



## 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).

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Luo Y, Gu Q, Wen X, Li Y, Peng W, Zhu Y, Hu W and Xi S (2021) Neurological Complications of Veno-Arterial Extracorporeal Membrane Oxygenation: A Retrospective Case-Control Study. Front. Med. 8:698242. doi: 10.3389/fmed.2021.698242 **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</p>

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:  $\mu g/kg/min$ )], 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



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 nonneurological 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)  $(8.12 \ [605, 13.81] \text{ vs. } 6.43 \ [4.45, 8.71] \text{ mmol/L}, P = 0.012),$ median concentration of troponin I (TNI) (16.7 [1.7, 88.8] vs. 5.0 [1.5, 7.5]  $\mu$ g/L, P = 0.041), median concentration of

#### TABLE 1 | Comparison of baseline characteristics of patients.

$\begin{array}{ c c c c c c c c c c c c c c c c c c c$		All patients	Neurological o	P	
App (years)         39 (20, 50.5) $50 (31, 60)$ $30 (24, 36)$ $-0.001$ Sex, R(s)         Mais $36 (60)$ $26 (66.7)$ $10 (47.6)$ $0.77$ Fermine $24 (40)$ $13 (53.3)$ $11 (83.4)$ $0.001$ Underlying diseases, $n$ (%)         Houstransion $15 (20)$ $14 (450.9)$ $10 (4.8)$ $0.011$ Houstransion $15 (20)$ $14 (35.3)$ $21 (53.6)$ $10 (0)$ $0.020$ CHD $5 (6.3)$ $5 (12.8)$ $0 (0)$ $0.021$ Mait $22 (65.7)$ $21 (53.6)$ $11 (4.8)$ $-0.001$ APM $29 (48.3)$ $22 (53.1)$ $14 (4.8)$ $-0.001$ APM $36 (10.0)$ $4 (10.3)$ $2 (45.3)$ $2 (45.3)$ $0.000$ CPP combine $6 (10.0)$ $4 (10.3)$ $2 (45.3)$ $2 (45.3)$ $0.001$ APA $36 (42.0)$ $7.7 (71.74 (53.3)$ $7.5 (73.5, 61.3)$ $0.002$ Probleme $6 (10.0)$ $7.7 (71.76 (53.3)$ $7.6 (73.5, 61.5)$ $0.002$		<i>n</i> = 60	Yes ( <i>n</i> = 39)	No ( <i>n</i> = 21)	
Sex, P(*)         Under         Under (%)         2 (80,7)         1 (45,3)         1 (45,3)           Inderlying diseases, P(%)          1 (45,3)         1 (45,3)         0.011           Dathering diseases, P(%)          0.021         0.031         0.021           Dathering diseases, P(%)          0.011         0.011         0.012           Dathering diseases, P(%)          0.023         0.021         0.023           Chilo         6.03,3         0.12(8,3)         1 (4.8)         0.001           APM         2.0(8,3)         2.2(8,3)         1 (4.8)         0.003           APM         2.0(8,3)         2.2(8,3)         1 (4.8)         0.003           CA         2.0(8,3)         2.2(8,3)         0.013         0.013           CA         2.0(8,3)         2.2(8,3)         0.013         0.013           CPM cmHig()         9.0(2,1,87,3)         7.7.7.17.8.5.31         2.8(7.8, 8,1)         0.026           PRO_C mmHig()         9.0(2,1,87,3)         7.4.6 (7.403,7.403)         0.026         0.026           PRO_C mmHig()         9.0(2,1,87,3)         9.0.102,03         3.1.01,9,87,9         0.026           PRO_C mmHig()         9.01(2,2,3,7,41 <t< td=""><td>Age (years)</td><td>39 (29, 59.5)</td><td>50 (31, 66)</td><td>30 (24, 35)</td><td>&lt;0.001</td></t<>	Age (years)	39 (29, 59.5)	50 (31, 66)	30 (24, 35)	<0.001
Mele         36 (40)         28 (65,7)         10 (47,6)         0.77           Finalla         24 (40)         18 (33,3)         11 (53,4)         0.01           Hypartansion         15 (25)         14 (35,5)         0.10         0.042           Dabelase         8 (13,3)         8 (20,5)         0.10         0.042           Ch5         5 (6,3)         5 (2,2)         0.10         0.042           AM         29 (46,3)         12 (63,8)         17 (43,0)         -0.00           MA         3 (5,0)         2 (16,3,3)         17 (43,0)         -0.00           Others         6 (10,0)         4 (10,3)         2 (43,3)         0.10           CA         3 (5,0)         7 (7 (7,1,7,85,3)         82.3 (73,8,91.5)         0.056           CMP cmrHq         29 (46,3)         7 (7 (7,1,7,85,3)         82.3 (73,8,91.5)         0.056           CMP cmrHq         9 (5,12)         7 .40 (7 (40,7,408)         7 .44 (7 (40,7,407,103)         0.356           CMP cmrHq         9 (5,13)         7 .45 (7 (40,7,408)         7 .44 (7 (40,7,507)         0.567           Pelo (mrHq)         15 (27,5,14)         16 (10,7,4,7,408)         7 .44 (7 (40,7,407,103)         0.42 (40,2,44)         0.620           CMP cmrHq) <td>Sex, n (%)</td> <td></td> <td></td> <td></td> <td></td>	Sex, n (%)				
Finnie (24,40)13,63.3)11,63.4)Underging diseases, n(%)Underging diseases, n(%)15,(25)14,(35.9)1,44.8)0.011Deckers6,(15.3)8,20.5)0.0(%)0.0.42CHD5,(63)5,12.8)0.0(%)0.0.42CHD5,(63)12,(50.8)14,49.0.0(%)0.0.00AMI22,(65.7)14,(63.9)14,69.0.0.00AMA3,(50.9)2,2,(50.4)17,(83.3)0.0.00CA22,(64.3)22,(50.4)7,(83.3)0.0.00Others6,(10.0)4,(10.3)2,2,(53.8,11.5)0.55CA post-CHO90,(12.1)8,66,(13)7,(7,17,7,8,53)23,2,(136,8,15.3)0.56CP (omf-O)90,(12.1)8,66,(13)7,(12,8,13.4)0.567PiaO_(mmf-b)13,19,27,5,44,0)23,2,(24,13,40)0.2020.327SoO_(mmf-b)13,19,27,5,44,0)23,2,2,(11,45,0)14,24,24,5,2710.0.10SoO_(mmf-b)13,19,27,5,44,0)10,9,(14,45,0)0.102,530.434,44,5,4710.501Chomb-Li24,50,45,134)10,64,13410,64,1340.402,4340.402,434Bull Immo/Li27,16,57,30.324,11,4590.404,44,54,5710.502Chomb-Li24,144,57,14410,64,144,140,0110,64,144,140,010.202Chomb-Li24,144,57,14410,64,144,140,010.2020.103,141,1400.204Bull Immo/Li25,172,2714,161,1314,161,100.204Chomb-Li24,144,57,144<	Male	36 (60)	26 (66.7)	10 (47.6)	0.176
Undergy diseases, n (%)         I (4,8)         I (4,8)         I (4,8)         O (1)           Display (5,1)         5 (25)         0 (0)         0,02           Ch D         5 (25)         1 (25,5)         0 (0)         0,02           Main         22 (5,7)         21 (5,0,8)         1 (4,8)         -0,00           MA         3 (5,0)         2 (5,1)         1 (4,8)         -0,00           MA         3 (5,0)         2 (5,1)         1 (4,8)         -0,00           MA         3 (5,0)         2 (6,0)         7 (7,1,3)         0,000           Ohma         6 (10,0)         4 (10,3)         2 (9,0,3,91(5)         0,050           Orpertorbo         9 (6,12)         5 (6,13)         7 (4,6,140,7,04)         0,060           Oxp0 (mmhg)         20 (013,02,9)         138 (10,1,30,0,0)         233 (150,26,01)         0,060           PROC (mmhg)         20 (013,02,9)         138 (12,0,130,0,0)         233 (150,26,01)         0,060           PROC (mmhg)         20 (13,02,9)         138 (12,0,130,0)         233 (150,26,01)         0,060           PROC (mmhg)         20 (13,02,9)         138 (12,0,130,0)         233 (150,26,01)         0,060           PROC (mmhg)         20 (10,0,4,01,40)         10 (2,0,1	Female	24 (40)	13 (33.3)	11 (53.4)	
Hypertansian         15 (28)         14 (82.8)         14 (82.8)         0 (0)         0.012           CHD         5 (8.3)         5 (12.8)         0 (0)         0.032           Initian         22 (8.7)         1 (8.5)         1 (4.6)         -0.001           APM         29 (8.3)         12 (80.6)         1 (4.6)         -0.001           APM         29 (8.3)         12 (80.6)         1 (4.6)         -0.001           APM         29 (8.3)         22 (66.4)         7 (83.3)         0.000           Others         6 (10.0)         4 (10.3)         23 (38.91.6)         0.000           Others         6 (10.0)         10 (8 (1.2)         5.0 (8 (1.3)         7 (0.1, 8 (1.6)         0.002           Others         7 (9 (2.1, 87.9)         7.7.7 (1.7, 80.3)         2.3 (108.2061)         0.002           Others         7 (9 (2.1, 87.9)         7.4 (8 (7.403, 7.401)         0.020         0.021         0.025         0.021           PAD cotted         9 (74.101.3)         9.4 (70.17.8)         9.4 (70.17.8)         0.020         0.021         0.025           PAD cotted         7 (17.2, 80.3)         8.1 (10.3, 0.32)         1.03 (14.20.5)         0.020         0.020           PAD cotted         7 (10.7,	Underlying diseases, n (%)				
Diabetes         8,1(1.3)         8,20,5)         0,0)         0,00,           CHO         5,(8.3)         5,(12.8)         0,00,         0,152           Initiat etiology, n, (%)	Hypertension	15 (25)	14 (35.9)	1 (4.8)	0.011
CHO         5 (8,3)         5 (12.8)         0 (0)         0.15 (2)           Initiate etiology, n (%)         2 (83.3)         1 (4.8)	Diabetes	8 (13.3)	8 (20.5)	O (O)	0.042
Initial stock general stock sto	CHD	5 (8.3)	5 (12.8)	O (O)	0.152
AMI         22 (86.7)         21 (5.8)         1 (4.8)         -0.001           AFM         29 (48.3)         12 (30.6)         17 (81.0)         -0.001           AA         3 (5.0)         25 (5.1)         11 (4.6)         1           CA         29 (48.3)         22 (56.4)         7 (33.3)         0.009           Others         6 (10.0)         4 (10.3)         21 (9.5)         1           ZA post-ECMO         9 (6, 12)         9.5 (6, 13)         7 (6, 12)         0.059           CVP (cmH-Q)         9 (6, 12)         9.5 (6, 13)         7.44 (7.408, 7.501)         0.567           PaO_(rmmHg)         200 (13, 002.9)         190 (120, 13.003.0)         233 (166, 280.1)         0.626           PaO_(rmmHg)         19 (27.5, 34.9)         32.2 (28.3, 35)         31 (28.8, 34)         0.205           ScAO_(rmmHg)         74.5 (66.9, 82.9)         70.9 (66.4, 0.3)         81 (7, 18.4, 57.7)         0.012           EV (rmmU1)         7.45 (66.9, 82.9)         70.9 (66.4, 0.3)         81 (7, 18.4, 57.7)         0.026           ScAO_(rmmHg)         31.9 (27.5, 34.9)         32.2 (28.1, 35.7)         0.128         0.206           EV (rmmU1)         7.45 (66.9, 82.9)         70.9 (66.4, 0.3)         81 (7, 18.7)         0.267	Initiate etiology, n (%)				
AFM         29 (48.3)         12 (20.8)         17 (81.0)         -0.001           MA         3 (6.0)         2 (6.1)         1 (4.8)         1           CA         29 (48.3)         22 (6.4)         7 (63.3)         0.103           Others         6 (10.0)         4 (10.3)         2 (9.5)         1           SH post-CMO         9 (6, 12)         9.5 (6, 13)         7 (5, 12)         0.037           PH         7.44 (7.409, 7.49)         7.49 (7.408, 7.50)         0.662         0.029           PaOC, ImmHg)         201 (13, 030.9)         139 (128, 1390.3)         233 (158, 286.1)         0.629           PaOC, ImmHg)         7.25 (5.74, 10.14)         8.12 (6.05, 1381)         6.43 (4.45, 8.71)         0.019           BUN ImmOLL         7.26 (5.74, 10.14)         8.12 (6.05, 1381)         6.43 (4.45, 8.71)         0.012           Ci (umoLL)         105.5 (64.5, 134)         108 (41, 156)         102 (75, 11.5)         0.083           Ci (umoLL)         105.5 (64.5, 134)         108 (44, 156)         102 (75, 11.5)         0.083           Ci (umoLL)         105.6 (64.5, 134)         108 (40, 156)         0.227         0.383 (1.14)         0.248           Ci (umoLL)         105.6 (64.5, 134)         108 (40, 168)         102 (27	AMI	22 (36.7)	21 (53.8)	1 (4.8)	<0.001
MA         3 (5.0)         2 (5.1)         1 (4.8)         1           CA         29 (48.3)         22 (56.4)         7 (63.3)         0.109           Ohres         6 (10.0)         4 (10.3)         2 (8.5)         1           24 past-ECMO          9.5 (6.13)         7 (5.12)         0.37           PMP (mHq)         9.07 (2.1, 87.9)         9.3 (19.1, 9.3)         2.33 (7.8.6, 9.1.5)         0.567           PAO_ (mHq)         20.01 (13, 002.9)         139 (129.1, 390.3)         2.33 (16.2, 90.1)         0.620           PAO_ (mHq)         20.11 (3.02.9)         139 (129.1, 390.3)         2.33 (16.2, 90.1)         0.620           PAO_ (mHq)         20.6 (57.4, 10.14)         8.12 (60.5, 13.81)         6.43 (4.45, 6.71)         0.001           SX0-0 (mmHq)         7.26 (57.4, 10.14)         8.12 (60.5, 13.81)         6.43 (4.45, 6.71)         0.012           SX0-0 (mmHq)         7.26 (57.4, 10.14)         8.12 (60.5, 13.81)         6.43 (4.45, 6.71)         0.021           SX0-0 (mmHq)         10.5 (5.3, 7.4)         10.6 (4.55)         10.7 (7.1, 8.7.)         0.63 (7.1, 7.5)         0.63 (7.1, 7.5)         0.63 (7.1, 7.5)         0.63 (7.1, 7.5)         0.63 (7.1, 7.5)         0.63 (7.1, 7.5)         0.63 (7.1, 7.5)         0.63 (7.1, 7.5)         0.63 (7.1, 7.5)	AFM	29 (48.3)	12 (30.8)	17 (81.0)	<0.001
CA         29 (43.)         22 (64.)         7 (3.3.)         0.100           Others         6 (10.0)         4 (10.3)         2 (9.5)         1           Zh post-ECMO             0.000           O'P (cmt-ly)         96 (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           PeO_ (mmt-lg)         30 (197, 3.49)         32.22 (28.3.3)         31 (28.3.4)         0.626           SerOo, (mmt-lg)         7.45 (68.9, 82.9)         7.0.9 (66.4, 80.3)         81 (7.1, 84.7)         0.091           EUN (mmol.1)         7.45 (68.9, 82.9)         7.0.9 (66.4, 80.3)         81 (7.1, 84.8)         0.626         0.702           K(mmol.1)         7.16 (1.6, 5.37.4)         1.28 (0.6, 1.37.5)         4.33 (14.2, 8.6, 7.1)         0.091           EUN (mmol.1)         9.15 (7.32, 10.91)         9.26 (68.9, 10.52)         8.8 (8.3.8, 11.4)         0.248           IB (µmol.1)         9.15 (7.3, 2.0191         9.26 (6.8, 10.52)         8.54 (8.3, 11.4)         0.248           ID (y1)         9.32 (60.8, 14.1.7)         9.32 (66.8, 10.52)         8.54 (8.3, 11.4)         0.248           IB (µmol.1)	MA	3 (5.0)	2 (5.1)	1 (4.8)	1
Others         6 (10.0)         4 (10.3)         2 (2.6.5)         1           21 part-ECMO         21	CA	29 (48.3)	22 (56.4)	7 (33.3)	0.109
24h post-ECMO         Virtuality         79 (21, 87, 9)         77, 717, 78, 63         62.3 (3.8, 91.5)         0.063           MAP (mnHg)         9 (6, 12)         9.3 (6, 13)         7 (5, 12)         0.371           PH         7.448 (7.400, 7.49)         7.466 (7.409, 7.488)         7.44 (7.408, 7.501)         0.667           PaO_ (mnHg)         319 (27, 5.49)         32.2 (28.3, 53)         311 (22.8, 54)         0.205           ScxOq (mnHg)         7.45 (68.9 (2.9)         7.0.9 (84.8 (0.3)         81 (71, 84.7)         0.009           ScxOq (mnHg)         7.26 (5.74, 10.14)         8.12 (60.5, 13.81)         6.43 (44.5, 6.71)         0.012           K(mmoLL)         4.14 (0.5, 4.53)         4.324 (41.4, 4.59)         4.94 (0.2, 4.40)         0.422           Cr (umoVL)         0.16 (5.64.5, 13.4)         10.8 (9.4, 150)         10.2 (75, 117.5)         0.083           TBil (umOL)         9.1 (7.32, 10.91)         9.26 (6.60, 10.52)         8.18 (13.14)         0.248           Ho (g/L)         9.4 (77, 117.25)         9.4 (75, 115)         9.4 (75, 115)         0.834           LU (mmOL)         9.1 (73.2, 10.91)         9.26 (6.60, 10.52)         8.18 (1.4, 19.7)         0.834           TI (g/L)         9.4 (75, 115, 7.5)         7.13 (7, 18)         0.047	Others	6 (10.0)	4 (10.3)	2 (9.5)	1
MAP (nmHg)         79 (72.1 87.9)         77.7 (71.7, 85.3)         82.3 (73.8, 91.5)         0.05           CVP (nmHg)         9 (6, 12)         9.5 (6, 13)         7 (6, 12)         0.37           PH         7.446 (7.409, 7.49)         7.466 (7.409, 7.48)         7.4 (7.40, 7.501)         0.567           PaO_ (nmHg)         200 (131, 302.9)         193 (121, 1303.3)         233 (138, 296.1)         0.682           PaO_Q (nmHg)         7.45 (66.9, 82.9)         70.9 (66.4, 60.3)         81 (71, 84.7)         0.004           SCNC (nmMl)         7.26 (5.74, 10.14)         8.12 (60.5, 13.81)         6.43 (44.56, 87.1)         0.012           K (nmol/L)         7.26 (5.74, 10.14)         8.12 (6.65, 10.51)         4.29 (40.2, 4.46)         0.428           C (µmol/L)         10.5 (45.4, 13.4)         10.08 (45.6)         10.02 (75, 11.75)         0.043           GLU (nmol/L)         2.01 (13.5, 37.4)         2.3 (15.1, 37.5)         15.4 (11.2, 26.5)         0.104           GLU (nmol/L)         9.15 (7.21, 0.91)         9.26 (85.5, 134.1)         9.6 (78.5, 139.5)         0.587           PT (a)         16.3 (14.1, 20.5)         17 (14.3, 21.7)         15.4 (11.2, 26.5)         0.041           ML (µT)         9.32 (68.5, 134.1)         9.6 (78.5, 316.7.5)         0.041	24 h post-ECMO				
CVP (cmH <sub>2</sub> O)         9 (6, 12)         9.5 (6, 13)         7 (6, 12)         0.371           PH         7.448 (7.409, 7.49)         7.456 (7.409, 7.482)         7.447 (7.406, 7.501)         0.567           PaO_ (mmHg)         200 (131, 302.9)         139 (122, 139.3)         233 (136, 266.1)         0.620           PaCO_ (mmHg)         31 (27, 5, 34.9)         32.2 (28, 335)         31 (23, 8, 34)         0.205           ScvO_ (mmHg)         7.45 (66, 8, 82.9)         7.0 9 (66, 4, 0.3)         81 (71, 84.7)         0.091           K (mmVL)         4.31 (4.05, 4.53)         4.32 (4.11, 4.59)         4.29 (4.02, 4.46)         0.426           Cr (umVL)         0.55 (48, 5, 134)         108 (94, 156)         102 (75, 117.5)         0.083           Bill (mmVL)         2.01 (13, 5, 37.4)         2.32 (15, 13, 75)         15.4 (11, 2, 76.5)         0.044           GLU (mmVL)         9.15 (7.2, 10.91)         9.26 (6.69, 10.52)         8.81 (8.38, 11.41)         0.248           Bill (moVL)         9.15 (7.32, 10.91)         9.26 (6.5, 134.1)         9.67 (62.3, 157.3)         0.934           TN (upL)         9.32 (60.8, 141.7)         9.32 (68.5, 134.1)         9.67 (62.3, 157.3)         0.934           GLU (mmVL)         6.17 (1.5, 45.4)         15 (17.17, 88.8)         5 (15.5, 75) <t< td=""><td>MAP (mmHg)</td><td>79 (72.1, 87.9)</td><td>77.7 (71.7, 85.3)</td><td>82.3 (73.8, 91.5)</td><td>0.059</td></t<>	MAP (mmHg)	79 (72.1, 87.9)	77.7 (71.7, 85.3)	82.3 (73.8, 91.5)	0.059
PH         7.448 (7.409, 7.49)         7.456 (7.409, 7.483)         7.44 (7.408, 7.501)         0.567           PaO <sub>2</sub> (mmHg)         200 (131, 302.9)         193 (129.1, 390.3)         233 (136, 296.1)         0.620           PaO <sub>2</sub> (mmHg)         319 (27.5, 34.2)         32.2 (28.3, 36)         31 (23.8, 34)         0.005           ScNO <sub>2</sub> (mmHg)         7.45 (66.9, 82.9)         7.0.9 (66.4, 80.3)         81 (71. 84.7)         0.001           BUN (mmol/L)         7.26 (5.7.4, 10.14)         8.12 (6.05, 13.81)         6.43 (4.45, 8.71)         0.012           C (mmol/L)         4.31 (4.05, 4.53)         4.32 (4.11, 4.59)         4.29 (4.02, 4.46)         0.426           C (mmol/L)         0.56 (84.5, 134)         106 (94.165)         102 (75, 117.5)         0.033           TBH (mmol/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)         2.6 (6.69, 10.52)         8.81 (8.88, 11.41)         0.248           Ho (yL)         9.17 (14.3, 21.7)         15.4 (14, 19.7)         0.327           APTT (a)         53.2 (60.8, 14.17)         93.2 (68.5, 134.1)         96 (15.7, 5)         0.004           LAC (mmol/L)         1.7 (12, 2.6)         1.8 (1.3, 3.3)         1.4 (1, 2)         0.33         0	CVP (cmH <sub>2</sub> O)	9 (6, 12)	9.5 (6, 13)	7 (5, 12)	0.371
PaG2 (mmHg)         200 (131, 302.9)         183 (129.1, 390.3)         233 (136, 296.1)         0.620           PaG2 (mmHg)         31.9 (27.5, 34.9)         32.2 (28.3, 55)         31 (23.8, 34)         0.205           Scv0z (mmHg)         7.26 (5.74, 10.14)         8.12 (6.6, 80.3)         81 (71, 184.7)         0.019           BUN (moulL)         7.26 (5.74, 10.14)         8.12 (6.05, 13.81)         6.43 (4.45, 8.71)         0.012           K (moulL)         4.31 (4.05, 4.53)         4.32 (4.11, 4.59)         4.29 (4.02, 4.48)         0.426           Cr (µmoulL)         0.16 (5.64 5, 13.4)         10.8 (94, 156)         102 (75, 117.5)         0.083           TBil (µmolL)         0.11 (13.5, 37.4)         23 (151, 37.5)         15.4 (11.2, 26.5)         0.104           GLU (mmoulL)         9.15 (73.2, 10.91)         9.26 (6.69, 10.52)         8.11 (8.38, 11.41)         0.248           Hb (g/L)         9.4 (77, 117.25)         9.4 (75, 11.5)         9.4 (78.5, 119.5)         0.587           PT (a)         3.2 (08.8, 141.7)         9.3 (80.8, 37.4)         0.690 (0.4, 6.61)         0.052           APTT (b)         9.3 (20.8, 134.1)         9.6 (2.6, 7.0)         0.067         0.057           PT (a) (1.4, 2.5, 5)         17 (14.3, 21.7)         15 (4.1, 0.2)         0.001         0.0	PH	7.448 (7.409, 7.49)	7.456 (7.409, 7.488)	7.44 (7.408, 7.501)	0.567
PaCO2 (mmHg)         31.9 (27.5, 34.9)         32.2 (28.3, 35)         31 (23.8, 34)         0.205           ScvO2, (mmHg)         74.5 (66.9, 82.9)         70.9 (66.4, 80.3)         81 (71, 84.7)         0.011           BUN (mmo/L)         7.26 (6.7.4, 10.14)         81.2 (6.05, 13.81)         64.3 (44.5, 8.71)         0.012           K(mmo/L)         4.31 (4.05, 4.63)         4.32 (4.11, 4.59)         4.29 (4.02, 4.46)         0.426           Cr (umo/L)         105.5 (84.5, 134)         108 (94, 166)         102 (75, 117.5)         0.003           TBil (umo/L)         20.1 (13.5, 37.4)         23 (15.1, 37.5)         15.4 (11.2, 26.5)         0.104           UL (mmo/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)         0.657           PT (6)         9.32 (60.8, 14.17)         9.32 (68.8, 13.41)         9.67 (13.2, 31.7.3)         0.304           LAC (mmo/L)         1.7 (12.2.6)         1.8 (1.3, 3.3)         1.4 (1.2)         0.033           CPP (mg/L)         6.5 (8.75, 81.75)         6.7 (32, 92)         52 (18.5, 70)         0.097           PCT (ug/L)         1.7 (12.2.6)         1.8 (1.3, 3.3)         1.4 (1.0, 2.0)         0.001     <	PaO <sub>2</sub> (mmHg)	200 (131, 302.9)	193 (129.1, 390.3)	233 (136, 296.1)	0.620
ScxO2 (nmHg)         74.5 (66.9, 82.9)         70.9 (66.4, 80.3)         81 (71, 84.7)         0.091           BUN (nmol/L)         7.26 (5.7.4, 10.14)         8.12 (6.05, 13.81)         6.43 (4.45, 8.71)         0.012           K (nmol/L)         4.31 (4.05, 4.53)         4.32 (4.11, 4.59)         4.29 (4.02, 4.46)         0.426           C (umol/L)         10.55 (84.5, 134)         10.06 (94, 156)         10.27 (5, 117.5)         0.083           TBI (umol/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 (8.36, 11.41)         0.248           Hb (g/L)         9.4 (77, 117.25)         9.4 (75, 115)         94 (785, 119.5)         0.637           APTT (a)         9.3.2 (60.8, 141.7)         93.2 (63.5, 134.1)         96.7 (62.3, 157.3)         0.934           TNI (gg/L)         6.7 (16.4, 54.4)         16.7 (17, 78.8.3)         1.4 (1, 2)         0.03           CFP (mg/L)         61.5 (28.75, 81.75)         67 (32, 92)         52 (18.5, 70)         0.097           PCT (gg/L)         16.3 (41.2)         1.4 (8.2)         .428 (0.38, 37.4)         0.69 (0.14, 6.61)         0.026           Pre-ECMO score         10.5 (12.25)         22 (18.31)         12 (6,	PaCO <sub>2</sub> (mmHg)	31.9 (27.5, 34.9)	32.2 (28.3, 35)	31 (23.8, 34)	0.205
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 (umol/L)         105.5 (84.5, 134)         108 (94, 156)         102 (75, 117.5)         0.063           BEI (umol/L)         9.15 (7.32, 10.91)         9.26 (6.66, 10.52)         8.81 (8.38, 11.41)         0.246           GLU (mmol/L)         9.15 (7.12, 10.91)         9.26 (6.66, 10.52)         8.81 (8.38, 11.41)         0.246           Hb (g/L)         9.47 (77, 117.25)         9.47 (75, 115)         9.47 (75, 115)         0.937           APTT (s)         9.32 (60.8, 141.7)         93.2 (65.5, 134.1)         96.7 (62.3, 157.3)         0.037           APTT (s)         9.32 (60.8, 141.7)         93.2 (63.5, 134.1)         96.7 (62.3, 157.5)         0.041           LAC (mmol/L)         1.7 (1.2, 2.6)         1.8 (1.3, 3.3)         1.4 (1.2)         0.037           PCT (ug/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (0.14, 6.61)         0.052           PCT (ug/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (0.14, 6.61)         0.052           PCT (ug/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (	ScvO <sub>2</sub> (mmHg)	74.5 (66.9, 82.9)	70.9 (66.4, 80.3)	81 (71, 84.7)	0.091
K (mmol/L)         4.31 (4.05, 4.53)         4.32 (4.11, 4.59)         4.29 (4.02, 4.46)         0.426           Cr (umol/L)         105 (84.5, 134)         108 (94, 156)         102 (75, 117.5)         0.033           TBil (umol/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)         13.3 (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 (63.5, 134.1)         96.7 (62.3, 157.3)         0.041           LAC (mmol/L)         1.7 (1.2, 2.6)         1.8 (1.3, 3.3)         1.4 (1, 2)         0.033           CPP (mg/L)         61.5 (28.75, 81.75)         67 (28.292)         52 (18.5, 70)         0.047           Der ECMO Score         2         2         8 (4, 10)         0.004           APACHE- II score         10 (7, 12)         11 (8, 12)         8 (4, 10)         0.004           APACHE- II score         19 (13, 24)         22 (17, 27)         13 (7, 18)         -0.001           APACHE- II score	BUN (mmol/L)	7.26 (5.74, 10.14)	8.12 (6.05, 13.81)	6.43 (4.45, 8.71)	0.012
Cr (µmol/L)         105.5 (84.5, 134)         108 (94, 156)         102 (75, 117.5)         0.083           TBi (µmol/L)         20.1 (13.5, 37.4)         23 (15.1, 37.5)         15.4 (11.2, 26.5)         0.104           GLU (µmol/L)         9.15 (7.32, 10.91)         9.26 (6.69, 10.52)         8.81 (8.38, 11.41)         0.2428           Hb (g/L)         94 (77, 117.25)         94 (75, 115)         0.537         0.337           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 (55.5, 134.1)         96.7 (62.3, 157.3)         0.934           TN (µg/L)         6.71 (1.6, 45.4)         16.7 (1.7, 88.8)         5 (1.5, 7.5)         0.004           LAC (mmol/L)         1.7 (12, 2.6)         14.8 (1.3, 3.3)         1.4 (1, 2)         0.033           CP (mg/L)         61.5 (28.75, 81.75)         67 (32, 92)         52 (18.5, 70)         0.007           PCT (µg/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (0.14, 6.61)         0.026           Pre-ECMO Score         50         22 (18, 31)         12 (6, 16.5)         <-0.001	K (mmol/L)	4.31 (4.05, 4.53)	4.32 (4.11, 4.59)	4.29 (4.02, 4.46)	0.426
TBI (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)         0.637           PT (s)         16.3 (14.1, 20.5)         177 (14.3, 21.7)         15.4 (14.14, 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 (16.45.4)         16.7 (17.88.8)         5 (1.5, 7.5)         0.041           LAC (mmol/L)         1.7 (12, 2.6)         1.8 (13.3.3)         1.4 (1.2)         0.037           PTC (µg/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (0.14, 6.61)         0.052           PTC-ECMO score         5         22 (18, 31)         12.6 (1.6.5)         -0.001           APACHE- II score         19.(13, 24)         22 (17, 27)         13 (7, 18)         -0.001           APACHE- II score         19 (13, 24)         22 (17, 27)         13 (7, 18)         -0.001           APACHE- II score         19 (13, 24)         12 (10, 14)         9 (5, 10)         -0.001           APACHE- II scor	Cr (µmol/L)	105.5 (84.5, 134)	108 (94, 156)	102 (75, 117.5)	0.083
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)         0.567           PT (s)         16.3 (14.1, 20.5)         17 (14.3, 2.17)         15.4 (14, 19.7)         0.327           APTT (s)         93.2 (60.8, 141.7)         93.2 (65.3 13.41)         96.7 (62.3, 157.3)         0.934           IN (ug/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)         0.033           CRP (mg/L)         61.5 (28.75, 81.75)         67 (32, 92)         52 (18.5, 70)         0.097           PCT (ug/L)         2.59 (0.27, 22.75)         4.28 (0.8, 37.4)         0.89 (0.14, 6.61)         0.050           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           APACHE- II score         19 (13, 24)         12 (10, 14)         9 (5, 10)         -0.001           APACHE- II score         19 (13, 24)         12 (17, 27)         13 (7, 18)         -0.001           APACHE- II score<	TBil (µmol/L)	20.1 (13.5, 37.4)	23 (15.1, 37.5)	15.4 (11.2, 26.5)	0.104
Hb (g/L)         94 (77, 117.26)         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 (55.5, 134.1)         96.7 (62.3, 157.3)         0.934           NI (ug/L)         6.71 (1.6, 45.4)         16.7 (1.7, 88.8)         5 (1.5, 7.5)         0.041           LAC (mmO/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 (ug/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (0.14, 6.61)         0.052           PCT ECMO score         52         22 (18, 31)         12 (6, 16.5)         -0.001           2M post-ECMO score         11 (8, 14)         12 (10, 14)         9 (5, 10)         -0.001           2M post-ECMO Score         11 (8, 14)         12 (10, 14)         9 (5, 10)         -0.001           2M post-ECMO Score         11 (8, 14)         12 (10, 14)         9 (5, 10)         -0.001           2M post-ECMO Score         11 (8, 14)         12 (10, 14)         9 (5, 10)         -0.001           2M post-ECMO Score	GLU (mmol/L)	9.15 (7.32, 10.91)	9.26 (6.69, 10.52)	8.81 (8.38, 11.41)	0.248
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           TN (µg/L)         6.7 (11.6, 45.4)         16.7 (17.8 8.8)         5 (15.7.5)         0.041           LAC (mmo/L)         1.7 (1.2, 2.6)         1.8 (1.3, 3.3)         1.4 (1, 2)         0.03           CRP (mg/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (0.14, 6.61)         0.052           PCT (µg/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (0.14, 6.61)         0.052           PCT (µg/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (0.14, 6.61)         0.052           PCT (µg/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (0.14, 6.61)         0.052           PCT (µg/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (0.14, 6.61)         0.052           PCT (µg/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (0.14, 6.61)         0.004           APACHE-II Iscore         19.5 (12, 25)         2 (218, 31)         12 (6, 16.5)         -0.001           APACHE-II Iscore         19 (13, 24)         2 (217, 27)         13 (7, 18)         -0.001	Hb (g/L)	94 (77, 117.25)	94 (75, 115)	94 (78.5, 119.5)	0.587
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 (12, 2.6)         1.8 (1.3, 3.3)         1.4 (1.2)         0.03           CRP (mg/L)         61.5 (28.7, 58.1.75)         67 (32, 92)         52 (18.5, 70)         0.097           PCT (µg/L)         2.59 (0.27, 22.75)         428 (0.38, 37.4)         0.69 (0.14, 6.61)         0.052           PTe-ECMO score         52         52 (18.5, 70)         0.097         0.097           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           APACHE- II score         19 (13, 24)         22 (17, 27)         13 (7, 18)         -0.001           APACHE- II score         19 (13, 24)         22 (17, 27)         13 (7, 18)         -0.001           APACHE- II score         19 (13, 24)         22 (17, 27)         13 (7, 18)         -0.001           APACHE- II score         19 (13, 24)         14 (8.7)         6 (28.6)         0.017           Pre-ECMO PCI         7 (11.7)         7 (17	PT (s)	16.3 (14.1, 20.5)	17 (14.3, 21.7)	15.4 (14, 19.7)	0.327
TN (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, 92.75)         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           2H post-ECMO score         19 (13, 24)         22 (17, 27)         13 (7, 18)         -0.001           APACHE: II score         19 (13, 24)         22 (17, 27)         13 (7, 18)         -0.001           APACHE: II score         19 (13, 24)         22 (17, 27)         13 (7, 18)         -0.001           APACHE: II score         19 (13, 24)         22 (17, 27)         13 (7, 18)         -0.001           APACHE: II score         19 (13, 24)         24 (17, 29)         0 (0.0)         -0.001           Pre-ECMO PCI         7 (11.7)         7 (17.9)         0 (0.0)         -0.029           Post-ECMO PCI         12	APTT (s)	93.2 (60.8, 141.7)	93.2 (58.5, 134.1)	96.7 (62.3, 157.3)	0.934
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)         0.652           Pre-ECMO score            0.69         0.14, 6.61)         0.692           Pre-ECMO score           11 (6, 12)         8 (4, 10)         0.004           APACHE- II score         19.5 (12, 25)         22 (18, 31)         12 (6, 16.5)         <0.001	TNI (µg/L)	6.71 (1.6, 45.4)	16.7 (1.7, 88.8)	5 (1.5, 7.5)	0.041
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-ECM0 score	LAC (mmol/L)	1.7 (1.2, 2.6)	1.8 (1.3, 3.3)	1.4 (1, 2)	0.03
PCT (μg/L)         2.59 (0.27, 22.75)         4.28 (0.38, 37.4)         0.69 (0.14, 6.61)         0.052           Pre-ECM0 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-ECM0 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           APACHE- II score         19 (13, 24)         22 (17, 27)         13 (7, 18)         <0.001           Other intervenes, <i>n</i> (%)         Pre-ECM0 PCI         7 (11.7)         7 (17.9)         0 (0.0)         0.0885           Post-ECM0 PCI         7 (11.7)         7 (17.9)         0 (0.0)         0.0885           Post-ECM0 PCI         7 (11.7)         7 (17.9)         0 (0.0)         0.0885           Post-ECM0 MV         50 (83.3)         34 (87.2)         16 (76.2)         0.2988           Post-ECM0 MV         50 (83.3)         34 (87.2)         16 (76.2)         0.2988           CRRT         33 (0.55)         27 (29.2)         5 (23.8)         0.2988           Othomes         I2	CRP (mg/L)	61.5 (28.75, 81.75)	67 (32, 92)	52 (18.5, 70)	0.097
Pre-ECMO 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	PCT (µg/L)	2.59 (0.27, 22.75)	4.28 (0.38, 37.4)	0.69 (0.14, 6.61)	0.052
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	Pre-ECMO score				
APACHE- II score         19.5 (12, 25)         22 (18, 31)         12 (6, 16.5)         <0.001           24 h post-ECMO score	SOFA score	10 (7, 12)	11 (8, 12)	8 (4, 10)	0.004
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	APACHE- II score	19.5 (12, 25)	22 (18, 31)	12 (6, 16.5)	<0.001
SOFA score11 (8, 14)12 (10, 14)9 (5, 10)<0.001APACHE- II score19 (13, 24)22 (17, 27)13 (7, 18)<0.001	24 h post-ECMO score				
APACHE- II score       19 (13, 24)       22 (17, 27)       13 (7, 18)       <0.001	SOFA score	11 (8, 14)	12 (10, 14)	9 (5,10)	<0.001
Other intervenes, n (%)         O (0.0)         0.085           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         11 (9, 17.5)         0.038         0.001         0.001           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	APACHE- II score	19 (13, 24)	22 (17, 27)	13 (7, 18)	<0.001
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 <b>Dutcomes</b> 11 (9, 17.5)         0.038         0.001         0.001           Hospital LOS (days)         14 (10, 21)         16 (11, 24)         11 (9, 17.5)         0.038           28-day mortality (%)         20 (33.3)         20 (51.3)         0 (0.0)         <0.001	Other intervenes, <i>n</i> (%)				
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         I         I (19, 17.5)         0.038           Hospital LOS (days)         19 (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	Pre-ECMO PCI	7 (11.7)	7 (17.9)	0 (0.0)	0.085
IABP25 (41.7)19 (48.7)6 (28.6)0.174Pre-ECMO MV50 (83.3)34 (87.2)16 (76.2)0.298Post-ECMO MV10 (16.7)5 (12.8)5 (23.8)0.298CRRT33 (0.55)27 (69.2)6 (28.6)0.003OutcomesICU LOS (days)14 (10, 21)16 (11, 24)11 (9, 17.5)0.038Hospital LOS (days)19.5 (13, 27)19 (13, 30)20 (13, 26.5)0.98128-day mortality (%)20 (33.3)20 (51.3)0 (0.0)<0.001	Post-ECMO PCI	12 (20.0)	11 (28.2)	1 (4.8)	0.042
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	IABP	25 (41.7)	19 (48.7)	6 (28.6)	0.174
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	Pre-ECMO MV	50 (83.3)	34 (87.2)	16 (76.2)	0.298
CRRT         33 (0.5)         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	Post-ECMO MV	10 (16.7)	5 (12.8)	5 (23.8)	0.298
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	CRRT	33 (0.55)	27 (69.2)	6 (28.6)	0.003
ICU LOS (days)14 (10, 21)16 (11, 24)11 (9, 17.5)0.038Hospital LOS (days)19.5 (13, 27)19 (13, 30)20 (13, 26.5)0.98128-day mortality (%)20 (33.3)20 (51.3)0 (0.0)<0.001	Outcomes	. ,	• /	· /	
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	ICU LOS (days)	14 (10, 21)	16 (11, 24)	11 (9, 17.5)	0.038
28-day mortality (%) 20 (33.3) 20 (51.3) 0 (0.0) <0.001	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<sub>2</sub>, Central venous oxygen saturation; PH, Potential of Hydrogen; PaO<sub>2</sub>, Arterial oxygen partial pressure; PaCO<sub>2</sub>, 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 <i>n</i> =60	Neurological complications		Р
		Yes ( <i>n</i> =39)	No ( <i>n</i> =21)	
ECPR, <i>n</i> (%)	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 <sub>2</sub> (%)	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 <sub>2</sub> O)	20 (16, 22)	21 (18, 24)	16 (15, 20)	0.003
PEEP (cmH <sub>2</sub> O)	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 nonpulsatile 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	Р	
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<sub>2</sub>O, P = 0.003) and positive end expiratory pressure (PEEP) (10 [8, 10] vs. 7 [5, 8] cmH<sub>2</sub>O, 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**).

## 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

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

	Time after discharge		
	1 month (n = 44)	3 months ( <i>n</i> = 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.

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 shortterm neurological complications during the ECMO support. Besides, the transfer of patients with ECMO support between departments inevitably involves high-risk or immediate-threatof-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-100 $\beta$ ) 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



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

Neurological complications	Long-term outcomes after discharge			
	1 month ( <i>n</i> = 44)	3 months (n = 44)	6 months (n = 44)	
Yes, <i>n</i> (%)	11 (25.0)	11 (25.0)	10 (22.7)	
No, <i>n</i> (%)	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 < 10mmHg 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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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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