# Risk factors for intracranial hemorrhage and mortality in adult patients with severe respiratory failure managed using veno-venous extracorporeal membrane oxygenation

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**Abstract**

**Background:** Intracerebral hemorrhage (ICH) is one of the most severe complications during veno-venous extracorporeal membrane oxygenation (VV-ECMO). This study aimed to determine the risk factors for ICH and mortality in such patients.

**Methods:** We analyzed the clinical data of 77 patients who received VV-ECMO due to severe respiratory failure from July 2013 to May 2019 at China-Japan Friendship Hospital. Demographical data, laboratory indices, imaging characteristics, and other clinical information were collected. Multivariable logistic regression analyses were performed to identify risk factors for ICH and mortality.

**Results:** Of 77 patients, 11 (14.3%) suffered from ICH, and 36 (46.8%) survived. The survival rate was significantly lower (18.2% [2/11] *vs.* 51.5% [34/66], $P = 0.040$) in patients with ICH than in those without ICH. Multivariable analysis revealed that factors independently associated with ICH were diabetes mellitus (adjusted odds ratio [aOR]: 12.848, 95% confidence interval [CI]: 1.129–146.188, $P = 0.040$) and minimum fibrinogen during ECMO (aOR: 2.557, 95% CI: 1.244–5.252, $P = 0.011$). Multivariable analysis showed that factors independently associated with mortality were acute hepatic failure during ECMO (aOR: 9.205, 95% CI: 1.375–61.604, $P = 0.022$), $CO_2$ retention before ECMO (aOR: 7.602, 95% CI: 1.514–38.188, $P = 0.014$), and minimum platelet concentration during ECMO (aOR: 0.130, 95% CI: 0.029–0.577, $P = 0.007$).

**Conclusions:** Diabetes mellitus and minimum fibrinogen concentration during ECMO are risk factors for ICH in patients with severe respiratory failure managed using VV-ECMO. This indicated that anticoagulants use and nervous system monitoring should be performed more carefully in patients with diabetes when treated with VV-ECMO due to severe respiratory failure.

**Keywords:** Veno-venous extracorporeal membrane oxygenation; Severe respiratory failure; Intracranial hemorrhage; Mortality; Risk factors

## Introduction

In recent years, the use of extracorporeal membrane oxygenation (ECMO) has become more common in clinical settings, and veno-venous ECMO (VV-ECMO) is used mainly for severe respiratory failure (SRF) caused by reversible disease or in patients waiting for lung transplantation.[1,2] Although the technology has been improving year by year, mortality remains high among ECMO patients, and neurological complications, especially intracerebral hemorrhage (ICH), are one of the main causes of death.[3,4] The prevalence of VV-ECMO-associated ICH ranges from 3.5%[5] to 16.4%.[6] During the outbreak of H1N1 influenza in 2009, the most common reason for death in patients supported with ECMO in Australian and New Zealand intensive care units (ICUs) was ICH (6/14).[7]

Few studies have specifically focused on ICH during VV-ECMO support for adults with SRF. Therefore, in this study, we explored the risk factors for ICH and mortality in such patients.

## Methods

### Ethical approval

This study was conducted in accordance with the *Declaration* of *Helsinki* and approved by the Ethics Committee of the China-Japan Friendship Hospital (No. 2015-ST-4). The requirement for informed consent was waived.

### Subjects

We identified patients admitted to the 4th Department of Pulmonary and Critical Care Medicine of the China-Japan

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Friendship Hospital and supported with VV-ECMO for SRF from July 2013 to May 2019. The clinical indications of VV-ECMO for SRF included a ratio of partial pressure of arterial oxygen ($PaO_2$) to the fraction of inspired oxygen ($FiO_2$) <50 mm Hg for >3 h, $PaO_2$:$FiO_2$ <80 mm Hg for >6 h, or an arterial blood pH <7.25 with a partial pressure of arterial carbon dioxide ($PaCO_2$) ≥60 mm Hg for >6 h, with the respiratory rate increased to 35 breaths per minute and mechanical-ventilation settings adjusted to maintain a plateau pressure of ≤32 cm $H_2O$ despite ventilator optimization (defined as $FiO_2$ ≥0.80, a tidal volume of 6 mL/kg predicted body weight, and a positive end-expiratory pressure of ≥10 cm $H_2O$). Patients were excluded for the following conditions: being supported with veno-arterial (VA) or veno-veno-arterial or veno-arterial-venous-ECMO; being supported with VV-ECMO for lung transplantation or other surgery; or being managed with low-flow extracorporeal carbon dioxide ($CO_2$) removal.

### Data collection

We collected and analyzed the following data: demographics; protopathy; complications; arterial blood gas analysis sampled 2 h before and after ECMO treatment (where multiple arterial blood gases were tested within 2 h, the test closest to the time of ECMO onset was selected); anticoagulation and fibrinolysis indices (including activated partial thromboplastin time [APTT], prothrombin time, fibrinogen, and D-Dimer, which were tested every 4–6 h during ECMO); complications during ECMO; and prognosis. The ECMO period was defined as the period from the beginning of ECMO up to the diagnosis of ICH, or up to withdrawal of ECMO, for patients without ICH. Survivors were defined as those who survived until hospital discharge. $CO_2$ retention was defined as $PaCO_2$ ≥50 mmHg. Acute hepatic failure was defined as total bilirubin ≥102 μmol/L in a patient without pre-existing liver disease. Change in arterial pH post-ECMO was defined as the pH value measured during arterial blood gas analysis within 2 h after ECMO minus the pH value measured during arterial blood gas analysis within 2 h before ECMO. Change in $PaO_2$ post-ECMO and change in $PaCO_2$ post-ECMO were defined in the same way as change in arterial pH post-ECMO. The diagnosis of diabetes was based on the patient's medical history. The presence of ICH was determined by computed tomography (CT) of the head. All scans were reviewed by a radiologist for confirmation of diagnosis and categorization of hemorrhage.

### Establishment and management with ECMO

All patients were treated using percutaneous, single-site, double-lumen catheterization. For drainage, a 21F cannula was placed in the femoral vein, and for return, a 17F cannula was placed in the jugular vein. All patients received an intravenous injection of 2000 to 3000 IU unfractionated heparin during ECMO catheterization according to coagulation indicators and body weight. The ECMO pump was maintained until the APTT reached 50 to 70 s. During ECMO treatment, APTT was measured every 6 to 8 h. If the platelet concentration was lower than $60 \times 10^9$/L, platelet transfusion was performed. Erythrocytes were transfused intermittently to maintain a hemoglobin concentration above 90 g/dL, and the fibrinogen concentration was maintained at a minimum of 2 g/L.

During ECMO treatment, neurological symptoms and signs were monitored regularly, patients were awakened every day, and their pupils were observed every two hours. When there were clinical indications of ICH, heparin transfusion was stopped, and CT of the head was performed within 3 h.

### Statistical analysis

IBM SPSS Statistics for Macintosh, Version 20.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Categorical variables were described as frequencies and percentages, while continuous variables were presented as means and standard deviations or median ($Q_1$, $Q_3$). Categorical variables were compared with the Chi-squared test or Fisher exact test, where appropriate. Continuous variables were compared using Student's $t$ test once normality was demonstrated; otherwise, the nonparametric Mann–Whitney $U$ test was performed.

Univariable and multivariable logistic regression analyses were performed to identify variables predictive of ICH and mortality (dependent variables). Variables with a $P$ value <0.05 upon univariable analysis were included in a multivariable, logistic, backward stepwise model. For all analyses, a two-tailed $P < 0.05$ was defined as a statistically significant result.

## Results

### Patient characteristics

Overall, we identified 309 patients supported with ECMO from July 2013 to May 2019, of which 33 received VA-ECMO, and 199 received ECMO for lung transplantation and other surgical reasons. As there was a remarkable difference in the anticoagulant regimen for perioperative patients of lung transplantation and patients with SRF due to other reasons, we excluded the former [Figure 1]. Ultimately, we included 77 patients with SRF managed with VV-ECMO. Of these, 11 (14.3%) suffered from ICH and 36 (46.8%) survived [Table 1].

We discovered statistically significant differences between the ICH and non-ICH groups in terms of median (interquartile range) pre-ECMO platelet count (102.0 [91.0, 131.5] $\times 10^9$/L *vs.* 155.5 [103.2, 229.2] $\times 10^9$/L, $U = 222.0$, $P = 0.040$); maximal bilirubin (24.3 [11.7, 76.4] μmol/L *vs.* 56.4 [27.4, 124.7] μmol/L, $U = 219.0$, $P = 0.036$) and creatinine (204.6 [181.5, 352.3] μmol/L *vs.* 130.4 [82.0, 190.9] μmol/L, $U = 186.0$, $P = 0.010$) concentrations during ECMO; minimum fibrinogen concentration during ECMO (3.11 [2.50, 4.44] g/L *vs.* 1.56 [1.16, 2.58] g/L, $U = 110.5$, $P < 0.001$); Acute Physiology and Chronic Health Evaluation II (24.0 [22.5, 28.0] *vs.* 19.0 [16.0, 24.8], $U = 198.5$, $P = 0.016$) and sequential organ failure assessment (12.0 [6.5, 13.0] *vs.* 8.0 [5.0, 9.0],

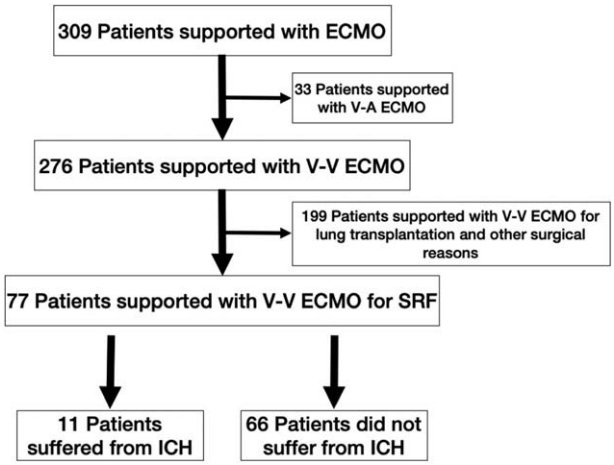


**Figure 1:** Inclusion and exclusion of patients in this study. ECMO: Extracorporeal membrane oxygenation; ICH: Intracerebral hemorrhage; SRF: Severe respiratory failure; V-A ECMO: Veno-arterial ECMO; V-V ECMO: Veno-venous ECMO.

$U = 224.5$, $P = 0.042$) scores at ICU admission; duration of ECMO support (4.0 [2.5, 6.5] days *vs.* 14.5 [9.0, 27.0] days, $U = 92.5$, $P < 0.001$); percentage of diabetes mellitus (63.6% *vs.* 15.2%, $P = 0.002$) and fungal pneumonia (54.5% *vs.* 21.2%, $P = 0.029$); and survival (18.2% *vs.* 51.5%, $P = 0.040$). There were also statistically significant differences between the non-survival and survival groups in terms of prior duration of mechanical ventilation before ECMO (3.0 [1.0, 8.0] days *vs.* 1.0 [0.0, 3.0] days, $U = 510.0$, $P = 0.018$); minimum platelet concentration during ECMO (33.0 [21.0, 64.5] $\times 10^9$/L *vs.* 65.5 [43.8, 108.0] $\times 10^9$/L, $U = 365.5$, $P < 0.001$); maximal bilirubin (109.0 [24.4, 180.9] μmol/L *vs.* 33.7 [24.1, 76.2] μmol/L, $U = 539.5$, $P = 0.043$), creatinine (117.0 [62.0, 256.5] μmol/L *vs.* 92.0 [62.0, 205.5] μmol/L, $U = 527.0$, $P = 0.031$) concentrations and APTT time (88.3 [74.4, 140.0] s *vs.* 116.8 [94.3, 148.4] s, $U = 528.5$, $P = 0.032$) during ECMO; duration of ECMO support (11.0 [4.0, 17.0] days *vs.* 15.5 [9.0, 33.0] days, $U = 486.5$, $P = 0.010$); incidence of $CO_2$ retention before ECMO (78.0% *vs.* 52.8%, $\chi^2 = 5.474$, $P = 0.019$); and incidence of acute kidney injury (AKI, 78.0% *vs.* 55.6%, $\chi^2 = 4.423$, $P = 0.035$), continuous renal replacement therapy (continuous renal replacement therapy [CRRT], 68.3% *vs.* 27.8%, $\chi^2 = 12.588$, $P < 0.001$), acute hepatic failure (39.0% *vs.* 8.3%, $P = 0.002$), and platelet transfusion (56.1% *vs.* 25.0%, $\chi^2$=7.633, $P = 0.006$) during ECMO.

### Clinical features in patients with ICH

On average, ICH occurred 4.3 days (range, 1–10 days) after ECMO was initiated. The clinical manifestations of suspected ICH included mydriasis (two patients), confusion (four patients), anisocoria (three patients), coma (two patients), and hemiplegia (one patient). Upon physical examination, seven patients exhibited a unilaterally or bilaterally positive Babinski sign, and four exhibited a negative Babinski sign.

All 11 cases of ICH were confirmed via CT of the head. Nine patients exhibited multiple parenchymal hemorrhages (five of them combined with subarachnoid hemorrhage) and one patient exhibited a single parenchymal hemorrhage. Six patients exhibited subarachnoid hemorrhage, and one patient exhibited subdural hemorrhage (combined with subarachnoid hemorrhage). Six patients exhibited more than one type of hemorrhage upon CT. The patient who survived was the one who exhibited only a single parenchymal hemorrhage on CT of head.

In total, nine of the 11 ICH patients died within one week after the diagnosis of ICH, and the other one patient was in a vegetative state and died one year later. Only one patient finally survived and recovered.

### Risk factors for ICH

Diabetes mellitus (odds ratio [OR]: 9.800, 95% confidence interval [CI]: 2.415–39.766, $P = 0.001$), fungal pneumonia (OR: 4.457, 95% CI: 1.184–16.778, $P = 0.027$), minimum fibrinogen concentration during ECMO (OR: 2.781, 95% CI: 1.521–5.085, $P = 0.001$), change in post-ECMO platelet concentration (OR: 1.015, 95% CI: 1.001–1.029, $P = 0.032$), and peak creatinine concentration during ECMO (OR: 1.008, 95% CI: 1.002–1.014, $P = 0.007$) were statistically significantly associated with ICH in the univariable logistic regression analyses. Among these variables, only diabetes mellitus (adjusted odds ratio [aOR]: 12.848, 95% CI: 1.129–146.188, $P = 0.040$) and minimum fibrinogen concentration during ECMO (aOR: 2.557, 95% CI: 1.244–5.252, $P = 0.011$) were risk factors for ICH in the multivariable analysis [Table 2].

### Risk factors for mortality

Acute hepatic failure (OR: 7.040, 95% CI: 1.847–26.834, $P = 0.004$), CRRT (OR: 5.600, 95% CI: 2.097–14.954, $P = 0.001$), platelet transfusion during ECMO (OR: 3.833, 95% CI: 1.446–10.157, $P = 0.007$), $CO_2$ retention before ECMO (OR: 3.181, 95% CI: 1.185–8.540, $P = 0.022$), minimum platelet concentration during ECMO (OR: 0.976, 95% CI: 0.963–0.990, $P = 0.001$) were significantly associated with mortality in the univariable logistic regression analyses. Among these variables, acute hepatic failure during ECMO (aOR: 9.205, 95% CI: 1.375–61.604, $P = 0.022$), $CO_2$ retention before ECMO (aOR: 7.602, 95% CI: 1.514–38.188, $P = 0.014$), and minimum platelet concentration during ECMO (aOR: 0.130, 95% CI: 0.029–0.577, $P = 0.007$) were risk factors for mortality in the multivariable analysis [Table 3].

## Discussion

ICH is one of the most severe complications during the ECMO treatment period. It may be caused by pre-ECMO factors such as hypoxia, reperfusion injury when establishing ECMO, the cascade reactions due to the ECMO pipeline and membrane lung, and coagulation disorders due to mechanical injury by the blood pump.[8,9] Currently, there are only a few studies specifically analyzing risk factors for ICH during VV-ECMO in adults. Nasr and Rabinstein[5] published the findings of a large clinical study including

**Table 1: Demographics and clinical characteristics of adult patients with severe respiratory failure managed using veno-venous ECMO.**

| Characteristics | All patients ($n=77$) | ICH group ($n=11$) | Non-ICH group ($n=66$) | Statistics | $P$ | Non-survival group ($n=41$) | Survival group ($n=36$) | Statistics | $P$ |
|---|---|---|---|---|---|---|---|---|---|
| Age (years) | 48.0 (33.0, 61.5) | 47.0 (33.0, 48.0) | 50.0 (33.0, 63.2) | 281.0* | 0.232 | 48.0 (35.0, 60.0) | 47.0 (31.0, 62.8) | 733.0* | 0.959 |
| BMI (kg/m$^2$) | 24.5 (21.6, 27.7) | 24.7 (23.5, 29.4) | 24.5 (21.5, 27.7) | 311.0* | 0.449 | 24.5 (21.4, 27.7) | 24.8 (22.1, 27.7) | 704.5* | 0.732 |
| Prior duration of mechanical ventilation (days) | 2.0 (0, 4.0) | 2.0 (0.5, 6.5) | 1.0 (0.2, 4.0) | 329.5* | 0.620 | 3.0 (1.0, 8.0) | 1.0 (0.0, 3.0) | 510.0* | 0.018 |
| Arterial pH pre-ECMO | 7.33 (7.21, 7.40) | 7.31 (7.18, 7.34) | 7.34 (7.24, 7.41) | 256.5* | 0.121 | 7.77 (7.18, 7.37) | 7.34 (7.24, 7.42) | 632.5* | 0.281 |
| $PaO_2/FiO_2$ pre-ECMO (mmHg) | 74.3 (65.1, 84.1) | 65.2 (54.6, 73.4) | 63.6 (51.5, 72.1) | 358.0* | 0.942 | 64.6 (49.6, 64.6) | 62.8 (52.8, 72.0) | 693.0* | 0.646 |
| $PaCO_2$ pre-ECMO (mmHg) | 49.9 (41.0, 70.1) | 51.3 (44.6, 71.65) | 49.6 (41.1, 65.4) | 340.0* | 0.738 | 52.8 (43.6, 76.0) | 49.0 (36.0, 63.1) | 590.0* | 0.131 |
| Change of arterial pH post-ECMO | 0.10 (0.04, 0.15) | 0.10 (0.10, 0.22) | 0.10 (0.03, 0.15) | 270.5* | 0.178 | 0.10 (0.06, 0.19) | 0.08 (0.02, 0.15) | 595.0* | 0.144 |
| Change of $PaO_2$ post-ECMO (mmHg) | 13.9 (−3.7, 28.5) | 12.1 (−6.5, 28.6) | 14.2 (0.6, 27.8) | 334.0* | 0.673 | 16.0 (1.5, 30.1) | 9.8 (−7.0, 24.3) | 667.0* | 0.405 |
| Change of $PaCO_2$ post-ECMO (mmHg) | −14.2 (−26.5, −4.2) | −12.9 (−39.0, −10.8) | −14.8 (−24.0, −4.2) | 299.5* | 0.355 | −17.2 (−31.6, −8.6) | −9.2 (−24.3, −3.6) | 572.5* | 0.091 |
| Platelet count pre-ECMO ($\times10^9$/L) | 146.0 (98.5, 224.0) | 102.0 (91.0, 131.5) | 155.5 (103.2, 229.2) | 222.0* | 0.040 | 129.0 (82.0, 203.5) | 151.5 (109.8, 229.0) | 566.0* | 0.079 |
| Minimum platelet during ECMO ($\times10^9$/L) | 52.0 (27.5, 89.0) | 59.0 (35.5, 89.0) | 49.0 (29.2, 83.2) | 347.0* | 0.816 | 33.0 (21.0, 64.5) | 65.5 (43.8, 108.0) | 365.5* | <0.001 |
| Change in post-ECMO platelet concentration ($\times10^9$/L) | −84 (−158, −46) | −40 (−85, −19) | −85 (−163, −51) | 524.0* | 0.020 | −85 (−160, −48) | −74 (−154, −49) | 748.0* | 0.919 |
| Peak bilirubin during ECMO (μmol/L) | 105.0 (81.6, 147.6) | 24.3 (11.7, 76.4) | 56.4 (27.4, 124.7) | 219.0* | 0.036 | 109.0 (24.4, 180.9) | 33.7 (24.1, 76.2) | 539.5* | 0.043 |
| Peak creatinine during ECMO (μmol/L) | 132.9 (82.6, 217.0) | 204.6 (181.5, 352.3) | 130.4 (82.0, 190.9) | 186.0* | 0.010 | 117.0 (62.0, 256.5) | 92.0 (62.0, 205.5) | 527.0* | 0.031 |
| Peak APTT during ECMO (s) | 105.0 (81.6, 147.6) | 79 (65.0, 122.3) | 107.55 (87.6, 150.6) | 231.0 | 0.054 | 88.3 (74.4, 140.0) | 116.8 (94.3, 148.4) | 528.5* | 0.032 |
| Peak heparin during ECMO (U·kg$^{-1}$·h$^{-1}$) | 13.3 (10.0, 18.0) | 12.6 (10.6, 18.3) | 13.5 (9.9, 17.8) | 352.5* | 0.878 | 13.3 (8.8, 17.0) | 13.9 (10.0, 19.7) | 623.5* | 0.242 |
| Minimum fibrinogen during ECMO (g/L) | 1.76 (1.26, 2.92) | 3.11 (2.50, 4.44) | 1.56 (1.16, 2.58) | 110.5* | <0.001 | 1.83 (1.30, 3.00) | 1.62 (1.22, 2.78) | 682.5* | 0.571 |
| APACHE II score at ICU admission | 20.0 (16.0, 25.5) | 24.0 (22.5, 28.0) | 19.0 (16.0, 24.8) | 198.5* | 0.016 | 22.0 (16.0, 26.0) | 18.5 (15.0, 25.5) | 611.5* | 0.196 |
| SOFA score at ICU admission | 8.0 (5.0, 10.0) | 12.0 (6.5, 13.0) | 8.0 (5.0, 9.0) | 224.5* | 0.042 | 8.0 (5.0, 11.5) | 7.5 (5.0, 9.8) | 676.0* | 0.523 |
| Duration of ECMO support (days) | 12.0 (6.0, 24.0) | 4.0 (2.5, 6.5) | 14.5 (9.0, 27.0) | 92.5* | <0.001 | 11.0 (4.0, 17.0) | 15.5 (9.0, 33.0) | 486.5* | 0.010 |
| Male | 55 (71.4) | 7 (63.6) | 48 (72.7) | – | 0.719 | 31 (75.6) | 24 (66.7) | 0.751† | 0.386 |
| Co-morbidity | | | | | | | | | |
| Hypertension | 15 (19.5) | 3 (27.3) | 12 (18.2) | – | 0.440 | 7 (17.1) | 8 (22.2) | 0.324† | 0.569 |
| Structural lung disease | 12 (15.6) | 1 (9.1) | 11 (16.7) | – | 1.000 | 6 (14.6) | 6 (16.7) | 0.060† | 0.806 |
| Diabetes | 17 (22.1) | 7 (63.6) | 10 (15.2) | – | 0.002 | 10 (24.4) | 7 (19.4) | 0.273† | 0.602 |
| Autoimmune disease | 13 (16.9) | 4 (36.4) | 9 (13.6) | – | 0.083 | 7 (17.1) | 6 (16.7) | 0.002† | 0.962 |
| Hematological system disease | 2 (2.6) | 1 (9.1) | 1 (1.5) | – | 0.267 | 2 (4.9) | 0 | – | 0.496 |
| Cause of respiratory failure | | | | | | | | | |
| Severe pneumonia | 63 (81.8) | 11 (100.0) | 52 (78.8) | – | 0.199 | 36 (87.8) | 27 (75.0) | 2.113† | 0.146 |
| Viral pneumonia | 47 (61.0) | 6 (54.5) | 41 (62.1) | – | 0.742 | 25 (61.0) | 22 (61.1) | <0.001† | 0.990 |
| Fungal pneumonia | 20 (26.0) | 6 (54.5) | 14 (21.2) | – | 0.029 | 13 (31.7) | 7 (19.4) | 1.499† | 0.221 |
| Acute interstitial lung disease | 11 (14.3) | 0 | 11 (16.7) | – | 0.348 | 5 (12.2) | 6 (16.7) | 0.313† | 0.576 |
| Pulmonary edema | 2 (2.6) | 0 | 2 (3.0) | – | 1.000 | 0 | 2 (5.6) | – | 0.215 |
| Asthma | 1 (1.3) | 0 | 1 (1.5) | – | 1.000 | 0 | 1 (2.8) | – | 0.468 |
| Complications | | | | | | | | | |
| Acidosis before ECMO | 43 (55.8) | 8 (72.7) | 35 (53.0) | – | 0.329 | 25 (61.0) | 18 (50.0) | 0.936† | 0.333 |
| $CO_2$ retention before ECMO | 51 (66.2) | 9 (81.8) | 42 (63.6) | – | 0.316 | 32 (78.0) | 19 (52.8) | 5.474† | 0.019 |
| AKI during ECMO | 52 (67.5) | 9 (81.8) | 43 (65.2) | – | 0.488 | 32 (78.0) | 20 (55.6) | 4.423† | 0.035 |
| CRRT during ECMO | 38 (49.4) | 7 (63.6) | 31 (47.0) | – | 0.347 | 28 (68.3) | 10 (27.8) | 12.588† | <0.001 |
| Acute hepatic failure during ECMO | 19 (24.7) | 2 (18.2) | 17 (25.8) | – | 0.722 | 16 (39.0) | 3 (8.3) | – | 0.002 |
| Platelet transfusion during ECMO | 32 (41.6) | 4 (36.4) | 28 (42.4) | – | 0.755 | 23 (56.1) | 9 (25.0) | 7.633† | 0.006 |
| ICH | 11 (14.3) | – | – | | – | 9 (22.0) | 2 (5.6) | – | 0.040 |
| Survival | 36 (46.8) | 2 (18.2)‡ | 34 (51.5) | – | 0.040 | – | – | – | – |

Data were presented as median ($Q_1$, $Q_3$), or $n$ (%). *$U$ values. †$\chi^2$ values. ‡One patient was in a vegetative state and died one year later. AKI: Acute kidney injury; APACHE II: Acute Physiology and Chronic Health Evaluation II; APTT: Activated partial thromboplastin time; BMI: Body mass index; $CO_2$: Carbon dioxide; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; $FiO_2$: Fraction of inspired oxygen; ICH: Intracranial hemorrhage; ICU: Intensive care unit; $PaCO_2$: Partial pressure of arterial carbon dioxide; $PaO_2$: Partial pressure of arterial oxygen; SOFA: Sequential organ failure assessment; –: Not applicable.

**Table 2: Univariable and multivariate logistic regression analyses of risk factors for intracerebral hemorrhage in adult patients with severe respiratory failure managed using veno-venous ECMO.**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| **Variables** | **OR** | **95% CI** | ***P*** | **OR** | **95% CI** | ***P*** |
| Diabetes | 9.800 | 2.415–39.766 | 0.001 | 12.848 | 1.129–146.188 | 0.040 |
| Fungal pneumonia | 4.457 | 1.184–16.778 | 0.027 | 7.420 | 0.618–89.057 | 0.114 |
| Minimum fibrinogen during ECMO | 2.781 | 1.521–5.085 | 0.001 | 2.557 | 1.244–5.252 | 0.011 |
| Change in post-ECMO platelet concentration | 1.015 | 1.001–1.029 | 0.032 | 0.962 | 0.925–1.001 | 0.056 |
| Peak creatinine concentration during ECMO | 1.008 | 1.002–1.014 | 0.007 | 1.007 | 0.998–1.015 | 0.116 |

CI: Confidence interval; ECMO: Extracorporeal membrane oxygenation; OR: Odds ratio.

**Table 3: Univariate and multivariate logistic regression analyses of risk factors for ICU mortality in adult patients with severe respiratory failure managed using veno-venous ECMO.**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| **Variables** | **OR** | **95% CI** | ***P*** | **OR** | **95% CI** | ***P*** |
| Acute hepatic failure during ECMO | 7.040 | 1.847–26.834 | 0.004 | 9.205 | 1.375–61.604 | 0.022 |
| CRRT | 5.600 | 2.097–14.954 | 0.001 | 1.006 | 0.998–1.015 | 0.151 |
| Platelet transfusion | 3.833 | 1.446–10.157 | 0.007 | 1.028 | 0.996–1.062 | 0.090 |
| $CO_2$ retention before ECMO | 3.181 | 1.185–8.540 | 0.022 | 7.602 | 1.514–38.188 | 0.014 |
| Minimum Platelet during ECMO | 0.976 | 0.963–0.990 | 0.001 | 0.130 | 0.029–0.577 | 0.007 |

CI: Confidence interval; $CO_2$: Carbon dioxide; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; OR: Odds ratio.

23,951 ECMO patients, and the rate of ICH was 3.6%. However, their study included adults, children, and infants, and they did not distinguish between VV- and VA-ECMO. In the study by Lockie *et al*,[6] of patients with SRF treated with VV-ECMO, the rate of ICH was 16.4%. According to a literature review conducted by Luyt *et al*,[9] the rate of ICH during ECMO ranges from 2% to 12%, and the average value is approximately 5%. In our study, the rate of ICH was 14.3%.

We discovered that diabetes mellitus was a risk factor for ICH during ECMO. Hyperglycemia and insulin resistance, related to diabetes, may result in impaired vascular endothelial function and a decrease in endothelium-dependent vasodilation, which is one of the early factors involved in vasculopathy.[10,11] Moreover, diabetes damages the endothelial environment, releases various proinflammatory factors, and causes oxidative stress and low-grade chronic inflammation, forming a vicious circle that further aggravates vascular disease.[12] The change in inflammatory factors is more obvious among non-elderly patients, and it increases the risk of cardiovascular complications independently of age.[13] Thus, diabetes can speed up vascular aging in multiple ways, which increases the risk of ICH threefold.[14,15] During ECMO, the use of anticoagulants may further increase this risk. Therefore, we suggest an appropriate lowering of the anticoagulation target for diabetes patients receiving ECMO, and an increased monitoring of nervous system signs.

In this study, the Acute Physiology and Chronic Health Evaluation II and sequential organ failure assessment scores of patients with ICH were higher than in those without ICH at ICU admission, which indicated that the conditions of patients with ICH were initially more severe than those without ICH. This result was in agreement with that in the study by Lockie *et al*.[6] A couple of authors have suggested that renal insufficiency before ECMO may be a risk factor for ICH during ECMO.[4,9] Luyt *et al*[9] also revealed that the rapid correction of hypercapnia before and after ECMO may be a risk factor for ICH during VV-ECMO. These two risk factors were also analyzed in our study, but no statistically significant differences were observed.

Anticoagulation treatment during ECMO may result in coagulation impairment, which may, in turn, lead to ICH.[16,17] As reported by Kasirajan *et al*,[18] 14 out of 74 VA-ECMO patients developed ICH, which was independently associated with a decrease in platelets. Our results indicated that minimum fibrinogen concentration during ECMO was a risk factor for ICH. ICH often occurs in the early stages of ECMO, and the average ECMO period before ICH was 4.3 days in our study. This may be related to the pipe stimulation that actively releases inflammatory factors at the beginning of ECMO establishment, resulting in a coagulation imbalance, *in vivo* and *in vitro*.

ICH is widely acknowledged to increase the mortality and disability rates of ECMO patients.[19] From data reported to the Extracorporeal Life Support Organization registry, the hospital survival of ICH patients was 10.5%,[3] and in our study, the hospital survival was 18.2%. Baek *et al*[20] found that age, use of nitrogen oxide and pH were significant independent prognostic factors for hospital mortality in patients with VV-ECMO. Data from the Montefiore Medical Center indicated that renal injury and

coagulation dysfunction were independent risk factors for 30-day mortality in ECMO patients.[21] In our study, acute hepatic failure during ECMO, $CO_2$ retention before ECMO, and minimum platelet concentration during ECMO were risk factors for mortality.

Our research also has certain limitations. First, this study was limited by its retrospective nature and small sample size. Second, other anticoagulant indexes, such as platelet function and changes during ECMO, were not measured. Third, most of our patients received blood products, but their impact on ICH and mortality was not included in the analysis. To further investigate the risk factors for ICH, we are in the process of conducting a prospective, randomized controlled trial, in which we are including more comprehensive parameters.

In conclusion, ICH occurred frequently in SRF patients managed with VV-ECMO, and was associated with a higher mortality. Diabetes mellitus and minimum fibrinogen concentration during ECMO are risk factors for ICH. This indicated that anticoagulants use and nervous system monitoring should be performed more carefully in patients with diabetes treated with VV-ECMO due to SRF.

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### Conflicts of interest

None.

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