circulating blood in the range of 7.25–7.55.

Drug Administration

When the temperature, flow rate, and pH of the ECMO circuits were stable, teicoplanin (120 mg), tigecycline (20 mg), micafungin (50 mg), meropenem (200 mg), polymyxin B (100,000 U), caspofungin (10 mg), cefoperazone-sulbactam (750 mg), and voriconazole (60 mg) were injected at 2-s intervals into a pre oxygenator injection site. These bolus doses were selected to produce concentrations similar to clinical concentrations. The order of administration was determined according to the half-life from long to short. According to the drug instructions, none of the drugs interact with each other (12). Two milliliters of physiological saline solution (0.9%) was used to flush the tube after injection of all drugs to avoid drug loss at the entrance of administration.

Blood Sample Collection

Whole blood was collected in polypropylene tubes containing ethylenediaminetetraacetic acid (EDTA) from a post-oxygenator site and chilled to 4°C until further processing. Blood samples were collected from the ECMO operation group at 5, 15, 30 min, 1, 3, 6, 12, and 24 h after drug administration (13, 14). The control group did not pass through the circuits but was kept at the same warming temperature to observe the spontaneous degradation of the drug. Ten milliliters of blood were collected 2 min after the injection of all the drugs, of which 8 ml was divided into 4 tubes and stored at 4°C after 3, 6, 12, and 24 h of immersion in a water bath at 37°C separately as a control group. The blood drug concentration of the remaining 2 ml sample was regarded as the baseline value of all sampling points.

Measurement of Drugs in Plasma Samples

All blood samples were stored at 4°C and centrifuged (10 min at 3,000 × g) within 8 h after sampling, and the plasma was separated and stored in clean polypropylene cryogenic vials at −80°C until analysis. The blood concentration of various drugs was measured through high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS).

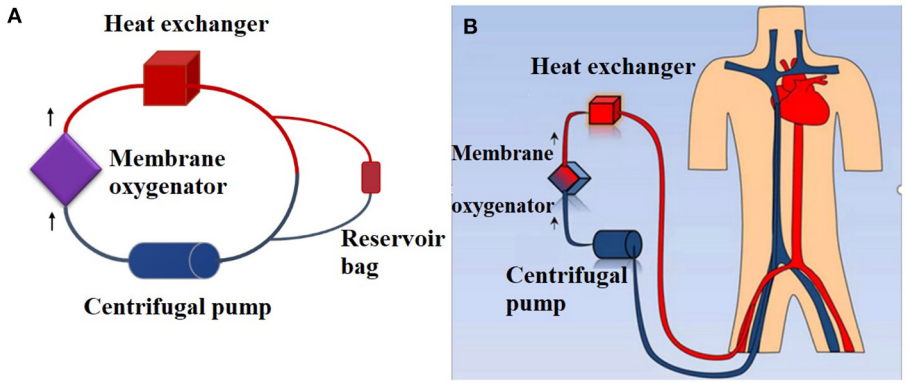

FIGURE 1 | Simulated closed loop ECMO circuits primed with fresh whole human blood. **(A)** *Ex vivo* ECMO circuit. A reservoir bag containing 30 mL of blood was used to construct a bypass to maintain the pressure of the circuit. A total of 800 mL of fresh whole human blood (<1 h) was used to prime the circuit. **(B)** *In vivo* ECMO circuit.

The recoveries of each drug after different times of circulation were calculated based on the blood concentration at 2 min.

Intra- and inter-assay means were within 15% of the target range value. For tigecycline, the linear calibration range was 0.07–8 ug/ml. For cefoperazone, the linear calibration range was 2.67–320 ug/ml. For sulbactam, the linear calibration range was 0.93–112 ug/ml. For teicoplanin, the linear calibration range was 1.6–192 ug/ml. For caspofungin, the linear calibration range was 0.53–64 ug/ml. For meropenem, the linear calibration range was 1–120 ug/ml. For voriconazole, the linear calibration range was 0.27–32 ug/ml. For micafungin, the linear calibration range was 0.54–64 ug/ml. For polymyxin B, the linear calibration range was 0.93–112 ug/ml.

Drug concentrations were measured using a Shimadzu (Kyoto, Japan) LC-20AD UHPLC system interfaced with a Shimadzu LCMS-8040 triple quadrupole mass spectrometer (MS/MS). Data acquisition and quantitative analysis were carried out using Shimadzu LabSolutions software.

Statistical Analysis

Statistical analysis was performed using SPSS software for Windows, version 26 (IBM Corp, Armonk, NY, USA). Paired *t*-tests were used to compare the differences in drug recoveries at 24 h between the ECMO operation group and the control group. A P-value < 0.05 was considered to indicate statistical significance. The concentration-vs.-time curves (mean ± standard error of the mean) were plotted using GraphPad Prism version 8.0 (GraphPad Software, Inc., La Jolla, CA, USA). Log P and protein binding rate for the individual drugs were obtained from DrugBank®, a web-accessible public database (12). We used simple linear regression to explore the relationship between the log P or protein binding rate of drugs and the extent of their loss in the circuit at the end of 24 h.

RESULTS

The *ex vivo* circuits were maintained under physiological conditions for 24 h with no complications during ECMO operation. The pH value in the individual circuits over the 24 h was between 7.226 and 7.504 (**Supplementary Material 2**). The circuit flow rate was 4.25–4.74 L/min. In this study, two experiments were carried out and 26 blood samples were analyzed. The first experiment was conducted with the Maquet ECMO circuit. The drugs studied were teicoplanin, tigecycline, meropenem, caspofungin, cefoperazone-sulbactam, and voriconazole. The blood samples collected at each time point were measured twice due to the uncertainty of the initial experiment. The second experiment was carried out with Sorin ECMO circuit, micafungin and polymyxin B were added in addition to the above drugs, and the blood samples were measured only once.

Drug Loss of Experimental Drugs in ECMO Circuits and Control Groups

A total of 26 samples were analyzed. After 24 h of operation of the two types of ECMO circuits, significant drug loss occurred in meropenem and voriconazole, and a small loss in cefoperazone, while no significant loss was observed in tigecycline and caspofungin in both ECMO circuits (**Figure 2**). In the Sorin circuit, significant drug loss occurred in teicoplanin, micafungin, and polymyxin B, while a small amount of drug loss occurred in sulbactam. There was no significant difference in the recovery rates of teicoplanin and sulbactam between the Maquet circuit and the control group. In the Maquet circuit, drug loss for voriconazole ($P = 0.018$) and at 24 h was significantly higher than the drug loss in control groups. But there were no other significant differences in drug loss for meropenem ($P = 0.301$), tigecycline ($P = 0.100$), caspofungin ($P = 0.559$), sulbactam ($P =$

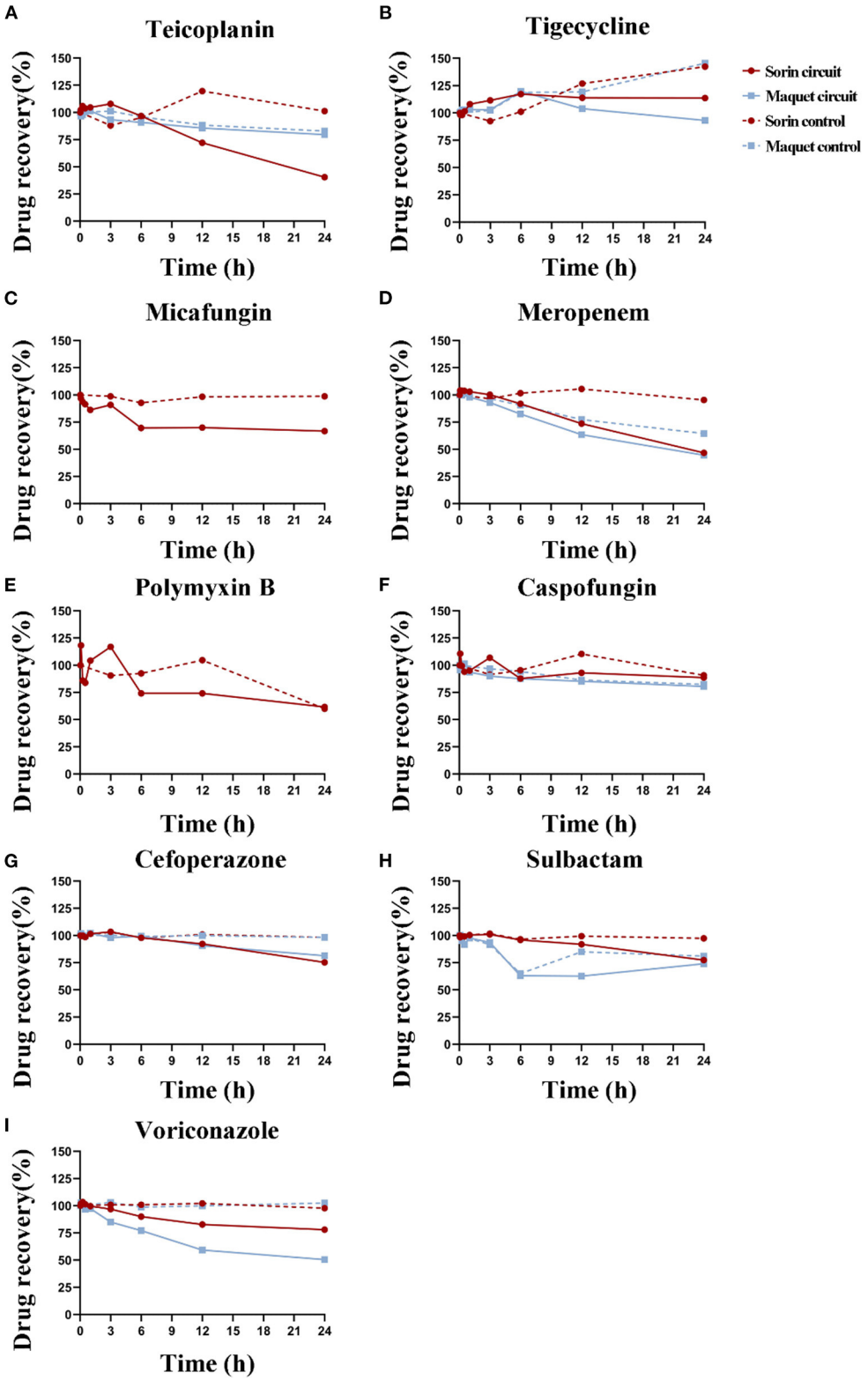

FIGURE 2 | Durg recovery of experimental drugs at different time points in Sorin and Maquet ECMO circuits and corresponding control groups. Average drug recovery vs. time for **(A)** teicoplanin, **(B)** tigecycline, **(C)** micafungin, **(D)** meropenem, **(E)** polymyxin B, **(F)** caspofungin, **(G)** cefoperazone, **(H)** sulbactam, and **(I)** voriconazole in the Maquet (blue) and Sorin (red) circuits and corresponding control groups.

TABLE 1 | The log P-value and protein-binding rate of drugs and the extent of their loss in the blood-primed circuit at 24 h.

Drug	Drug recovery (%) from circuits at 24 h	Drug recovery (%) from control group at 24 h	Lipophilicity (log P)†	Protein binding rate (%)
Teicoplanin	66.64 (24.37)	89.06 (14.40)	−1.1	90–95
Tigecycline	100.03 (13.68)	144.54 (2.31)	0.8	71–89
Micafungin	66.85 (-)*	98.82 (-)*	−1.5	99
Meropenem	45.37 (3.58)	74.84 (19.10)	−0.6	2
Polymyxin B	61.66 (-)*	60.10 (-)*	−4.861	79–92
Caspofungin	83.26 (6.17)	85.24 (7.93)	−2.798	97
Cefoperazone	79.41 (19.16)	98.30 (1.17)	−0.74	82–93
Sulbactam	75.15 (6.50)	86.55 (11.31)	−0.92	38
Voriconazole	59.70 (16.00)	101.01 (2.85)	2.561	58

Data are presented as the mean (SD).

**The data of polymyxin B data were only available in the Sorin circuit; therefore, they had no standard deviation.*

†Log P and protein-binding rate for the individual drugs were obtained from DrugBank®, a web-accessible public database.

0.105), cefoperazone ($P = 0.079$) and teicoplanin ($P = 0.094$) at 24 h between circuit and control group.

The average drug recoveries from the ECMO circuits and control groups at 24 h relative to baseline were 67 and 89% for teicoplanin, 100 and 145% for tigecycline, 67 and 99% for micafungin, 45 and 75% for meropenem, 62 and 60% for polymyxin B, 83 and 85% for caspofungin, 79 and 98% for cefoperazone, 75 and 87% for sulbactam, and 60 and 101% for voriconazole, respectively (**Table 1**). Detailed data on drug recovery for each drug at different time points in each circuit are shown in **Supplementary Materials 3, 4**.

The Difference in Drug Loss Between the Maquet Circuit and the Sorin Circuit

The drug recovery rates of tigecycline, caspofungin, meropenem, and cefoperazone in these two circuits were similar. In the Sorin circuit, significant drug loss occurred in teicoplanin, and a small amount of drug loss occurred in sulbactam, while in the Maquet circuit, the drug recovery rates of teicoplanin ($P = 0.094$) and sulbactam ($P = 0.105$) were not significantly different from those in the control group. Voriconazole showed significant drug loss after 3 h of operation in the Maquet circuit, while it remained unchanged in the first 3 h of operation in the Sorin circuit. The recovery rate of voriconazole at 24 h was 53% in the Maquet and 78% in the Sorin circuit.

Correlation Between Drug Recovery and Log P or Protein Binding Rate

The relationship between drug recovery and lipophilicity (represented as log P) or protein binding rate was analyzed using linear regression. The log P, protein binding rate, and average drug recovery rates of all drugs were summarized in **Table 1**. The correlation between log P of drugs and the extent of their loss in the blood-primed circuit at 24 h was not significant ($r^2 = 0.008$, $P = 0.225$), nor was the protein binding rate of drugs ($r^2 = 0.168$, $P = 0.479$).

DISCUSSION

To the best of our knowledge, this is the first *ex vivo* experiment to evaluate the sequestration of teicoplanin, tigecycline, polymyxin B, cefoperazone, and sulbactam in ECMO circuits.

Teicoplanin showed a large loss in the Sorin circuit (59%), which may due to its high protein binding rate (90–95%). Similar to our findings, Chen et al. (15, 16) recommended four doses of teicoplanin administered within the initial 72 h at a dose of 12 mg/kg/dose, a higher than the normal dose, which could successfully achieve a therapeutic serum trough concentration of teicoplanin (>10–15 mg/L). Previous studies have also pointed out that critically ill patients who did not receive ECMO support also need to increase the dosage of teicoplanin: compared with patients receiving lower loading dose (6 mg/kg/ dose, 4 doses), critically ill patients receiving high loading dose of teicoplanin (12 mg/kg/ dose, 4 doses) are more likely to reach sufficient blood concentration (17). Combined with the above studies and the results of this experiment, the drug loss of teicoplanin during ECMO support may be the result of the drug adsorption by the ECMO circuit and the pathophysiological changes caused by critical diseases. Therefore, we suggest that patients receiving Sorin ECMO support should increase the dosage of teicoplanin to ensure the therapeutic effect. It is worth noting that there is almost no drug loss of teicoplanin in the Maquet circuit, which may be related to the differences of membrane oxygenator and PVC pipeline coating between the two types of ECMO. However, there are no other studies to compare the difference of teicoplanin drug loss in these two types of ECMO. More *ex vivo* and *in vivo* experiments are needed to guide the administration of teicoplanin during ECMO support.

At present, only one study has reported that ECMO has no effect on tigecycline pharmacokinetics (18). Similar to this case report, no drug loss of tigecycline was observed in the Maquet/Sorin circuit in our study, which may be due to its weak lipophilicity (log P 0.8). The average Vd of tigecycline in critically ill patients is 398 L, which is therefore unlikely to be noticeably increased simply by dilution into the system. Present studies have shown that ECMO does not affect the pharmacokinetic

parameters of tigecycline. However, researches conducted in critically ill patients have recommended a high-dose tigecycline regimen (LD 200 mg, MD 100 mg, BID) (19, 20). Therefore, it is suggested that the plasma concentration of tigecycline be monitored regularly during ECMO support to prevent the failure of anti-infection treatment.

We detected a significant drug loss of polymyxin B in the Sorin circuit at 6 h. The drug recovery was 74% in the Sorin circuit group and 93% in the control group. Unexpectedly, the drug recovery in the Sorin circuit and the control group was 62 and 60% at 24 h, respectively. Polymyxins are highly surface-active; therefore, their drug loss from aqueous solutions onto the surfaces of the apparatus used during the collection and processing of samples may have an impact on recovery (21). Since we experimented with the Sorin circuit only once, we hypothesized that the recovery rate of polymyxin B at 24 h in the control group (60%) might be reduced due to its adherence to the collection device during processing. The results of our study need to be confirmed by more experiments with a large sample size.

Cefoperazone-sulbactam is a hydrophilic drug, which makes the sequestration of Cefoperazone-sulbactam in the ECMO circuit less likely than that of lipophilic drugs. In our study, Cefoperazone-sulbactam showed slight drug loss after 24 h of ECMO operation, further *in vivo* experiments are needed to figure out whether clinical dosage needs to be adjusted during ECMO operation.

No significant drug sequestration of caspofungin was observed in this study, the average drug recovery at 24 h was 83 and 85% in the ECMO circuit and control group, respectively. This is contrary to other *ex vivo* and *in vivo* experiments. An *ex vivo* experiment conducted by Shekar et al. found that the average drug recovery of caspofungin at 24 h in the ECMO circuit was 56% (6). A case report (22) observed that the standard dose of caspofungin failed to reach the target plasma concentration level during ECMO support. However, other *in vivo* studies (23–25) have suggested that ECMO does not affect the pharmacokinetic characteristics of caspofungin. Caspofungin is hydrophilic (log P −2.798) but has a high protein binding rate (97%), which may lead to significant differences in its recovery in different types of ECMO circuits. Given the large variation among patients and the extremely limited sample size of the above studies, it is difficult to draw a unified conclusion. Therefore, the dose of caspofungin during ECMO support still needs to be adjusted according to the monitoring results of plasma concentration.

Similar to caspofungin, micafungin is hydrophilic (log P −1.5) and has a high protein binding rate (>99%). An *ex vivo* study conducted by Watt et al. (26) showed that the average drug recovery of micafungin in the ECMO loop was 26–43% at 24 h, compared to 57% in the control group. Watt explained that drug degradation is the most likely mechanism of loss in the controls. Micafungin is known to degrade in light, neither the ECMO circuit nor the control group was light-avoiding, which might lead to a large amount of degradation of micafungin. However, in our study, the drug recovery of micafungin was 67% in the Sorin loop and 99% in the control group at 24 h, which was much higher than the results of Watt's research. Therefore, the drug degradation of micafungin may not explain its significant drug loss in the ECMO circuit. *In vivo* studies found that in infants on ECMO, the Vd of micafungin was 20–90% higher than that reported in infants not on ECMO (27). However, a prospective observational study carried out in 12 adult patients on ECMO found no significant changes in the pharmacokinetic parameters of micafungin (28). Infants have less blood volume than adults, so ECMO circuits might have a greater effect on the Vd of micafungin in infants. Both *ex vivo* and *in vivo* studies in infants have shown remarkable drug loss of micafungin during ECMO support, therefore, we recommend increasing the dose of micafungin in infants on ECMO. As for adult patients on ECMO, we could maintain the conventional dose and adjust the dose regimen of micafungin according to the plasma concentration.

Previous *ex vivo* experiments have shown that the drug recovery of voriconazole at 24 h in the ECMO circuit was only 29% (5). This study detected an average 24 h recovery of 60% for voriconazole in the ECMO circuit, which also showed significant drug loss. Consistent with the results of *ex vivo* experiments, *in vivo* experiments also showed insufficient plasma concentrations of voriconazole in patients under ECMO. Plasma concentration monitoring of voriconazole in two adult patients under ECMO showed that more than 50% of the measured plasma concentration levels were below the detection lower limit (5). Existing researches have shown that due to the high lipophilicity of voriconazole (log P 2.561), substantial drug loss of voriconazole occurs during the ECMO process, requiring a routine increase in the dose of voriconazole. It is worth noting that indiscriminately increasing the dose of voriconazole may cause its plasma concentration to exceed the treatment window and lead to adverse events (23). Therefore, in the treatment of voriconazole during ECMO support, the peak concentration and trough concentration should be closely monitored at the same time.

The sequestration of meropenem in ECMO circuits in our research was comparable to previous reports. Consistent with previous reports [80% loss at 24 h (9); 17% loss at 3 h (9)], the average meropenem loss at 24 h in the circuits was 55% in our study. The drug loss of meropenem can be attributed to its instability at physiological temperature. Patrick suggested that optimization of meropenem treatment during ECMO requires either more frequent dosing, a dose increase, or prolonged infusion due to its degradation and significant sequestration in the ECMO circuit after 4–6 h of treatment (29). However, in a case-control study conducted by Donadello et al., ECMO therapy did not significantly influence meropenem pharmacokinetics compared with well-matched non-ECMO controls (30). Another 2 studies (31, 32) also pointed out that in patients receiving meropenem on ECMO, standard dosing (1 g 8 h) should achieve routinely targeted plasma concentrations. However, incremental dosing or continuous infusion may be needed when targeting higher plasma concentrations and/or in patients with elevated creatinine clearance.

Previous studies have shown that different types of pumps and circuits affect drug sequestration during ECMO therapy. Wildschut et al. (10) found that the recovery of midazolam and fentanyl in centrifugal pump circuits with hollow-fiber membrane oxygenators was significantly higher than that

in neonatal roller pump circuits with silicone membranes. According to Park's research (33), the tubing material could be the source of the cause of drug loss rather than the coating material used for the ECMO circuit. The difference between Maquet and Sorin ECMO circuits is the surface coating material. Maquet is coated with Bioline (an albumin-heparin coating in which heparin is covalently bonded to albumin immobilized on the surface), and Sorin is coated with choline phosphate. Teicoplanin, which has low lipophilicity, lost far more Sorin than Maquet circuits. Therefore, when the tubing material is the same, the coating material will become the primary cause of drug loss in ECMO circuits, which is associated with drug lipophilicity.

Simple linear regression did not find any significant correlation between log P ($r^2 = 0.008$, $P = 0.225$) or protein binding rate ($r^2 = 0.168$, $P = 0.479$) of drugs and the extent of their loss in the blood-primed circuit at 24 h. We failed to find their correlation using non-linear regression analysis. Shekar et al. declared that drugs with significantly reduced concentrations at 24 h were either highly protein-bound (>80%), highly lipophilic (log P > 2.3), or both. However, in our research, the concentration of highly protein-bound drugs, such as cefoperazone, remained relatively stable after 24 h of circulation; drugs with a low protein-binding rate and low lipophilicity, such as sulbactam and meropenem, showed important losses in ECMO circuits. More research is needed on these drugs to understand their adsorption in ECMO circulation.

Our *ex vivo* study has some limitations. First of all, due to the high cost of the ECMO equipment, we only conducted one experiment for each type of ECMO circuit, the solidity of the results might suffer from too few replicates of the experiment. More replicates on these drugs are needed in the future to clarify the influence of the ECMO circuit on them. Secondly, the concurrent presence of 9 physically compatible drugs in the circuit and control groups may have had an impact on competitive binding to plasma proteins or the circuit components, thereby influencing the results. And lastly, a reservoir bag was necessary to construct a bypass to maintain pressure on the circuit, which may have influenced the circuit drug loss because of its own drug absorption. Similarly, the drug lost in the control groups due to the binding of drugs to the polypropylene tubes was immeasurable.

In conclusion, in the two ECMO circuits, meropenem and voriconazole were significantly lost, cefoperazone was slightly lost, while tigecycline and caspofungin were not lost. Drugs with high lipophilicity were lost more in the Maquet circuit than in the Sorin circuit. This study needs more *in vivo* studies with larger samples for further confirmation, and it suggests that therapeutic drug concentration monitoring should be strongly considered during ECMO.

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 Medical Ethics Committee of NanFang Hospital of Southern Medical University (NFEC-2020-021). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZC designed and coordinated the study. YZ and HH collected and analyzed data and developed the manuscript for publication. QO and TS assisted with the operation of ECMO circuits. QZ guided antimicrobial dosage. HZ was in charge of the blood collection from volunteers. JW and ZZ assisted with statistical analysis. JL was responsible for the measurement of drug concentration. All authors provided final approval of the version submitted for publication.

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SUPPLEMENTARY MATERIAL

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Early Enteral Nutrition Tolerance in Patients With Cardiogenic Shock Requiring Mechanical Circulatory Support

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Background: Enteral nutrition (EN) is recommended within the first 24–48 h for patients with hemodynamic stability, following admission to an intensive care unit (ICU). However, for patients with approximate stable hemodynamics requiring mechanical circulatory support and vasoactive drugs, the application of early EN remains controversial. We sought to evaluate the tolerance of early EN in patients with cardiogenic shock who required vasoactive drugs and mechanical circulatory support after cardiac surgery.

Methods: This single-center, prospective observational study included patients with cardiogenic shock, requiring vasoactive drugs and mechanical circulatory support after cardiac surgery, undergoing EN. The primary endpoint was EN tolerance and secondary endpoints were mortality, length of mechanical ventilation, and length of ICU stay.

Results: From February 2019 to December 2020, 59 patients were enrolled, of which 25 (42.37%) developed intolerance within 3 days of starting EN. Patients in the EN intolerant group had a longer median length of mechanical ventilation (380 vs. 128 h, $p = 0.006$), a longer median ICU stay (20 vs. 11.5 days, $p = 0.03$), and a higher proportion of bloodstream infections (44 vs. 14.71%, $p = 0.018$). The median EN calorie levels for all patients in the first 3 days of EN were 4.00, 4.13, and 4.28 kcal/kg/day, respectively. Median protein intake levels of EN in the first 3 days were 0.18, 0.17, and 0.17 g/kg/day, respectively. No significant difference was observed in the median dose of vasoactive drugs between the groups (0.035 vs. 0.05 μg/kg/min, $p = 0.306$).

Conclusions: Patients with cardiogenic shock after cardiac surgery had a high proportion of early EN intolerance, and patients with EN intolerance had a worse prognosis, but no significant correlation was identified between EN tolerance and the dose of vasoactive drugs.

Keywords: enteral nutrition, cardiogenic shock, mechanical circulatory support, vasoactive drugs, tolerance

INTRODUCTION

According to the guidelines from the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN), enteral nutrition (EN) is recommended for patients admitted to an intensive care unit (ICU) once hemodynamics are stable (1). Similarly, the European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines also recommend that if oral intake is not possible, early EN (within 48 h) in critically ill adult patients should be performed/initiated rather than delaying it (2). Early EN nourishes the intestinal mucosa, maintains intestinal integrity, maintains intestinal microbial diversity, and improves immunity and metabolic function (3). Therefore, when compared with delayed EN, early EN reduces infectious complications (4–20).

Although early EN is recommended for most critically ill patients, the European Society of Intensive Care Medicine (ESICM) guidelines advocate seven scenarios that require delayed EN, including uncontrolled shock and failure to achieve hemodynamic and tissue perfusion targets (14). Some studies have demonstrated that vasoactive drugs aggravate visceral vasoconstriction and intestinal metabolic disorders caused by shock, and this may lead to intestinal ischemia (21). Similarly, early EN was speculated to cause abdominal distension, diarrhea, vomiting, aspiration, and possibly death (22–25). However, a recent study reported that intestinal ischemia is rare in patients receiving vasoactive drugs during EN; the incidence is 0.3–3.8% (21). However, while previous studies have focused on septic shock patients, data on EN safety in patients with cardiogenic shock are limited, and critically, conclusions are inconsistent (26–31). Furthermore, a consensus has not been reached on safe vasoactive drug doses during early EN.

Patients with cardiac surgery frequently present with circulatory failure for various reasons (32–35). Vasoactive drugs and mechanical circulatory support are thus required to achieve hemodynamic targets. In this study, we investigated the tolerance of early EN in patients taking vasoactive drugs and undergoing mechanical circulatory support after cardiac surgery to determine the effects of different vasoactive drug doses on the safety of early EN administration.

MATERIALS AND METHODS

Study Design

This was a single-center prospective observational study. From February 2019 to December 2020, patients were continuously enrolled from a cardiac surgery ICU of a tertiary hospital. The ICU has 40 beds and accommodates various cardiac surgery perioperative patients. The study was approved by the ethics committee of Zhongshan Hospital, Fudan University (Approval No. B2019-075R), and patients or family members provided informed consent prior to study commencement.

Participant Selection

Inclusion criteria were as follows: (1) age $\geq$ 18 years, (2) patients with cardiogenic shock receiving vasoactive drugs and mechanical circulatory support, including extracorporeal membrane oxygenation (ECMO) or intraaortic balloon pump (IABP), (3) mean arterial pressure $\geq$ 65 mmHg, (4) starting

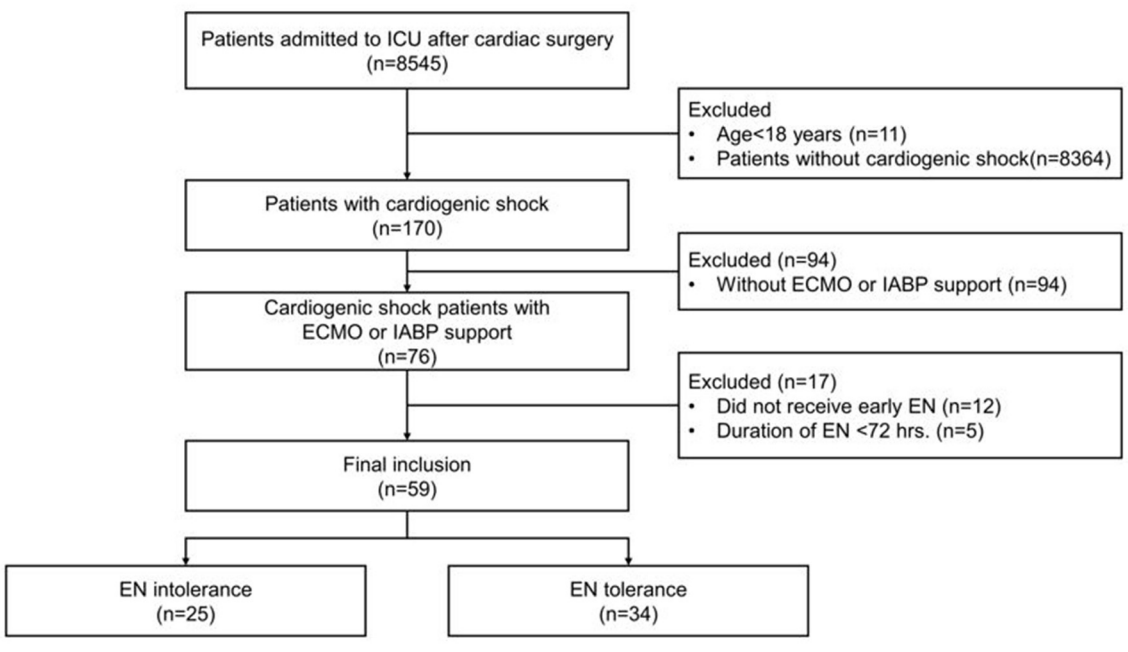

FIGURE 1 | Flowchart of patient selection. ICU, intensive care unit; EN, enteral nutrition.

EN within 48 h after hemodynamic stability, and estimated EN duration ≥ 72 h.

Exclusion criteria included were as follows: (1) discontinued vasoactive drugs and mechanical circulatory support within 1 h after EN commencement, (2) situations where ESICM guidelines recommended EN should be delayed, i.e., uncontrolled hypoxemia and acidosis, uncontrolled gastric intestinal bleeding, overt bowel ischemia, bowel obstruction, abdominal compartment syndrome, and gastric aspirate volume > 500 ml/6 h. Cardiogenic shock was defined as a state of critical end-organ hypoperfusion due to reduced cardiac output (36).

Data Collection and Outcome Definitions

According to the EN tolerance of patients, they were divided into EN tolerant and EN intolerant groups. EN intolerance was defined as gastric residual volume (GRV) > 250 ml on any day or any kind of EN complication (vomiting, abdominal distension, diarrhea, intestinal ischemia, and aspiration) within 3 days of EN (10, 12). Aspiration was defined as digestive fluid or EN solution in the respiratory tract by bronchoscope. Continuous gastrointestinal decompression was performed 1 h after the end of EN, and the amount of gastrointestinal decompression was defined as the GRV.

Patient baseline data were collected within 24 h after ICU admission, including patient characteristics, such as age, gender, height, weight, body mass index (BMI), types of mechanical circulatory support, comorbidity, previous cardiac surgery, left ventricular ejection fraction (LVEF) before surgery, acute physiology and chronic health evaluation (APACHE) II scores, surgery time, cardiopulmonary bypass time, and laboratory data such as liver function, renal function, cardiac biomarker, and serum lactate indices. Nutrition-related data were collected for 3 consecutive days after the start of EN and included daily GRV, EN volume, protein levels, calories provided by EN, calories provided by parenteral nutrition (PN), and calories provided by propofol. These data were derived from the in-house electronic medical record system and nurse-record sheets.

Information on vasoactive drug types and doses in the first 3 days of EN were collected. The following formula was used to calculate the equivalent dose of norepinephrine, where equivalent dose of norepinephrine = norepinephrine (μg/min) + dopamine (μg/min) ÷ 2 + epinephrine (μg/min) +

TABLE 1 | Patient baseline characteristics grouped by EN intolerance or tolerance.

Characteristics	Total (*n* = 59)	Intolerance (*n* = 25)	Tolerance (*n* = 34)	*P*-value
Age (y)	63 (55–67)	62 (52–66)	63 (55–68)	0.628
Gender (male, %)	46 (77.97)	23 (92.00)	23 (67.65)	0.030
Weight (kg)	65 (60–75)	65 (62–73)	64 (60–79)	0.718
Height (cm)	168.93 ± 8.70	172.04 ± 7.74	166.65 ± 8.77	0.020
BMI (kg/cm^2)	23.54 ± 4.41	22.67 ± 4.04	24.17 ± 4.62	0.425
ECMO (*n*, %)	16 (27.12)	12 (48.00)	4 (11.76)	0.003
IABP (*n*, %)	46 (78.00)	14 (56.00)	32 (94.10)	0.001
LVEF before surgery (%)	49.05 ± 13.88	51.36 ± 12.35	47.35 ± 14.85	0.326
APACHE II	10 (7–18)	13 (7–19)	9.5 (7–13)	0.177
Surgery time (min)	293 (219–380)	277 (178–395)	305 (240.5–365)	0.179
Cardiopulmonary bypass time (min)	137 (0–191)	130 (0–207)	146 (48–187)	0.895
TBil (μmol/L)	13.89 ± 7.60	15.49 ± 8.04	12.72 ± 7.14	0.187
Total protein (g/L)	65.42 ± 6.28	63.80 ± 7.35	66.62 ± 5.15	0.112
Albumin (g/L)	39.37 ± 4.49	38.24 ± 5.20	40.21 ± 3.76	0.113
AST (U/L)	23 (14–36)	23 (14–35)	24 (14–38)	0.794
ALT (U/L)	23 (17–36)	24 (18–36)	22 (17–36)	0.908
cTnT (ng/ml)	1 (0.50–2.73)	0.86 (0.52–2.72)	1.61 (0.47–3.55)	0.634
NT-proBNP (pg/ml)	2,994 (1,410–8,199)	2,914 (1,322–6,293)	3,239.5 (1,606–9,757)	0.586
Lactate (mmol/L)	4.6 (1.5–8.3)	4.6 (1.4–9.0)	4.55 (1.6–7.7)	0.914
eGFR (ml/min/1.73 m^2)	68 (62–89)	65 (61–81)	71 (63–90)	0.205
Hypertension (*n*, %)	29 (49.15)	13 (52.00)	16 (47.06)	0.795
Diabetes mellitus (*n*, %)	14 (23.73)	6 (24.00)	8 (23.53)	1.000
CKD (*n*, %)	7 (11.86)	5 (20.00)	2 (5.88)	0.122
Cerebral infarction (*n*, %)	6 (10.17)	3 (12.00)	3 (8.82)	0.691
Myocardial infarction (*n*, %)	2 (3.39)	1 (4.00)	1 (2.94)	1.000
Cardiac surgery (*n*, %)	10 (16.95)	4 (16.00)	6 (17.65)	1.000

EN, enteral nutrition; BMI, body mass index; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; TBil, total bilirubin; ALT, alanine transaminase; AST, aspartate transaminase; cTnT, cardiac troponin T; NT-proBNP, N-terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate.

Categorical variables are expressed as n (%). Continuous variables are expressed as mean ± SD or median (Q1–Q3).

TABLE 2 | The primary and secondary outcomes, grouped by EN intolerance or tolerance.

Characteristics	Total ($n = 59$)	Intolerance ($n = 25$)	Tolerance ($n = 34$)	*P*-value
Norepinephrine equivalents (μg/min)	3.17 (1.33–7.14)	3.83 (2.42–6.57)	2.25 (1.13–10.96)	0.330
Norepinephrine equivalents (μg/kg/min)	0.04 (0.02–0.10)	0.05 (0.04–0.09)	0.03 (0.01–0.135)	0.306
Initial dose of EN (mL)	200 (200–450)	250 (200–500)	200 (200–300)	0.234
Average dose for the first 3 days of EN (mL)	317 (233–450)	256.67 (233.33–458.34)	316.67 (224.17–412.50)	0.829
CRRT (*n*, %)	15 (25.4)	9 (36.0)	6 (17.6)	0.137
Length of mechanical ventilation (h)	216 (77–408)	380 (102–576)	128 (58.5–300)	0.006
Length of ICU stay (day)	16 (7–25)	20 (11–31)	11.5 (7–18)	0.030
Length of hospital stay (day)	28 (20–43)	31 (19–46)	25.5 (20–37)	0.519
Mortality (*n*, %)	17 (28.81)	10 (40.00)	7 (20.59)	0.147
Infection rate (*n*, %)	40 (67.80)	20 (80.00)	20 (58.82)	0.100
Pulmonary infection (*n*, %)	39 (66.10)	20 (80.00)	19 (55.88)	0.094
Wound infection (*n*, %)	2 (3.39)	1 (4.00)	1 (2.94)	1.000
Urinary tract infection (*n*, %)	2 (3.39)	0	2 (5.89)	0.503
Bloodstream infection (*n*, %)	16 (27.12)	11 (44.00)	5 (14.71)	0.018

EN, enteral nutrition; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; CRRT, continuous renal replacement therapy; ICU, intensive care unit. Categorical variables are expressed as n (%). Continuous variables are expressed as mean ± SD or median (Q1–Q3).

phenylephrine (μg/min) ÷ 10 + vasopressin (U/h) × 8.33 (26). Based on previous practices, according to vasoactive drug doses, patients were divided into low- and high-dose groups: the average equivalent dose of norepinephrine <0.1 μg/kg/min during EN was defined as the low-dose group, whereas ≥0.1 μg/kg/min was defined as the high-dose group (27).

The primary study endpoint was patient EN intolerance. Secondary endpoints were the length of mechanical ventilation, length of ICU stay, length of stay in the hospital, in-hospital mortality, the incidence of infection, and the site of infection (e.g., pulmonary, wound, urinary system, and bloodstream infection). Intolerance signs were also recorded, including GRV > 250 ml and EN-related adverse events (e.g., vomiting, abdominal distension, diarrhea, intestinal ischemia, and aspiration).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 20. After using the KS test to evaluate data normality, normally distributed data were represented by the mean (±SD), and non-normally distributed data were represented by the median [interquartile range (IQR)]. The χ^2-test was used for categorical variables and the *t*-test or Mann–Whitney *U*-test for continuous variables. A $p < 0.05$ value was considered statistically significant.

RESULTS

Baseline Patient Characteristics

From February 2019 to December 2020, 8,545 patients, after cardiac surgery, were admitted to the cardiac surgery ICU. In total, 170 adult patients were diagnosed with cardiogenic shock with an ICU stay >72 h. Of these, 94 patients were excluded because they did not receive mechanical circulatory support, 12 were excluded because they did not receive early EN, and five were excluded because the EN duration was <72 h. Therefore, 59 patients were finally enrolled and divided into two groups; 25 in the EN intolerant group and 34 in EN tolerant group (**Figure 1**).

Patient baseline data are shown in **Table 1**. The median age was 63 years old, the majority were male (77.97%), and the average BMI was 23.5 kg/cm^2. Sixteen patients received ECMO, 46 received IABP, and 10 had received cardiac surgery prior to this admission. The median APACHE II score was 10, the average LVEF before surgery was 49%, the median surgery time was 293 min, the median cardiopulmonary bypass time was 137 min, the median cardiac troponin T (cTnT) level was 1 ng/mL, the median N-terminal probrain natriuretic peptide (NT-proBNP) level was 2,994 pg/mL, and the median lactate level was 4.6 mmol/L. The proportion of men in the EN intolerant group was significantly higher (92 vs. 68%, $p = 0.03$). In the EN intolerant group, the proportion of patients receiving ECMO was higher (48 vs. 11.76%, $p = 0.003$). We observed no statistical differences between groups in terms of age, BMI, comorbidity, pre-operative cardiac functions, APACHE II scores, surgery time, cardiopulmonary bypass time, and indices for liver function, renal function, cardiac biomarkers, and serum lactate levels.

Primary and Secondary Outcomes

As indicated, 25 (42.37%) patients were EN intolerant. As shown in **Table 2**, the median dose of norepinephrine equivalent in EN tolerant and intolerant groups was not statistically different (0.035 vs. 0.05 μg/kg/min, $p = 0.306$). The median length of mechanical ventilation in the EN intolerant group was significantly longer (380 vs. 128 h, $p = 0.006$). In addition, the median length of ICU stay for the EN intolerant group was longer than the EN tolerant group (20 vs. 11.5 days, $p = 0.03$), but no

TABLE 3 | Signs for intolerance ($N = 25$).

Signs for intolerance	*N* (%)
GRV > 250 mL	9 (36)
Aspiration	7 (28)
Diarrhea	6 (24)
Vomiting	3 (12)
Abdominal distention	5 (20)
Intestinal ischemia	0 (0)

GRV, gastric residual volume.
Variables are expressed as n (%).

significant difference in the length of hospital stay was observed between the groups (31 vs. 25.5 days, $p = 0.519$). Although the mortality rate between groups was not statistically different, the mortality rate of the EN intolerant group was almost twice that of the EN tolerant group (40 vs. 20.59%, $p = 0.147$). Moreover, the proportion of patients receiving CRRT was slightly higher in the EN intolerant group (36 vs. 17.65%, $p = 0.137$).

We observed no statistical difference in the dose of enteral feeding on the first 3 days between the groups. In terms of post-operative infections, the bloodstream infection rate in the EN intolerant group was higher than the EN tolerant group (44 vs. 14.71%, $p = 0.018$). Pulmonary infection was more common in the EN intolerant group, although no statistical differences were identified between the groups (80 vs. 55.88%, $p = 0.094$).

Among EN intolerant patients, nine (36%) had GRV > 250 mL, seven (28%) experienced aspiration, six (24%) had diarrhea, three (12%) experienced vomiting, and five (20%) had abdominal distension. No bowel ischemia occurred in this study (**Table 3**).

The calorie and protein intake of all patients in the first 3 days are shown (**Table 4**). The median calorie levels of EN in the first 3 days were 4.00, 4.13, and 4.28 kcal/kg/day, respectively, with an upward trend each day. The median calorie levels of PN in the first 3 days were 7.28, 6.55, and 6.10 kcal/kg/day, respectively, indicating a daily downward trend. The median total calories in the first 3 days were 10.87, 10.84, and 10.28 kcal/kg/day, respectively, which were basically the same. The median EN volume for patients in the first 3 days was 200, 280, and 400 mL, respectively, indicating an increasing trend. The median protein intake of EN in the first 3 days was 0.18, 0.17, and 0.17, respectively, whereas the median total protein intake was 0.61, 0.73, and 0.57 g/kg/day, respectively (**Table 4**). However, no significant differences were observed in either calorie or protein intake between the groups.

According to vasoactive drug doses, the average equivalent dose of norepinephrine <0.1 μg/kg/min was defined as the low-dose group, whereas norepinephrine ≥0.1 μg/kg/min was defined as the high-dose group. Surgery time (278.5 vs. 443.0 min, $p = 0.01$) and cardiopulmonary bypass time (115.5 vs. 174.0 min, $p = 0.04$) were significantly shorter in the low-dose group. Levels of cTnT after surgery in the low-dose group were lower (0.84 vs. 2.16 ng/mL, $p = 0.005$), and NT-proBNP levels in the low-dose group exhibited a lower trend (2,889.5 vs. 4,714

TABLE 4 | Patients' energy and protein intake in the first 3 days.

Characteristics	Day 1				Day 2				Day 3			
	Total	EN intolerance	EN tolerance	*P*-value	Total	EN intolerance	EN tolerance	*P*-value	Total	EN intolerance	EN tolerance	*P*-value
Calorie received from EN (kcal/kg/day)	4.00 (2.92–5.00)	4 (0.85–6.93)	4 (2.97–4.35)	0.618	4.13 (1.56–7.52)	3.47 (0.77–7.51)	4.21 (2.09–7.81)	0.228	4.28 (2.53–7.00)	3.88 (2.14–7.69)	4.52 (2.51–6.80)	0.976
Calorie received from propofol (kcal/kg/day)	0 (0–2.00)	0 (0–1.67)	0.48 (0–2.15)	0.226	0 (0–0.59)	0 (0–0)	0 (0–1.42)	0.099	0 (0–0.35)	0 (0–0.65)	0 (0–0.45)	0.916
Calorie received from PN (kcal/kg/day)	7.28 (5.88–8.85)	6.52 (6.01–9.05)	7.50 (5.67–8.78)	0.866	6.55 (5.31–8.35)	6.74 (5.66–8.19)	6.38 (4.79–8.43)	0.434	6.10 (4.40–7.52)	6.55 (4.78–7.55)	6.09 (3.75–7.51)	0.576
Total calorie received (kcal/kg/day)	10.87 (9.47–13.27)	11.87 (8.74–16.30)	12.18 (10.01–14.88)	0.963	10.84 (8.10–14.91)	10.16 (8.08–14.87)	12.14 (8.59–15.70)	0.510	10.28 (7.2–13.67)	12.35 (7.01–15.12)	10.24 (7.05–15.02)	0.794
Dose of EN (mL)	200 (200–450)	250 (200–500)	200 (200–300)	0.234	280 (200–500)	250 (200–500)	350 (237.5–500)	0.241	400 (200–500)	450 (200–500)	400 (200–500)	0.691
Protein received from EN (g/kg/day)	0.18 (0.13–0.21)	0.18 (0–0.27)	0.18 (0.13–0.2)	0.536	0.17 (0–0.29)	0.16 (0–0.29)	0.19 (0–0.32)	0.476	0.17 (0–0.28)	0.17 (0–0.30)	0.16 (0–0.28)	0.771
Total protein received (g/kg/day)	0.61 (0.48–0.80)	0.65 (0.53–0.88)	0.59 (0.39–0.76)	0.160	0.73 (0.49–0.92)	0.74 (0.56–0.92)	0.67 (0.38–0.95)	0.386	0.57 (0.33–0.85)	0.58 (0.57–0.99)	0.56 (0.32–0.85)	0.490

EN, enteral nutrition; PN, parenteral nutrition.
Continuous variables are expressed as median (Q1–Q3).

TABLE 5 | Patient baseline characteristics, grouped by the dose of norepinephrine equivalents.

Characteristics	Low dose (<0.1 μg/kg/min) *n* = 44	High dose (≥0.1 μg/kg/min) *n* = 15	*P*-value
Age (y)	62.50 (55.25–67.75)	64.00 (48.00–65.00)	0.507
Gender (male, %)	36 (81.8)	10 (66.7)	0.192
Weight (kg)	65.00 (60.00–75.00)	65.00 (55.00–74.00)	0.656
Height (cm)	168.95 ± 8.03	168.87 ± 10.77	0.818
BMI (kg/cm^2)	23.57 ± 4.11	23.42 ± 5.35	0.108
LVEF before surgery (%)	47.36 ± 13.80	54.00 ± 13.33	0.848
ECMO (*n*, %)	14 (31.8)	2 (13.3)	0.145
IABP (*n*, %)	33 (75)	13 (86.7)	0.290
APACHE II	10.00 (7.00–14.75)	13.00 (9.00–22.00)	0.074
Surgery time (min)	278.50 (219.00–327.50)	443.00 (293.99–600.00)	0.010
Cardiopulmonary bypass time (min)	115.50 (0–188.00)	174.00 (132.00–367.00)	0.040
TBil (μmol/L)	13.86 ± 7.58	13.99 ± 7.91	0.652
Total protein (g/L)	65.36 ± 5.98	65.60 ± 7.32	0.752
Albumin (g/L)	39.48 ± 4.24	39.48 ± 4.24	0.595
AST (U/L)	25.00 (14.50–36.00)	21.00 (14.00–45.00)	0.571
ALT (U/L)	23.50 (17.00–39.75)	22.00 (19.00–26.00)	0.423
cTnT (ng/ml)	0.84 (0.35–2.44)	2.16 (1.00–6.00)	0.005
NT-proBNP (pg/ml)	2,889.50 (1,338.00–6,776.50)	4,714.00 (1,654.00–18,221.00)	0.247
Lactate (mmol/L)	3.55 (1.53–7.48)	5.30 (1.50–10.70)	0.370
eGFR (ml/min/1.73 m^2)	68 (62–89)	66 (60–78)	0.338
Hypertension (*n*, %)	19 (43.2)	10 (66.7)	0.101
Diabetes mellitus (*n*, %)	13 (29.5)	1 (6.7)	0.067
CKD (*n*, %)	4 (9.1)	3 (20.0)	0.243
Cerebral infarction (*n*, %)	3 (6.8)	3 (20.0)	0.165
Myocardial infarction (*n*, %)	0	2 (13.3)	0.061
Cardiac surgery (*n*, %)	6 (13.6)	4 (26.7)	0.218

EN, enteral nutrition; BMI, body mass index; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; TBil, total bilirubin; ALT, alanine transaminase; AST, aspartate transaminase; cTnT, cardiac troponin T, NT-proBNP, N-terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate.

Categorical variables are expressed as n (%). Continuous variables are expressed as mean ± SD or median (Q1–Q3).

pg/mL, $p = 0.247$). Serum lactate levels after surgery in both the groups were not significantly different (3.55 vs. 5.30 mmol/L, $p = 0.37$).

For other baseline data, no significant differences were recorded between the groups (**Table 5**). Clinical outcomes are shown in **Table 6**. The CRRT rate in the high-dose group was higher (60 vs. 13.6%, $p = 0.001$). The length of mechanical ventilation tended to be prolonged in the high-dose group (348 vs. 150 h, $p = 0.095$), and the mortality rate also tended to increase in the high-dose group (46.7 vs. 22.7%, $p = 0.078$). No significant difference in GRV was observed between high- and low-dose groups (83.33 vs. 33.33 mL, $p = 0.235$). As shown in **Figure 2**, the equivalent dose of norepinephrine and GRV was discretely distributed in the scatter plot, and R^2 was 2.200×10^{-6}, which indicated no correlation between the equivalent dose of norepinephrine and GRV. No significant difference was observed in the EN intolerance rates between high- and low-dose groups (33.3 vs. 45.5%, $p = 0.305$).

DISCUSSION

In our study, 25/59 patients (42.37%) with cardiogenic shock after cardiac surgery were intolerant to EN, similar to previous studies (26–28). Merchan et al. reported for patients with sepsis receiving vasoactive drugs that 62/120 were EN tolerant, indicating an intolerance rate of 48.33% (26). However, in another study, 259 patients with vasoactive drug support had an EN intolerance rate of 25.1% (27). For patients undergoing mechanical ventilation, a previous study with 1,888 ICU patients showed an EN intolerance rate of 30.5% (28). Thus, differences in EN intolerance rates between these studies may have arisen due to different patient populations and non-uniform definitions of EN intolerance. In patients who received mechanical ventilation >72 h after cardiovascular surgery, an EN intolerance rate of 43.68% was determined (28), similar to our data. This result suggested that patients with cardiogenic shock had a higher rate of EN intolerance during vasoactive drug and mechanical

TABLE 6 | The primary and secondary outcome, grouped by the dose of norepinephrine equivalents.

Characteristics	Low dose (<0.1 μg/kg/min) *n* = 44	High dose (≥0.1 μg/kg/min) *n* = 15	*P*-value
Norepinephrine equivalents (μg/min)	2.25 (1.05–3.79)	14.00 (10.39–20.49)	<0.001
Norepinephrine equivalents (μg/kg/min)	0.04 (0.01–0.05)	0.22 (0.13–0.32)	<0.001
Enteral nutritional intolerance (*n*, %)	20 (45.5)	5 (33.3)	0.305
GRV (mL)	33.33 (5.00–125.00)	83.33 (33.33–113.33)	0.235
Initial dose of EN (mL)	200.00 (200.00–487.50)	200.00 (200.00–250.00)	0.783
Average dose for the first 3 days of EN (mL)	320.00 (228.34–487.50)	316.67 (233.33–350.00)	0.643
CRRT (*n*, %)	6 (13.6)	9 (60)	0.001
Length of mechanical ventilation (h)	150 (73.25–393.00)	348.00 (132.00–456.00)	0.095
Length of ICU stay (day)	15.00 (7.00–23.75)	17.00 (10.00–26.00)	0.276
Length of hospital stay (day)	27.00 (20.00–41.00)	30.00 (20.00–47.00)	0.464
Mortality (*n*, %)	10 (22.7)	7 (46.7)	0.078
Infection rate (*n*, %)	30 (68.2)	10 (66.7)	0.576
Pulmonary infection (*n*, %)	29 (65.9)	10 (66.7)	0.609
Wound infection (*n*, %)	1 (2.3)	1 (6.7)	0.447
Urinary tract infection (*n*, %)	1 (2.3)	1 (6.7)	0.447
Bloodstream infection (*n*, %)	12 (27.3)	4 (26.7)	0.623

EN, enteral nutrition; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; CRRT, continuous renal replacement therapy; ICU, intensive care unit. Categorical variables are expressed as n (%). Continuous variables are expressed as median (Q1–Q3).

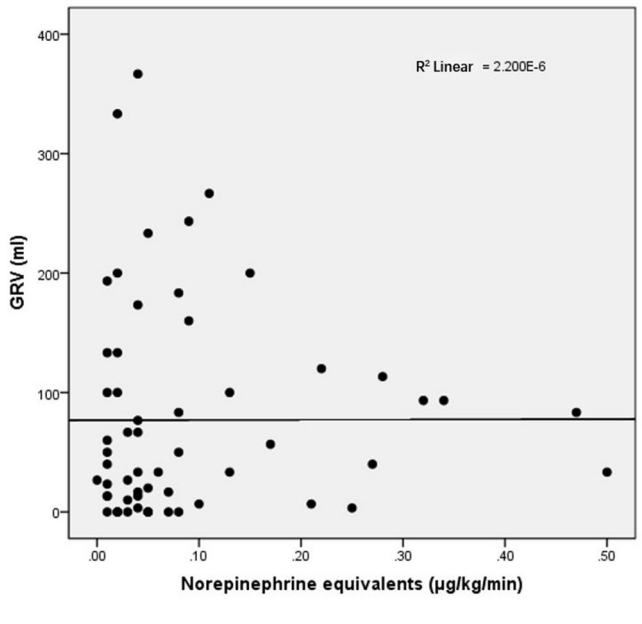

FIGURE 2 | Relationship between vasoactive drug dosage and GRV. GRV, gastric residual volume.

circulatory support. Therefore, caution should be exercised when these patients commence EN.

It was previously demonstrated that patients with EN intolerance had higher mortality, shorter length of mechanical ventilation free time, longer ICU stays, reduced calorie intake, and poorer outcomes (26, 28). Our study confirmed these findings. Patients with EN intolerance had significantly longer mechanical ventilation time, longer ICU stays, and a higher incidence of bloodstream infections. Although no statistical differences in mortality were observed between groups, mortality in the EN intolerant group was approximately twice that of the EN tolerant group. Our research demonstrated that 28% of EN intolerant patients experienced aspiration issues, which may be partially explained by the high incidence of pulmonary infections in these patients. Unfortunately, there was no statistical difference in mortality due to the small sample size.

In previous studies, the caloric compliance rate of EN in some patients with shock was between 40 and 89.8% (28, 29), among which EN intolerant patients received approximately 10.9–12 kcal/kg/d (26, 27). Our ICU had previously adopted a trophic nutrition strategy for patients with cardiogenic shock. Both calorie and protein intake levels were lower than previous studies. This may have been due to the high rate of EN intolerance in this study, and also the requirement for patients with cardiogenic shock to be fluid restricted. Hence, calorie and protein nutrition from EN and PN were both low. Furthermore, based on our previous findings, the implementation of a soybean-based intravenous fat emulsion restriction diet in cardiac surgical patients was associated with a reduced post-operative nosocomial infection rate (37). It also reduced the length of ICU/hospital stay, hospital costs, mechanical ventilation time, and a lower incidence of cholestasis. Therefore, our cardiovascular center implemented a soybean-based intravenous fat emulsion restriction diet for cardiac surgical patients. This factor was the cause of relatively low calorie and protein levels.

The relationship between vasoactive drug doses and tolerance and prognosis of early EN is inconsistent in the literature. Mancl et al. reported that in patients with septic shock, the incidence of EN intolerance was positively correlated with vasoactive drug doses (27). Therefore, many studies have sought to determine safe vasoactive drug doses when implementing early EN. Ohbe et al. compared differences in clinical outcomes for early (<48 h) or late (≥48 h) EN in shock patients on mechanical ventilation taking vasoactive drugs. Patients were divided into three groups based on the norepinephrine equivalent: low (<0.1 μg/kg/min), medium (0.1–0.3 μg/kg/min), and high (>0.3 μg/kg/min) doses. The 28-day mortality rate was significantly lower in the early EN than in the late EN groups in low- and medium-dose groups. In the high-dose group, the 28-day mortality rate did not differ significantly between the early EN and the late EN groups. Additionally, no significant difference was observed in the non-obstructive mesenteric ischemia rate (0.2 vs. 0.3%) between the early and the late EN groups (28). Thus, when supported by low and medium vasoactive drug doses, early EN was considered safe and it improved patient outcomes. Another study revealed it was safe to commence early EN in mechanically ventilated septic shock patients, with norepinephrine usage <0.14 μg/kg/min (26). However, early EN is not always safe for patients taking vasoactive drugs and those who are on mechanical ventilation support. Reignier et al., compared patient outcomes in those receiving EN and PN who were under mechanical ventilation and vasoactive drug support. Although no differences in mortality were determined, intestinal ischemia was significantly increased in patients on EN. It should be noted these patients received a very high vasopressor dose (average 0.53 μg/kg/min) (21). This observation suggested that when high-dose vasoactive drugs are used, EN should be administered with caution.

In our study, based on the vasoactive drug dose, the EN intolerance rate was 45.5% in the low-dose group and 33.3% in the high-dose group. Furthermore, no significant correlation between the average GRV and vasoactive drug dose was observed. This result was inconsistent with previous studies (28) and maybe related to our small sample size. Previous studies reported it was unsafe to commence EN when high-dose vasoactive drugs were used, and the rate of EN tolerance was negatively correlated with the dose of vasoactive drugs. The reported safe dosage is <0.14–0.32 μg/kg/min (26, 31). In our study, the overall vasoactive drug dose was relatively low, and most patients were within safe doses, as reported previously. This possibly explained the non-significant correlation between the average GRV and the vasoactive drug dose. In addition, serum lactate levels in low- and high-dose groups exhibited no statistical differences, suggesting that the timing of EN initiation cannot be based only on the vasoactive drug dose and serum lactate levels. Thus, the optimal timing for EN initiation requires further investigation.

Our study had some limitations. First, the sample size was small, with only 59 patients; thus, some bias may have been introduced. Second, the overall dose of vasoactive drugs was low, and most were within safe doses as indicated by previous studies; however, this factor may have restricted analyses of the relationships between vasoactive drug doses and the rate of EN intolerance. Third, patient calorie and protein intakes were low, which may have been related to fluid restriction and the high EN intolerant rate generated by cardiogenic shock.

CONCLUSIONS

Patients with cardiogenic shock, taking vasoactive drugs, and undergoing mechanical circulatory support had a high proportion of early EN intolerance, which was associated with adverse prognoses. However, no significant correlations were identified between EN tolerance and vasoactive drug doses.

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 Ethics Committee of Zhongshan Hospital, Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

W-jL, JZ, G-wT, and ZL: conception and design. G-wT and ZL: administrative support. JZ, J-cL, and J-fM: collection and assembly of data. W-jL and JZ: data analysis and interpretation. All authors: manuscript writing and final approval of manuscript.

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Veno-Arterial Extracorporeal Membrane Oxygenation for Patients Undergoing Heart Transplantation: A 7-Year Experience

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Objective: Primary graft dysfunction (PGD) is the leading cause of early death after heart transplantation. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) can provide temporary mechanical circulatory support and time for functional recovery of the transplanted heart. The purpose of this study was to analyze the timing and prognoses of VA-ECMO in patients with severe PGD after heart transplantation.

Methods: A total of 130 patients underwent heart transplantation at the Zhongshan Hospital Affiliated with Fudan University between January 2014 and December 2020. All patients received basiliximab immunoinduction and a classic double vena cava anastomosis orthotopic heart transplantation. Among them, 29 patients (22.3%) developed severe PGD in the early postoperative period. VA-ECMO was performed in patients with difficulty weaning from cardiopulmonary bypass (CPB) or postoperative refractory cardiogenic shock. Patients were divided into two groups according to whether or not they were successfully weaned from VA-ECMO (patients who survived for 48 h after weaning and did not need VA-ECMO assistance again). The perioperative clinical data were recorded, and all patients were followed up until discharge. Early outcomes were compared between groups.

Results: A total of 29 patients with VA-ECMO support after heart transplantation were included in this study. The proportion of patients receiving VA-ECMO was 22.3% (29/130). Nineteen patients (65.5%) needed VA-ECMO due to difficulty with weaning from CPB, and 10 patients required VA-ECMO for postoperative cardiogenic shock. Nineteen patients (65.5%) were successfully weaned from VA-ECMO. Overall, in-hospital mortality of VA-ECMO support patients was 55.2%. The main causes of death were ventricular fibrillation (four cases), major bleeding (three cases), infection (four cases), and graft failure (five cases).

Conclusion: Despite advances in heart transplantation, severe PGD remains a lethal complication after heart transplantation. At present, the treatment for severe PGD after

heart transplantation is a challenge. VA-ECMO provides an effective treatment for severe PGD after heart transplantation, which can promote graft function recovery.

Keywords: heart failure, heart transplantation, primary graft dysfunction, veno-arterial extracorporeal membrane oxygenation, cardiogenic shock

INTRODUCTION

At present, orthotopic heart transplantation is the most effective treatment for patients with end-stage heart disease. According to the 36th Annual Adult Heart Transplantation Registry report published by the International Society of Heart and Lung Transplantation (ISHLT) registry in 2019, a total of 1,31,249 adult heart transplants were completed by June 30, 2018, although >90% of the ISHLT data came from North America and Europe (1). The perioperative success rate of heart transplantation is about 90%. Shortage of donor hearts and time of donor heart ischemia are the main limitations restricting the development of heart transplantation (2).

Early primary graft dysfunction (PGD) after heart transplantation, especially right heart failure, is an important factor leading to perioperative death, affecting 7.4–36% of heart transplant recipients (3–5). The 30-day all-cause mortality for PGD has been reported to be about 19–30% (3, 4, 6). Although advances have been achieved in the field of transplantation in the past few decades, factors leading to PGD and associated treatment remain unclear (7). ISHLT has proposed a consensus definition for PGD in 2014, which standardized and graded its diagnosis. Inotropes can be used for mild to moderate PGD to restore myocardial contractility and maintain hemodynamic stability, including catecholamines, phosphodiesterase inhibitors, and levosimendan or intraaortic balloon counterpulsation (IABP). However, for patients with severe PGD, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is needed to maintain hemodynamic stability and perfusion of vital organs (3).

Veno-arterial extracorporeal membrane oxygenation is a temporary cardiopulmonary support technology that can provide effective circulation for critically ill patients with heart failure caused by a variety of reasons (8). In heart transplantation, VA-ECMO is mainly used in patients waiting for donor hearts before the operation and in patients with cardiogenic shock or PGD after the surgery. The survival rate in patients on VA-ECMO support is notably lower, especially in the early posttransplantation period. The Zhongshan Hospital Affiliated with Fudan University started to offer ECMO support therapy in 2009 and has achieved favorable therapeutic effects. This study aimed to investigate the timing and outcomes of VA-ECMO in patients with severe PGD after heart transplantation according to the ISHLT criteria.

MATERIALS AND METHODS

Patients

This retrospective single-center study reviewed the records of 130 adult patients who underwent orthotopic heart transplantation at Zhongshan Hospital, Fudan University (Shanghai, China) between January 2014 and December 2020. According to the ISHLT criteria, patients with severe PGD who received VA-ECMO support within 24 h after heart transplantation surgery were included in this study. Exclusion criteria included age of <18 years and/or pregnancy. The study was approved by the Ethics Committee of Zhongshan Hospital. Patients were divided into two groups according to whether successful weaning from VA-ECMO occurred (patients were defined as successfully weaned from VA-ECMO if they survived for longer than 48 h after VA-ECMO explantation) (9, 10). Baseline variables, including age, sex, body mass index, comorbidities, laboratory tests, and heart failure etiology, together with outcome variables, which included VA-ECMO support time, VA-ECMO weaning rate, mechanical ventilation time, length of stay in intensive care unit (ICU), length of hospital stay, complications, and in-hospital mortality, were compared between the two groups. Preoperative laboratory tests refer to the tests made on the day or the day before the heart transplantation. The changes in the Sequential Organ Failure Assessment (SOFA) score and lactate (Lac) level from baseline to day 5 were retrospectively analyzed. All data were collected from the patients' hospital records by two residents (YJ-Z and JY-H).

Surgical Procedures

After successful anesthesia, median sternotomy was performed to establish cardiopulmonary bypass (CPB). The superior vena

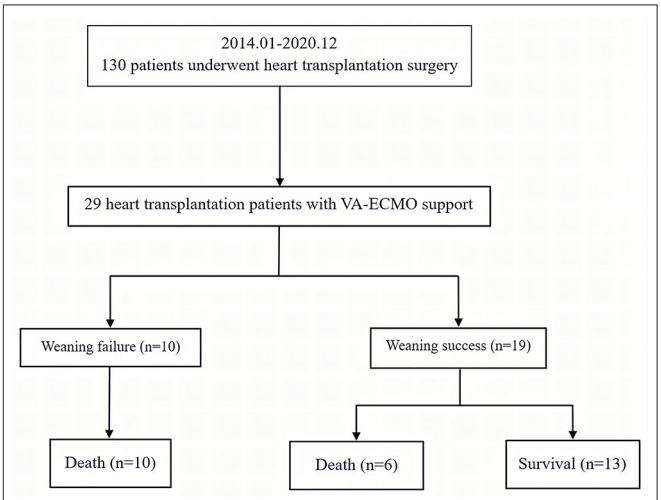

FIGURE 1 | Enrollment, allocation, and follow-up for heart transplant patients who received VA-ECMO. VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

TABLE 1 | Demographic and clinical characteristics of ECMO patients prior to surgery.

Variables	Total ($n = 29$)	Wean-from ECMO		*p*-value
		Success ($n = 19$)	Failure ($n = 10$)	
Age, *y*	48 (36,59)	54 (39,58)	41 (32,64)	0.77
Male, *n* (%)	23 (79)	17 (89)	6 (60)	0.14
BMI, (kg/m^2)	23.03 (21.0,25.61)	23.03 (20.76,25.96)	21.84 (21.14,23.77)	0.46
Comorbidities, *n* (%)				
Hypertension	3 (10)	2 (11)	1 (10)	1.00
Diabetes mellitus	2 (7)	1 (5)	1 (10)	0.96
CKD	3 (10)	1(5)	2 (20)	0.27
Atrial fibrillation	3 (10)	2 (11)	1 (10)	1.00
Pulmonary hypertension	7 (24)	4 (21)	3 (30)	0.66
Diagnosis				
Ischemic heart disease	2 (7)	2 (11)	0 (0)	0.53
Dilated cardiomyopathy	19 (66)	14 (73)	5(50)	0.24
Congenital heart disease	4 (14)	1 (5)	3 (30)	0.10
Valvular heart disease	4 (14)	2 (11)	2 (20)	0.59
Previous cardiac surgery, n (%)	8 (28)	3 (16)	5 (50)	0.08
Preoperative PVR, (wood units)	2.9 (2.2,4.5)	3.3 (2.0,4.4)	2.8 (2.2,5.2)	0.88
Laboratory tests				
cTnT, (ng/ml)	0.03 (0.02,0.07)	0.03 (0.02,0.06)	0.04 (0.01,0.09)	0.67
BNP, (pg/ml)	4890 (2406,9728)	4890 (2479,10930)	4273 (2168,9628)	0.51
Hb, (g/L)	137 (124,147)	139 (128,147)	129 (95,146)	0.33
Hct, (%)	40.6 (35.1,44.3)	41.2 (39.4,44.2)	37.4 (31.3,44.5)	0.31
WBC, ($\times 10^{12}$/L)	6.94 (4.99,8.47)	6.81 (4.89,8.34)	7.22 (5.45,9.21)	0.70
Neutrophils, (%)	69.2 (59.6,73.6)	68.8 (57.9,73.0)	69.8 (62.2,75.6)	0.54
PLT, ($\times 10^9$/L)	182 (152,223)	176 (134,222)	206 (159,238)	0.23
ALB, (g/L)	43 (37,46)	42 (35,46)	43 (38,46)	0.95
TBIL, (μmol/L)	27 (19,47)	28 (18,44)	27 (22,51)	0.74
DBIL, (μmol/L)	10 (6,21)	9 (6,20)	16 (8,24)	0.43
ALT, (U/L)	28 (18,43)	30 (19,46)	25 (12,29)	0.18
AST, (U/L)	30 (25,38)	37 (26,41)	30 (22,35)	0.40
Cr, (μmol/L)	101 (82,118)	101 (81,118)	107 (77,127)	0.80
BUN, (mmol/L)	9 (7,11)	9 (8,11)	9 (6,12)	0.80
CRP, (mg/L)	2.3 (1.5,11.7)	2.3 (1.5,10.5)	2.2 (1.5,14.2)	0.91
T3, (nmol/L)	1.3 (1.1,1.5)	1.3 (1.0,1.5)	1.3 (1.1,1.5)	0.94
T4, (nmol/L)	98.4 (85.7,105.9)	96.5 (82.6,107.0)	99.7 (93.7,106.8)	0.60
TSH, (uIU/mL)	3.54 (2.15,5.58)	3.54 (2.16,5.69)	3.02 (2.13,6.02)	1.0
PT, (s)	16.5 (13.3,19.3)	15.8 (12.2,20.1)	18.0 (16.1,19.0)	0.25
INR	1.4 (1.1,1.7)	1.4 (1.1,1.8)	1.5 (1.4,1.7)	0.31
APTT, (s)	32.7 (27.2,36.7)	31.3 (26.9,35.2)	33.8 (28.1,40.5)	0.18
Fib, (mg/dL)	264 (221,333)	264 (208,332)	276 (222,349)	0.70
EuroSCORE	8 (6,11)	7 (5,9)	10 (9,12)	0.01
APACHE II	14 (7,22)	13 (7,18)	20 (7,28)	0.14
LVEF, (%)	28 (25,35)	27 (25,29)	32 (24,41)	0.33

Continuous data are presented as the mean (SD) or median (IQR). Categorical data are presented as counts (%).
ECMO, extracorporeal membrane oxygenation; BMI, body mass index; cTnT, cardiac troponin T; BNP, brain natriuretic peptide; Hb, hemoglobin; PLT, platelet; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, serum creatinine; BUN, blood urea nitrogen; CRP, C-reactive protein; TSH, thyroid stimulating hormone; PT, prothrombin time; INR, international normalized radio; APTT, activated partial thromboplastin time; Fib, fibrinogen; EuroSCORE, European System for Cardiac Operative Risk Evaluation; APACHE II, Acute Physiology and Chronic Health Evaluation; LVEF, left ventricular ejection fraction.

TABLE 2 | Intraoperative and postoperative clinical characteristics.

Variables	Total ($n = 29$)	Wean-from ECMO		p-value
		Success ($n = 19$)	Failure ($n = 10$)	
Intraoperative conditions				
Operation time (min)	420 (370,503)	420 (355,472)	470 (380,575)	0.15
CPB time (min)	245 (210,304)	230 (193,290)	275 (218,332)	0.12
Aortic cross clamp time (min)	53 (44,62)	54 (45,82)	51 (37,57)	0.27
Donor organ ischemic time (min)	285 (127,370)	230 (134,360)	342 (120,382)	0.57
Post-ECMO support conditions				
Red blood cell transfusion (U)	14 (9,20)	15 (12,19)	11 (7,22)	0.20
Frozen plasma (ml)	2000 (900,3000)	2000 (1400,3000)	1700 (600,2800)	0.46
Drainage in first three days	1670 (1260,2320)	1590 (1270,2260)	2165 (1238,3085)	0.29
Peak cTnT (ng/ml)	2.61 (1.88,5.28)	2.16 (1.78,5.75)	3.58 (2.00,4.85)	0.70
Peak BNP (pg/ml)	15565 (8012,29527)	15565 (6495,25646)	14936 (8603,48817)	0.74
Peak lactate (mmol/L)	12.0 (10.4,19)	12.0 (9.0,15.5)	15.4 (11.7,20)	0.13
Peak TBIL (μmol/L)	76.5 (46.2,93.1)	75.6 (39.9,92)	85.0 (58.3,140.7)	0.38
Peak DBIL (μmol/L)	51.0 (26.1,69.5)	40.0 (25.3,67.6)	60.7 (24.1,124.4)	0.27
Peak ALT (U/L)	51 (27,137)	39 (25,57)	141 (51,806)	0.01
Peak AST (U/L)	136 (92,275)	128 (84,151)	275 (162,1506)	0.01
Peak Cr (mmol/L)	228 (193,301)	221 (182,295)	247 (216,336)	0.46

ECMO, extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass; cTnT, cardiac troponin T; BNP, brain natriuretic peptide; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, serum creatinine.

cava (SVC), inferior vena cava (IVC), and ascending artery were blocked. The main trunk of the aorta and pulmonary artery, SVC, and IVC was cut off. The donor heart was pruned, and the posterior wall of the left atrium between the donor heart and the recipient heart was sutured continuously. The donor heart and recipient aorta were also sutured continuously, followed by aortic crossclamp removal to regain rhythmic contractions in the graft. The anastomosis with IVC, pulmonary artery, and SVC was accomplished in the beating heart to reduce the ischemia time of donor hearts.

Definition of PGD

The specific diagnostic criteria were based on the 2013 ISHLT consensus (3). The PGD diagnosis was based on the evidence of cardiac dysfunction in the first 24 h after heart transplantation, including left, right, or total heart dysfunction. The clinical manifestation included severe hemodynamic instability with cardiogenic shock, excluding acute graft failure caused by other reasons, such as pericardial tamponade and hyperacute rejection. Although the ISHLT consensus committee recommended a distinction between PGD-LV and PGD-RV, it was not feasible to include it in this study because left and right ventricular assist devices (LVADs and RVADs) were not available in our center. VA-ECMO has become the preferred treatment for patients with refractory cardiogenic shock.

Indications for VA-ECMO

The decision to use VA-ECMO was made by the cardiac surgeon in the operating room or by the intensivist in the cardiac surgery ICU. Indications for VA-ECMO therapy included difficulty weaning from CPB or postoperative refractory cardiogenic shock despite adequate volumes and high doses of inotropes, such as norepinephrine, dobutamine, epinephrine, and milrinone. A femoral venous cannula placed from the femoral vein to the right atrium was used as the VA-ECMO venous cannula. The femoral artery is most commonly used for arterial catheterization in adult patients. When femoral ECMO was initiated, an additional 8-Fr cannula was inserted distally into the femoral artery to prevent lower extremity ischemia.

General Management During VA-ECMO Support

The optimal management of VA-ECMO involves several aspects, including circulatory support, anticoagulation, infection prevention, and nutritional support (11). The VA-ECMO support management protocol has been previously described (12). Briefly, the VA-ECMO blood flow and vasoactive drug dose were adjusted to maintain the mean arterial pressure above 65 mmHg. Several indices were used for the assessment of peripheral perfusion in VA-ECMO patients, such as clinical assessment (urinary output, skin mottling, capillary refill time, and consciousness), lactate level, mixed venous oxygen saturation, central venous oxygen saturation, and regional saturation of tissue oxygen. Cardiac function and hemodynamic conditions were routinely assessed by transesophageal or transthoracic echocardiography. Heparinization therapy was titrated according to the activated clotting time (ACT) and activated partial thromboplastin time (APTT). The target ACT was maintained at 180–200 s and APTT at 50–70 s (13). Platelets were transfused when the patient's platelet count fell below 50×10^9/L (14). Major bleeding was defined if there was clinically overt bleeding

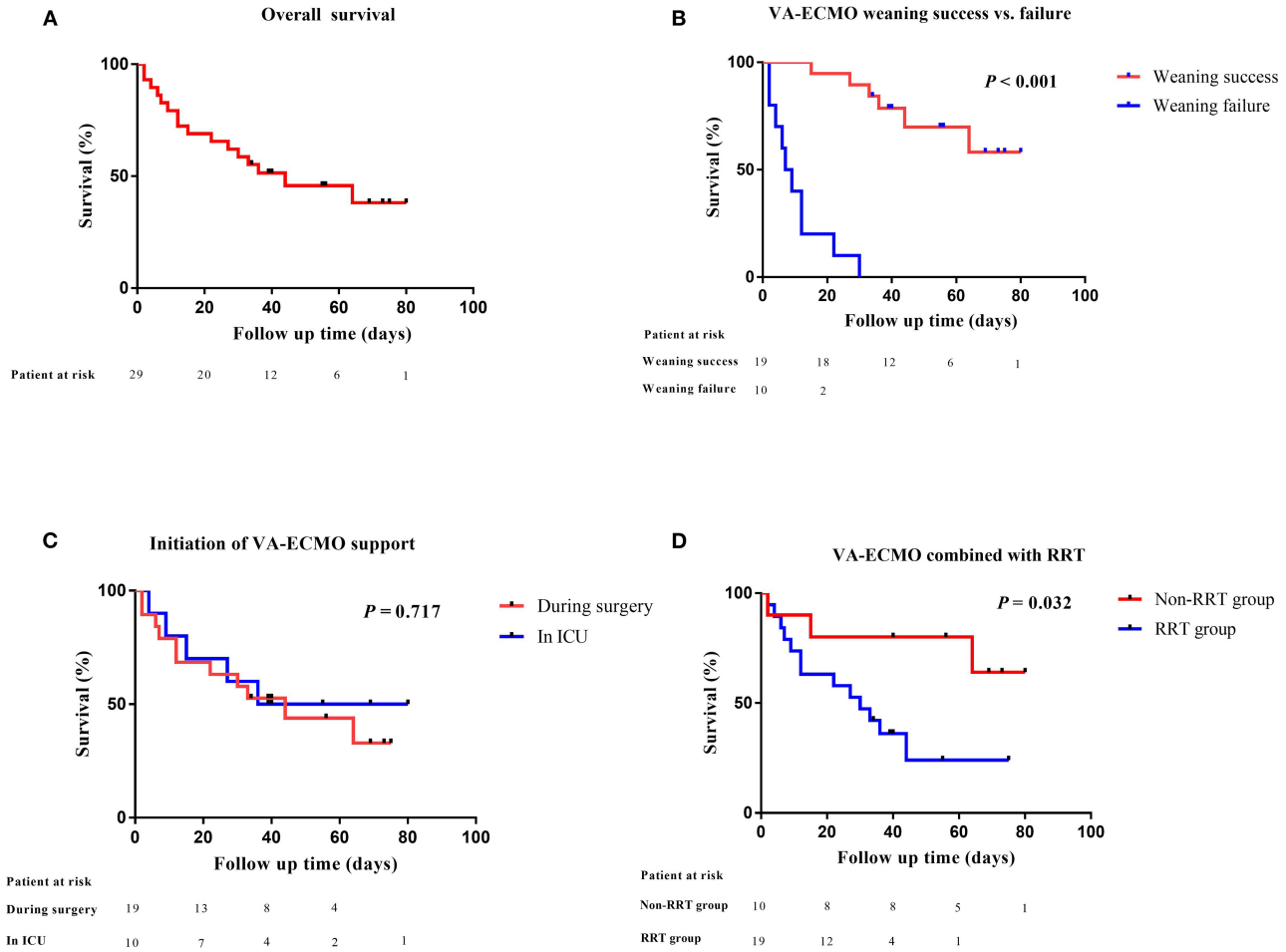

FIGURE 2 | Comparative survival in heart transplant patients after VA-ECMO support. **(A)** Kaplan–Meier analysis of overall survival in heart transplant patients supported by VA-ECMO from 2014 to 2020 ($n = 29$); **(B)** VA-ECMO weaning success or failure; **(C)** initiation of VA-ECMO support; **(D)** VA-ECMO combined with RRT. VA-ECMO, veno-arterial extracorporeal membrane oxygenation; ICU, intensive care unit; RRT, renal replacement therapy.

recorded in the medical and/or nursing charts associated with either administration of 2 or more RBC units in 24 h or a drop in hemoglobin >2 g/L over 24 h, or if there was a hemothorax, central nervous system, or retroperitoneal bleeding, or if bleeding required surgical intervention. Midazolam and remifentanil were used for sedation.

Weaning Protocol

When the patient showed signs of partial circulatory recovery and the echocardiographic evaluation demonstrated improvement in ventricular contractility, a VA-ECMO weaning test was performed by gradually reducing the pump flow to 1.5–2 L/min (15). In this setting, the removal of VA-ECMO support was considered if the patient's hemodynamic status remained stable, the left ventricular ejection fraction (LVEF) was ≥20–25%, the left ventricular outflow tract velocity time integral was ≥10 cm, and tissue Doppler lateral mitral annulus peak systolic velocity was ≥6 cm/s under minimal VA-ECMO support (16). Epinephrine was routinely used during the weaning process. In addition, when VA-ECMO combined with continuous renal replacement therapy (CRRT) or IABP was used, VA-ECMO could be removed first, and CRRT or IABP could be removed after the condition was further improved.

Statistical Analysis

Continuous data were expressed as median (IQR). Categorical variables were expressed as percentages (%). Quantitative variables were analyzed using the Mann–Whitney U test. Categorical variables were analyzed by the chi-squared test or Fisher's exact methods as appropriate. Log-rank testing and Kaplan–Meier survival curves were used for survival analysis. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using the SPSS software (version 20.0; SPSS, Inc., Chicago, IL, USA).

RESULTS

A total of 130 patients underwent an orthotopic heart transplantation procedure between January 2014 and December 2020. Twenty-nine patients who were supported with VA-ECMO following heart transplantation surgery were enrolled in the study (**Figure 1**). None of the patients received mechanical circulatory support preoperatively. The overall incidence of severe PGD was 22.3%. The mean recipient age was 47 ± 14 years and 23 (79%) of the recipients were men. All of the patients had a pulmonary artery catheter inserted preoperatively. Demographics, comorbidities, laboratory tests, and clinical manifestations in the successful (n = 19) and failed (n = 10) weaning groups are summarized in **Table 1**. Most variables were similar between the two groups. However, patients in the successful group were likely to have a lower EuroSCORE (7 ± 2 vs. 10 ± 3; $p < 0.01$) compared to those in the failure group.

Perioperative details of the 29 patients who were supported with VA-ECMO are shown in **Table 2**. Although there were no significant differences in operation, CPB, or graft ischemia durations between the two groups, the durations in the failed group were longer than those in the successful group (411 ± 81 vs. 484 ± 116 min; 236 ±65 vs. 280 ± 66 min; 246 ± 118 vs. 274 ± 129 min, $p > 0.05$). Postoperative peak alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were both significantly higher in patients who failed to wean from VA-ECMO(39 [25–51] vs. 141 [51–806] U/L; 128 [84–151] vs. 275 [162-1,506] U/L, respectively; $p < 0.01$). Nineteen patients received VA-ECMO support in the operating room due to difficulty with weaning from CPB. Ten patients had VA-ECMO initiated in the cardiac surgery ICU because of refractory postoperative cardiogenic shock. The median time from the end of the operation until VA-ECMO implantation was 8.6 h in the ICU group.

After a median support period of 5 days, 19 patients (66%) were successfully weaned from VA-ECMO support, whereas six patients died in the hospital despite successful weaning from VA-ECMO. Thirteen patients (45%) survived until hospital discharge. No patient developed leg ischemia or leg fasciotomy due to femoral arterial cannulation. The Kaplan–Meier survival curves for patients with severe PGD who required perioperative VA-ECMO support are shown in **Figure 2**. SOFA scores were significantly higher in the weaning failure group on days 3 and 5, whereas the difference in Lac level was significant only on day 3 (**Figure 3**).

Additionally, six of the patients who were successfully weaned from VA-ECMO died, including four patients died of infection or sepsis (21, 59, 8, and 30 days after weaning), one patient died of ventricular arrhythmia (31 days after weaning), and one patient died of neurological complications (19 days after weaning). No patient was lost to follow-up during this period. In addition, VA-ECMO treatment of severe PGD had no adverse effect on graft function among survivors. Details for VA-ECMO implementation and outcomes in this patient are outlined in **Table 3**.

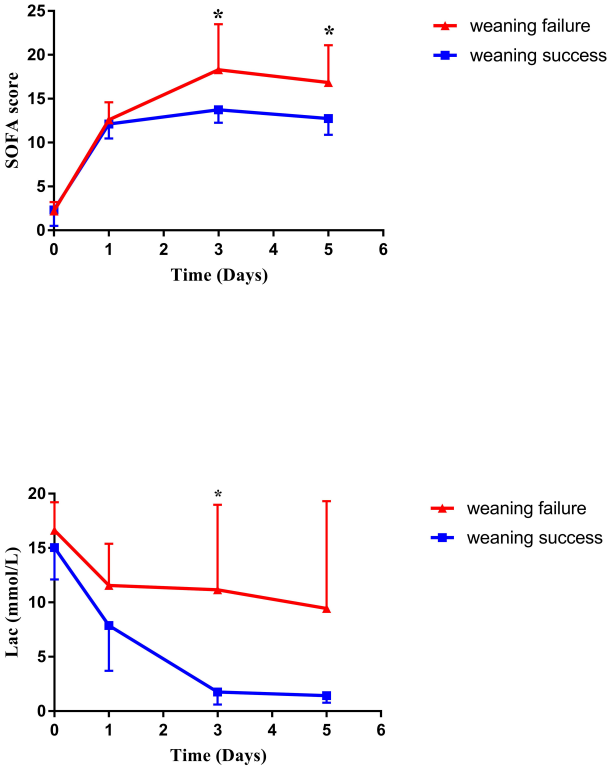

FIGURE 3 | Changes in SOFA score and lactate level during VA-ECMO support. SOFA, sequential organ failure assessment; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

DISCUSSION

In this single-center study, 29 out of 130 heart transplant recipients received VA-ECMO and achieved relatively satisfactory results. Because LVADs and RVADs were not available in our center, VA-ECMO was the only effective treatment for patients with severe PGD after heart transplantation. To the best of our knowledge, this study is the first to apply the new ISHLT criteria to Chinese patients to investigate outcomes of severe PGD at high-volume transplantation centers.

Over the last several decades, orthotopic heart transplantation has become the standard treatment for select patients with advanced and refractory heart failure. However, severe PGD remains a major cause of perioperative death after heart transplantation. Several studies have investigated the incidence of severe PGD using the ISHLT consensus statement criteria and found that the incidence rate was 7–23% with in-hospital mortality of 19–65% (4, 6, 17–21). VA-ECMO is a viable extracorporeal life support technique for cardiac surgery patients who are difficult to wean from CPB or those with postoperative cardiogenic shock. In this study, the successful weaning rate and mortality following VA-ECMO were 66 and 55%, respectively, which are comparable to those published by Alessandro et

TABLE 3 | ECMO implementation and clinical outcomes.

Variables	Total ($n = 29$)	Wean-from ECMO		*p*-value
		Success ($n = 19$)	Failure ($n = 10$)	
Initiation of ECMO support (*n*)				0.41
During surgery	19 (66)	11 (58)	8 (80)	
In ICU	10 (34)	8 (42)	2 (20)	
ECMO duration (*d*)	5 (3,7)	5 (5,7)	5 (1,7)	0.38
MV time (*d*)	10 (7,18)	13 (9,19)	6 (2,11)	0.01
CRRT, *n* (%)	19 (66)	10 (53)	9 (90)	0.10
IABP, *n* (%)	4 (14)	1 (5)	3 (30)	0.10
Cause of death, *n* (%)				
Major bleeding	3 (10)	0 (0)	3 (30)	0.01
Infection/sepsis	4 (14)	4 (21)	0 (0)	0.27
VT/VF	3 (10)	1 (5)	2 (20)	0.10
Neurological complications	2 (7)	1 (5)	1 (10)	0.27
Graft failure	4 (14)	0 (0)	4 (40)	0.01
ICU stay (*d*)	20 (10,29)	24 (17,38)	6 (2,11)	0.01
Hospital stay (*d*)	36 (11,56)	40 (36,69)	8 (4,12)	0.01
In-hospital mortality, *n* (%)	16 (55)	6 (32)	10 (100)	0.01

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; IABP, intra aortic balloon counterpulsation; VT, ventricular tachycardia; VF, ventricular fibrillation.

al. (weaning: 60%, survival: 46%) (20). We believe that the main causes of this higher incidence rate and mortality may be associated with marginal donors, basic patient conditions, surgical strategies, longer cold ischemia duration, and indication for VA-ECMO despite its likelihood to be multifactorial (4, 5, 22).

The timing of VA-ECMO implantation is an important factor influencing patient outcomes. A previous study has shown that prompt implementation of VA-ECMO allows for adequate organ perfusion and promotes the recovery of graft function, while avoiding multiple organ dysfunction and complications caused by large doses of inotropic or vasoactive agents (17). This study compared outcomes in patients with different VA-ECMO initiation times and found no significant differences between the two groups in terms of weaning success rate or in-hospital mortality. It should be noted that the median time from the end of the operation to the start of VA-ECMO was 8.6 h in the ICU group. It has been shown that delayed VA-ECMO initiation for longer than 24 h in heart transplant recipients with refractory cardiogenic shock can lead to poor outcomes (6, 17, 23). Based on our previous experience, we were more aggressive in using VA-ECMO as a therapy for severe PGD in the ICU.

It has been reported that successful weaning from VA-ECMO does not mean patient survival. Several studies have assessed the predictors of death after VA-ECMO weaning in postcardiotomy shock patients. VA-ECMO implantation time, poor renal and liver function, high lactate levels, and high SOFA scores were reported to be predictors of death after weaning (24–26), which is similar to the results in this study. Many scoring systems are routinely used in cardiac surgery ICU. SOFA was developed to objectively evaluate the degree of severity in ICU patients and to simplify the prediction of patients' risk of mortality (27). Nevertheless, in patients with VA-ECMO support, the performance of the SOFA score in predicting short-term mortality is still controversial (25, 28).

Complications during VA-ECMO support may directly lead to recipient's death or forced weaning from VA-ECMO. The leading causes of death in this study were surgical bleeding, graft failure, and septic shock. The causes of major postoperative bleeding are multifactorial (29–33). Excessive loss of coagulation factors during operation, longer CPB time, thrombocytopenia, massive perioperative blood transfusion, and postoperative VA-ECMO support can lead to coagulation dysfunction and relentless bleeding. Three patients died of major bleeding in this study. Therefore, it is very important to strictly maintain hemostasis during the operation, provide infusion of fresh frozen plasma, platelets, fibrinogen, and prothrombin complex, closely observe drainage after the operation, and conduct a secondary thoracotomy if necessary. How to best maintain the balance between bleeding and clotting in VA-ECMO patients remains a challenge.

There were several limitations in this study. First, this was a single-center retrospective study. Second, although the analyses were based on the experience over the past 7 years, the sample size was too small and the follow-up time was relatively short, which meant that detailed risk factor analysis was not possible. Third, due to privacy protection, we are unable to obtain donor information. In the future, multicenter studies with large patient populations are needed to optimize management strategies and to improve outcomes in this rare but complex cardiac emergency.

CONCLUSION

In conclusion, the application of VA-ECMO in the perioperative period of heart transplantation provided a "bridge to recovery" in patients with severe PGD. Further research is needed to determine the optimal time for VA-ECMO use and how to prevent complications to improve patient prognosis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, 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 Zhongshan Hospital affiliated to Fudan University (No. B2020-169). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

J-yH, G-wT, and ZL contributed to study design. XL, Y-jZ, J-lZ, and J-fM contributed to participant enrollment. K-fG and S-gY contributed to study management and data collection. J-yH and S-gY contributed to manuscript writing. G-wT and ZL contributed to data analyses and manuscript revision. All authors have read and approved the final manuscript.

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Sedation, Analgesia, and Muscle Relaxation During VV-ECMO Therapy in Patients With Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2): A Single-Center, Retrospective, Observational Study

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Objective: The pharmacokinetics and pharmacodynamics of ECMO-supported sedative, analgesic, and muscle relaxants have changed, but there are insufficient data to determine the optimal dosing strategies for these agents. Sedation, analgesia and muscle relaxation therapy for patients with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) receiving ECMO support are more specific and have not been fully reported. This study observed and evaluated the use of sedative and analgesic drugs and muscle relaxants in SARS-CoV-2 patients treated with VV-ECMO.

Methods: This study was a single-center, retrospective and observational study. Our study includes 8 SARS-CoV-2 patients treated with VV-ECMO in an intensive care unit at Shanghai Public Health Center from February to June 2020. We collected the demographic data from these patients and the dose and course of sedation, analgesia, and muscle relaxants administered during ECMO treatment.

Results: The doses of sedative, analgesic and muscle relaxant drugs used in patients with VV-ECMO were significant. Over time, the doses of drugs that were used were increased, and the course of muscle relaxant treatment was extended.

Conclusion: Sedation, analgesia, and muscle relaxant use require individualized titration in patients with SARS-CoV-2 who have respiratory failure and who are receiving VV-ECMO.

Keywords: VV-ECMO, SARS-CoV-2, sedation, analgesia, muscle relaxant

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is an important technique for the rescue of critically ill patients, and it is used as an adjunct therapy for critically ill patients with heart failure and/or severe respiratory failure. Patients with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) complicated with severe respiratory failure require ECMO support. It is essential that ECMO support includes a strategy for sedation, analgesia, and muscle relaxation during therapy. Sedation and excessive analgesia can lead to the delayed removal of the endotracheal tube, a prolonged time for mechanical ventilation, and the development of deep vein thrombosis. Long-term deep sedation during mechanical ventilation in patients with SARS-CoV-2 may delay the discovery and diagnosis of cerebrovascular side effects (1, 2). If the sedation and analgesia are too shallow, it will lead to patient agitation, man-machine confrontation, pipeline dropping, an imbalance of the oxygen supply and demand, an unstable ECMO flow, and other serious consequences and can even increase the risk of infection with the novel coronavirus in the doctors and nurses. It has been reported in the literature that a reasonable sedation and analgesia strategy can reduce the asynchrony between patients and ventilators and prevent man-machine confrontation (3); it can also reduce the oxygen consumption by reducing spontaneous muscle activity (4). Current ICU analgesia/sedation guidelines first advocate the assurance of adequate analgesia, minimizing sedation, preventing patient awakening, preventing delirium, and early recovery to facilitate ventilator weaning and early ICU weaning. However, these strategies are not always applicable to patients with ARDS who sometimes require deep sedation. Patients with severe ARDS are underrepresented in analgesic and sedative studies, and the currently recommended strategy may not be feasible (5).

An international study involving 394 ECMO centers showed that up to 75% of patients with VV-ECMO had deep sedation and 25% had light sedation (6). Shekar et al. reported that patients with VV-ECMO require a higher dose of sedatives relative to patients with VA-ECMO (7). Because more studies on neuromuscular blockers are conducted in ARDS patients undergoing mechanical assisted ventilation, relevant studies for ECMO-supported patients are scarce. The ELSO (The Extracorporeal Life Support Organization) guidelines recommend the use of muscular blockers when establishing ECMO circuits with intravenous intubation to avoid air embolism due to the patient's spontaneous breathing. The use of muscular blockers may be considered when the ECMO flow is unstable and is not recommended during other times (8, 9). The ELSO guidelines recommend minimal sedation, analgesia, and muscle relaxation in ARDS patients receiving ECMO support (8, 9), but whether this guideline is applicable to SARS-CoV-2 patients receiving VV-ECMO is unclear.

Due to the severe hypoxia, hemodynamic instability, multisystem involvement and strong infectious nature of SARS-CoV-2 patients, the strategies of sedation, analgesia and muscle relaxation need to be specific. This study was designed to summarize our team's experience with sedation, analgesia, and muscle relaxation in ECMO-supported patients with SARS-CoV-2.

MATERIALS AND METHODS

Case Selection

This study reviewed 8 routine patients with SARS-CoV-2 supported by VV-ECMO who were admitted to the Intensive Care Unit of Shanghai Public Health Center from February 1, 2020 to June 1, 2020. The research protocol was approved by the Ethics Committee of the Sixth People's Hospital Affiliated to Shanghai Jiao Tong University [Approval No.: 2021-KY-094(K)].

Patient Grouping

The 8 patients were divided into two groups according to death ($n = 4$) and survival ($n = 4$). Group A was the death group, and Group B was the survival group.

Research Methods

The ECMO cannulation sites of the eight patients were all jugular and femoral veins. The oxygen saturation probe was routinely placed at the blood introduction end and the perfusion end to maintain a peripheral oxygen saturation SPO2 > 90% and a mixed venous oxygen saturation > 70%. All patients received VV-ECMO with a protective lung ventilation strategy of FIO2 < 40%, a tidal volume of 2–4 ml/kg (ideal body weight), a platform pressure < 25 cmH_2O, and a respiratory rate of 8–10 breaths/min. The tidal volume was reduced if the platform pressure was above 25 cmH_2O. Pressure control was often used before ECMO evacuation. If the patient's P/F ratio (PaO2/FiO2) was not good enough, priority was given to the ECMO parameters instead of the ventilator parameters.

Because of the patient's anxiety and oxygen demand, a bedside titration method was used for sedation, analgesia and muscle relaxation. Our goals for sedation, analgesia, and muscle relaxation are, first, to ensure a peripheral oxygen saturation of greater than 90%. However, we have found in practice that such patients with severe pneumonia need deep sedation and enough analgesia to maintain an adequate peripheral oxygen saturation. Therefore, we maintained the RASS (Richmond Agitation-Sedation Scale) score at less than or equal to −4 (deep sedation) and the analgesic CPOT (Critical Care Pain Observation Tool) score at <3 points during ECMO. The bispectral index (BIS) and train of four stimulation (TOF) were used to record the specific sedation and muscle relaxation values. In addition, the pupillary light reflex and pathological reflexes of the patients were observed regularly every day for a timely detection of possible cerebrovascular accidents. Once the patient's lung condition had improved and when patients were ready to be weaned from ECMO, the doses of muscle relaxants and sedative and analgesic drugs were gradually reduced until they were eventually discontinued. Then, antipsychotic drugs were added.

Data Collection

We recorded the demographic characteristics of the patients and the usage data of sedative, analgesic and muscle relaxants at three time points: the start date of ECMO (Start), the interim period of

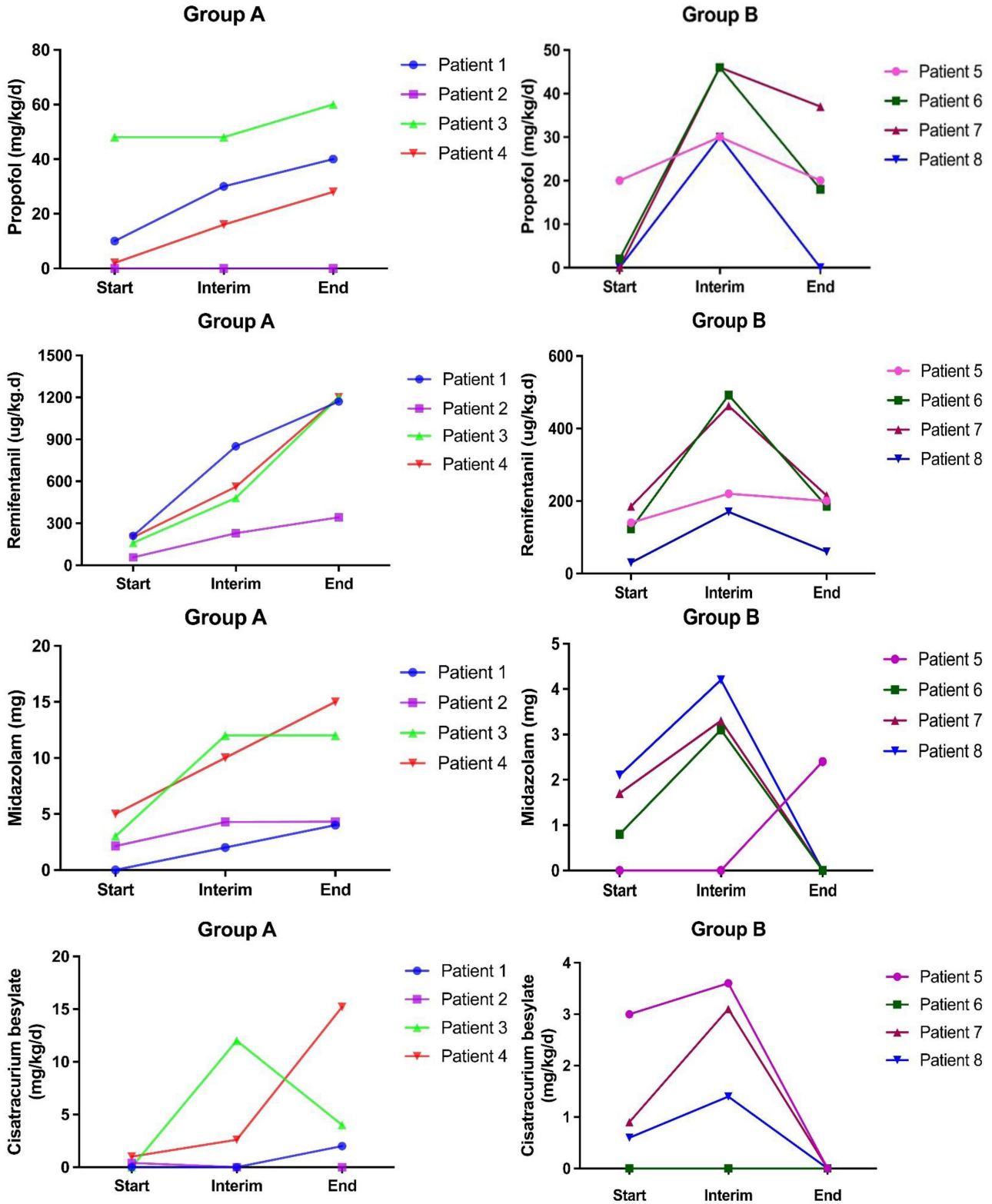

FIGURE 1 | Use of sedative, analgesic and muscle relaxants during ECMO treatment: Group A was the death group, and Group B was the survival group. The usage period was divided into three main time points, namely, the ECMO start date (Start), the ECMO support interim period (Interim), and the ECMO support end date (End). The dose units used for propofol, midazolam, and cisatracurium were mg/kg/d, and those for remifentanil were ug/kg/d.

ECMO support (INTERIM) and the end date of ECMO support (END) (see **Figure 1**).

Outcome

The primary study endpoint was the dose and time of sedation and the analgesia and muscle relaxation drugs given to the patient. The ECMO days, duration of mechanical ventilation (MV) and ICU stay were recorded as secondary study endpoints.

Statistical Analyses

Consecutive variables were expressed as means ± standard deviation, and classified variables were represented by counts. All analyses were performed using SPSS 20.0. The line graph was drawn using GraphPad Prism 8.0.

RESULTS

General Information

We collected 8 SARS-CoV-2 patients treated with VV-ECMO for respiratory failure: 7 males (88%) and 1 female (12%). The youngest was 25 years old, the oldest was 81 years old, and they had a median age of 64 (25, 81) years old. All eight patients had coexistent diseases, including four patients with hypertension, two with diabetes, one with coronary heart disease, one with bladder cancer, and one with chronic renal insufficiency. The risk factors in the 25-year-old patient were obesity: a body weight of 100 kg and a BMI of 33.4. The median duration of mechanical ventilation before ECMO treatment was 2 (0, 4) days in the survival group and 8 (0, 21) days in the death group. The median number of days ECMO support was 37.5 (8, 46). The P/F ratio was 96.6 (58, 155.6), and all of the patients had moderate to severe ARDS (**Table 1**).

Use of Sedative and Analgesic Drugs and Muscle Relaxants During ECMO Treatment

The sedative drugs used in this study were mainly midazolam and propofol. The analgesic drug was remifentanil, and the muscle relaxant was cisatracurium. The usage period was divided into three main time points, namely, the ECMO start date (Start), the ECMO support interim period (INTERIM) and the ECMO support end date (END). The specific dosages of the drugs are shown in **Figure 1**. Antipsychotic drugs were added to reduce the degree of sedation and analgesia in the four patients who were successfully taken off ECMO. Clonazepam 2 mg was administered orally three times a day, or olanzapine 5 mg was administered orally once a day.

The overall trend is that from the start of ECMO to the intermediate stage of ECMO support (Interim) (along with the prolongation of ECMO treatment), the doses of remifentanil, propofol and midazolam in eight patients were increased to different degrees, and the doses were generally high, resulting in a long treatment course. From the Interim ECMO support (INTERIM) to the end of ECMO, the doses of sedative and analgesic drugs used in the death group continued to increase, while the doses of the drugs were decreased in the survival group due to the disease remission in these patients and the improvement of the diseased lungs.

Monitoring of the Depth of Sedation, Analgesia, and Muscle Relaxation

The degree of sedation was monitored using RASS and BIS (BIS value 0 stands for flat line; 0–40 indicates deep sleep and outbreak inhibition; 40–60 represents general anesthesia; 70 represents deep sedation; >70 represents mild to moderate sedation). The RASS scores for the two time points of ECMO Start and Interim ECMO support (INTERIM) were−5 and−5, respectively, and the BIS monitoring results were 58.5 (46, 76) and 79 (59, 89), respectively, both of which were deep sedations. The survival group gradually transitioned to a mild sedation plane before ECMO removal. The RASS score of the survival group was 1 at the end of ECMO, while the death group was still in a deep sedation state. The BIS monitoring results were 58.5 (46, 76), respectively. The RASS score was −5. The CPOT score was used for analgesic monitoring so that the CPOT score was <3 points. The muscle tone of the patients was monitored using TOF. The TOF monitoring values at the start of ECMO and the intermediate stage of ECMO support (Interim) were 65.6 (56, 70) and 77.5 (65, 86), respectively. The muscle relaxants were discontinued in the survival group and were decreased but not completely discontinued in the death group at the end of ECMO.

Adverse Effects

The four patients who were successfully weaned from ECMO did not develop any severe adverse reactions. Three patients had different degrees of muscle tremors, with obvious facial manifestations, and one patient had pharyngeal paralysis and dysphagia. The patients who developed muscle tremors received subsequent TCM and rehabilitation physiotherapy, and their symptoms quickly improved.

DISCUSSION

The explanation of our finding: the treatment strategies may be slightly different due to the group responsibility system in our ward, but this does not affect the overall trend. In Group A, patient 2 did not receive propofol during the whole course, and our ECMO therapy was in an exploratory phase because this patient was the first to see the doctor, considering that propofol might affect the life of ECMO oxygenator. In Group B, patient 5 had a relatively mild illness, and midazolam was not used for ECMO at the beginning. However, due to the large dose of muscle relaxant, our attempt to reduce the dose of the muscle relaxant had failed, and our patient's target oxygen saturation could not be maintained. Hence, we were forced to use the muscle relaxant again, and midazolam was added to assist with sedation.

The muscle relaxants were used for much longer than 48 h. From the start of ECMO to the interim stage of ECMO support (INTERIM), the doses of muscle relaxants showed an increasing trend in both the death group and the survival group, except for two patients. Patient 1 did not receive muscle relaxants in the early stage, but in the late stage, it was difficult to reach the standard due to the worsening oxygen

TABLE 1 | Patients' clinical characteristics.

Patient no.		1	2	3	4	5	6	7	8	Mean ± SD
Age (years)		64	62	65	75	25	75	63	81	63 ± 6
Gender		M	M	M	M	M	M	F	M	/
Body weight (kg)		65	65	70	80	100	75	50	70	72 ± 5
MV[a] time (days)		4	0	4	0	0	8	21	10	6 ± 3
ECMO parameters[b]	Blood Pump Speed (rpm)	3,240	3,200	3,200	3,435	3,500	3,200	3,600	3,000	3,296 ± 70
	Blood pump flow (L/min)	4.9	3.6	3.6	4.4	4.9	4.0	4.1	3.2	4.1 ± 0.2
	Airflow velocity (L/min)	4.0	3.5	3.5	4.0	5.0	4.0	6.0	3.0	4.1 ± 0.3
Arterial blood gas[b]	P/F	58	66	156	65	58	133	100	97	92 ± 13
	PH	7.4	7.4	7.4	7.4	7.2	7.3	7.3	7.4	7.3 ± 0.03
	PCO_2 (mmHg)	55	42	45	34	58	45	91	49	52 ± 6
Disease severity score[c]	Murray lung injury	3	4	4	3	3	3	4	3	3.3 ± 0.2
	APACH E-II	19	11	20	21	19	23	23	18	19 ± 1
	SOFA	13	5	19	10	18	11	12	18	13 ± 2
Prognosis indicator	ECMO support days	39	46	21	16	9	36	39	46	32 ± 5
	ICU length of stay (days)	69	75	71	58	23	49	69	56	57 ± 8
	Outcome	Alive	Alive	Alive	Alive	Dead	Dead	Dead	Dead	/

MV, mechanical ventilation; ECMO, Extracorporeal Membrane Oxygenation; P/F, PO_2/FIO_2; PCO_2, Partial Pressure of Carbon Dioxide; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit.
[a]The day before ECMO; [b]The day of starting ECMO; [c]The day of admission to ICU.

saturation. After a muscle relaxant was added, the patient's condition improved, and the dose showed an increasing trend. Patient 2, who was given small dose of muscle relaxant in the early stage and who did not receive any muscle relaxants in the middle and late stages, met the recommendations of the guidelines, but his oxygen saturation and blood pressure were always low, which made it was difficult to keep him alive. The four surviving patients in Group B progressed from the intermediate stage of ECMO support (Interim) to the end of ECMO with gradually reduced doses of the muscle relaxants until the muscle relaxants were eventually discontinued due to improvement in the patients' conditions. From interim ECMO support (INTERIM) to the end of ECMO (END), the doses of sedatives used in patient 1 and patient 4 in Group A increased with the prolongation of ECMO treatment. Patient's 3 muscle relaxant dose was gradually reduced because his lung condition was actually improving, and the muscle relaxant dose could be reduced. However, the patient eventually died due to complicated gastrointestinal bleeding.

The ELSO guidelines recommend minimizing sedation, analgesia, and muscle relaxation in patients with ARDS receiving ECMO support (8, 9). This study found that the sedative, analgesic and muscle relaxant strategies of patients with SARS-CoV-2 supported by ECMO were different from those in the ELSO guidelines, and the overall dose of these drugs was higher, resulting in a longer course of treatment. The doses of sedative, analgesic and muscle relaxants need to be continually increased while maintaining the same degree of sedation, analgesia and muscle relaxation. Four of the eight ECMO patients were successfully weaned from the ventilator, and the other four died due to an ineffective management of their complications. All four successful patients received relatively large doses of sedative and analgesic drugs as well as muscle relaxants. From the start of ECMO to the middle stage of ECMO support, the doses of sedative and analgesic drugs were increased instead of decreased in order to maintain a stable oxygen supply and consumption. This study suggested that deep sedation, analgesia and muscle relaxation could temporarily improve oxygenation, allow for treatment opportunities, give time to allow for the control of later primary disease, and could allow for the opportunity to wean the COVID-19 patients from ECMO when the patients developed uncorrectable hypoxemia or man-machine confrontation.

In this study, the doses of the sedative and analgesic drugs that we used were higher, and the course of treatment was longer. The cause of these findings were analyzed. The long course of treatment was related to the long course of SARS-CoV-2 itself. Only when the lung lesions improved could the use of sedative and analgesic drugs be reduced. Attempts to reduce the depth of sedation and analgesia during the course of the disease were unsuccessful because of our patients' restlessness and the difficulty in maintaining the oxygen saturation of the patients at an ideal level. In addition, the doses of sedative and analgesic drugs are not reduced with the usual process, but the dose demand is gradually increased. The main reasons were considered to be the following: doctors and nurses wearing protective clothing and goggles played a certain role in blocking the observation of the patient's condition and the catheters were easily pulled out due to the shallow depth of sedation. Our data show that the depth of sedation in the middle stage of ECMO treatment was still deep sedation, which was inconsistent with the guidelines, and this was related to the inability to reduce the depth of sedation and analgesia during the actual operation of ECMO. From the perspective

of the doses of sedative and analgesic drugs used, the doses of these drugs were increased without changing the degree of the sedative and analgesic effects, and the BIS score was not decreased. An *in vitro* study by Shekar et al. demonstrated for the first time that there was a significant reduction in midazolam and fentanyl in the circuit of 24-h extracorporeal membrane oxygenation in adults (10). This may partly explain the increased dose requirements for these sedative and analgesic drugs during ECMO.

For ARDS patients supported by ECMO, the use of muscle relaxants can reduce ventilator-associated lung injury, and 25–45% of ARDS patients receive neuromuscular blockers (NMBAs), with an average time of 1 2 days (11). In this study, all eight patients were treated with muscle relaxants at doses greater than the regular dose and for a longer period of time. We also tried to reduce the dose of the muscle relaxants or even stop using them, but once the dose was reduced, the patient immediately developed tachypnea, ventilator resistance and difficulty in maintaining the peripheral oxygen saturation. During this time, the doses of the sedative and analgesic drugs were already relatively high, and the P/F ratio could be improved after the dose of muscle relaxants was again increased. In our analysis, we considered that patients with SARS-CoV-2 had severe lung lesions and long ECMO support times, so the course of treatment for muscle relaxants was long. In addition, severe patients often suffer from obvious abdominal flatulence, and their diaphragm moves upwards. On the one hand, this will affect lung ventilation and aggravate hypoxia. On the other hand, abdominal distension can easily affect the flow rate of ECMO, and an unstable flow rate will lead to decreased oxygenation. Studies have reported that when hypoxia occurs, adequate sedation and analgesia and muscle relaxation can reduce spontaneous respiratory movement, thus reducing the oxygen consumption (4). In addition, in this study, it was also found that the degree of muscle relaxation in the intermediate stage of ECMO support (Interim) was shallower than the start date of ECMO. However, the dose of muscle relaxants was actually increased instead of decreased. These results suggest that the pharmacodynamics and pharmacokinetics of muscle relaxants may also be altered by ECMO.

ECMO may cause significant changes in the pharmacokinetics (PK) of a drug in three ways (12, 13): (I) the retention of the drug in the ECMO lines; (II) an increase in the apparent volume of distribution (Vd); and (III) a decreased drug clearance. The drug retention is affected by the oxygenator material, the type of conduit, the life of the circuit, and the composition of the prefilled fluid. The ECMO circuit includes a conduit and a membrane oxygenator that adds additional body surface volume, and the drug is trapped in the circuit, resulting in an increase in the apparent volume of distribution and a decrease in the plasma drug concentration (12, 14). ECMO may change the apparent volume of distribution (VD) of drugs through the following mechanisms: (I) drug retention; (II) hemodilution; and (III) ECMO-related physiological changes. It is common for critically ill patients treated with ECMO to develop PK changes associated with systemic inflammatory response syndrome, which may lead to an increase in the Vd of hydrophilic drugs (15). In addition, significant changes in the blood pH may occur in patients receiving ECMO therapy, resulting in further changes in the drug distribution, ionization level, and protein binding (16). It should be noted, however, that much of the PK data in the ECMO setting are from neonates (17), and extrapolation from these data must be used with caution due to the differences in the neonatal immature glomerular and renal tubular function as well as the developing liver function (18). In general, the plasma clearance (CL) of drugs was lower in ECMO patients than in those not treated with ECMO (14) due to the hepatic and renal hypoperfusion and hypoxemia (19). The effects of the decreased drug clearance were partially offset by an increased cardiac output due to an initial inflammatory response, aggressive fluid therapy, and positive inotropic drug use (15).

CONCLUSION

When patients with SARS-CoV-2 receive adjuvant support with VV-ECMO, they require special protection and isolation, and their disease may involve multiple systems, resulting in refractory hypoxemia. In addition, the pharmacokinetics of drugs are changed, which requires the use of increased doses of sedative and analgesic drugs, and the time while using these drugs is relatively long. Therefore, the PK of the drugs should be considered in the diagnosis and treatment of these patients, and individualized titration and adjustment should be performed in combination with the actual clinical situation.

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.

AUTHOR CONTRIBUTIONS

YL and YG conceived this research. FW, ML, ZZ, and JS collected data. FW and ML completed the statistics. FW and YG made the table and figure. FW and YG completed the writing of the full text of the paper. YL reviewed the entire paper. All authors approved it for publication.

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CASE REPORT
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Case Report: Respiratory Management With a 47-Day ECMO Support for a Critical Patient With COVID-19

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This paper reports a complete case of severe acute respiratory distress syndrome (ARDS) caused by coronavirus disease 2019 (COVID-19), who presented with rapid deterioration of oxygenation during hospitalization despite escalating high-flow nasal cannulation to invasive mechanical ventilation. After inefficacy with lung-protective ventilation, positive end-expiratory pressure (PEEP) titration, prone position, we administered extracorporeal membrane oxygenation (ECMO) as a salvage respiratory support with ultra-protective ventilation for 47 days and finally discharged the patient home with a good quality of life with a Barthel Index Score of 100 after 76 days of hospitalization. The purpose of this paper is to provide a clinical reference for the management of ECMO and respiratory strategy of critical patients with COVID-19-related ARDS.

Keywords: COVID-19, ARDS, mechanical ventilation, ECMO, critical care

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INTRODUCTION

COVID-19 first occurred in Wuhan, China, at the end of 2019, and by April 21, 2021, there were more than 14.4 million cases in 210 countries. About 5–7% of patients with COVID-19 are critically ill and need admission to intensive care units (ICUs) (1). Among critical patients, 71% needed invasive mechanical ventilation, and 67% have ARDS (2). COVID-19 patients with ARDS have a hospital mortality rate of about 28.8–88% (3, 4). Respiratory support is crucial for critical cases due to the lack of specific anti-virus therapy. The World Health Organization (WHO), the Surviving Sepsis Campaign (SSC), and the National Institutes of Health (NIH) issued guidelines regarding respiratory support for patients with COVID-19 (5–7). However, there are uncertainties about the pathogenesis and pathophysiology of COVID-19 pneumonia and what respiratory support strategies are suitable for patients with COVID-19-related ARDS.

We report a patient who experienced rapid development of critical COVID-19 despite escalation to invasive mechanical ventilation support. The patient was finally discharged home and remained

good quality of life after 76 days of hospitalization with the treatment of ECMO as a salvage respiratory support for 47 days. This patient was in few of those who received a long-time ECMO support together with comprehensive respiratory management yet back to normal life without apparent sequelae.

The patient was a 62-year-old male (height: 176 cm, weight: 75 kg) with an unremarkable medical history who entered Shanghai from Wuhan on January 22, 2020. Before admission to hospital, he did not have to take medications. On January 27, he presented with a fever but no evidence of other symptoms. A reverse transcriptase polymerase chain reaction (RT-PCR) test of a pharyngeal swab was positive for SARS-CoV-2 on January 29, leading to a diagnosis of COVID-19 pneumonia and transfer to the designated hospital on January 30.

On admission, he was febrile but without dyspnea, and a physical examination indicated that his heart rate was 76 beats per minute, the blood pressure was 119/78 mmHg, the respiratory rate (RR) was 18 times per minutes, and the pulse oxygen saturation (SpO2) was 100% under 5L/min of oxygen through nasal catheter. There was evidence of leukocytopenia (white blood cell counts $3.34*10^9$/L), lymphocytopenia (lymphocyte counts $0.87*10^9$/L), elevated C-reactive protein (CRP, 0.87 mg/dL), and decreased $CD3^+$, $CD8^+$, and $CD4^+$ T cells. Arterial blood gas (ABG) analysis indicated the PaO_2 was 16.5 kPa [5 L/min through nasal catheter, PaO_2/FiO_2 (P/F) ratio: 309 mmHg], and the $PaCO_2$ was 4.9 kPa. Other organ function parameters were normal. A chest CT indicated bilateral scattered mottled ground glass shadows in the lungs (**Table 1**; **Figure 1**).

THERAPEUTIC INTERVENTIONS

Interventions Before ECMO Support

After admission, we prescribed low-flow nasal catheter oxygen therapy, darunavir/cobicistat tablets (800 mg once per day for five days), and a nebulizer with interferon-α. His daily peak temperature was 38.5–39.2°C, RR was about 20/min, and SpO_2 was 95–98% with 5 L/min oxygen supplied *via* a nasal catheter.

On February 3, he presented with progressive dyspnea with a RR of 30/min. An arterial blood gas (ABG) analysis indicated the PaO_2 was 9.94 kPa (P/F ratio: 181 mmHg) and $PaCO_2$ was 4.83 kPa, and the elevated CRP and lymphocytopenia remained. Another chest CT showed more advanced bilateral diffusive ground glass shadows. Thus, we administered intravenous immunoglobulin (20 g/day) and high-flow nasal cannulation (HFNC). However, he developed rapidly progressive respiratory distress with a RR of 40/min, and the CT lesions continued to deteriorate, so we transferred him to the ICU three days after the onset of respiratory distress. His P/F ratio rapidly decreased to 66 mmHg despite increased flow rate and FiO_2 of HFNC (flow rate: 60 L/min, FiO_2: 0.9). However, because he could not maintain oxygenation, we intubated him as soon as he was transferred to ICU. During his exacerbation, we did not try to self-prone him before intubation.

After intubation, he was deep sedated with midazolam, propofol and remifentanil, and paralyzed with rocuronium. The initial compliance of the respiratory system (Crs) was 13.5 mL/cmH2O. Although the tidal volume was set to provide protective ventilation (350 mL) and the PEEP was titrated to 12 cmH_2O, his plateau pressure was 38 cmH_2O, and driving pressure was 26 cmH_2O, thus necessitating an ultra-protective ventilation strategy. Furthermore, with the support of FiO_2 of 1.0 and a PEEP of 12 cmH_2O, he remained desaturated (SpO_2 < 90%). His lungs had no response to high PEEP or high FiO_2, so we placed him in a prone position, but his P/F ratio remained 60 mmHg after 3 h.

Initiation and Maintenance of ECMO Support as a Salvage Therapy

Thus, eight hours after intubation, we initiated venous-venous (V-V) ECMO with deep sedation, analgesia, and paralysis (**Tables 2**, **3**). There was no extrapulmonary organ dysfunction, and conservative fluid therapy was managed.

On February 13, lymphocytopenia and an elevated CRP and interleukin-6 remained. We tried to discontinue neuromuscular blockade agent (NMBA), however, this led to increased respiratory drive and patient-ventilator mismatch. Therefore, we maintained paralysis and ECMO and titrated the PEEP to 8 cmH_2O using electrical impedance tomography (EIT). Another evaluation on February 19 indicated his Crs remained too low (10 mL/cmH_2O) to wean from ECMO support.

First Trial off From ECMO Support

On February 29, he still had lymphocytopenia, but a decreased CRP, an improved Crs, a chest X-ray showing absorption of lung lesions, and the EIT showed improved ventilation. ABG analysis indicated the pH was 7.35, PaO_2 was 22.6 kPa, and $PaCO_2$ was 7.26 kPa, and bronchoscopy indicated no evident airway secretions. Therefore, we discontinued the NMBA and then turned off the airflow from the ECMO to evaluate the possibility of weaning. One h after the air source was closed, an ABG analysis indicated the pH was 7.35, PO_2 was 13.7 kPa, $PaCO_2$ was 7.96 kPa, and P/F ratio was 202 mmHg. However, after the airflow was clamped, the respiratory drive increased significantly, and patient-ventilator mismatch occurred again. Another ABG analysis indicated gradual decreases in PaO_2 (8.93–9.87 kPa) and the P/F ratio (134–144 mmHg), a gradual increase of the $PaCO_2$ (8–8.5 kPa), and the pH was 7.33–7.34. The patient's respiratory drive was apparent, with a respiratory rate of 35/min and an increase of tidal volume indicating increasing transpulmonary pressure. At meantime, paradoxical breathing could be observed. For adequate ventilation and oxygenation could not be maintained, so we resumed airflow 36 h after clamping.

Second Trial off and Weaning From ECMO Support

On March 20, his lymphocyte count normalized, pharyngeal swabs and feces were PCR-negative, the CRP declined, and the Crs improved (24 mL/cmH_2O). A chest X-ray showed further absorption of the lung lesions. The PaO_2 remained above 14.67 kPa when the FiO_2 of ECMO decreased to 0.4, and the $PaCO_2$ remained at about 6 kPa when the airflow gradually declined to 2 L/min. On March 21, we clamped the airflow again after the cessation of NMBA. The patient developed synchronization

TABLE 1 | Laboratory and ventilator parameters before ECMO support (from Jan 30th to Feb 6th).

Event or parameters		30-Jan	3-Feb	5-Feb		6-Feb	
Day of hospitalization		Day 1	Day 5	Day 7		Day 8	
Clinical event		Onset of fever	Onset of dyspnea			Intubation NMBA Higher PEEP PP for 3 h	ECMO
Inflammation	Tmax (°C)	38.5	39.0	38.5	39.0		
	CRP (mg/dL)	0.89	4.63		6.36		
	WBC (×10^9/L)	3.34	4.55		9.82		
	Lymphocyte count (×10^9/L)	0.87	0.8		0.61		
	PCT (ng/ml)	0.03	0.05		0.14		
	IL-6 (pg/ml)						
Immunity	IgA (mg/L)	1.71					
	IgG (mg/L)	10.9					
	IgM (mg/L)	0.74					
	CD3 (/ul)	411					
	CD8 (/ul)	203					
	CD4 (/ul)	198					
ABG	PH	7.44	7.43	7.42	7.41	7.26	
	PaCO2 (kpa)	4.9	4.83	5	5.62	9.32	
	PO2 (kpa)	16.5	9.94	8.55	7.44	8	
	BE (mmol/L)	0.6	−0.4	0.1	2	2	
	P/F ratio (mmHg)	309	181	106	66	60	
Oxygen therapy		Nasal Catheter (5 L/min)		HFNC (60 L/min, FiO2 90%)		IMV	
Ventilator settings	Mode					VCV	PCV
	PEEP (cmH2O)					12	10
	FiO2					1.0	0.4
	PC above PEEP (cmH2O)						16
	PS above PEEP (cmH2O)						
	Tidal volume (ml)					350	160
	RR (breath per minute)					15	8
Respiratory mechanics	Driving pressure (cmH2O)					26	15
	Pplat (cmH2O)					38	25
	Crs (ml/H2O)					13.5	13
ECMO parameters	Rotation speed (rpm)						3,270
	Blood flow (L/min)						3.7
	Air flow (L/min)						4

NMBA, neuromuscular blockade agent; ECMO, extracorporeal membrane oxygenation; PP, prone position; CRP, C-reactive protein; WBC, white blood cell count; PCT, procalcitonin; IL-6, interleukin-6; HFNC, high-flow nasal cannulation; IMV, invasive mechanical ventilation; VCV, volume control ventilation; PCV, pressure control ventilation; PEEP, positive end expiratory pressure; RR, respiratory rates; Pplat, plateau pressure; Crs, respiratory system compliance.

with the ventilator, and an ABG analysis showed increasing normalization (pH: 7.44–7.45, PaO_2: 13.6–20 kPa, PaCO2: 6–6.67 kPa, P/F ratio: 280–350 mmHg). Finally, he weaned from ECMO on March 23. After ECMO-weaning, we set the ventilator setting as pressure control mode, with pressure support of 19 cmH2O, PEEP of 6 cmH2O, FiO2 of 0.4, and respiratory rate of 20/min. The next day, we changed the mode to pressure support mode, with pressure support of 18 cmH2O, PEEP of 6 cmH2O, FiO2 of 0.35 (**Table 2**).

An evaluation of cardiac function by dynamic echocardiography showed no abnormality in left ventricular ejection fraction (LVEF, 60–70%) and normal pulmonary artery systolic pressure. There were no signs of myocardial injury or dysfunction of other organs.

ECMO Associated Adverse Events During Support

During the 47 days of ECMO support, the oxygenator was replaced thrice due to thrombosis. Heparin was used as anticoagulation therapy with 8–14 U/kg/h to maintain activated clotting time (ACT) between 160–210 s and activated partial thromboplastin time (APTT) between 50–60 s. During ECMO support, hemorrhinia had been observed, and local compression was used to stop bleeding in his nasal cavity. Except for

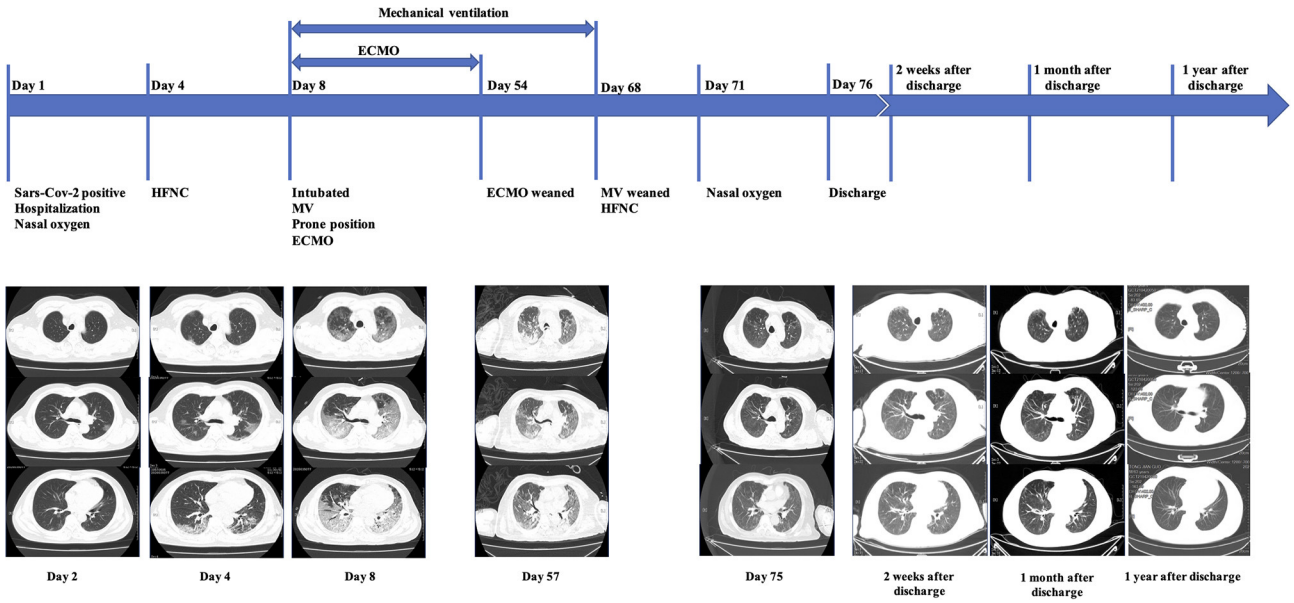

FIGURE 1 | On admission, the patient presented with fever but without dyspnea. A chest CT showed bilateral scattered ground-glass opacities. On Day 4, although the patient still denied dyspnea, a chest CT showed progressive bilateral ground-glass opacities. On Day 8, the patient experienced a rapid decline of the P/F ratio, and a chest CT showed bilateral heterogeneous diffusive ground-glass opacities with consolidation in dorsal areas, much worse than previously, leading to intubation and then ECMO. After the patient had been weaned from ECMO, chest CT exams on Day 57 and Day 75 showed significant resolution of the consolidation and ground-glass opacities, which corresponded to a de-escalation of respiratory support. After being discharged from hospital, the patient had chest CT scanned 2 weeks after discharge, 1 month after discharge, and 1 year after discharge, respectively. These images revealed further resolution of former opacities.

hemorrhinia, no fatal ECMO-related complications occurred in this case.

De-escalation of Respiratory Support

On April 6, he weaned from the ventilator and de-escalated to HFNC. On April 9, we administered a low-flow nasal cannula for oxygen therapy. Subsequent CT exams indicated increasing absorption of lung lesions. After rehabilitation, the patient was able to perform basic daily activities by himself, and he had a grade 3 on the modified British Medical Research Council (mMRC) dyspnea scale. We discharged him on April 15, 76 days after the onset of the disease.

FOLLOW-UP AND OUTCOMES

We followed up with this patient for one year after he had been discharged home. At the time of his discharge, he could accomplish basic daily activities such as bathing himself and could bear some physical exercises. He had a grade 2 on the mMRC dyspnea scale two weeks after being discharged. On May 14, one month after his discharge, his mMRC dyspnea scale score improved to grade 1, and a CT scan showed further absorption of lung lesions (**Figure 1**). One year after his discharge, the pulmonary function testing showed normal pulmonary ventilation and diffusion function. His respiratory function has been improving to an mMRC dyspnea scale of grade 0 and a Barthel Index Score of 100 one year after discharge. In addition, his muscle strengths also have been recovering after rehabilitation.

DISCUSSION

Our COVID-19 patient had rapidly progressing pneumonia that led to severe ARDS. Remarkably, after 76 days of intensive care and support, he survived with a good quality of life. We report this case to provide a whole picture of a fatal COVID-19 ARDS case with ECMO support as salvage therapy. Of note, the patient was one of the COVID-19 patients who received the most prolonged time of ECMO support.

The patient deteriorated rapidly 8 days after onset, consistent with the earlier published data (8, 9). His P/F ratio decreased from 181 to 66 mmHg in 3 days, and he rapidly progressed to severe ARDS, necessitating invasive mechanical ventilation. Thus, this COVID-19 patient is among the ∼5% of those with the fastest deterioration and worst outcomes (1).

There still remains uncertainties regarding the pathogenesis of COVID-19 ARDS. Wang et al. performed postmortem examinations of 2 cases (10) and reported lungs with severe injury with diffuse alveolar damage. However, the pathology of the lungs is somewhat different for SARS-CoV-2 and SARS infections. Gattinoni et al. found that severely hypoxemic patients with COVID-19 had different presentations, suggesting that infection with the same virus can lead to different manifestations and pathophysiologies (11). They hypothesized two COVID-19 ARDS phenotypes: type L (low elastance,

TABLE 2 | Ventilation parameters after initiation of ECMO support (from Feb 7th to Apr 14th).

Events or parameters		7-Feb	13-Feb	23-Feb	29-Feb	1-Mar	2-Mar	10-Mar	20-Mar	21-Mar	22-Mar	23-Mar	31-Mar	6-Apr	14-Apr
Day of hospitalization/day of ECMO		Day 9/2	Day 15/8	Day 25/18	Day 31/24	Day 32/25	Day 33/26	Day 41/34	Day 51/44	Day 52/45	Day 53/46	Day 54/47	Day 62	Day 68	Day 76
Clinical event					D/C NMBA		Restart ECMO air flow	NMBA		D/C NMBA		Wean from ECMO			
				Clamp ECMO air flow					Clamp ECMO air flow						
ABG	PH	7.47	7.37	7.46	7.35	7.36	7.42	7.44	7.47	7.43	7.43	7.44	7.46	7.45	7.52
	PaCO2 (kpa)	4.64	6.07	6.06	7.26	8.12	6.97	6.35	5.63	6.04	6.07	5.8	4.68	4.37	5.24
	PO2 (kpa)	8.8	8.17	13.90	22.60	9.05	13.70	14.00	23.33	14.4	17.33	20.6	20.13	22.00	16.00
	BE (mmol/L)	1.2	1.30	8.40	4.20	8.60	9.50	7.60	7.20	6.6	5.7	5.5	1.1	−1.6	9
	P/F ratio (mmHg)											386	431	471	414
Oxygen therapy		Invasive mechanical ventilation and ECMO											IMV	HFNC	
Ventilator settings	Mode	PCV	PCV	PCV	PCV	PCV	PCV	PCV	PCV	PCV	PCV	PCV	PSV	PSV	
	PEEP (cmH2O)	10	10	8	8	8	8	8	8	6	6	6	6	4	
	FiO2	0.4	0.4	0.4	0.5	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.35	0.35	
	PC above PEEP (cmH2O)	16	16	20	22	22	17	20	16	19	19	19			
	PS above PEEP (cmH2O)												18	10	
	Tidal volume (ml)	180	180	200	340	340	280	300	400	450	450	460	500	450	
	RR (breath per minute)	8	13	16	24	22	16	14	15	18	18	20	23	25	
Respiratory mechanics	Driving pressure (cmH2O)		18	18	25			18	16						
	Pplat (cmH2O)		28	26	33			26	24						
	Crs (ml/H2O)		10	11	16			17	24						
ECMO parameters	Rotation speed (rpm)	3,270	3,270	3,010	3,175	3,355	3,355	3,550	3,215	3,255	3,585				
	Blood flow (L/min)	3.7	3.8	3.5	3.69	4.07	4.03	4.14	3.82	3.80	4.20				
	Air flow (L/min)	4	4	4	4	0	5	5	2	0	0				

D/C, discontinue; NMBA, neuromuscular blockade agent; ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; HFNC, high-flow nasal cannulation; VCV, volume control ventilation, PCV, pressure control ventilation; PEEP, positive end expiratory pressure; RR, respiratory rates; Pplat, plateau pressure; Crs, respiratory system compliance.

TABLE 3 | Laboratory parameters after initiation of ECMO support (from Feb 7th to Apr 14th).

Events or parameters		7-Feb	13-Feb	23-Feb	29-Feb	1-Mar	2-Mar	10-Mar	20-Mar	21-Mar	22-Mar	23-Mar	31-Mar	6-Apr	14-Apr
Day of hospitalization/		Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day
day of ECMO		9/2	15/8	25/18	31/24	32/25	33/26	41/34	51/44	52/45	53/46	54/47	62	68	76
Clinical event					D/C NMBA		Restart ECMO AF	NMBA		D/C NMBA		Wean ECMO			
				Clamp ECMO AF					Clamp ECMO AF						
Inflammation	Tmax (°C)	37.0	38.4	37.4	37.5	38.0	37.3	36.8	37.4	37.5	37.6	38.2	37.3	37.0	36.7
	CRP (mg/dL)	4.14	8.52	6.74	7.00	9.14	10.55	4.75	1.91	1.97	2.68	1.53	1.62	0.59	0.87
	WBC (×10^9/L)	7.98	6.77	8.86	7.69	7.91	7.76	9.06	7.43	6.88	7.92	7.2	6.4	7.55	7.27
	Lymphocyte count (×10^9/L)	0.44	0.53	0.85	0.58	0.65	0.66	1.13	1.91	1.61	2.32	2.36	1.65	1.96	2.78
	PCT (ng/ml)	0.09	0.49	0.08	0.17	0.16	0.17	0.48	0.41	0.35	0.27	0.23	0.11	0.06	0.05
	IL-6 (pg/ml)		135.94	123.00		26.45		4.93							
Immunity	IgA (mg/L)	1.37		3.00	2.86	2.72	2.57	2.18		2			1.91		
	IgG (mg/L)	17		14.60	13.90	13.90	12.60	11.10		12.8			14.2		
	IgM (mg/L)	0.62		2.56	1.80	1.69	1.47	0.97		0.98			1.26		
	CD3 (/ul)	130	265	533	381	364	393	668		1,267			1,469		
	CD8 (/ul)	63	101	214	162	148	176	370		989			1,149		
	CD4 (/ul)	63	158	308	201	202	210	278		247			308		

D/C, discontinue; NMBA, neuromuscular blockade agent; ECMO, extracorporeal membrane oxygenation; CRP, C-reactive protein; WBC, white blood cell count; PCT, procalcitonin; IL-6, interleukin-6.

ventilation-to-perfusion ratio, lung weight, and recruitability) and type H (high elastance, right-to-left shunt, ventilation-to-perfusion ratio, lung weight, and recruitability). These differences might be due to differences in SARS-CoV-2 phenotype, virus load, host responses, or different stages of the disease (12).

Our patient presented with progressive hypoxemia unresponsive to FiO_2, indicating pulmonary venous admixture and a higher ratio of airflow/blood flow (5–6 to 3.5–4 L/min) required during ECMO support indicating an increase of the physiological dead space. After intubation, his Crs was only 13.5 mL/cmH_2O, indicating type H phenotype.

Different phenotypes may require different respiratory treatments, and Gattinoni et al. proposed respiratory support strategies be modified according to phenotype (11). For phenotype H patients, they recommended treatment as severe ARDS. Clinical practice recommendations for COVID-19 suggest treating this cohort similarly to ARDS due to other causes (6).

Our patient's decline of respiratory function led to our escalation from a nasal catheter, then HFNC, to the implementation of mechanical ventilation. This patient continued to deteriorate under HFNC, and his P/F ratio decreased rapidly even after he was transferred to ICU and intubated. We intubated this patient according to his persistent respiratory distress as well as failure to maintain $SpO_2 > 90\%$ with other non-invasive respiratory interventions. For the timing of intubation in COVID-19 patients, COVID-19 appeared early in China, and this patient was among the early infected cohorts. At that time, the timing of intubation and the potential risks for exposure to the virus during intubation remained unclear. In an early demographic study of 221 COVID-19 patients from Wuhan showed intubation rate was 29.1% in severe COVID-19 cohorts, and invasive mechanical ventilation plus ECMO rate was 18.2%. The median time of onset of symptoms to dyspnea was 10 days and onset of symptoms to intubation was 11 days, indicating the intubation time was close to the onset of dyspnea (13). The most consistent triggers to intubate patients were altered mental status, hemodynamic instability, and failure to maintain $SpO_2 >$ 90% with other non-invasive respiratory interventions (14).

After intubation, he was deep sedated with midazolam, propofol and remifentanil, and paralyzed with rocuronium. We sedated and paralyzed him due to his respiratory system compliance and high respiratory drive which make unable to protect his lungs by lung protective strategy. Of note, this patient had been deep sedated and paralyzed until 45 days after initiation of ECMO. In addition, he still responded poorly to high PEEP and prone position. This failure of the prone position might have been due to the patient's rapid deterioration, which prone position failed to have enough time to take effect. Based on chest CT results, we wondered whether invasive mechanical ventilation and prone position would be helpful if he had been intubated earlier was not clear. Finally, we had to implement ECMO as a salvage treatment. The indication we intubated and initiated ECMO was his desaturation and his significant respiratory drive that could have led to further injury of the lung. Based on previous evidence for ARDS, we believe that a protective pulmonary ventilation strategy, reducing the driving

pressure, and avoiding ventilator-induced lung injury are the cornerstones of treatment for COVID-19 ARDS (14).

Some clinicians suggest alternate methods of respiratory support, such as ECMO. The EOLIA trial reported that ECMO provided some benefit in patients with severe ARDS (15), but this remains for use when standard therapy fails. The Extracorporeal Life Support Organization (ELSO) guidelines for adult respiratory failure state that two weeks of no lung function in a patient who is not a transplant candidate is considered futile in many centers (16). The largest report to date from the ELSO registry included patients with COVID-19 from 213 centers across 36 countries (17). Data on 1035 patients with COVID-19 supported with ECMO showed an estimated cumulative incidence of in-hospital mortality 90 days after ECMO initiation of 37%. Of the 968 patients with a final disposition of death or hospital discharge, 380 (39%) died. 309 (81%) of 380 patients died within 24 h of discontinuation of ECMO support, and 322 (85%) were discontinued from ECMO support because of a poor prognosis. Among patients with COVID-19, how long and how such a patient could recover from COVID-19 ARDS remains unclear. This patient was different from our non-COVID ARDS patients for his very long time for recovery, both long time for virus eradication and lung infiltrates absorption. The patient's RT-PCR test only became negative nearly seven weeks after onset, and his chest images indicated improvements three weeks after onset, indicating that COVID-19 ARDS patients might require a longer recovery time than patients with ARDS from other causes. During the 47 days of ECMO support, the oxygenator was replaced thrice due to thrombosis, but there were no fatal ECMO-related complications. Thus, from an ethical view, the applicability and duration of ECMO in these patients remain uncertain (18). ECMO can serve as a bridge to recovery and provide more chances for critical COVID-19 ARDS patients to survive. Nasa et al. developed an international expert consensus on the respiratory management of COVID-19 related acute respiratory failure in areas where evidence is absent or limited. 82.8% experts agreed that V-V ECMO may be considered only in patients with refractory hypoxemia, who do not respond to other adjuvant therapies (14). Patient selection is crucial when considering ECMO and those who are inappropriately selected stand a much lower chance of survival. VV-ECMO should be reserved for patients for whom the potential benefits outweigh the associated risks (including hemorrhagic, ischemic and infectious complications), and for whom a meaningful recovery from COVID-19 is a possibility. Providers must undertake rigorous evaluations to prevent a "bridge to nowhere" situation (19).

In conclusion, for patients with COVID-19-related ARDS, optimized and intensive respiratory support based on an understanding of the pathophysiology is crucial while lacking specific drugs against coronavirus. The most appropriate respiratory support still awaits further exploration. More data and expert consensus support the application of ECMO in these patients as a salvage therapy. The selection of appropriate patients is of cardinal importance, especially during such pandemics. And for those treated with ECMO, all we can do for these patients is to give them time to recover while minimizing extra damage.

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

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

WX and RT: conceptualization and writing – original draft preparation. JH, SQ, SX, and BL: data curation. YQ, YX, and FL: validation. HQ: writing - review and editing. YL, YG, and XL: supervision. All authors contributed to the article and approved the submitted version.

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Clinical Characteristics of 10 Pregnant and Postpartum Women With Extracorporeal Membrane Oxygenation: A Retrospective Study

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Background: The aim of study was to summarize the clinical characteristics and experience of extracorporeal membrane oxygenation (ECMO) in pregnant and postpartum patients.

Methods and Results: We retrospectively reviewed 131 consecutive ECMO patients at our center from May 2015 to May 2021. A total of 10 Chinese patients were pregnant or postpartum at the time of ECMO initiation. Patients ranged in age from 25 to 36 years (median age 30.5 years). The ECMO duration ranged from 3 to 31 days (median duration 8 days). There was a stabilizing trend of acid-base balance and decreasing lactic acid over the 3 days following ECMO initiation. Seven (70%) patients survived at least 48 h after weaning from ECMO. Four (40%) patients survived until discharge, and four (40%) fetuses survived until discharge.

Conclusion: ECMO provides a suitable temporary cardiopulmonary support for pregnant and postpartum patients. ECMO shows a favorable effect on short-term stability in critical obstetric patients.

Keywords: extracorporeal membrane oxygenation, pregnant, obstetric, postpartum, critical care, clinical characteristics

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is an extracorporeal life-support technology for patients suffering from refractory cardiac shock and/or respiratory failure. In ECMO, venous blood is oxygenated and pumped back into the patient's vessels *via* a centrifugal pump located outside the body, in order to meet the body's demands (1–3). To best treat different conditions in patients, venoarterial (VA) and venovenous (VV) are the two basic types of ECMO, and these use different cannulation vessels. In certain centers, some additional, modified types of ECMO are accepted because additional venous or arterial cannulation can help manage several clinical challenges.

A jugular venous backflow cannula is commonly added in cases with concomitant severe lung failure on VA-ECMO [i.e., for veno-arterio-venous (VAV) support], whereas venous drainage cannula (VVA) or arterial backflow cannula (VAA) additions are rarely chosen to support the circulation (4).

In recent decades, ECMO has been widely used as an approach for treating critically ill patients, especially infants with congenital diaphragmatic hernia or pneumonia, as well as adults with fulminant myocarditis (5, 6). Clinicians are more likely to initiate an ECMO procedure in these specific populations, given the clear and significant benefits. Previous cardiopulmonary resuscitation (CPR) is also an indication for ECMO use because it allows patients to recovery from refractory cardiac arrest (7).

Pregnant and postpartum women often have a rapid onset of symptoms complicated with underlying disease. Even for experienced physicians, the decision to use ECMO is challenging because a number of unique factors (e.g., the fetus, hypercoagulability, liquid burden) must be taken into consideration separately. These various factors create clinical situations that are intractable with respect to diagnosis and/or management. According to the Extracorporeal Life Support Organization (ELSO), a progressive increase of ECMO use has been seen in recent decades (8). However, published studies involving ECMO use in pregnant and postpartum women are significantly lacking, especially those concerning Asian obstetric patients (9). ECMO data from pregnant and postpartum women are sometimes published together with information from non-obstetric patients. However, there is a great degree of variability in pregnant and postpartum patients, which makes it difficult to evaluate the effectiveness of ECMO treatment when data are not provided separately. Here, we reviewed our clinical records from the most recent 6 years; we report data on ECMO use in pregnant and postpartum women and provide additional characteristics of our study population.

MATERIALS AND METHODS

We completed a retrospective review of all patients treated with ECMO who were admitted to our hospital between May 2015 and May 2021; the first pregnant patient treated with ECMO in our hospital was in 2015. A total of 131 ECMO procedures were performed in our center during this time. Of these, 10 patients were pregnant or postpartum women, and all consecutive patients are included in this study. Postpartum patients were only included if ECMO cannulation occurred within 8 weeks of delivery. Data were collected from our institution's electronic medical record system. History of illness, past medical history, laboratory tests, rescue therapies, and discharge status were recorded for all patients.

Our hospital performed its first ECMO procedure in 2009, and has since become a leading ECMO regional center. Our hospital also works as a regional center for critically ill perinatal women and, therefore, our center sees a higher rate of ECMO use in pregnant women. All 10 patients were treated in our general intensive care unit (ICU), regardless of the type of ECMO performed.

Two ECMO systems were on service in our center during the time of this study: (1) the Rotaflow Centrifugal Pump (Maquet Inc, Rastatt, Germany) combined with a Quardox D oxygenator, and (2) the Cardiohelp System (Maquet Inc, Rastatt, Germany). Both systems are commonly used in China. We preferred to use the right femoral vein for drainage cannulation followed by the left femoral vein, because the left femoral vein is more commonly curved. For backflow cannulation, either femoral artery was used for VA-ECMO and either jugular vein was used for VV-ECMO. If an additional cannulation was needed for VAV ECMO, either jugular vein was used. However, decisions were made after considering the bilateral femoral vascular ultrasound.

In our ICU, decisions to initiate ECMO treatment were made by the same ECMO team leader after discussing the state of patient illness in our workgroup, or sometimes more quickly in emergency situations. Since our hospital is a regional center for critically ill perinatal women, patients can be canulated and administered ECMO treatment in local clinical departments, and later transferred to our center for monitoring and further treatments. While a patient was being considered as candidate for ECMO, our ICU colleagues would review patient history and evaluate with ultrasound. Through discussion, our team leader would then decide whether to initiate ECMO and where to perform the cannulations. All 10 ECMO cannulations were completed using the advanced Seldinger puncture technique with ultrasound guidance, and the location of guide wires and drainage cannulations was confirmed.

For circulatory failure, VA-ECMO serves to improve oxygen supply and delivery. The drainage catheter tip was typically placed in the left atrium, and a primary blood flow of 3.5–4.5 L/min was set to maintain a mean arterial pressure of 60–70 mmHg, or sometimes 70–80 mmHg in external cardiopulmonary resuscitation (ECPR) patients to achieve better cerebral perfusion. Blood flow through the aortic valve was frequently monitored with ultrasound doppler because a high VA-ECMO blood flow can lead to an elevated afterload, causing thrombosis in the left ventricle or the left atrium. If circulation improved, adjustment of blood flow was considered in order to keep the aortic valve activated; an intra-aortic balloon pump (IABP) was used as an alternative to decompress the left ventricle. Continuous renal replacement therapy (CRRT) was commonly prioritized to maintain a stable internal environment unless the patient had not suffered any aggravated kidney injury or oliguria.

With regard to VV-ECMO in respiratory failure, low volume protective ventilation and prone position ventilation were typically administered prior to ECMO, and were needed after ECMO initiation. We were extremely careful to ensure that the drainage cannulation tip was positioned in the inferior vena cava to minimize recirculation. Additionally, we adjusted the flow and oxygen concentration of VV-ECMO to improve oxygen supply and remove excess carbon dioxide. In our institution, we aim for 88–95% blood oxygen saturation and 35–45 mmHg PCO_2. No awake VV-ECMO procedures were performed in this study, and rapid frequency of breath did improve, but a rapid and shallow breath still existed after ECMO initiation. In order to avoid further lung injury caused by elevated driving pressure, we continued to reduce oxygen

TABLE 1 | Basic characteristics of patients.

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
ECMO type	**VA**					**VAV**	**ECPR**		**VV**	
Age (year)	30	31	31	33	28	26	25	31	36	25
BMI (kg/m^2)	32.04	27.58	N/A	N/A	23.94	28.83	19.53	N/A	27.34	17.58
History of pregnancy	G5P1	G1P0	G2P0	G1P0	G2P1	G2P0	G3P0	G1P0	G5P1	G1P0
GA when admitted to our hospital	33 weeks 3 days	34 weeks 1 day	12 weeks 6 days	32 weeks 1 day	2 days after delivery	39 weeks 2 days	After induced abortion	32 weeks 5 days	54 days after delivery	12 weeks 5 days
GA when admitted to ICU	33 weeks 3 days	0 day after delivery	12 weeks 6 days	32 weeks 1 day	0 day after delivery	39 weeks 2 days	After induced abortion	0 day after delivery	51 days after delivery	12 weeks 5 days
GA when ECMO initiated	2 days after delivery	1 day after delivery	12 weeks 6 days	32 weeks 1 day	2 days after delivery	0 day after delivery	After induced abortion	32 weeks 5 days	54 days after delivery	37 days after delivery
Time of MV before ECMO initiated	0 day	1 day	0 day	0 day	0 day	0 day	0 day	0 day	3 days	38 days
Where ECMO Initiated	ICU Bedside	ICU Bedside	ICU Bedside	Local hospital ER	ICU Bedside	ICU Bedside	Local hospital ER	ER	Local hospital ICU bedside	ICU Bedside
Regular obstetric examination	NO	NO	YES	YES	YES	YES	YES	YES	YES	YES
Fetus when ECMO initiated	C-section, survived	C-section, survived	Normal fetal	Normal fetal	C-section, intrauterine demise	C-section, survived	Induced abortion, intrauterine demise	Intrauterine demise	Stillbirth	Spontaneous abortion

ECPR, external cardiopulmonary resuscitation; BMI, body mass index; GA, gestational age; MV, mechanical ventilation; ER, emergency room; C-section, Cesarean section.

consumption and protect lung function through sedation and analgesia.

As far, specific ECMO removal suggestions for pregnant patients were rarely described in prior studies while the situations could be complicated. In particular, anticoagulant contraindications and high risk for thrombosis could exist in a same special person. In our center, readiness for weaning from ECMO and bedside echocardiography evaluation were performed daily. Aortic VTI $\geq$ 10 cm, LVEF $>$ 20–25%, and lateral mitral annulus peak systolic velocity >6 cm/s were recommended in some literatures with non-pregnant patients associated with successful weaning (10, 11). Similar VA-ECMO removal criteria were adopted in our study. Before removal of VV-ECMO, regular trials with the sweep gas turned off were required in our center. Weaning criteria from VV-ECMO based on EOLIA study are: $P_aO_2 \geq 60$ mmHg, $S_aO2 \geq 90\%$, with $FiO_2 \leq 60\%$; $P_aCO_2 \leq 50$ mmHg or PH $\geq$ 7.36, with respiratory rate $\leq$ 28/min; $P_{plat} \leq 28$ cmH_2O; and no signs of acute cor-pulmonale (12).

Once-daily fetal monitoring was routinely performed by obstetricians in patients who were still pregnant at the time of ECMO initiation. Intrauterine fetal demise was commonly induced, or fetuses were actively delivered by Cesarean section. In the case of fetal survival, corticosteroids were more likely used first to promote fetal lung maturation and to prepare for unexpected regular uterine contractions. For patients in the early stages of pregnancy, we discussed with the department of obstetrics to assess the need to continue the pregnancy. In the third trimester, an early Cesarean section was the preferred approach to decompress the patient's circulatory and respiratory load.

RESULTS

In this study, 10 pregnant and postpartum women received ECMO treatment in our center from May 2015 to May 2021; patient characteristics are listed in **Table 1**. All patients were from China, and relatively few cases have been previously reported in Asian patients. Of the 10 patients in this study, seven (70%) had ECMO initiated at our hospital, of which six (60%) were catheterized in our ICU and one (10%) was transferred to ICU after catheterization in the emergency room. The other three (30%) patients were transferred to our ICU after ECMO catheterization at local hospitals. The patients ranged in age from 25 to 36 years (median age 30.5 years). At admission, two (20%) patients were in the first trimester, five (50%) patients were in the third trimester, and three (30%) patients had delivered or miscarried. ECMO was initiated in three (30%) patients prior to delivery; two (20%) patients did not undergo regular obstetric examination during pregnancy; one (10%) patient was examined for splenic aneurysm and was recommended splenic aneurysm surgery or termination of pregnancy, but resolutely refused these treatments.

After reviewing medical history and treatment process for each patient in the electronic medical record system, we summarized patient information at the time of ECMO initiation in **Table 2**. Various etiologies in our study were Eisenmenger syndrome, cardiac arrest secondary to induced abortion syndrome, fulminant cardiomyopathy, pulmonary thrombosis, cardiac arrest after hemorrhagic shock, interstitial pneumonia, infection-induced acute respiratory distress syndrome (ARDS), and cardiogenic shock after aortic dissection. Among these, cardiac arrest after induced abortion syndrome and hemorrhagic shock were rarely reported. Patients receiving VA-ECMO all had severe circulatory failure for various reasons. Moreover, both patients receiving VV-ECMO could not maintain oxygen delivery after conventional treatment (e.g., low tidal volume ventilation or prone positioning), and were treated with ECMO as a salvage treatment.

Data from laboratory tests in **Table 3** show that nine (90%) patients presented with normal blood urea nitrogen and creatinine at the time of ECMO initiation. Despite different etiologies, all 10 (100%) patients showed an elevation of liver enzyme indicators related to poor condition. Coagulation disorders occurred in nine (90%) patients, of which one was treated with thrombolytic therapy. Five (50%) patients had thrombocytopenia, two (20%) patients had slightly elevated bilirubin, and almost all patients had decreased albumin, reflecting the complexity of disease management in maternal patients.

Due to different etiologies and various treatments performed, rather than focusing on the direct relationship between ECMO and final prognosis, we instead recorded arterial blood gas at the start of ECMO and on each of the following 3 days. The data show a stabilizing trend of acid-base balance and decreasing lactic acid over 3 days following the initiation of ECMO (**Figure 1**). This demonstrates a promising effect of ECMO with respect to short-term stability in critical obstetric patients. Patient outcomes are listed in **Table 4**; seven (70%) patients survived at least 48 h after weaning from ECMO; four (40%) patients were discharged; four (40%) fetuses were discharged, while the rest were aborted or stillborn upon admission. The ECMO duration ranged from 3 to 31 days (median duration 8 days).

DISCUSSION

We reviewed recent reports and literature of ECMO uses in the obstetric population, and found that although cases reports have increased in the last 5 years, they still remain scarce. In our study, seven of 10 patients were successfully weaned off of ECMO and survived for at least 48 h; one of these patients received a double lung transplant and survived. As reported previously by Abenhaim et al., the maternal survival to discharge rate for ECMO patients was 79.3% in published cases (13), and our study shows a similar excellent success of ECMO in the obstetric population. However, other characteristics in this population, such as gestation age, ECMO indication, neonatal survival, and long-term prognosis seem to be discriminative, which requires more attention. As these data showed, the disease of patients who needed VA-ECMO initiated seemed to progress more rapidly than those patients on VV-ECMO. Before VV-ECMO was initiated, several days of mechanical ventilation treatment may

TABLE 2 | Information of patient disease.

Patient	Reasons for admission to the ICU	Basis disease	Conditions at ECMO initiation	Other main treatment
VA				
1	Eisenmenger syndrome	Congenital heart disease, PDA, thrombocytopenia	PASP > 150 mmHg, SBP 120 mmHg,PaO_2/FiO_2 = 55 with high-dose NE	PGI2, S-G, CRRT, Vasoconstrictor
2	Stanford type A aortic dissection		Circulation failure after Bentall and C-section surgery, increasing lac 17.4 mmol/L, PaO_2/FiO_2 = 54.7 with high-dose NE and inotropic drugs, hypoxia	CRRT, IABP, Vasoconstrictor
3	Fulminant carditis, ROSC		Poor heart contractility after CPR, cardiac edema, EF 18%, increasing lac 14.1 mmol/L with high dose inotropic drugs and NE	CRRT, IABP, Vasoconstrictor
4	Circulation failure after ROSC	Pulmonary hypertension detected in obstetric test	Consideration of massive PE, increasing lac 13.8 mmol/L with high-dose NE, hypoxia,	CRRT, thrombolytic therapy, Vasoconstrictor
5	Severe metabolic acidosis intrauterine demise	Left femur fracture 3 months ago	Consideration of AFE, thrombocytopenia, certain low-risk PE, lac > 20 mmol/L with high-dose NE and steroid	CRRT, Vasoconstrictor
VAV				
6	Eisenmenger syndrome	Congenital heart disease, VSD	PASP > 150 mmHg, SBP 110–120 mmHg, PaO_2/FiO_2 = 41 with high-dose NE	PGI2, S-G, Vasoconstrictor
ECPR				
7	Induced abortion syndrome	Intrauterine demise, CA	Hardly maintain SBP > 35 mmHg even with NE and epinephrine I.V	Vasoconstrictor
8	Hemorrhage shock, intrauterine demise	Ruptured splenic artery aneurysm, CA	CA upon admission, no ROSC after 30 min, HB 64 g/L after blood transfusion, increasing lac 15.7 mmol/L	CRRT, uterine water bag oppression, Vasoconstrictor
VV				
9	Interstitial pneumonia, pneumocystis carinii infection	CADM	Misdiagnosed in local hospital, RP-ILD, PaO_2/FiO_2 = 53.1, pneumomediastinum	Prone position, low tidal volume ventilation, RM, NMB
10	Infection-induced ARDS	Cerebral hemorrhage	ARDS, PH 7.16, lac 9.3 mmol/L, PaO_2/FiO_2 = 45, sepsis, pneumomediastinum	Prone position, low tidal volume ventilation, RM, NMB

PASP, pulmonary arterial systolic pressure; NE, norepinephrine; PGI2, prostaglandin-2; S-G, Swan-Ganz catheter; RM, recruitment maneuvers; NMB, neuromuscular blocking agent; ARDS, acute respiratory distress syndrome; CADM, clinical asymptomatic dermatomyositis; RP-ILD, rapidly progressive interstitial pneumonia; CA, cardiac arrest; ROSC, restoration of spontaneous circulation; IV, intravenous; HB, hemoglobin; CRRT, continuous renal replacement therapy; IABP, intra-aortic balloon pump; PDA, patent ductus arteriosus; VSD, ventricular septal defect; SBP, systolic blood pressure; EF, ejection fraction; CPR, cardiopulmonary resuscitation; C-section, Cesarean section; lac, lactic acid; AFE, amniotic fluid embolism; PE, pulmonary embolism.

always be applied for temporary respiratory support. But what we can't ignore is that patients with slow progressing peripartum cardiomyopathy which were lacked in our study can also benefit from VA-ECMO (14). Due to sustained organ failure (i.e., liver failure and neurologic complications), only five of 10 patients survived longer than a month post-ECMO. It is worth noting that two cases of severe Eisenmenger syndrome, secondary to congenital heart disease, occurred in 2016 when we did not have access to treatments such as nitric oxide inhalation. Both patients saw improvement in conditions after ECMO support, but sadly, neither could afford heart or/and lung transplantation surgery and refused to continue treatments. Considering all factors, ECMO provided great recovery opportunities for obstetric patients, and treatment plans should be individually optimized in the future for better long-term prognosis.

Prognosis varies for pregnant women in different areas and societies due to various cultural and social security mechanisms (15). Cases of pregnant and postpartum women treated with ECMO are rarely reported in the Asian population, especially with Chinese women (16). In our study, all patients were 36 years of age or younger, which likely implies better basic organ function in these patients. Upon further analysis of laboratory tests in **Table 3**, it appears that liver enzyme indicators were more sensitive and potentially showed damage from ECMO initiation, whereas renal function indicators remained largely normal due to favorable basic renal function. Similar to other clinical studies (17–19), our data suggest that early application of ECMO obviously improves patient perfusion and leads to more favorable outcomes.

TABLE 3 | Laboratory tests at the time of ECMO initiation.

Patient	1	2	3	4	5	6	7	8	9	10	Normal value
GPT (U/L)	44	48	70	403	37	21	162	370	63	160	9–50
GOT (U/L)	60	247	166	2231	137	25	185	419	79	163	15–40
LDH (U/L))	515	859	884	2515	404	497	370	724	482	877	24–195
TBIL (μmol/L)	43.3	9.6	12.4	21.9	19	7.5	19	4.6	3.8	11.8	3.4–20.5
TB (g/L)	54.9	42	52.3	34.1	61.4	49.9	64.7	24.9	49.7	53.9	65–85
ALB (g/L)	28.4	28	28.2	16.3	35.5	28.4	44.6	14.9	24.7	28.3	40–55
WBC (10^9/L)	11.5	14.3	12.8	10.8	15.7	18.1	36.3	8.8	13.8	4.2	3.5–9.5
HB (g/L)	97	100	114	89	109	75	103	64	81	87	130–175
PLT (10^9/L)	63	94	100	139	194	159	343	13	333	83	125–350
INR	1.07	1.54	1.1	5.12	1.11	1.02	1.44	2.31	1.26	1.41	0.8–1.4
APTT (s)	40.1	111.4	28.5	>160	34.1	38.8	36.4	117.5	111	48.3	25–31.3
D-D (μg/L)	2050	5400	870	92530	4480	4820	32630	31200	6540	3680	
CR (μmol/L)	55	64	55	112	84	53	82	76	49	42	41–111
BUN (mmol/L)	2.63	3.16	3.09	7.1	4.27	3.45	6.18	3.74	5.94	2.53	3.1–8.8

GPT, glutamic pyruvic transaminase; GOT, glutamic oxaloacetic transaminase; LDH, lactic dehydrogenase; TBIL, total bilirubin; TB, total albumin; ALB, albumin; WBC, white blood cell; HB, hemoglobin; PLT, platelets; INR, international normalized ratio; APTT, activated partial thromboplastin time; D-D, d-dimer; CR, creatinine; BUN, blood urea nitrogen.

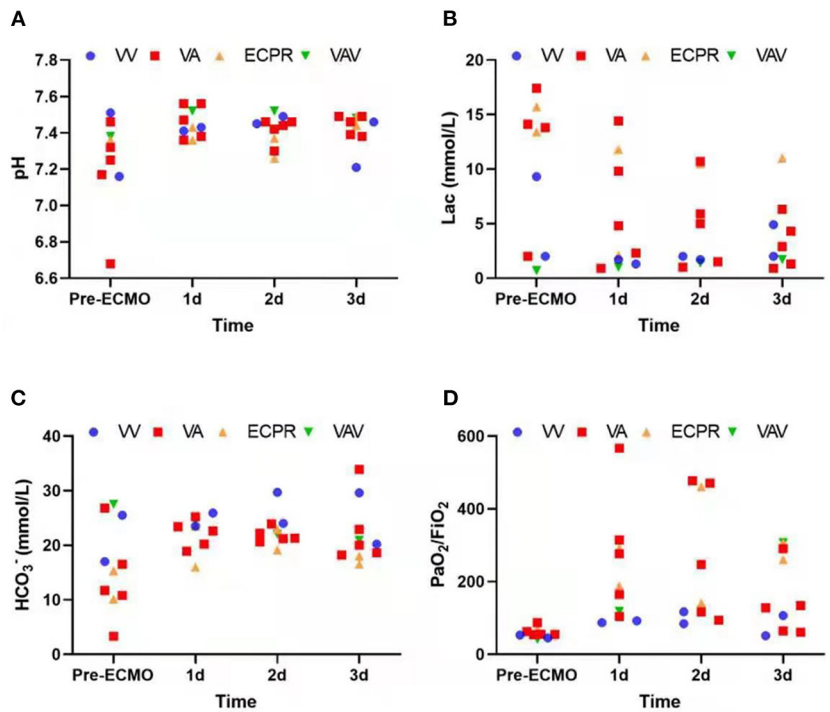

FIGURE 1 | (A–D) Arterial blood gas trends before and during first three ECMO days.

In obstetric patients, an excellent 73.9% neonatal survival rate was reported in a recent review, while intrauterine fetal demise occurred only in 8.9% of patients (13). In contrast, five of 10 patients in our study had an abortion or intrauterine demise prior to admission, and only 40% of infants survived until discharge. There are several objective factors that may account for this discrepancy. For instance: four patients experienced cardiopulmonary resuscitation before or during ECMO initiation; four patients were in the first trimester, which made it difficult to continue the pregnancy; and three patients were admitted to a local hospital before being transferred to our center. Two pregnant patients in their third trimester were sent to a hospital with intrauterine demise, despite receiving regular obstetric examination. Although these patients were not treated at disease onset, severe acidosis or cardiac arrest occurred upon admission. Perhaps improved obstetric examinations

TABLE 4 | Outcomes of ECMO and prognosis of patients.

Patient	1	2	3	4	5	6	7	8	9	10
Maternal survival when ECMO weaned off 48 h later	Dead	Survived	Survived	Survived	Survived	Dead	Survived	Survived	Dead	Survived
Maternal survival when discharged	Dead	Survived	Dead	Survived	Survived	Dead	Survived	Dead	Dead	Dead
Organ failure remained	Dead	None	Dead	Coma	None	Dead	None	Dead	Dead	Dead
Reason for death	Eisenmenger syndrome	N/A	Liver failure	N/A	N/A	Eisenmenger syndrome	N/A	Liver failure and sepsis	Respiratory failure and sepsis	Neurological complications after transplantation and relatives' decision
Fetal survival when discharged	Survived	Survived	Dead	Survived	Dead	Survived	Dead	Dead	Dead	Dead
Time on ECMO	14 days	7 days	8 days	11 days	8 days	8 days	4 days	3 days	7 days	31 days
Time in hospital	16 days	35 days	16 days	43 days	34 days	12 days	11 days	15 days	1 days	36 days

could reduce the probability of rapid intrauterine fetal demise outside the hospital due to maternal disease. As mentioned earlier, the two patients with severe Eisenmenger syndrome secondary to congenital heart disease struggled to maintain their pregnancies due to their condition; they were also unable to regularly participate in obstetric examinations, and pulmonary artery pressure was difficult to control upon admission. Both cases happened in 2016 we did not encounter additional obstetric patients with such severe pulmonary hypertension during the next 5 years. We now have more effective treatment measures, such as nitric oxide inhalation and heart or/and lung transplantation surgery. China is still a developing country, and many people are limited by economic conditions or low education level. Furthermore, we would like to suggest that improvement to social security mechanisms may improve the maternal death rate.

In addition to this, circumscribed retroperitoneal hematoma occurred in one patient who was 12 weeks pregnant and had fulminant myocarditis, which was considered to be a complication of ECMO. Fortunately, this patient survived after intra-abdominal hypertension for several days; after ECMO initiation, we offered to induce labor. Operating on pregnant patients requires heightened attention, regardless of gestational stage. Antoine et al. proposed a technique of ECMO cannulation using a left lateral tilt position of 15–30° during femoral cannula insertion to avoid aortocaval compression (20). We have found that careful cannula insertion with ultrasound or X-ray can help, but more clinical studies are required to confirm this finding.

Until now, no certain criteria for ECMO indication in pregnant and postpartum women had been proposed. Considering the favorable outcomes, similar criteria for ECMO in other populations seems acceptable for clinical application. Previous reports show that the most common causes leading to ECMO use in the general population are influenza-induced ARDS, pulmonary embolisms, and peripartum cardiomyopathy (14, 21, 22). However, in this study, our findings differ for pregnant and postpartum women; peripartum cardiomyopathy (80.0%) and postpartum hemorrhage (88.9%) were associated with impressive survival rate. Young patients often present with better basic conditions, and are less likely to have chronic coronary ischemia, long-term diabetes, or hypertension. Positive strategies to reverse these diseases can influence outcomes for ECMO and, therefore, the time of organ hypoperfusion can be decreased. Of note, we present two ECPR cases with unusual etiologies that contributed to cardiac arrest. One patient with induced abortion syndrome was unable to maintain effective blood pressure with continuous high-dose infusion of norepinephrine and epinephrine. The other patient with hemorrhage shock suffered cardiac arrest upon admission; rapid CPR and blood transfusion could not maintain restoration of spontaneous circulation. After ECMO initiation, an exploratory laparotomy and excision of a ruptured splenic artery aneurysm was completed. Circulation was significantly improved in both patients after ECMO initiation, and both patients survived at least 1 week post-ECMO. These cases suggest that more proactive decision-making is necessary, especially with in-hospital cardiac arrest (IHCA), considering that most etiologies resulting in cardiac arrest are reversible.

More effort needs to be focused on ECMO management for obstetric women. The complex management of anticoagulation is one of the main factors that distinguishes this population from others (23). Conventional ECMO management commonly maintains anticoagulation through heparin transfusion, which aims for 180–200 sec for activated clotting time (ACT) or 40–60 sec for activated partial thromboplastin time (APTT). Although maternal patients are often in a state of hypercoagulation, many of these patients are conversely at very high risk of bleeding from thrombocytopenia. At present, there is not a recommendation for management of anticoagulation in pregnant

and postpartum women. In our clinical experience, continuous anticoagulation in patients with embolism is associated with patient outcome. When it comes to severe bleeding patients, anticoagulation can be temporarily paused; frequent monitoring of membrane function and whether there is any intracardiac thrombosis is required. ECMO can be weaned off as early as possible if conditions permit, but further studies are necessary to confirm.

CRRT has been widely used in combination with ECMO. Several studies show that CRRT decreases inflammation in an animal hemorrhage-reperfusion ECMO model (24–26). Ning Li et al. reports that CRRT alleviates the intestinal mucosal dysfunction and bacterial translocation during VV-ECMO in a porcine model (27). No significant differences have been observed in CRRT implementation in maternal ECMO. An early CRRT can help stabilize acid-base balance and liquid load management. Nevertheless, studies on long-term outcomes are lacking. Intra-aortic balloon pump (IABP), another common assistive device, is recognized for its effect on left ventricle afterload decompression (28); despite this, there is limited evidence for the effectiveness on 30-day mortality in the IABP-SHOCK II study (29). We suspect that for pregnant ECMO women, IABP can not only achieve left cardiac decompression, but also prevent a blood flow stasis (30–32). This may indirectly decrease the difficulty of anticoagulation management, and further studies are needed to confirm this.

For patients who are pregnant during ECMO, delivery of the fetus can lower aortic compression, reduce abdominal pressure, and improve maternal oxygen delivery, such that an early induction of the inviable fetus should be acceptable. In contrast, for a fetus still in gestation, individualized delivery programs must be established. The use of corticosteroids may not be clearly recommended, but is widely adapted from the literature and accelerating fetal lung maturation may improve fetal survival (33). Continuation of pregnancy is only recommended for fetuses that will survive with a follow-up short-term pregnancy. Mazzeffi et al. suggested that general obstetric indications should be retained, but more studies are expected (17). There are some limitations in our study; for example, the etiologies of cases are relatively scattered and the cases are low in number. In addition, retrospective collection of cases is prone to some bias. Thankfully, increasing numbers of ECMO studies are examining the pregnant and postpartum population, and more data will be collected and analyzed.

CONCLUSION

Most pregnant women are young and have few chronic diseases. ECMO, as an auxiliary device for temporary cardiopulmonary support, can effectively stabilize the short-term condition of obstetric women and is an effective, feasible salvage treatment. For reversible disease or ECPR, aggressive strategies can be adopted to reduce the duration of patient hypoperfusion for better outcomes. Pregnant women on ECMO require more attention, especially with respect to anticoagulation and fetal management. IABP and CRRT can serve as valid adjuncts, and more studies are needed to clarify management protocols in this population.

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

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

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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CASE REPORT
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Successful Use of Extracorporeal Life Support and Continuous Renal Replacement Therapy in the Treatment of Cardiogenic Shock Induced by Tumor Lysis Syndrome in a Pediatric Patient With Lymphoma: A Case Report

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The use of extracorporeal membrane oxygenation (ECMO) in the treatment of cardiopulmonary failure in children with malignant tumors is controversial. There are few reports on the use of ECMO in the treatment of children with tumor lysis syndrome. This article reports a case of a 9-year-old girl who presented with hyperkalemia and cardiogenic shock. The discovery of an abdominal mass with critical ultrasound provided key evidence for the initial diagnosis of tumor lysis syndrome. Cardiopulmonary resuscitation was performed for 1 h. Veno-arterial ECMO was installed at the bedside to provide cardiopulmonary support for the patient and was combined with continuous renal replacement therapy (CRRT) to improve her internal environment. The patient was ultimately diagnosed with mature B-cell lymphoma with tumor lysis syndrome. A severe electrolyte disorder led to cardiogenic shock. After the electrolyte imbalance was corrected, the patient's heart function gradually improved, ECMO was successfully weaned, and chemotherapy was continued with the support of CRRT. One month after ECMO weaning, the organ function of the patient had recovered and there were no serious complications. In this case report, we paid attention to the rapid diagnosis of the etiology behind a patient's shock with critical ultrasound as well as the initiation and management of extracorporeal cardiopulmonary resuscitation (ECPR), which provided us with valuable experience using VA-ECMO on critically ill children with tumors. It is also important evidence for the use of ECMO in the treatment of children with cardiopulmonary arrest secondary to malignancy.

Keywords: ECMO (extracorporeal membrane oxygenation), tumor lysis syndrome, continuous renal replacement therapy (CRRT), pediatric, case report

INTRODUCTION

Extracorporeal cardiopulmonary resuscitation (ECPR) can greatly improve the survival rate of both in-hospital and out-of-hospital cardiac arrest. Early diagnosis of the cause of cardiogenic shock can greatly improve treatment efficiency, shorten time on extracorporeal membrane oxygenation (ECMO), and reduce the economic cost of medical care. Bedside critical ultrasound can guide the diagnosis and treatment of patients in cardiogenic shock and is also an important bedside assessment method for guiding the initiation of ECPR.

Tumor lysis syndrome (TLS) is a critical complication of malignancy that frequently occurs in children with leukemia and lymphoma. TLS is characterized by internal environmental disorders such as hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia, which cause renal failure and severe cardiac arrhythmias (1). ECMO has been shown to benefit children in severe respiratory or cardiac failure, but its use in patients with malignancies is still controversial, especially in children (2). The chief concerns regarding ECMO in patients with cancer focus on the poor prognosis of malignancy and the serious complications of ECMO, such as infection and bleeding. As the long-term prognosis of most childhood tumors has greatly improved, more medical centers have begun to explore the beneficial effects of ECMO in children with malignancies. However, the timing and contraindications of ECMO in children with tumors still require further clinical exploration (3).

In this study, we report the case of a 9-year-old girl who was admitted to the pediatric intensive care unit (PICU) in shock with ventricular arrhythmia. We rapidly diagnosed the cause of her cardiogenic shock and TLS within 30 min of admission based on cardiopulmonary ultrasound findings, the discovery of an abdominal mass, and internal environmental characteristics such as hyperkalemia and hypocalcemia. Extracorporeal cardiopulmonary resuscitation (ECPR) was performed at the bedside after an additional 30 min, and the child received ECMO + continuous renal replacement therapy (CRRT) for 3 days. The child was successfully weaned off ECMO and discharged after completing chemotherapy.

CASE REPORT

Patient Information

A 9-year-old girl with a history of "arthritis" over the prior 2 months was admitted to the pediatric intensive care unit (PICU) for 1 day of abdominal distension and 30 min of dyspnea. An electrocardiogram showed short bursts of ventricular tachycardia. Her initial diagnosis in the outpatient clinic was "fulminant myocarditis, ventricular arrhythmia, and cardiogenic shock (compensated period)." The child took 10 mg of methotrexate for "arthritis" 1 day ago and denied any other past medical history.

Clinical Findings

Physical examination suggested that the child was in the compensatory period of shock: she was irritable, dyspneic with 86% transcutaneous oxygen saturation under mask oxygen, her heart rate was 120 beats/min, her blood pressure was 70/42 mmHg, and her capillary refill time was 4–5 s. Other positive physical examination findings included: fine wet rales in her lungs, reduced heart sounds, and a suspicious mass in her lower abdomen.

Diagnostic Assessment

The patient's bedside electrocardiogram showed a ventricular arrhythmia (**Figure 1A**), and her blood gas analysis showed hyperkalemia, hypocalcemia, and metabolic acidosis (**Table 1**). After admission, the child had repeated episodes of pulseless ventricular tachycardia requiring bedside conventional cardiopulmonary resuscitation (CCPR). A tracheal intubation ventilator was used to support breathing. Intravenous drugs (calcium, insulin, adrenaline) were immediately used. An emergency bedside ultrasound revealed a significant decrease in the patient's left ventricular systolic function, with a velocity–time integral of 2 cm, a left ventricular ejection fraction (LVEF) of 15%, volume overload (enlargement of the right ventricle), and a right pleural effusion. However, the results of the outpatient blood test showed cardiac troponin (c-TNI) 0.06 μg/L and CK-MB(m) 1.90 μg/L, which are not in line with the common characteristics of fulminant myocarditis. The cause of the patient's cardiogenic shock was therefore difficult to diagnose: was it really cardiogenic shock caused by fulminant myocarditis that led to an imbalance of the patient's homeostasis? Could an alternative reason result in internal environmental imbalance (low calcium, high potassium) and then cause cardiogenic shock? A bedside abdominal ultrasound at the bedside provided a key piece of evidence: an abdominal pelvic effusion with a substantial mass in the pelvic cavity (**Figure 1C**). The patient's outpatient computed tomography (CT) also showed pleural effusion and a pelvic space mass (**Figure 1B**), but due to the emergency situation, her CT images were not uploaded to the hospital imaging network on time. The patient's preliminary diagnosis was therefore "pelvic neoplasm, TLS, hyperkalemia, ventricular arrhythmia, and cardiogenic shock." On the second hospital day, a diagnosis of mature B-cell lymphoma (stage IV, R4) was confirmed *via* flow cytometry of the ascites.

Therapeutic Intervention

Within 30 min of admission, the child had experienced four episodes of pulseless ventricular tachycardia and required three electrical cardioversions. Spontaneous circulation was restored 2–4 min after CCPR after the first three arrests. During the fourth episode of ventricular fibrillation, EPCR was initiated. Continuous advanced CPR was performed for another 40 min under invasive arterial blood pressure monitoring (MAP > 60 mmHg). Veno-arterial ECMO (VA-ECMO) was then performed *via* peripheral cannulation of the right femoral artery using 15 Fr arterial cannulae [Medtronic], a 19 Fr right femoral vein cannula catheter [Medtronic], and a distal perfusion tube 6 Fr

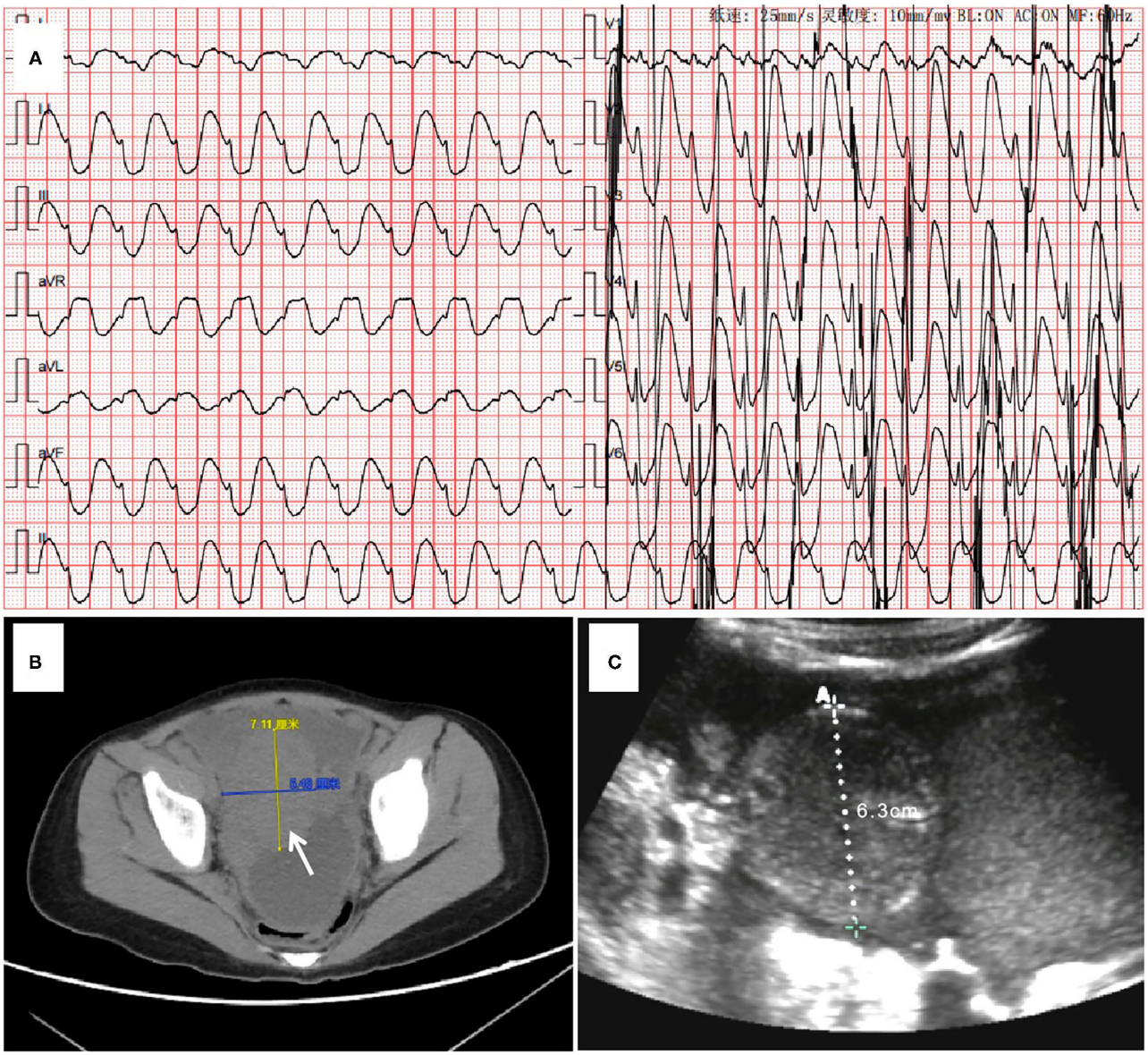

FIGURE 1 | Sequential imaging evaluations performed on Day 0. **(A)** The electrocardiogram on admission indicates ventricular tachycardia. **(B)** The abdominal CT indicates the presence of space. **(C)** The rapid bedside abdominal B-ultrasound prompts abdominal occupation.

[Tyrmer], which took the surgeon 40 min. The ECMO circuit was previously circulated with Ringer acetate (500 ml), 20% albumin (50 ml), and heparin (10 mg). A red blood cell suspension (1 U) was then pre-filled throughout the whole line to ensure hematocrit > 30%. A Maquet (Rastatt; Baden-Württemberg, Germany) PLS Membrane and Rotaflow centrifugal Pump (Maquet Cardiopulmonary AG, Hirrlingen, Germany) were utilized. Support was initiated using 90 mL/kg/h pump flow, 2,100 revolutions per minute (RPM) at a 3,000 mL/min sweep, and a 50% fraction of inspired oxygen. Considering that the cause of the patient's cardiogenic shock was an internal environmental disturbance such as hyperkalemia induced by TLS, CRRT is synchronized to prepare and pre-charge for an operation to correct the internal environmental disturbances and replace the kidneys to reduce capacity load. CRRT was connected to the ECMO circuit, with the access line connected after the oxygenator and the return line connected before the oxygenator. A CVVHDF mode was adopted. Blood flow speed was 250 ml/min (6.25 ml/kg/min), dialysate speed was 2,000 ml/h (50 ml/kg/h), the replacement fluid speed was 1,000 ml/h (25 ml/kg/h), and the dehydration speed was adjusted over time. During the ECMO maintenance, the fluid balance was mainly kept positive to preserve ECMO flow and blood pressure. The patient's condition improved significantly 4 days after admission,

TABLE 1 | Hemodynamic and laboratory measurements over the course of the ECMO treatment of the patient.

Time after ICU admission	Day 0 Peri-ECMO	Day 1 Under-ECMO	Day 2 Under-ECMO	Day 3 ECMO weaning	Day 4 Post-ECMO
Hemodynamic parameters					
ECMO Flow (L/min)	2.79	2.39	2.4	1.5	-
Blood pressure (mmHg)	72/60	79/61	71/60	95/62	110/55
CVP (cm H2O)	8	12	9	8	12
ScvO2 (%)	75	63	66	69	55
PCO2 gap	10	11	10	4.3	7.1
LVOT-VTI (cm)	2	4	8	13	14
Fluid balance (ml)	+2,854	+640	+550	+194	−11
Adrenaline (μg/kg/min)	0.5	0.4	0.3	0.25	0.05
Norepinephrine (μg/kg/min)	0.5	0.2	0	0	0
Homeostasis parameters					
PH	6.72	7.36	7.33	7.39	7.4
PaO2 (mmHg)	81.3	118	115	210	99.1
PaCO2 (mmHg)	53.2	38.7	39.1	38.5	38.8
Lac (mmol/L)	26	12	4.9	1.2	1
K+ (mmol/L)	9.03	6.11	3.98	4	3.47
Free Ca2+ (mmol/L)	1.3	1.78	1.8	2.16	2.1
Phosphorus (mmol/L)	8.4	3.98	1.38	1.01	0.66
Uric acid (μmol/L)	2,620	1,198	471	-	85.5
Creatinine (μmol/L)	177	73	42	-	48

CVP, central venous pressure; ScvO2, central venous oxygen saturation; PCO2 gap, central venous to arterial carbon dioxide partial pressure difference; LVOT-VTI, left ventricular outflow tract velocity time integral; PH, Potential of Hydrogen; Lac, lactic acid.

and reverse fluid resuscitation began to be achieved (**Table 1**). The ventilator was set to PC mode, with peep 5 cm H2O, a peak inspiratory pressure (PIP) of 18 cm H2O, a tidal volume (VT) of ∼200 ml (4–5 ml/kg), a respiratory rate (RR) of 13 times/min, and a FiO2 (fraction of inspired oxygen) of 80%. Considering the higher risk of bleeding in the patient, we adopted a conservative anticoagulation strategy of whole-body heparinization with heparin sodium 5–10 IU/kg/h for intravenous maintenance. The patient's activated clotting time was ∼180 s and her activated partial thromboplastin time was ∼60 s (**Table 2**). Since the total CCPR time was up to 1 h, to avoid secondary damage to the brain the following measures were taken: (1) control the child's temperature at 35°C through the ECMO device within 4 h after running. After a total of 2 days of mild hypothermia treatment, the day before ECMO weaning the patient was slowly rewarmed at 0.2°C/h until her body temperature was 36.5°C; and (2) combined use of sedative and analgesic drugs and muscle relaxants to maintain a deep sedative and analgesic level with a Richmond Agitation—Sedation Scale (RASS) of −4 to −5 points and a bispectral index (BIS) of 40–50; (3) cerebral blood flow signals monitored by transcranial doppler to preserve the time-average flow velocity of the middle cerebral artery at 70–100 cm/s by adjusting vasoactive drugs or ECMO flow. Local cerebral oxygen saturation (nirs-sco2) was maintained at more than 60%. As ECMO catheterization is an invasive operation, vancomycin combined with ceftazidime was used intravenously for infection prophylaxis. On the third day of ECMO, the patient's C-reactive protein (CRP) and procalcitonin levels increased significantly. Antibiotics were therefore changed to vancomycin combined with meropenem to fight the infection. With the use of tumor chemotherapy drugs, the patient's white blood cell count was reduced to 0.5*10^9/L but her CRP remained high 6 days after admission. Caspofungin was therefore added as empiric antifungal treatment.

Follow-Up and Outcomes

With ECMO and CRRT treatment, the patient's hyperkalemia was quickly corrected (6 h after the start of CRRT), her cardiac ejection function improved, and her blood lactate gradually fell. Three days after admission, the patient's heart function recovered and ECMO was weaned. Tumor induction chemotherapy was started on day 4, the patient's lung function significantly improved, the ventilator was withdrawn on day 9, and CRRT treatment was discontinued on day 11. Twenty-one days after admission the patient's organ function had recovered well and she was awake and able to communicate normally (**Figure 2**). Brain function assessment by the Paediatric Cerebral Performance Category got 1 point. Only a small subdural hemorrhage was seen on cranial MRI, and the patient was transferred to the general ward. The patient was discharged 31 days after admission after she completed the first phase of chemotherapy and her bone marrow minimal residual disease (MRD) was negative. In total her ECPR time was 1 h, her ECMO support time was 71 h, her ventilator support time was 190 h, and her CRRT operation time was 247 h. No serious ECMO complications occurred. At the

TABLE 2 | Additional biologic parameters, treatments, and relevant data during the ECMO treatment.

Timeline after ICU admission	Day 0 Peri-ECMO	Day 1 Under-ECMO	Day 2 Under-ECMO	Day 3 ECMO weaning	Day 4 Post-ECMO
Coagulation parameters					
Heparin (UI/kg/h)	5	7.5	10	7.5	0
ACT (S)	220	190	204	180	-
APTT (S)	69	45	69	67	36
Anti-X (IU/ml)	0.03	0.01	0.17	0.16	-
AT (%)	-	33	-	27	-
Platelet(x10^9/L)	103	88	21	13	18
Infection and inflammation parameters					
CRP (mg/L)	73	53	120	140	106
Procalcitonin (ng/ml)	1.27	-	-	75	-
White blood cell (x10^9/L)	20.6	10.6	1.38	1.15	0.99
Neutrophil (%)	39	30.7	55	43	39
Lymphocyte (%)	53	64.5	39	50.4	53.5
Monocyte (%)	5.9	2.6	2.2	1.7	3
Ferritin(ng/ml)	-	314	-	6,000	-
Interleukin-6 (pg/ml)	-	-	-	5,378	-
Etiology			Sputum/Blood/Urine Culture (-)		
Antibiotics		VA + CAZ		VA + MEM	
Cerebral function monitoring parameters					
Analgesics-sedatives			Midazolam + Fentanyl + Rocuronium		
RASS	−5	−5	−4	−2	−2
NIRS-ScO2	55	60	61	65	68
BIS	40	45	51	60	-
TAP (cm/s)	-	72	86	106	100
Perfusion index	-	1.92	1.36	1.04	0.58
Other parameters					
Amylopsin (U/L)	69	357	219	72	30
Lipase (U/L)	1,048	1,884	1,317	384	131
cTNI (μg/L)	0.06	1.53	2.64	1.42	0.68
NT-proBNP (pg/ml)	1,874	-	3,589	3,726	1,994
ALT(U/L)	31	460	293	259	215
AST(U/L)	190	1,805	1,027	920	785
TBIL (μmol/L)	5.4	11.2	22.8	23.6	33.6

ACT, activated clotting time; APTT, activated partial thromboplastin time; AT-III, antithrombin-III; CRP, C-reactive protein; PCT, procalcitonin; VA, Vancomycin; CAZ, Ceftazidime; MEM, meropenem; RASS, Richmond Agitation Sedation Scale; NIRS-ScO2, Cerebral oxygen saturation monitoring by near-infrared spectroscopy; BIS, bispectral index; cTNI, cardiac troponin I; NT-proBNP, N-terminal pro-b-type natriuretic peptide; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin.

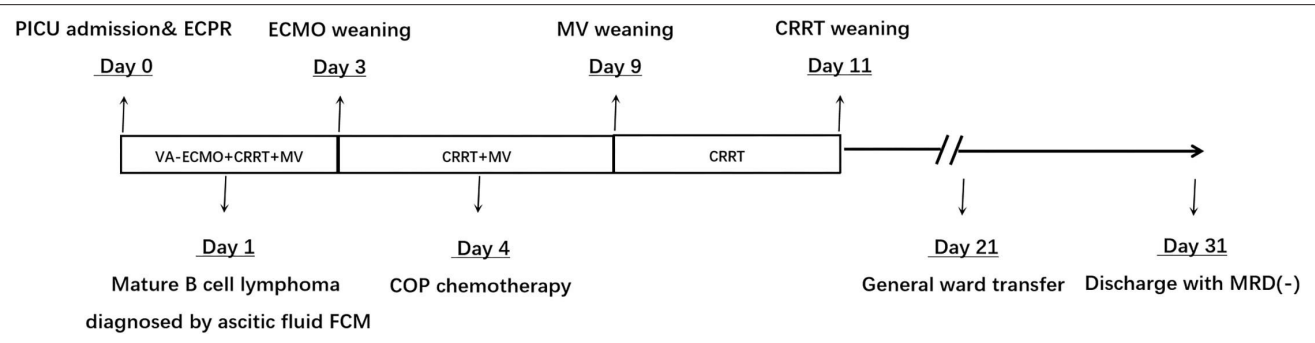

FIGURE 2 | The clinical timeline of the patient.

time of discharge, the patient had a good mental function and other organ functions were normal.

DISCUSSION

The diagnosis and treatment of this patient's case provided us with three important experiences: (1) the use of critical ultrasound technology in the rapid diagnosis and treatment of the cause of shock and critical illness; (2) valuable experience with ECMO management and in the use of craniocerebral ultrasound monitoring of cerebral blood flow; (3) childhood malignant tumors should not be contraindications to the use of ECMO in children, but its use should only be following a comprehensive assessment of their condition.

Shock is a common critical illness in the ICU. ICU care permits the rapid identification of the type of shock and accurate interventions to achieve early recovery and improve long-term prognosis. Critical Care Ultrasound is a problem-oriented, multi-objective integrated dynamic bedside evaluation process under the guidance of critical care medicine theory and the use of ultrasound technology for critically ill patients. It is an important means to determine critical care, especially the direction of hemodynamic therapy and guide fine adjustments (4). We performed a thorough assessment of the patient's heart using the bedside ultrasound, identifying a full lower cavity, enlarged right heart, and a decreased left ventricular ejection fraction. Once the patient's shock type was determined to be cardiogenic, and combined with the appearance of her electrocardiogram, the internal environmental characteristics of high potassium, low calcium, and high phosphorus levels suggest what pathophysiological process was occurring. The contents of the lower abdomen were evaluated using an abdominal ultrasound, and conclusive evidence of a tumor was finally found. The characteristic changes in electrolyte levels caused by tumor lysis syndrome led to arrhythmia, which in turn caused a cardiogenic shock. The characteristics of the course of tumor lysis syndrome lets us know that conventional potassium-lowering methods cannot quickly stabilize the child's internal environment. CRRT is an important medical technique that can quickly correct the body's water, sodium, and electrolyte balance. Therefore, an initial treatment plan of ECMO combined with CRRT was therefore developed to correct the child's internal environment in the shortest possible time. ECMO machine time was minimized, reducing the risk of serious complications that can occur in the patient. The early diagnosis of the cause of this patient's cardiogenic shock using critical ultrasound provided an important basis for the early initiation of ECPR.

In this case, the total CCPR time experienced by the child is close to 1 h, and continuous CCPR time is up to 40 min. The results of a large multi-center cohort study in North America showed that continuous CCPR for more than 21 min without ROSC may worsen neurological prognosis (5). Hence, how to protect the patient's organs, especially her brain, was the focus of ECMO management during her ECMO support period. First, targeted temperature management (TTM) and sedation and analgesia are considered to be important strategies that can improve the neurological prognosis after ECPR (6). Studies have shown that sub-hypothermia treatment can reduce brain oxygen consumption, reduce the production of oxygen free radicals, and significantly improve the prognosis of patients with a traumatic brain injury. International resuscitation guidelines recommend TTM at 32°C−36°C in unconscious patients with out-of-hospital cardiac arrest for at least 24 h (6, 7). Considering the TTM complications such as deterioration of hemodynamics and bleeding, we set the target temperature to 35°C (anal temperature). Combined with deep sedation and analgesia, TTM management lasted for 48 h, and hemodynamic deterioration and chills related to TTM did not occur. In addition, we also adjust the blood pressure and ECMO flow of children by monitoring indicators such as cerebral blood flow, cerebral oxygen, and arterial carbon dioxide partial pressure. We monitored the brain blood flow of the middle cerebral artery (MCA) daily by cranial ultrasound and continuous cerebral oxygen saturation by near-infrared spectroscopy (NIRS). When the ECMO flow is maintained at 80–90 ml/kg/ min and the mean arterial pressure (MAP) > 65 mmHg, the cerebral blood flow TAP can reach more than 70 cm/s, and the cerebral oxygen can also be maintained at 60–80%. It should be noted that CCPR was performed under the monitoring of intraarterial blood pressure (MAP > 60 mmHg), which could ensure a high-quality CPR. There is a greater risk of bleeding and nosocomial infections in patients with cancer when ECMO treatment is performed. At the beginning of treatment, the patient's diagnosis allowed us to predict the possibility of early weaning after a short period of ECMO support. We therefore adopted a more conservative anticoagulation strategy and maintained APTT around 60 s *via* heparin treatment (5–10 U/kg/h). With respect to antibiotics, meropenem and vancomycin were used to prevent infection. Despite this, on the third day of ECMO support, the patient's laboratory reports showed a reduced number of white blood cells, and significantly increased CRP and inflammatory indicators. We used intravenous immunoglobulins to improve the patient's immunity. Furthermore, early weaning is a key factor to preventing nosocomial infections.

The incidence of pediatric malignancies has increased, and they have become the second leading cause of death in children. TLS can cause a malignant arrhythmia due to high potassium and low calcium levels. It is one of the most common emergencies related to malignant tumors. ECMO is rarely used in the management of severe cardiopulmonary failure caused by TLS. Prabhu reported that a 16-month-old child with acute myeloid leukemia developed TLS combined with a respiratory syncytial virus infection after induction chemotherapy, resulting in acute respiratory and circulatory failure. VA-ECMO was used to treat the patient's shock successfully for 16 days (8). Sanford reported an 8-year-old boy with metastatic alveolar rhabdomyosarcoma who developed severe TLS with pulmonary edema and right ventricular failure after chemotherapy. The patient successfully improved after 5 days of VA-ECMO support (9). These two reports are based on tumor lysis and have unique characteristics that suggest that effective ECMO support is possible in children with malignancies. The characteristics of the case in this report are as follows: (1) the child was hospitalized due to sudden cardiogenic shock directly induced by TLS; (2) based on rapid diagnosis of TLS, the treatment of ECMO combined with CRRT was reasonable, ECPR provided a time window for the

pathological diagnosis and treatment of the child's tumor; and CRRT enabled the rapid correction of the patient's internal environment, permitted the rapid weaning of ECMO and avoided serious complications. In addition, the child has been in good health history. Therefore, in this case, ECMO+CRRT is an accurate treatment plan.

Tumors are no longer an absolute contraindication to the use of ECMO in critically ill patients. Beyond TLS, ECMO is reported to treat pediatric tumor patients in other critical care situations. First, tumors are space-occupying lesions that can lead to airway and/or cardiac vascular obstruction. ECMO can be used to bridge surgery or chemotherapy. There are many reports about adult cases using ECMO. Bourcier reported five adult patients with respiratory and circulatory failure caused by huge mediastinal tumors at a single center. They had different degrees of obstructive shock when they entered the ICU. After emergency VA-ECMO support, they were diagnosed with cancer and received chemotherapy (10). With respect to pediatrics, Ward reported three successful instances of planned VV-ECMO to bridge surgery in infants with airway obstruction caused by airway tumors. ECMO was weaned soon after surgery without any serious complications (11). Although there have been no rigorous large-scale clinical studies on the topic, a large number of successful cases of ECMO have been reported in cancer patients, which suggests that ECMO may be a rare emerging strategy for the treatment of obstructive shock caused by a primary mediastinal malignancy (12–14).

Second, severe infections can lead to acute respiratory distress syndrome (ARDS) or septic shock, requiring salvage ECMO support during cancer treatment. Children often have long-term immunosuppression and bone marrow hematopoietic insufficiency after chemotherapy or hematopoietic stem cell transplantation (HSCT), which increases their risk of ECMO complications, in particular severe bleeding and infection. Stecher retrospectively analyzed the prognosis of 25 patients with malignant tumors or HSCT who received ECMO for ARDS at a single center. The results showed that all 25 patients had leukopenia/thrombocytopenia due to anti-cancer treatment or underlying disease and that 17 patients (68%) died of ECMO. Among them, four patients had serious bleeding events (15). Bojic et al. retrospectively analyzed the relevant characteristics and results of patients with long-term ECMO managed at a single center (16). The proportion of patients with cancer was significantly lower in the long-term survivor group, and the main complication was an infection. Accordingly, providing ECMO for tumor patients with immunosuppression is still controversial.

In addition, several cases of secondary circulatory crises in patients with pheochromocytoma have been reported along with a summary of cases that used VA-ECMO transitional support therapy (13, 17, 18). Severe respiratory and circulatory failure due to chemotherapy drug-related cardiopulmonary injuries can also require ECMO support. Odish reported six cases of VV-ECMO used for the salvage treatment of lung injuries caused by bleomycin in adult tumor patients, with a cumulative survival rate of 33% (2/6) (19).

In conclusion, there are significant differences in the clinical details of patients with malignancies. There is no standardized protocol for when to provide ECMO. In this case, a girl with primary B-cell lymphoma was previously healthy. The use of ECMO support during an emergency undoubtedly won valuable time for the child. The combined use of ECMO and CRRT considerably shortened the patient's ECMO support time and avoided common complications of ECMO in tumor patients such as bleeding and infection. Decision-makers must balance factors such as disease prognosis, reversibility, the possibility of treatment-related complications, and appropriate use of clinical resources. Under no circumstances should ECMO for potential survivors be rejected simply because of the presence of a malignancy. Centers should continuously improve the management quality of ECMO for this kind of patients, which should improve corresponding results.

PATIENT PERSPECTIVE

I still remember when I was sent to the PICU, I had trouble breathing and chest tightness. I thought I was dying and was terrified. When I woke up I couldn't remember many things, and just felt a little dizzy and in pain. However, the doctor said that my illness had improved a lot and I can return to school again in the future. Now I just need to see my doctor regularly.

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

Written informed consent was obtained from the child's legal guardian for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

This work was performed at Shanghai Children's Medical Center, HR contributed to conception and design of the study. ZW organized the database and wrote the first draft of the manuscript. HR and WW has edited and revised the first draft. All authors contributed to manuscript revision, read, and approved the submitted version.

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Cytokine Hemoadsorption as Rescue Therapy for Critically Ill Patients With SARS-CoV-2 Pneumonia With Severe Respiratory Failure and Hypercytokinemia

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Introduction: A dysregulated inflammatory response, known as "cytokine storm", plays an important role in the pathophysiology of coronavirus 2019 disease (COVID-19). Identifying patients with a dysregulated inflammatory response and at high risk for severe respiratory failure, organ dysfunction, and death is clinically relevant, as they could benefit from the specific therapies, such as cytokine removal by hemoadsorption. This study aimed to evaluate cytokine hemoadsorption as rescue therapy in critically ill patients with SARS-CoV-2 pneumonia, severe respiratory failure refractory to prone positioning, and hypercytokinemia.

Methods: In this single center, observational and retrospective study, critically ill patients with SARS-CoV-2 pneumonia, severe acute respiratory failure, and hypercytokinemia were analyzed. All the patients underwent cytokine hemoadsorption using CytoSorb® (Cytosorbents Europe, Berlin, Germany). The indication for treatment was acute respiratory failure, inadequate clinical response to the prone position, and hypercytokinemia.

Results: Among a total of 343 patients who were admitted to the intensive care unit (ICU) due to SARS-CoV-2 infection between March 3, 2020 and June 22, 2020, six patients received rescue therapy with cytokine hemoadsorption. All the patients needed invasive mechanical ventilation and prone positioning. A significant difference was found in the pre- and post-treatment D-dimer (17,868 mcg/ml [4,196–45,287] vs. 4,488 mcg/ml [3,166–17,076], $p = 0.046$), C-reactive protein (12.9 mg/dl [10.6] vs. 3.5 mg/dl [2.8], $p = 0.028$), ferritin (1,539 mcg/L [764–27,414] vs. 1,197 ng/ml [524–3,857], $p = 0.04$) and interleukin-6 (17,367 pg/ml [4,539–22,532] vs. 2,403 pg/ml [917–3,724], $p = 0.043$) levels. No significant differences in the pre- and post-treatment interleukin-10 levels

(22.3 pg/ml [19.2–191] vs. 5.6 pg/ml [5.2–36.6], $p = 0.068$) were observed. Improvements in oxygenation (prehemoadsorption PaO_2/FIO_2 ratio 103 [18.4] vs. posthemoadsorption PaO_2/FIO_2 ratio 222 [20.9], $p = 0.029$) and in the organ dysfunction (prehemoadsorption SOFA score 9 [4.75] vs. posthemoadsorption SOFA score 7.7 [5.4], $p = 0.046$) were observed. ICU and in-hospital mortality was 33.7%.

Conclusions: In this case series, critically ill patients with COVID-19 with severe acute respiratory failure refractory to prone positioning and hypercytokinemia who received adjuvant treatment with cytokine hemoadsorption showed a significant reduction in IL-6 plasma levels and other inflammatory biomarkers. Improvements in oxygenation and SOFA score were also observed.

Keywords: SARS-CoV-2 pneumonia, hemoadsorption, acute respiratory distress syndrome (ARDS), hypercytokinemia, COVID-19

INTRODUCTION

Clinicians face several challenges when taking care of patients with coronavirus 2019 disease (COVID-19) (1), as the disease presents three distinct stages of disease progression. Each stage corresponds to the different clinical profiles according to individual responses to therapy and different prognoses (2). These three stages determine the severity of SARS-CoV-2 pneumonia: early, pulmonary, and hyperinflammatory. The hyperinflammatory stage is characterized by a multisystemic inflammatory syndrome, in which serum levels of inflammatory biomarkers increase, resulting in a high risk of organ dysfunction and death (3). The "cytokine storm" plays a central role in the pathophysiology of the disease (4). In the former reports from China, the cytokine storm was recognized as a clinical feature associated with the severity of the clinical condition (5).

As a consequence, the resulting inflammatory response is not homogeneous throughout the course of the disease (6, 7). During the asymptomatic phase, hypercytokinemia is not clinically evident, and, in the subsequent stages, massive cytokine release worsens the clinical course of the disease (8). This progression correlates with the fact that although an important cytokine elevation begins in the first 24 or 48 h of presentation, the clinical hyperinflammatory state becomes evident on days 7–10 from the onset of symptoms. At this stage, clinical deterioration is ubiquitous, and acute respiratory failure occurs progressively. In the lung, hypercytokinemia leads to diffuse alveolar damage, hyaline membrane formation, thrombus formation, fibrin exudates, and fibrotic healing (9), resulting in acute respiratory distress syndrome (ARDS) (10), whose frequency is up to 26% in SARS-CoV-2 infection (11, 12).

However, potentially useful adjuvant treatments do not fit all the patients. Early in the course of COVID-19, avoiding immunosuppression is recommended. In advanced stages, immunomodulation is a cornerstone for treatment interventions. Thus, it is relevant to identify the subgroup of patients who develop a hyperinflammatory response (13), as they could benefit from specific therapies, such as immunomodulation using blood purification strategies (14). Cytokine hemoadsorption therapy could be a promising therapeutic intervention in patients with severe acute respiratory failure (15–17).

This study hypothesizes that cytokine hemoadsorption may improve the hyperinflammatory profile and organ dysfunction in the selected critically ill COVID-19 patients. This study aimed to evaluate cytokine hemoadsorption as rescue therapy in critically ill patients with severe SARS-CoV-2 pneumonia, acute respiratory failure refractory to standard maneuvers, and hypercytokinemia.

METHODS

Patients and Ethics Approval

In this single center, observational, and retrospective study, critically ill patients with COVID-19 who received cytokine hemoadsorption using CytoSorb® (Cytosorbents Europe, Berlin, Germany) adsorbent, between March 3, 2020 and June 22, 2020 were eligible. All patients were admitted to the ICU of Vall d'Hebron University Hospital, Barcelona, Spain. The study was approved by the local Clinical Research Ethics Committee (PR (AG) 270/2020), and the need for informed consent was waived.

Inclusion and Exclusion Criteria

The inclusion criteria were the presence of acute respiratory failure (PaO_2/F_IO_2 [arterial oxygen pressure (P_aO_2), inspired fraction of oxygen (F_IO_2)] ratio < 150) with poor response to the prone position, hyperinflammatory state, manifested as interleukin-6 (IL-6) hypercytokinemia (IL-6 > 1,000 pg/ml), and increased levels of ferritin and D-dimer (DD). Poor response to prone positioning was considered when PaO_2/FiO_2 ratio remained <150 after the prone position. The exclusion criteria were all patients who did not meet the aforementioned criteria or had a limitation of life-sustaining care, pregnant patients, or patients who had other indications for cytokine hemoadsorption.

Analyzed Data and Scores

The plasma concentrations of inflammatory biomarkers were analyzed, including IL-6, IL-10, DD, and C-reactive protein (CRP) on ICU admission, immediately before hemoadsorption initiation (prehemoadsorption), and after the procedure (posthemoadsorption). The severity of the disease was evaluated with the Acute Physiology and Chronic Health disease Classification System (APACHE) II (18) and Sequential

Organ Failure Assessment (SOFA) scores (19). Both scores were calculated using the worst parameters measured during the first 24 h of admission. Organ dysfunction was assessed by calculating the SOFA score before and after the treatment with hemoadsorption.

Acute respiratory distress syndrome was defined according to the Berlin definition criteria (20). Data on the incidence of acute kidney injury (AKI) or failure, and the need for the continuous renal replacement therapy (CRRT), were collected according to the latest kidney disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline criteria (21). P_aO_2/F_IO_2 ratio was calculated before and after each hemoadsorption session. Also, the use of high doses of methylprednisolone (∼1.5–2 mg/kg), systemic anticoagulation (22), number of days on mechanical ventilation, duration of ICU stay, and ICU and in-hospital mortality were collected. The study fulfilled the "Strengthening the reporting of observational studies in epidemiology (STROBE)" checklist for the observational studies (23).

CytoSorb® and Continuous Renal Replacement Therapy

CytoSorb® is a highly bio- and hemocompatible cytokine adsorber approved for use in conditions with increased levels of cytokines. The device is composed of porous polymer beads within a huge and efficient surface area. It allows for adsorption and permanent binding of molecules in the 5–60 kDa range. This range includes the vast majority of cytokines and other inflammatory molecules.

The CytoSorb® filter was connected posthemofilter *via* a close loop circuit to the CRRT pump (Prismaflex, Gambro Lundia AB, Lund, Sweden). CRRT was delivered using the continuous hemodiafiltration mode using an MA 150® hemofilter (Baxter, Illinois, US) at a blood flow rate of 200 ml/min. Anticoagulation was performed with citrate or heparin.

Measurement of Plasmatic Levels of Cytokines

Plasmatic levels of IL-6 were measured using the automated quantitative immunoassay Cobas® (Roche diagnostics International Ltd, Switzerland), following the instructions of the manufacturer. Circulating levels of IL-10 and soluble CD25 (IL-2Ra) were determined using the microfluidics-based quantitative immunoassay, ELLA® (ProteinSimple, California, US), following the instructions of the manufacturer.

Statistical Analysis

According to the variable distribution, descriptive data were expressed as mean (SD) or median (interquartile range [IQR], 25–75%). Mann-Whitney U-test was used to compare continuous variables and Fisher's test for categorical variables. All the statistical tests were 2-sided, and a p-value < 0.05 was considered statistically significant. An analysis of the required sample size was not performed because of the observational characteristics of the study. Data analysis was conducted using the statistical software package PASW Statistics for Windows, Version 18.0 (SPSS Inc, Chicago, Illinois, US).

RESULTS

Characteristics of the Study Population

Among a total of 343 patients who were admitted to the ICU due to severe infection of SARS-CoV-2, six patients received treatment with CytoSorb® (**Table 1**). During the study period, hemoadsorption was performed in another patient whose indication was refractory septic shock secondary to the intestinal perforation. This patient was excluded from this study.

From a total of six patients, 5 (83.0%) were male; mean age 57.0 years (10.5). Patient characteristics, other treatments received, and outcomes are presented in **Table 1**. All the patients fulfilled the Berlin criteria for severe ARDS. All patients required mechanical ventilation and prone positioning. The mean SOFA score was 5.2 (1.5) at ICU admission, and the mean P_aO_2/F_iO_2 ratio was 97.5 (14.6). The levels of DD were 559 mcg/ml (254–2,643), CRP 19.5 mg/dl (13.4), ferritin 967 mcg/L (682–2,116) and IL-6 1,163 pg/ml (52–2,775).

The mean duration of the mechanical ventilation was 15.2 days (7.2). Three (50%) patients developed COVID-19-associated AKI and required CRRT. The mean ICU stay was 17.2 days (8.0), and ICU and in-hospital mortality was 33.7%.

Hemoadsorption

Patient eligibility for the cytokine hemoadsorption was assessed between days 3 and 4 of ICU admission. At inclusion, clinical parameters of the organ dysfunction and inflammation had worsened in all patients. The mean SOFA score was 9 (4.75), and P_aO_2/F_iO_2 ratio was 103 (18.4). Levels of DD were 17,868 mcg/ml (4,196–45,287), CPR 12.9 mg/dl (10.6), ferritin 1,539 mcg/L (764–27,414), IL-6 17,367 pg/ml (4,539–22,532), and IL-10 22.3 pg/ml (19.2–191) (**Table 2**). All the patients underwent cytokine hemoadsorption (5 patients received one session of CytoSorb® hemoadsorption [each session of variable duration], and one patient received two 24-h sessions). The mean perfusion time was 16 (9) h. The circuit patency determined the duration of hemoadsorption sessions in 3 patients (circuit clotting occurred at 3, 8, and 16 h).

Inflammatory Parameters and Organ Dysfunction

All inflammatory parameters, except for IL-10 levels, significantly decreased after treatment (posthemoadsorption DD levels 4,488 mcg/ml [3,166–17,076], $p = 0.046$; posthemoadsorption CRP 3.5 mg/dl [2.8], $p = 0.028$; posthemoadsorption ferritin levels 1,197 mcg/L [524–3,857], $p = 0.046$; posthemoadsorption IL-6 levels 2.403 pg/ml [917–3.724], $p = 0.043$; and posthemoadsorption IL-10 levels 5.6 pg/ml [5.2–36.6], $p = 0.068$).

Improvements in oxygenation (posthemoadsorption P_aO_2/F_iO_2 ratio 222 (20.9), $p = 0.029$) and the organ dysfunction were also observed (posthemoadsorption SOFA score 7.7 [5.4], $p = 0.046$) (**Table 2**).

DISCUSSION

Main Findings of This Study

This retrospective study describes the potential benefits of CytoSorb® hemoadsorption in critically ill patients with

TABLE 1 | Clinical patient characteristics.

Variable	Result
Characteristics of the study population	
Male gender	5 (83.0%)
Age (years)	57.0 (10.5)
APACHE II	19.5 (6.1)
Body mass index	29 (3)
Comorbidities	
History of smoking (*n*, %)	2 (33.3%)
Arterial Hypertension (*n*, %)	3 (50%)
Diabetes mellitus (*n*, %)	2 (33.3%)
Chronic Obstructive Pulmonary Disease (*n*, %)	0 (0%)
Malignant condition or immunosuppression (*n*, %)	0 (0%)
Chronic kidney disease (*n*, %)	0 (0%)
Liver disease (*n*, %)	0 (0%)
Congestive heart disease (*n*, %)	0 (0%)
Coronary heart disease (*n*, %)	0 (0%)
Organ dysfunction and supportive treatment	
SOFA ICU admission	5.2 (1.5)
PaO_2/F_IO_2 ratio	97.5 (14.6)
Prone position (*n*, %)	6 (100%)
Sepsis (*n*, %)	0 (0%)
Shock (*n*, %)	1 (16.7%)
AKI (*n*, %)	3 (50.0%)
CRRT (*n*, %)	3 (50.0%)
Tocilizumab (*n*, %)	4 (66.7%)
Corticoesteroids 2 mg/kg (*n*, %)	1 (16,7%)
Anticoagulation (*n*, %)	4 (66.7%)
VAP (*n*, %)	2/6 (33.3%)
Hemoadsorption	
Duration hemoadsorption (h)	16.0 (9.0)
N° sessions hemoadsorption	1.2 (1.0)
Inflamatory parameters on admission	
DD (n.v. < 0.5mcg/ml)	559 (254–2643)
CRP (n.v. < 0.5mg/dl)	19.5 (13.4)
Ferritin (n.v.<336 mcg/L)	967 (682–2116)
IL-6 (n.v. < 4.3 pg/ml)	1163 (52–2775)
Outcomes	
Days on mechanical ventilation	15.2 (7.0)
ICU stay (days)	17.2 (8.0)
ICU Mortality (*n*, %)	2 (33.3%)
Inhospital Mortality (*n*, %)	2 (33.3%)

AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health disease Classification System II; CRRT, continuous renal replacement therapy; CRP, C-reactive protein; DD, D-dimer; ICU, intensive care unit; SOFA, sequential organ failure assessment; VAP, ventilator-associated pneumonia.

refractory acute respiratory failure due to COVID-19 and hypercytokinemia. Hemoadsorption was associated with a reduction in inflammatory biomarkers, improved oxygenation, and multiorgan dysfunction.

Previous Experience With Cytokine Hemoadsorption

Several recommendations regarding the use of cytokine hemoadsorption in SARS-CoV-2 pneumonia have been published recently. The National Health Commission and National Administration of Traditional Chinese Medicine recommends CytoSorb® hemoadsorption to treat severe and critical cases of COVID-19 (24). The Brescia Renal Covid Task Force recommends CytoSorb® hemoadsorption in the patients with COVID-19 admitted to ICU who have ARDS or AKI-requiring CRRT (25). The Panamanian Association of Critical Medicine and Intensive Therapy recommends using CytoSorb® in patients with hyperlactatemia and high-dose vasopressors who do not respond to standard therapy. Patients with severe ARDS with high-ventilatory support requirements or candidates for the use of extracorporeal membrane oxygenation (ECMO) therapy are also considered (26). The Colombian consensus suggests using CytoSorb® in patients with cytokine storm syndrome when there is a lack of treatment response, and while evaluating the individual prognosis of the patient (27). On April 10, 2020, the United States of America Food and Drug Administration issued an Emergency Use Authorization for CytoSorb® to treat patients with 18 years of age or older with confirmed COVID-19 admitted to the ICU with confirmed or imminent respiratory failure and specifically early ARDS, severe disease or life-threatening disease defined as respiratory failure, septic shock or the multiorgan dysfunction (28). Despite these recommendations, clinical experience is scarce and comes mainly from case reports and some case series (29–31).

Characteristics of the Study Population. Target Patient Population

The selection of patients with COVID-19 for receiving cytokine hemoadsorption is critical and should be individualized. There are two clinical phenotypes of the patients with COVID-19 (11). One phenotype is characterized by a mild or moderate disease with low-viral loads. These patients have preserved interferon responses with regulated production of cytokines and show rapid recovery from initial lymphopenia. Thus, they are unlikely to benefit from cytokine hemoadsorption. However, selected patients in the second phenotype, characterized by a severe disease with a high risk of death, high-viral loads, insufficient interferon response, sustained lymphopenia, and a very significant elevation of cytokines, could benefit from cytokine hemoadsorption. In this study, patients were more suitable to receive cytokine hemoadsorption if they were more severely ill and developed severe acute respiratory failure refractory or poorly responsive to prone positioning, in association with a hyperinflammatory state (determined by very high levels of biomarkers, such as IL-6, ferritin, and DD). All patients in this study presented a considerable deleterious clinical condition, with a mean PaO_2/F_IO_2 ratio of 103 (18.4).

There is a lack of studies evaluating cytokine hemadsorption in critically ill patients with COVID-19, and some of them have included heterogeneous populations of critically ill patients. Rampino et al. (32) reported a case series of 9 consecutive

TABLE 2 | Comparison of prehemoadsorption (pre-HA) and posthemoadsorption (post-HA) parameters.

	ICU admission	Pre-HA	Post-HA	*p*-value
SOFA	5.2 (1.5)	9 (4.75)	7.7 (5.4)	$p = 0.046$
PaO_2/FiO_2 ratio	97.5 (14.6)	103 (18.4)	222 (20.9)	$p = 0.029$
DD (n.v. < 0.5 mcg/ml)	559 (254–2,644)	17,868 (4,196–45,287)	4,488(3,166–17,076)	$p = 0.046$
CRP (n.v. < 0.5 mg/dl)	19.5 (13.4)	12.9 (10.6)	3.5 (2.8)	$p = 0.028$
Ferritin (n.v. < 336 mcg/L)	967 (682–2,116)	1,539 (764–27,414)	1,197 (524–3,857)	$p = 0.046$
IL-6 (n.v. < 4.3 pg/ml)	1,163 (52–2,775)	17,367 (4,539–22,532)	2,403 (917–3,724)	$p = 0.043$
IL-10 (n.v. < 7.8 pg/ml)	–	22.3 (19.2–191)	5.6 (5.2–36.6)	$p = 0.068$

DD, D-dimer; Fb, fibrinogen; HA, hemoadsorption; IL-6, interleukin 6; IL-10, interleukin 10; CRP, C-reactive protein; n.v., normal values; SOFA, Sequential Organ Failure Assessment score.

critically ill patients with SARS-CoV-2 and acute respiratory failure requiring continuous positive airway pressure. In this study, no patients required invasive mechanical ventilation. Their eligibility criteria were confirmed SARS-CoV-2 pneumonia and a sum of P_aO_2/F_iO_2 ratio < 200 mm Hg, CRP levels >10 mg/dl, and a lymphocyte count <1,500/mm^3. Damiani et al. (33) delivered hemoadsorption with CytoSorb® for 24 to 48-h sessions to 11 patients with COVID-19 requiring mechanical ventilation due to rapidly progressive ARDS after a median of 3 days (range 0–4 days) from hospital admission. Nassiri et al. (34) used CytoSorb® in 26 patients with COVID-19-associated moderate ARDS (P_aO_2/F_iO_2 ratio < 200) and hyper inflammation (CRP > 50 mg/L and ferritin > 1,500 mcg/L). Of all patients, 46.2% received mechanical ventilation. Paisey et al. (35) reported a case series of 15 patients with severe COVID-19 that received cytokine hemoadsorption (five HA-330 cartridges and 10 CytoSorb® adsorbents). All the patients needed invasive mechanical ventilation and CRRT, and 11 received ECMO support. In a multicenter study, Villa et al. (36) evaluated 37 patients who had received cytokine hemoadsorption using the oXiris® membrane. The indication for oXiris® was biochemical and clinical evidence of systemic inflammation associated with AKI, hemodynamic instability, or multiorgan dysfunction. All the patients received mechanical ventilation.

Biomarker Levels and Organ Dysfunction Throughout Hemoadsorption in Relation to Outcomes

In general, critically ill patients with COVID-19 do not show increased plasma levels of biomarkers as other populations of critically ill patients (e.g., septic shock or sepsis with patients with ARDS). Previous studies have found mild-to-moderate elevations of CRP, IL-6, and ferritin. (37) However, there are no well-defined thresholds of biomarkers to consider the initiation of cytokine hemoadsorption. Given the heterogeneity of individual responses and the numerous underlying factors that affect levels of biomarker, it is uncertain whether valid thresholds will be determined shortly.

The results of this study are engaging and coincide with the previous studies. Rampino et al. (32) documented reductions in proinflammatory cytokines (e.g., IL-6) in patients receiving cytokine hemoadsorption therapy. All patients who received the treatment survived, and only two of them needed endotracheal intubation. Damiani et al. (33) showed the median values of IL-6 before hemoadsorption were 355 pg/ml (IQR 263–466), 118 pg/ml (IQR 19–221, $p = 0.003$) at treatment end and 169 pg/ml (IQR 61–253, $p = 0.03$) 24 h after therapy. A significant decrease in CRP and an increase in P_aO_2/F_iO_2 ratio were also observed. The improvement in the inflammatory profile was associated with progressive improvements in the respiratory function. Nassiri et al. (34) reported that the P_aO_2/F_iO_2 ratio, SOFA score, and inflammatory biomarkers (procalcitonin, CRP, and ferritin) improved significantly, and the authors reported a mortality rate of 19.2%. A potential limitation of this study is that cytokine levels were not reported. Paisey et al. (35) proposed hemoadsorption as an adjunctive treatment leading to a reduction in ferritin, CRP, procalcitonin, and lactate levels. Yet, no significant differences were found in IL-6 and IL-10 pre- and post-treatment levels. In these patients, hypercytokinemia was moderate, although they showed a hyperinflammatory profile based on ferritin and CPR levels. Villa et al. (36) delivered the hemoadsorption therapy after a median of 3.6 days (IQR 3.7) from ICU admission and 14 days (IQR 10.0) from the symptom onset. The decrease of IL-6 concentration was significant, especially during the first 24 h of treatment (from baseline levels of 1,230 pg/ml [IQR 895] to 479 pg/ml [IQR 531] at 24 h after treatment, 320 pg/ml [IQR 259] at 48 h, and 160 pg/ml [IQR 141] at 72 h [$p = 0.001$ for each time point]). The reduction in serum IL-6 concentration levels correlated with improved organ function, particularly hemodynamic and pulmonary function. A slight decrease in the observed mortality rate compared with the predicted mortality rate, calculated by the APACHE IV score, was also observed.

The results of this study are different from the recently published CYCOV trial (38), in which 34 patients with severe COVID-19 pneumonia requiring ECMO were included. Seventeen patients were treated with cytokine hemoadsorption for 72 h. No significant differences in IL-6 levels were observed between the two groups after 72 h of cytokine hemoadsorption. The median IL-6 concentrations decreased from 357 pg/ml (IQR 177.4–118.0) to 98.6 pg/ml (71–192.8) in the cytokine adsorption group and from 289.0 pg/ml (87–787.0) to 110.0 pg/ml (48–198.5) in the control group. In contrast, the median baseline IL-6 levels were very high (17,367 pg/ml [4,539–22,532]), and the reduction in IL-6 levels and inflammatory biomarkers was substantial. The results of the CYVOV trial are not comparable

with the results of this study, as the rate of cytokine removal by hemoadsorption depends on the presence of baseline high-concentration levels of cytokines in plasma (39).

In this study, the strategy for delivering cytokine hemadsorption was different from other studies that used fixed hemoadsorption regimens. Single 24-h sessions of hemoadsorption were planned to be delivered (only one patient required two sessions of 24 h). Real-time IL-6 levels were monitored during the hemoadsorption sessions, which allowed us to withhold the treatment at 24 h if IL-6 levels had been reduced, and the patient had clinical improvement. As observed by Damiani et al. (33) and Paisey et al. (37), no significant differences were found in the reduction of IL-10 levels. However, the lack of effect over IL-10 levels may be secondary to the slightly increased baseline levels and the small sample size.

Cytokine hemoadsorption could be considered an effective and safe rescue therapy for highly selected critically ill patients with COVID-19. Further studies and randomized controlled trials in critically ill patients with COVID-19 with refractory acute respiratory failure and hypercytokinemia should be conducted to accurately narrow the indications and clinical benefits of the cytokine hemoadsorption.

Limitations

This study has some limitations. First, this is a single-center study including a small number of patients with no control group. Thus, the findings of this study should be confirmed in larger comparative studies and cannot be extrapolated to other ICU settings; moreover, the complexity of the conferred difficulty of the patients in determining the effect of CytoSorb® alone on patient outcomes. Second, the patient inclusion process was not consecutive. Given the unprecedented pandemic situation, it was impossible to ensure that all patients meeting the inclusion criteria were evaluated for eligibility. Third, we have not performed the sample size calculation because of the observational characteristics of the study.

CONCLUSIONS

In this case series, critically ill patients with COVID-19 with severe acute respiratory failure refractory to prone positioning and hypercytokinemia who received adjuvant treatment with cytokine hemoadsorption showed a significant reduction in IL-6 plasma levels and other inflammatory biomarkers. Improvements in oxygenation and SOFA score were also observed. Cytokine hemoadsorption could be a safe and effective rescue therapy for patients with refractory COVID-19 acute respiratory failure.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was approved by the Local Clinical Research Ethics Committee (PR (AG) 270/2020), and the need for informed consent was waived. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors involved in providing care for the patient and writing and reviewing the manuscript.

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Cox-LASSO Analysis for Hospital Mortality in Patients With Sepsis Received Continuous Renal Replacement Therapy: A MIMIC-III Database Study

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Background: Sepsis remains the leading cause of mortality in-hospital in the intensive care unit (ICU). Continuous renal replacement therapy (CRRT) is recommended as an adjuvant therapy for hemodynamics management in patients with sepsis. The aim of this study was to develop an adaptive least absolute shrinkage and selection operator (*LASSO*) for the *Cox* regression model to predict the hospital mortality in patients with Sepsis-3.0 undergoing CRRT using Medical Information Martin Intensive Care (MIMIC)-III v1.4.

Methods: Patients who met the Sepsis-3.0 definition were identified using the MIMIC-III v1.4. Among them, patients who received CRRT during ICU hospitalization were included in this study. According to the survival status, patients were split into death or survival group. Adaptive *LASSO* for the *Cox* regression model was constructed by STATA software. At last, nomogram and Kaplan-Meier curves were drawn to validate the model.

Results: A total of 181 patients who met Sepsis 3.0 criteria received CRRT were included in the study, in which, there were 31 deaths and 150 survivals during hospitalization, respectively. The overall in-hospital mortality was 17.1%. According to the results of multivariate *Cox-LASSO* regression analysis, use of vasopressor, international normalized ratio (INR) $\geq$1.5, and quick sequential organ failure assessment (qSOFA) score were associated with hospital mortality in patients with sepsis who underwent CRRT, but lactate level, mechanical ventilation (MV) support, PaO_2/FiO_2, platelet count, and indicators of acute kidney injury (AKI), such as blood urea nitrogen (BUN) and creatinine, were not independently associated with hospital mortality after adjusted by qSOFA. The risk nomogram and Kaplan-Meier curves verified that the use of vasopressor and INR $\geq$1.5 possess significant predictive value.

Conclusions: Using the *Cox-LASSO* regression model, use of vasopressor, INR ≥1.5, and qSOFA score are found to be associated with hospital mortality in patients with Sepsis-3.0 who received CRRT. This finding may assist clinicians in tailoring precise management and therapy for these patients who underwent CRRT.

Keywords: MIMIC-III, Sepsis-3.0, *LASSO*, *Cox* regression, mortality, CRRT

INTRODUCTION

Sepsis is a major condition with high morbidity and mortality in intensive care unit (ICU) patients (1). Severe sepsis and septic shock are characterized by vasoplegia and alterations of microcirculation, resulting in aggressively hemodynamic alterations that render the patient hypotensive or with organ dysfunction (2–5). During sepsis, fluid responsiveness or the use of vasopressors could guide fluid administration (6), but the response to therapy is highly variable (7, 8). Improvement of hemodynamic may not be related to the improvement of microcirculation (4, 9). Septic shock is defined as a microcirculation disease, and many trials showed that the severity of microvascular alterations is associated with outcomes in patients with septic shock (10–14). Evaluation of the response for hemodynamic management is critical for the prognosis of sepsis.

According to the 2020 Surviving Sepsis Campaign (SSC) guidelines, renal replacement therapy (RRT)/continuous RRT (CRRT) has emerged as the preferred modality for critically ill patients to treat acute kidney injury (AKI), fluid overload, particularly, those with hemodynamic instability who are unresponsive to fluid restriction and diuretic therapy (15). In adult septic patients who underwent RRT, microcirculation was improved despite no significant variation in macro-hemodynamics (16). Sepsis-induced aggressively hemodynamic alterations are mainly caused by endothelial dysfunction resulting in the activation of inflammation and coagulation processes (5, 17). CRRT plays an important role in removing toxins and inflammatory factors, and higher TNF-α removal could be related to the lower mortality observed in patients with AKI (18). In addition, patients with sepsis suffer from a higher risk of bleeding and clotting. Anticoagulation is necessary for the effective delivery of CRRT, and anticoagulation for CRRT should be adapted to the patient's characteristics (19). Given the complex roles of CRRT in improving inflammatory response, fluid management, and anticoagulation involved in CRRT management, assessment of the prognosis in patients with sepsis who underwent CRRT could be especial. Until now, the risk factors of worse prognosis in patients with sepsis who received CRRT are limited to be reported.

In the current study, we conducted a retrospective study based on Medical Information Martin Intensive Care (MIMIC) III v1.4 to develop a model based on the potential risk factors related to the outcome of patients with sepsis who need CRRT. The results could be helpful for clinicians to make precise management of these patients.

Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; *CI*, confidence intervals; CRRT, continuous renal replacement therapy; *HR*, hazard ratio; ICD, International Classification of Diseases; ICU, intensive care unit; INR, international normalized ratio; LODS, Logistic Organ Dysfunction System; MIMIC, Medical Information Mart for Intensive Care; PaO_2/FiO_2, the ratio of the partial pressure of oxygen in arterial blood (PaO_2) to the inspired oxygen fraction (FiO_2); qSOFA, quick sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; SpO_2, oxyhemoglobin saturation; SSC, surviving sepsis campaign; WBC, white blood cells.

METHODS

Database and Study Population

Study data were acquired from the MIMIC-III database v1.4, which encompasses > 60,000 ICU admissions between 2001 and 2012 for > 46,000 unique patients at Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts between 2001 and 2012 (20). The information available in MIMIC-III includes dates of admission to the ICU and hospital, demographic, clinical features, laboratory and microbiology test results, fluid balance, critical illness scores, diagnosis codes, and hospital mortality. Use of the MIMIC-III database was approved by the Institutional Review Boards of BIDMC and the Massachusetts Institute of Technology.

Firstly, data extraction adhered to the original Sepsis-3.0 definition as closely as possible (21, 22). According to the report of Johnson (23), the patients who fulfilled the Sepsis-3.0 criteria were automatically extracted using pgAdmin PostgreSQL tools (version 1.22.1). Of these patients, patients who aged over 18-year-old received CRRT during hospitalization were included. We excluded those with conditions who may be associated with hospital mortality, such as: (1) the length of ICU stay <24 h; (2) with chronic kidney disease (International Classification of Diseases [ICD]9-code: 5859); (3) metastatic cancer and solid tumor without metastasis (metastatic cancer: icd9_code: 1960–1991, 20970–20975, 20979, 78951; solid tumor without metastasis: icd9_code: 1400–1729, 1740–1759, 179–1958, 20900–20924, 20925–2093, 20930–20936, 25801–25803); or (4) surgery plan. Patients were divided into two groups based on the record of the hospital expire flag (in-hospital death recorded in the hospital database). The detailed process of patients' selection and data extraction is shown in **Figure 1**.

Outcomes

The primary outcome was hospital mortality at the first ICU admission. The secondary outcomes were the length of ICU and hospital stay, use of vasopressor, and mechanical ventilation (MV) support.

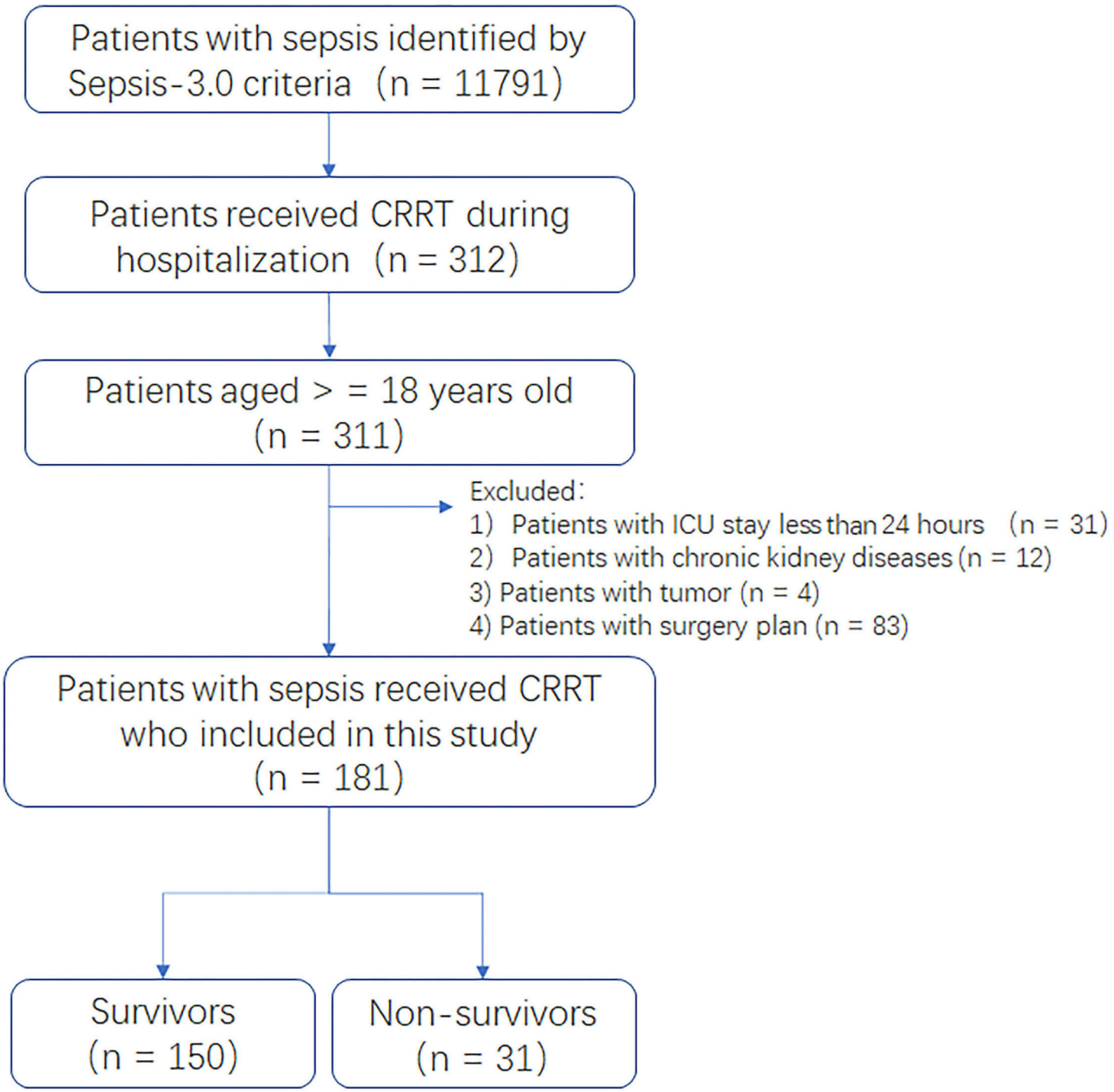

FIGURE 1 | Flow chart of patient selection and data extraction.

Data Extraction and Variables Collection

Variables extracted from MIMIC-III database v1.4 included demographics, severity accessed by SOFA, qSOFA, systemic inflammatory response syndrome (SIRS), and Logistic Organ Dysfunction System (LODS) scores, source of patients, vital signs, such as heart rate (HR), systolic blood pressure (BP), diastolic BP, mean arterial pressure (MAP), temperature, respiratory rate (RR), arterial blood gas, such as oxyhemoglobin saturation (SpO_2) and PaO_2/FiO_2, serum laboratory variables that include the minimum of albumin, platelet, the maximum of bilirubin, creatinine, lactate, international normalized ratio (INR), blood urea nitrogen (BUN), and white blood cells (WBC), and the test results of blood infection. Furthermore, oxygen therapy support mode, duration of ventilation, use of vasopressor, and vasopressor duration were accessed. Patient demographics and all necessary variables were calculated using data from the first 24 h of the ICU stay. Furthermore, we set categorical variables based on the values of laboratory indexes within 24 h after ICU admission as below: (1) systolic BP <100 mmHg, (2) whether or not need vasopressor, (3) INR ≥ 1.5, (4) platelet $<100 \times 10^9$/L, (5)

TABLE 1 | Baseline characteristics in patients with sepsis who received CRRT.

Parameters	Total ($n = 181$)	Survivors ($n = 150$)	Non-survivors ($n = 31$)	*P*
Demographic variables				
Gender male, *n* (%)	109 (60.2)	89 (59.3)	20 (64.5)	0.591
Age, year, mean (SD)	61.9 (14.82)	61.2 (15.11)	65.0 (13.12)	0.196
Ethnicity, n 0.530				
White	101	81	20	0.283
Black	34	32	2	0.053
Hispanic	12	11	1	0.403
Others	34	26	8	0.272
Severity, median (IQR)				
SOFA	7 (5–10)	6 (5–9)	11 (8–16)	<0.001
qSOFA	2 (1–2)	2 (1–2)	2 (2–3)	<0.001
SIRS	3 (2–4)	3 (2–3)	3 (2–4)	0.033
LODS	6 (5–8)	6 (4–7)	9 (7–13)	< 0.001
First service, *n*				0.546
CMED	24	18	6	
MED	152	127	25	
NMED	2	2	0	
OMED	3	3	0	
Blood infection, *n*	68	54	14	0.338
Mechanical ventilation, *n* (%)	76 (42)	53 (35.3)	23 (74.2)	< 0.001
Length of ICU stay, days, median (IQR)	2.9 (1.8–5.7)	2.8 (1.8–5.7)	3.3 (1.7–7.2)	0.778
Length of hospital stay, days, median (IQR)	7.7 (4.1–4.0)	9.8 (5.1–15.6)	3.4 (1.6–9.8)	< 0.001

SOFA, sequential organ failure assessment; qSOFA, Quick SOFA; SIRS, systemic inflammatory response syndrome; LODS, Logistic Organ Dysfunction System.

lactate $\geq$4 μmol/L, (6) impaired pulmonary function was defined as PaO_2/FiO_2 >300 mmHg, 200 mmHg < $PaO_2/FiO_2 \leq$ 300 mmHg, 100 mmHg < $PaO_2/FiO_2 \leq$ 200 mmHg, and $PaO_2/FiO_2 \leq$ 100 mmHg. Ultimately, we obtained the list of data based on anonymized patients with Sepsis-3.0 who received CRRT.

Statistical Analysis

All the data analyses were conducted using STATA 15.0 MP (College Station, TX, USA). Variables were displayed and compared between survivors and non-survivors. Normally and non-normally distributed continuous variables were expressed as the mean ± SD and the median (interquartile range, IQR), respectively. Continuous variables of normal distribution were tested by Student's *t*-test. Mann-Whitney *U*-test was used to compare continuous data of non-normally distribution. Categorical variables were summarized as numbers or percentage and assessed using the Chi-square test. A $p < 0.05$ was defined as statistically significant.

Cox survival analysis and least absolute shrinkage and selection operator (LASSO) regression univariable regression analyses were performed to assess the association of each variable with hospital mortality, and values of $p < 0.05$ were selected as a candidate variable. The method of LASSO was used to select predictors. Multivariate *Cox* regression was further performed to assess the prognostic value of selected variables, with qSOFA as an adjustment factor. The hazard ratio (HR) and 95% CI were estimated by *Cox* proportional hazards regression model.

Construction and Validation of a Prognostic Nomogram for Hospital Mortality

Nomogram were constructed to calculate an individual's probability of hospital mortality by using STATA software. In the nomogram, the patient was scored according to the variables entered multivariate *Cox* proportional hazards regression model. The final sum of the scores was expected to be the corresponding hospital mortality probability. Kaplan-Meier curves were drawn and compared the differences in hospital mortality between groups divided by the variables of the nomogram.

RESULTS

Baseline Characteristics

There were 11,791 patients with Sepsis-3.0 between 2008 and 2012. In this cohort, 312 patients received CRRT during hospitalization. One patient aged less 18-year-old, 31 cases with the length of ICU stay <24 h, 12 patients with chronic kidney disease, 4 patients with tumor, and 83 patients with surgery plan were excluded. Finally, there were 181 patients with Sepsis-3.0 who underwent CRRT during hospitalization, in which, there were 31 deaths and 150 survivals during hospitalization, respectively.

In these patients, the age, gender, ethnicity, first service type, blood infection, and the length of ICU stay showed no significant difference between survival and non-survival groups. The ratio of

TABLE 2 | Laboratory indexes within 24 h after ICU admission in patients with sepsis who received CRRT.

Parameters	Total ($n = 181$)	Survivors ($n = 150$)	Non-survivors ($n = 31$)	*P*
Vital signs, median (IQR) if not otherwise specified				
Maximum heart rate (/min), mean (SD)	105 (22)	104 (22)	109 (21)	0.241
Minimum systolic BP (mmHg)	87 (77–103.5)	90 (81–107)	73 (62–80)	< 0.001
Systolic BP group, (mmHg)				0.002
Systolic BP ≥ 100, *n*	53	51	2	
Systolic BP < 100, *n*	128	99	29	
Minimum diastolic BP (mmHg)	40 (33–49)	41 (35–49)	35 (27–44)	0.005
Diastolic BP group, (mmHg)				0.370
Diastolic BP ≥ 60, *n*	20	18	2	
Diastolic BP < 60, *n*	161	132	29	
Minimum MAP (mmHg)	54 (47–63)	55.5 (48–64)	47 (40–51)	< 0.001
MAP group, (mmHg)				0.327
MAP ≥ 70, *n*	28	25	3	
MAP < 70, *n*	153	125	28	
Maximum respiratory rate (/min)	28 (23–32)	27 (23–31)	33 (28–35)	< 0.001
Respiratory rate group, (/min)				0.226
Respiratory rate ≤ 20, *n*	16	15	1	
Respiratory rate > 20, *n*	165	135	30	
Maximum temperature (°C), mean (SD)	37.4 (1.0)	37.5 (0.9)	37.3 (1.4)	0.432
Serum laboratory variables, median (IQR) if not otherwise specified				
Maximum lactate (μmol/L)	2.2 (1.4–4.6)	1.9 (1.4–3.3)	4.8 (2–9.9)	< 0.001
Lactate group, (μmol/L)				0.068
Lactate < 4, *n*	97	85	12	
Lactate ≥ 4, *n*	84	65	19	
Maximum creatinine (μmol/L)	5.4 (3.7–8.2)	5.8 (3.6–9)	4.7 (3.8–5.7)	0.036
Maximum glucose (mg/dL)	166 (122–243)	161 (121–230)	213 (132–290)	0.062
Maximum bilirubin (mg/dL)	0.65 (0.4–1.5)	0.5 (0.3–0.9)	1.8 (0.6–4.1)	0.001
Bilirubin group, (mg/dL)				0.797
Bilirubin < 4, *n*	119	98	21	
Bilirubin ≥ 4, *n*	62	52	10	
Minimum platelet ($\times 10^9$/L)	167 (106–229)	174.5 (111–30.5)	121 (76–182)	0.045
Platelet group, ($\times 10^9$/L)				0.038
Platelet ≥ 100, *n*	142	122	20	
Platelet < 100, *n*	39	28	11	
Maximum INR	1.4 (1.2–1.9)	1.3 (1.2–1.6)	2 (1.4–2.7)	< 0.001
INR group				0.004
INR < 1.5, *n*	95	86	9	
INR ≥ 1.5, *n*	86	64	22	
Maximum BUN, (mmol/L)	52.5 (41–79)	53 (41–79)	49 (43–81)	0.887
Minimum WBC ($\times 10^9$/L)	8.6 (5.8–13.7)	8.3 (5.9–13.2)	9.1 (5.4–14.6)	0.894
Maximum WBC ($\times 10^9$/L)	11.8 (7.8–19.5)	11.4 (7.8–17.9)	14.8 (7.5–20.4)	0.327
Minimum albumin (g/dL)	3.1 (2.6–3.8)	3.25 (2.7–3.8)	2.6 (2.3–3.1)	0.001
Albumin group, (g/dL)				0.252
Albumin ≥ 4, *n*	87	75	12	
Albumin < 4, *n*	94	75	19	
Pulmonary parameters, median (IQR) if not otherwise specified				
SpO_2	96 (92.5–97.5)	96 (93–98)	95.5 (89.5–97)	0.184
PaO_2/FiO_2, mmHg	112.5 (74.5–91)	122(80–196.7)	90 (63–140)	0.132
Impaired pulmonary function group				< 0.001
$PaO_2/FiO_2 \geq 300$, *n*	119	108	11	

(Continued)

TABLE 2 | Continued

Parameters	Total ($n = 181$)	Survivors ($n = 150$)	Non-survivors ($n = 31$)	*P*
300<$PaO_2/FiO2 \leq 200$, *n*	8	5	5	
200<$PaO_2/FiO_2 \leq 100$, *n*	25	20	5	
PaO_2/FiO_2 <100, *n*	29	17	12	
Vasopressor				< 0.001
No, *n* (%)	109 (60.2)	104 (69.3)	5 (16.1)	
Yes, *n* (%)	72 (39.8)	46 (30.7)	26 (83.9)	
Vasopressor duration, hours	44.8 (23.0–20.0)	41.8(15.5–24.2)	63.8 (27.6–15.7)	0.281
Respiratory support model, *n* (%)				< 0.001
None, *n* (%)	19 (10.5)	19 (12.7)	0 (0)	
Oxygen therapy, *n* (%)	82 (45.3)	76 (50.7)	6 (19.4)	
Mechanical ventilation, *n* (%)	80 (44.2)	55 (36.7)	25 (80.6)	
Ventilation durations, hours	65.6 (27.9–67.5)	82 (30.8–89.8)	60 (27.4–98.2)	0.338

SD, standard deviation; IQR, inter quartile range; BP, blood pressure; SpO_2, pulse oxygen saturation; PaO_2/FiO_2, the ratio of the partial pressure of oxygen in arterial blood (PaO_2) to the inspired oxygen fraction (FiO_2); INR, international normalized ratio.

MV was higher in non-survivors than survivors, and the length of hospital stay was shorter in non-survivors than survivors (**Table 1**).

Laboratory Indexes Within the First 24 h After ICU Admission

Minimum systolic BP, minimum diastolic BP, minimum MAP, maximum RR, maximum lactate, maximum creatinine, maximum bilirubin, minimum platelet, maximum INR, minimum albumin, ratio of vasopressor needed, and respiratory support were significantly different between survivors and non-survivors. However, maximum HR, maximum temperature, maximum glucose, maximum BUN, minimum WBC, maximum WBC, SpO_2, PaO_2/FiO_2, vasopressor duration, and ventilation durations showed no significant difference between the two groups (**Table 2**).

Relationship Between Clinical and Laboratory Indexes and Hospital Mortality

Overall hospital mortality was 17.1% (31/181). The ratio of MV needed was 44.2% (80/181), and the ratio of use of vasopressor was 39.8% (72/181). The hospital mortality was 36.1% (26/72) in patients who received vasopressor and 4.6% (5/109) in patients without vasopressor support ($p < 0.001$). In a subgroup of patients who received MV support, the hospital mortality was 31.3 (25/80), which was significantly higher than that 7.3% (6/82) in patients with oxygen therapy, and all 19 patients without any oxygen therapy were survival.

Identification of Risk Factors of Hospital Mortality by *Cox-LASSO* Analysis

According to the results of **Table 2**, laboratory variables and categorical variables with statistically significant differences between survivors and non-survivors were entered in the Univariate *Cox* analysis. The results showed that systolic BP < 100 mmHg, the use of vasopressor, INR ≥1.5, maximum lactate, maximum creatinine, and impaired severity of pulmonary function were associated with hospital mortality in patients with sepsis undergoing CRRT (all $p < 0.05$; **Table 3**). Furthermore, *LASSO* regression analysis was used to screen these variables. Adaptive *LASSO* regression analysis indicated that the categorical variables, such as the use of vasopressor, INR ≥ 1.5, impaired severity of pulmonary function, but not the absolute values of laboratory indexes, were entered multivariate *Cox* regression model (**Figure 2**). Finally, multivariate *Cox* regression model based on the adaptive LASSO displayed that the use of vasopressor and INR ≥ 1.5 were risk factors of hospital mortality in patients with Sepsis-3.0 who received CRRT adjusted by qSOFA (**Table 4**).

TABLE 3 | Univariate *Cox* analysis of factor related to hospital mortality in patients with sepsis received CRRT.

Parameters	*HR* (95% *CI*)	*P*
Minimum systolic BP	0.956 (0.938–0.976)	< 0.001
Systolic BP <100 mmHg	5.327 (1.268–22.388)	0.022
Use of vasopressor	6,860 (2.622–17.947)	< 0.001
Maximum INR	1.231 (1.127–1.346)	< 0.001
INR ≥ 1.5	2.639 (1.208–5.767)	0.015
Minimum platelet	0.998 (0.995–1.001)	0.270
Platelet < 100 *10^9/L	1.890 (0.901–3.967)	0.092
Maximum lactate	1.140 (1.071–1.213)	< 0.001
Lactate ≥ 4 μmol/L	2.017 (0.978–4.158)	0.057
Maximum creatinine	0.873 (0.772–0.987)	0.031
PaO_2/FiO_2	0.997 (0.991–1.002)	0.244
Severity of impaired pulmonary function	1.580 (1.203–2.076)	0.001
qSOFA	2.523 (1.455–4.374)	0.001

HR, hazard ratio; CI, confidence interval; BP, blood pressure; PaO_2/FiO_2, the ratio of the partial pressure of oxygen in arterial blood (PaO_2) to the inspired oxygen fraction (FiO_2); INR, International normalized ratio; qSOFA, quick sequential organ failure assessment.

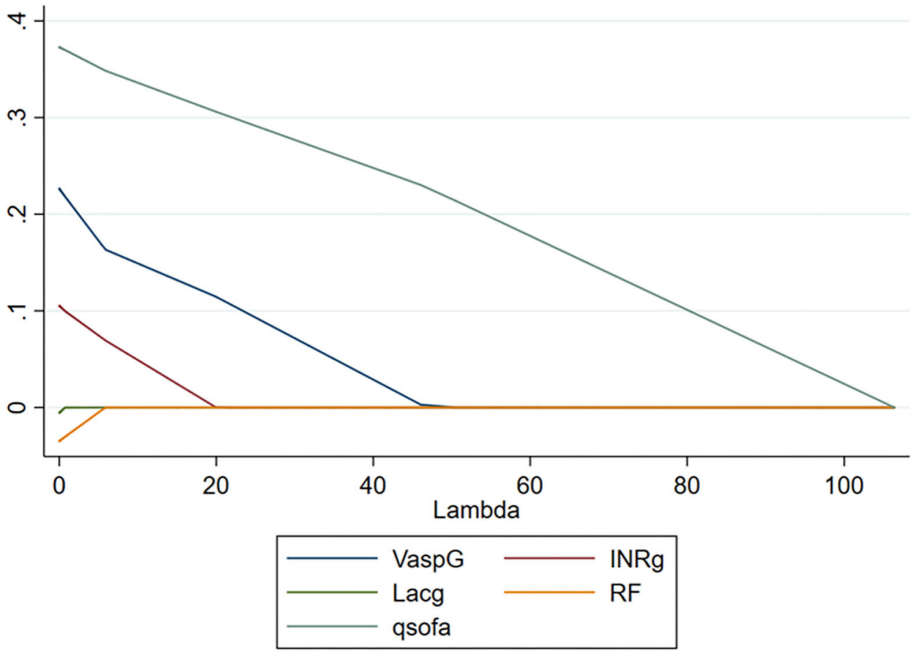

FIGURE 2 | LASSO regression analysis for hospital mortality in patients with Sepsis-3.0 who received CRRT. VaspG (blue line): use of vasopressor; INRg (purple line): INR >1.5; Lacg (green line): lactate ≥4 μmol/L; RF (orange line): severity of impaired pulmonary function (defined as PaO_2/FiO_2 (PF) >300 mmHg, 200 mmHg < PF ≤ 300 mmHg, 100 mmHg < PF ≤ 200 mmHg, PF ≤ 100 mmHg); qSOFA (dark green line): qSOFA score. LASSO, least absolute shrinkage and selection operator; CRRT, continuous renal replacement therapy; qSOFA, quick sequential organ failure assessment; INR, international normalized ratio.

A New Prognostic Nomogram for Patients With Sepsis-3.0 Who Underwent CRRT

To provide a quantitative method for clinical outcome prediction, we constructed a prognostic nomogram, such as the use of vasopressor, INR ≥ 1.5, the severity of impaired pulmonary function, and qSOFA, to predict the hospital mortality of patients with Sepsis-3.0. As shown in **Figure 3**, total scores were derived from the sum of the individual scores of various risk factors. In this nomogram, a higher total number of points indicated worse hospital mortality.

Stratified Analysis of Prognostic Factors Using Kaplan-Meier Curves

Further, we evaluated the prognostic value of the use of vasopressor, INR > 1.5, the severity of impaired pulmonary function, and qSOFA score for the patients with Sepsis-3.0 who received CRRT. A significant difference in clinical outcomes was observed between with and without vasopressor support (**Figure 4A**, $p < 0.001$), INR > 1.5 compared with INR ≤ 1.5 (**Figure 4B**, $p = 0.012$), among different severity of impaired pulmonary function indicated with the value of PaO_2/FiO_2 (**Figure 4C**, $p < 0.001$), and with or without MV support (**Figure 4D**, $p < 0.001$).

TABLE 4 | Multivariate *Cox* analysis of factor related to hospital mortality based on LASSO regression in patients with sepsis received CRRT.

Parameters	*HR* (95% *CI*)	*P*
Use of vasopressor	4.564 (1.575–13.223)	0.005
INR ≥ 1.5	2.475 (1.114–5.497)	0.026
Severity of impaired pulmonary function	1.066 (0.782–1.454)	0.685
qSOFA	2.514 (1.322–4.780)	0.005

HR, hazard ratio; CI, confidence interval; INR, International normalized ratio; qSOFA, quick sequential organ failure assessment; Continuous renal replacement therapy.

DISCUSSION

Sepsis-induced aggressive hemodynamic alterations are one of the main causes for high mortality in patients with sepsis. CRRT, as a recommended management for hemodynamic stable, is paid more attention in recent years. In the present study, the retrospective study based on MIMIC-III v1.4 developed a *Cox-LASSO* model to show that use of vasopressor and INR ≥ 1.5 are found to be risk factors of hospital mortality in patients with sepsis who received CRRT. These findings may assist clinicians in tailoring precise management and therapy for these patients who underwent CRRT.

According to the international guideline for the management of sepsis in 2016 (24), CRRT is suggested to be used to facilitate the management of fluid balance in hemodynamically unstable septic patients. In the present study, the ratio of CRRT support in patients who met the criteria of Sepsis-3.0 was 2.6% (312/11791). There were about 5–6% of ICU patients with AKI who will receive RRT (25). This result is much lower than the ratio of CRRT application in patients with sepsis in adult ICU in China (16.3%) (26) and in pediatric ICU according to our previous

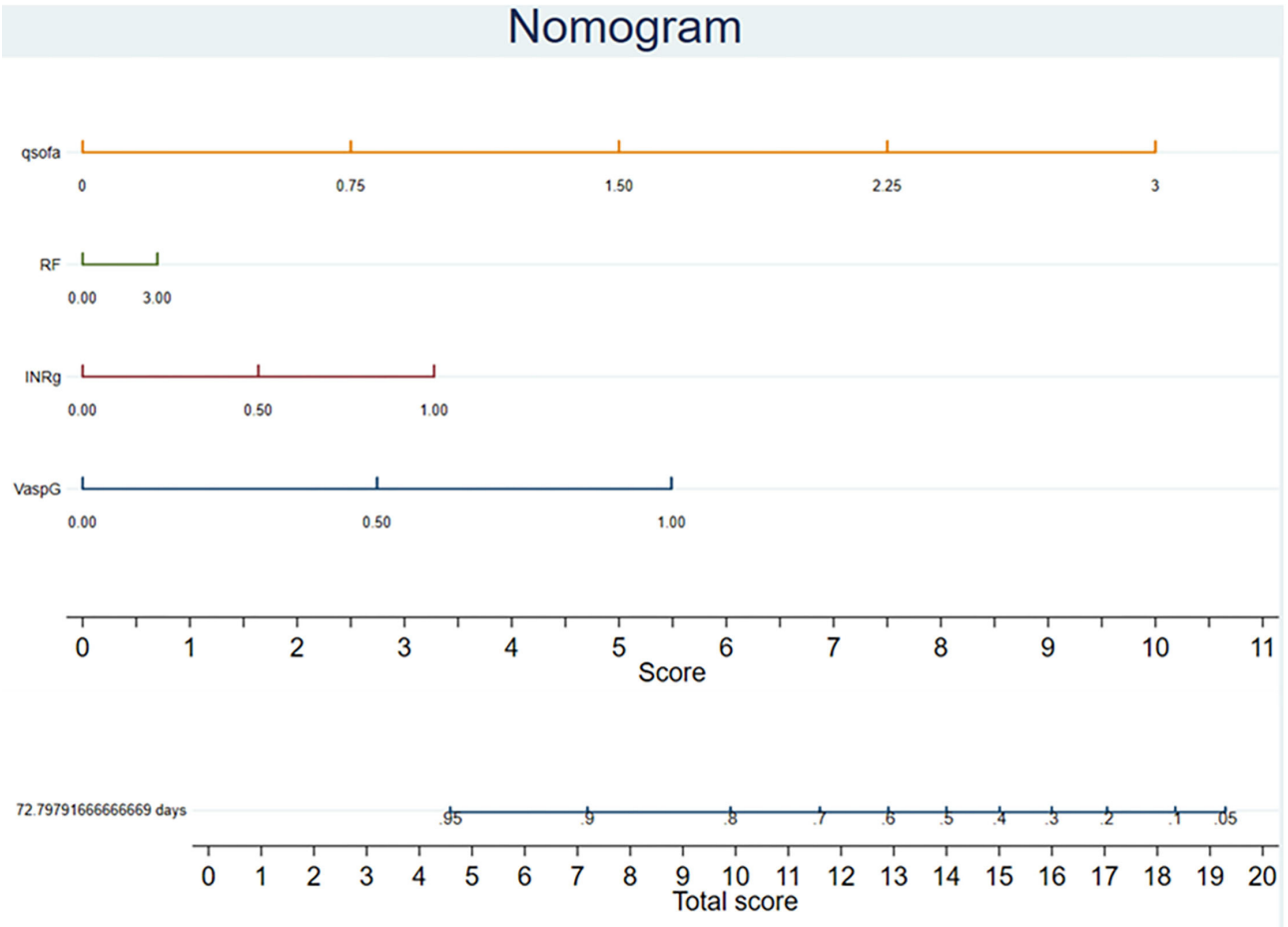

FIGURE 3 | Top features were selected using multivariate *Cox-LASSO* regression analysis and the corresponding variable importance score. The X-axis indicates the importance score, which is the relative number of a variable that is used to distribute the data, the Y-axis indicates the top-weighted variables. qSOFA (orange line): quick sequential organ failure assessment; RF (green line): impaired severity of pulmonary function (defined as PaO_2/FiO_2 [PF]) > 300 mmHg, 200 mmHg < PF ≤ 300 mmHg, 100 mmHg < PF ≤ 200 mmHg, PF ≤ 100 mmHg). INRg (purple line): INR > 1.5; VaspG (blue line): use of vasopressor. LASSO, least absolute shrinkage and selection operator; CRRT, continuous renal replacement therapy; qSOFA, quick sequential organ failure assessment; INR, international normalized ratio.

study (10.7%) (27). As reported, the ratio of CRRT used in a patient with COVID-19-induced that AKI was from 3.9% (225/5700) to 8.7% (280/3235) in the USA (28). MIMIC-III v1.4 did not include detailed information about the indications for CRRT in each patient. According to the baseline characteristics of patients with sepsis who received CRRT, there were high ratio (70.7%, 128/181) of systolic BP <100 mmHg, high lactate levels (≥ 4 μmol/L) (46.4%, 84/181), high ratio of vasopressor support (39.8%, 72/181), and a high ratio of MV support (44.2%, 80/181). Miao et al. (29) reported the indications of CRRT in pediatric severe sepsis (http://links.lww.com/CCM/E733). Whether there are more detailed differences in CRRT application between pediatric and adult patients with sepsis who need further investigation in a well-designed study.

In adult ICU, hospital mortality and 28-day mortality ranged from 50.4 to 64.5% in patients with septic AKI under CRRT (30, 31). The recent insights and results from large randomized and non-randomized trials in the area of RRT applied for sepsis-induced AKI do not seem to improve survival or renal recovery (32). Our previous study indicated that CRRT decreases hospital mortality rate from 32.4% (44/136) to 21.3% (29/136) in pediatric patients with severe sepsis (29). Moreover, there is no evidence to indicate that high-volume hemofiltration (HVHF) is superior to standard-volume continuous veno-venous hemofiltration (CVVH) in the aspect of reducing 28-day mortality in pediatric patients with severe sepsis (24.7 vs. 33.8%, $p = 0.216$) (33). In our present study, the total hospital mortality was 17.1% (31/181). In the subgroup, the hospital mortality was 22.6% (19/84) in patients with lactate ≥ 4 μmol/L, 22.6% (29/128) with systolic BP <100 mmHg, 31.3% with MV support, and 36.1% (26/72) with vasopressor support. These findings give an overview of the clinical benefits of CRRT in adult sepsis.

Hypotension or the need for vasoactive drugs was associated with mortality (34). In our present study, the need for vasoactive drugs, but not hypotension (defined as systolic BP < 100 mmHg), on ICU admission was entered the *LASSO* model for mortality in a patient with sepsis under CRRT. In addition, thrombocytopenia prior to the initiation of CRRT and severe thrombocytopenia

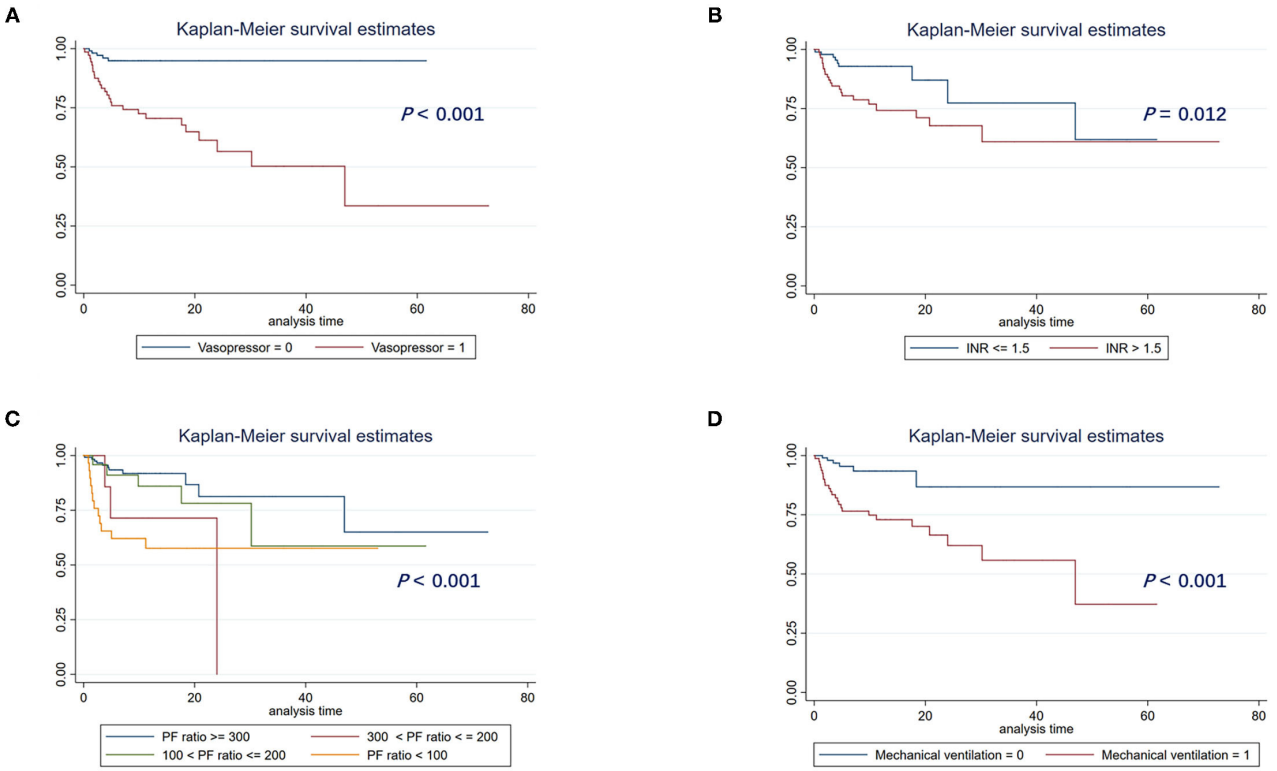

FIGURE 4 | Kaplan-Meier survival curve analysis of hospital mortality in patients stratified by prognostic factors based on *Cox-LASSO* analysis. **(A)** With vs. without vasopressor; **(B)** INF ≤ 1.5 vs. INR >1.5; **(C)** PaO_2/FiO_2 (PF) >300 mmHg vs. 200 mmHg < PF ≤ 300 mmHg vs. 100 mmHg < PF ≤ 200 mmHg vs. PF ≤ 100 mmHg); **(D)** with or without mechanical ventilation support. LASSO, least absolute shrinkage and selection operator; INR, international normalized ratio.

prior to and following the initiation of CRRT were associated with increased ICU mortality (35). In the present study, though the ratio of patients with platelets $<100 \times 10^9$/L was higher in non-survivors than survivors, the ratio of patients with platelets $<100 \times 10^9$/L on admission was not an independent factor for mortality in patients under CRRT support. Moreover, AKI is a main indication for CRRT initiation, but the levels of serum creatinine were relatively lower in non-survivors than survivors, and there were no differences in the levels of BUN between the two groups. Consistently, there was a report that the severity of the AKI at the time of CRRT start did not have a significant relationship with the burned patient outcome with CRRT (36). Otherwise, in sepsis patients with AKI treated with CRRT, age, Acute Physiology and Chronic Health Evaluation (APACHE) II, SOAF, and grade IV of cardiac function were independent risk factors for death (37). In this study, qSOFA score was associated with mortality in patients treated with CRRT.

There are several limitations in this study. Firstly, we could not collect the detailed information about fluid overload in patients with sepsis. Secondly, the indications for CRRT were lacking in this study. Thirdly, as a database study, the interval time between sepsis occurrence and CRRT initiation was lacking. All these limitations could lead to bias for the present conclusions of this study, which needs further confirmation in a well-designed prospective study.

CONCLUSIONS

In summary, we found that the use of vasopressor, INR ≥ 1.5, and qSOFA score are outcome of patients with sepsis who received CRRT based on MIMIC-III v1.4. After adjusted by qSOFA score, either lactate level or MV support is independently associated with the hospital mortality. These findings may assist clinicians in tailoring precise management of hemodynamics and coagulation disorders for these patients who underwent CRRT.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

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 for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CW and YZ conceptualized the research aims. CW planned the analyses, guided the literature review, and drafted the manuscript. JZ extracted the data from the MIMIC-III database. CW, JZ, and JW participated in processing the data and doing the statistical analysis. LZ and YZ provided comments and approved the final manuscript. All authors read and approved the final manuscript.

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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.2021.778536/full#supplementary-material

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