Prevalence and Neurological Outcomes of Comatose Patients with Extracorporeal Membrane Oxygenation

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Abstract

Background: Coma and disorders of consciousness is understudied in patients on extracorporeal membrane oxygenation (ECMO). The objective of our study was to investigate the prevalence, risk factors, and in-hospital outcomes of comatose ECMO patients.

Method: This is a retrospectively observational cohort study in a tertiary academic hospital. All adults (age≥18) who received venoarterial (VA) or venovenous (VV) ECMO support between 11/2017 and 04/2022 were included. We defined "24-hour off sedation" as no sedative infusion (except dexmedetomidine) or paralytics administration over a continuous 24-hour period while on ECMO. "Off-sedation coma" (coma_{off}) was defined as GCS ≤8 after achieving 24-hour off sedation. "On-sedation coma" (coma_{on}) was defined as GCS≤8 during the entire ECMO course without off-sedation for 24 hours. Neurological outcomes were assessed at discharge using the modified Rankin scale (good 0-3 and poor 4-6).

Results: The cohort consisted of 230 ECMO patients (VA-ECMO 143, median age 54, male 65%). "24-hour off sedation" was achieved in 32.2% VA-ECMO and 26.4% VV-ECMO patients. Among all patients off sedation for 24 hours (n=69), 56.5% VA-ECMO and 52.2% VV-ECMO patients experienced coma_{off}. Among those unable to be sedation-free for 24 hours (n=161), 50.5% VA-ECMO and 17.2% VV-ECMO had coma_{on}. Coma_{off} was associated with poor outcomes (p<0.05) in both VA-ECMO and VV-ECMO groups while coma_{on} only impacted the VA-ECMO group outcomes. In a multivariable analysis, the number of packed red blood cell (pRBC) transfusion (aOR=1.16, 95% CI=1.04-1.28), average lactate level (aOR=1.91, 95% CI=1.11-3.30), and acute brain injury (ABI) (aOR=6.41, 95% CI=1.17-35.26) during ECMO support were independent risk factors for coma_{off} after adjusting for renal replacement therapy, ECMO configuration (VA vs. VV), worst pre-ECMO PaO₂ and PaCO₂.

Conclusions: Coma_{off} was common in ECMO patients and was associated with poor neurological outcomes at discharge. The number of pRBC transfusions, high lactate levels, and ABI were independent risk factors.

INTRODUCTION

Since the first successful application of extracorporeal membrane oxygenation (ECMO) in patients in the 1970s \cite{1,2}, ECMO has become an increasingly utilized lifesaving technique for patients with refractory cardiopulmonary failure. It serves as a bridge to recovery, other mechanical circulatory support device, or heart/lung transplant \cite{3,4}. It has been reported that close to 50% of the adult ECMO patients survive to hospital discharge \cite{5}. However, acute brain injury (ABI) during ECMO support is a major contributing factor to poor functional outcomes and mortality \cite{6}. ABI includes intracranial hemorrhage (ICH), ischemic stroke, seizure, hypoxic-ischemic brain injury (HIBI), brain death, and cerebral edema \cite{7}. ABI has been reported in
more than 15% of the venoarterial (VA)-ECMO patients and 7–18% of the venovenous (VV)-ECMO patients\textsuperscript{7}. In a meta-analysis of extracorporeal cardiopulmonary resuscitation (ECPR) patients, ABI occurred in 27% of patients\textsuperscript{8}. The reported incidence of ABI is higher in the autopsy studies\textsuperscript{9,10}, likely due to underdiagnosis in ECMO patients with underutilization of neuroimaging studies.

Persistent coma in ECMO may be a unique manifestation of clinically significant ABI or the effects of metabolic derangement without identifiable organic brain injuries. As ECMO patients commonly have multi-organ failure and require heavy and prolonged sedation, determining whether coma is from significant ABI or sedation can be challenging. Notably, in one cohort, 12.6% (11 of 87) of the ECMO patients had unexplained coma without relevant imaging findings during ECMO support, which accounted for only 26% of all patients with ABI\textsuperscript{11}. In an autopsy study of 4 ECMO patients who had persistent coma, in 2 of the 4 cases, the comatose status was not explained by the neuropathology findings\textsuperscript{12}. Despite these observations and clinical experience, the prevalence of coma and its clinical implication in ECMO patients is unknown. There are no reports on the in-hospital outcomes of comatose ECMO patients. And yet, persistent coma and a presumed poor neurological outcome is an association that is frequently used in end-of-life discussions in ECMO patients. Here, we aimed to better define the neurological outcomes of ECMO-associated coma. We hypothesized that the persistent coma while off sedation represented a surrogate for poor neurologic outcomes at hospital discharge.

**METHODS**

**Study Design**

A retrospective observational cohort study was conducted on VA- and VV-ECMO patients at a tertiary medical center. All adults (age \(\geq 18\)) who received ECMO support between November 2017 and April 2022 were included. All patients were admitted to the cardiovascular surgical or cardiac intensive care unit and were followed by the neurocritical care team from day 1 of ECMO cannulation according to our standardized neuromonitoring protocol until hospital discharge or death\textsuperscript{6}. This study adhered to the ethics statement of the International Society for Heart and Lung Transplantation and was approved by the Johns Hopkins Medicine Institutional Review Board. Informed consent was obtained from all study participants through their legally authorized representatives (IRB00216321: An Observational Registry of Patients who Received Extracorporeal Membrane Oxygenation at Johns Hopkins Hospital, approved on 12/28/2020). All procedures were followed in accordance with the ethical standards of the institutional committee on human experimentation and with the Helsinki Declaration of 1975.

**Definitions**

"24-hour off sedation" was defined as no sedative infusion (except dexmedetomidine) or paralytics administration over a continuous 24-hour period while on ECMO. Pro Re Nata (PRN) boluses with sedatives and/or analgesics were allowed. Glasgow Coma Scale (GCS) was assessed every 1–4 hours.
"Off-sedation coma" or "coma off" was defined as GCS remained \( \leq 8 \) despite achieving the first 24 hours off sedation. If a patient had one GCS recording \( \geq 9 \) during that 24-hour period, this patient was considered as "off-sedation non-coma" or "non-coma\textsubscript{off}". "On-sedation coma" or "coma on" was defined as GCS \( \leq 8 \) during the entire ECMO course without being off sedation for 24 hours. If a patient had one GCS recording \( \geq 9 \) during the same period, this patient was considered as "on-sedation non-coma" or "non-coma\textsubscript{on}".

We defined ABI as a newly developed acute neurological insults during ECMO support, including ischemic stroke, ICH, subdural hematoma (SDH), subarachnoid hemorrhage (SAH), seizure, HIBI, brain death, cerebral edema, and central nervous system (CNS) infection.

**Clinical Protocol and Outcomes**

Neurological exams were performed at least daily by the primary team and/or the neurocritical care consult team, and the exams were attempted at the time while the patients on minimal amount of sedation or completely off sedation. According to the sedation protocol of our institution, attempts to wean off sedating medications were made daily, and sedation holidays were routinely given to patients if deemed safe \(^6\).

Based on whether the 24-hours off sedation was achieved and whether the patient continued to exhibit a GCS \( \leq 8 \) despite being off-sedation for 24 hours, each group of patients, those supported with VV-ECMO and those supported with VA-ECMO, were divided into 4 subgroups (Fig. 1): off-sedation coma (coma\textsubscript{off}), off-sedation non-coma (non-coma\textsubscript{off}), on-sedation coma (coma\textsubscript{on}), and on-sedation non-coma (non-coma\textsubscript{on}). For those in coma\textsubscript{off} group, we continued to track GCS until hospital discharge or death and recorded the best GCS.

The primary outcome was the patient’s neurological functional status at discharge: good if modified Rankin scale (mRS) \( \leq 3 \) or poor if mRS \( \geq 4 \). Outcomes were compared between comatose patients and non-comatose patients. We further explored possible associations of relevant variables (both pre-ECMO and post-ECMO) with the coma status.

**Statistical Analysis**

We did not embark upon a prior sample size and power calculations but rather intended to include all ECMO patients cared for in our institution during the study period. Demographic and clinical data were reported as the number of counts with percentage or the median with interquartile range (IQR). Those variables between patients with or without coma were compared using Wilcoxon rank-sum test for continuous variables and Fisher’s exact test for binary or categorical variables.

We performed a Kaplan-Meier (KM) survival analysis and compared differences between the subsets of data using the log-rank test. Neurological outcomes upon discharge were compared between patients with coma\textsubscript{off} and non-coma\textsubscript{off}. Time zero was defined as ECMO cannulation date, and patients were followed until hospital discharge or death. We built a multivariable logistic regression statistical model.
Selected clinically relevant covariates were included in the multivariable logistic regression analysis to identify risk factors for being in a coma when off sedation. A two-way interaction analysis was conducted on the selected covariates. Two-tailed P value < 0.05 was considered statistically significant. Odds ratios and 95% confidence intervals were calculated. STATA version 18.0 (STATA Corp, College Station, Texas, USA) was used for statistical analysis. Prism 9.5.1 (GraphPad Software, Boston, MA, USA) was used to generate tables and graphs.

RESULTS

Baseline Characteristics

A total of 230 adult patients were included in the cohort. Of those, 143 (62%) were on VA-ECMO support and 87 (38%) were on VV-ECMO support. The baseline demographics and characteristics of the cohort are shown in Table 1. Among the VA-ECMO patients, 64.3% were males with the median age of 58 years (IQR = 45–68). In the VV-ECMO group, 66.7% were males with the median age of 48 years (IQR = 39–56). The median duration of ECMO support was 5.4 days in the VA-ECMO group and 21.1 days in the VV-ECMO group. Please refer to Supplementary Fig. 1 for more details.
Table 1
Baseline Characteristics of Patients undergo VA or VV ECMO.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>VA-ECMO patients</th>
<th>VV-ECMO patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>58 (45–68)</td>
<td>48 (39–56)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>92 (64.3%)</td>
<td>58 (66.7%)</td>
</tr>
<tr>
<td>BMI, kg/m² (IQR)</td>
<td>29.4 (25.0-35.6)</td>
<td>33.2 (28.2–37.3)</td>
</tr>
<tr>
<td>Race (W/B/H/A/Other)</td>
<td>82/45/3/5/8</td>
<td>32/29/20/3/3</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>103</td>
<td>35</td>
</tr>
<tr>
<td>Diabetes</td>
<td>47</td>
<td>14</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>78</td>
<td>29</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Prior ischemic stroke</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Prior hemorrhagic stroke</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hospital stay</strong> (days), median (IQR)</td>
<td>20 (8–47)</td>
<td>49 (24–77)</td>
</tr>
<tr>
<td><strong>ECMO length</strong> (days), median (IQR)</td>
<td>5.4 (2.9–8.8)</td>
<td>21.1 (10.2–42.3)</td>
</tr>
</tbody>
</table>

Abbreviations: ECMO, extracorporeal cardiopulmonary oxygenation; IQR, interquartile ratio; W, white; B, black; H, Hispanic; A, Asian; BMI, body mass index

VA-ECMO

Coma_{off}

A continuous 24-hour off-sedation period was achieved in 46 patients (32.2%) with a median off-sedation duration of 2.5 days (IQR = 2.0–5.0). Among those patients, 26 (56.5%) patients remained GCS ≤ 8 (coma_{off}) while 20 (43%) patients recovered to at least one GCS score ≥ 9 (non-coma_{off}). The coma_{off} group had significantly fewer good neurological outcomes compared with the non-coma_{off} group (n = 0, 0%, vs. n = 6, 30%, p = 0.004) (Fig. 2A). The KM survival curve also demonstrated that the coma_{off} group had significantly lower probability of good neurological outcomes (p = 0.0001) (Fig. 2B). Among the 26
patients with coma_{off}, 2 patients (7.7%) had an improvement in GCS score to $\geq 9$ during the hospital course. However, both had poor neurological outcomes at discharge (mRS 5 and 6).

Among the 46 patients who achieved 24-hour off sedation, 20 (43.5%) had at least one type of ABI. There was a non-statistically significant trend towards higher prevalence of ABI in coma_{off} patients vs. non-coma_{off} patients ($n = 14, 53.8\%$, vs. $n = 6, 30.0\%, p = 0.14$) (Fig. 2C). Among the 14 coma_{off} patients with ABI, ischemic stroke and HIbl were the most common types (Fig. 2D).

**Coma_{on}**

In our cohort, 97 patients never achieved 24-hour off sedation while on ECMO. 48 (49.5%) had at least one GCS score $\geq 9$ (non-coma_{on}) and 49 (50.5%) remained GCS $\leq 8$ (coma_{on}) during the ECMO course. The coma_{on} group had significantly fewer good neurological outcomes compared with the non-coma_{on} group ($n = 3, 6.1\%$, vs. $n = 21, 43.8\%, p < 0.0001$) (Supplementary Fig. 2A). The prevalence of ABI in the coma_{on} and the non-coma_{on} groups can be found in Supplementary Materials and Supplementary Fig. 2B.

**VV-ECMO**

**Coma_{off}**

A continuous 24-hour off sedation period was achieved in 23 (26.4%) patients undergoing VV ECMO with the median off-sedation duration of 3.0 days (IQR = 2.0–9.0). Among those patients, 12 (52.2%) remained GCS $\leq 8$ (coma_{off}) while 11 (47.8%) had recovered to at least one GCS score $\geq 9$ (non-coma_{off}). The coma_{off} group had significantly fewer good neurological outcomes compared with the non-coma_{off} group ($n = 1, 8.3\%$, vs. $n = 7, 63.6\%, p = 0.009$) (Fig. 3A). The KM survival curve also demonstrated the coma_{off} group had significantly lower probability of good neurological outcomes ($p = 0.0003$) (Fig. 3B). Among the 12 coma_{off} patients, 2 (16.7%) had an improvement in GCS score to $\geq 9$. However, both had poor neurological outcomes at discharge (mRS 4 and 6).

Among the 23 patients who achieved 24-hour off sedation, 9 (39.1%) had at least one type of ABI. The prevalence of ABI was similar between the coma_{off} patients vs. the non-coma_{off} patients ($n = 5, 41.8\%, vs. n = 4, 36.4\%, p > 0.99$) (Fig. 3C). Among the 5 coma_{off} patients with ABI, ICH and SAH were the most common types (Fig. 3D).

**Coma_{on}**

Of the 64 patients who never achieved 24-hour off sedation while on ECMO, 53 (82.8%) had at least one GCS score $\geq 9$ (non-coma_{on}) and 11 (17.2%) remained GCS $\leq 8$ (coma_{on}) during the ECMO course. The coma_{on} group had a non-statistically significant trend towards fewer good neurological outcomes compared with the non-coma_{on} group ($n = 3, 27.3\%$, vs. $n = 22, 41.5\%, p = 0.50$) (Supplementary Fig. 2C).
The prevalence of ABI in the coma_on and the non-coma_on groups can be found in Supplementary Materials and Supplementary Fig. 2D.

**Risk Factors for Coma_{off}**

In the multivariable analysis statistical model, a higher number of packed red blood cell (pRBC) transfusions while on ECMO (aOR = 1.16, 95% CI = 1.04–1.28), a higher average lactate level during the ECMO course (aOR = 1.91, 95% CI = 1.11–3.30), and the presence of ABI while on ECMO (aOR = 6.41, 95% CI = 1.17–35.26) were significant risk factors for coma_{off} after adjusting for renal replacement therapy (RRT), ECMO configuration, pre-ECMO PaO$_2$ and PaCO$_2$ (worst within 24 hours before cannulation) (Tables 2–3). A two-way interaction analysis was conducted on all 7 selected covariates and there was no significant interaction effect between any 2 covariates.
Table 2

Univariable logistic regression analysis of off-sedation coma (coma$_{off}$) in both VA and VV ECMO patients. RRT renal replacement therapy, HTN hypertension, CHF chronic heart failure, DM diabetes, HLD hyperlipidemia, CKD chronic kidney disease, A-fib atrial fibrillation, pRBC packed red blood cell, ABI acute brain injury, MAP mean arterial pressure.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ECMO worst PCO2</td>
<td>0.99</td>
<td>0.97–1.01</td>
<td>0.421</td>
</tr>
<tr>
<td>Pre-ECMO worst PO2</td>
<td>1.00</td>
<td>1.00–1.00</td>
<td>0.623</td>
</tr>
<tr>
<td>ABI</td>
<td>2.1</td>
<td>0.78–5.62</td>
<td>0.140</td>
</tr>
<tr>
<td># of PRBC transfused</td>
<td>1.06</td>
<td>1.01–1.12</td>
<td><strong>0.015</strong></td>
</tr>
<tr>
<td>ECMO type</td>
<td>1.19</td>
<td>0.44–3.25</td>
<td>0.732</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1.17</td>
<td>0.40–3.40</td>
<td>0.772</td>
</tr>
<tr>
<td>BMI</td>
<td>1.11</td>
<td>1.02–1.21</td>
<td><strong>0.011</strong></td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>0.98–1.06</td>
<td>0.262</td>
</tr>
<tr>
<td>Gender</td>
<td>0.73</td>
<td>0.27–1.98</td>
<td>0.536</td>
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<tr>
<td>Race</td>
<td>1.27</td>
<td>0.83–1.94</td>
<td>0.276</td>
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<tr>
<td>RRT</td>
<td>4.39</td>
<td>1.43–13.50</td>
<td><strong>0.010</strong></td>
</tr>
<tr>
<td>Arterial line MAP</td>
<td>0.93</td>
<td>0.86–1.02</td>
<td>0.119</td>
</tr>
<tr>
<td>Covid 19</td>
<td>2.09</td>
<td>0.58–7.60</td>
<td>0.261</td>
</tr>
<tr>
<td>HTN</td>
<td>1.53</td>
<td>0.53–4.43</td>
<td>0.429</td>
</tr>
<tr>
<td>CHF</td>
<td>0.32</td>
<td>0.11–0.93</td>
<td><strong>0.036</strong></td>
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<tr>
<td>DM</td>
<td>1.17</td>
<td>0.40–3.40</td>
<td>0.772</td>
</tr>
<tr>
<td>HLD</td>
<td>2.17</td>
<td>0.83–5.73</td>
<td>0.115</td>
</tr>
<tr>
<td>CKD</td>
<td>1.52</td>
<td>0.40–5.78</td>
<td>0.535</td>
</tr>
<tr>
<td>A-fib</td>
<td>0.55</td>
<td>0.18–1.70</td>
<td>0.302</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.57</td>
<td>1.11–2.24</td>
<td><strong>0.012</strong></td>
</tr>
<tr>
<td>AST</td>
<td>1.00</td>
<td>1.00–1.00</td>
<td><strong>0.045</strong></td>
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<tr>
<td>ALT</td>
<td>1.01</td>
<td>1.00–1.01</td>
<td><strong>0.042</strong></td>
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</table>
Table 3

Multivariable logistic regression analysis of off-sedation coma (coma\textsubscript{off}) in both VA and VV ECMO patients. RRT renal replacement therapy, pRBC packed red blood cell, ABI acute brain injury.

<table>
<thead>
<tr>
<th>Variables</th>
<th>aOR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECMO type</td>
<td>0.24</td>
<td>0.017–3.36</td>
<td>0.290</td>
</tr>
<tr>
<td>ABI</td>
<td>6.41</td>
<td>1.17–35.26</td>
<td>0.033</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.91</td>
<td>1.11–3.30</td>
<td>0.020</td>
</tr>
<tr>
<td>Number of pRBC transfusions</td>
<td>1.16</td>
<td>1.042–1.28</td>
<td>0.006</td>
</tr>
<tr>
<td>Pre-ECMO worst PCO\textsubscript{2}</td>
<td>0.95</td>
<td>0.89–1.01</td>
<td>0.095</td>
</tr>
<tr>
<td>Pre-ECMO worst PO\textsubscript{2}</td>
<td>1.00</td>
<td>0.99–1.00</td>
<td>0.227</td>
</tr>
<tr>
<td>RRT</td>
<td>2.40</td>
<td>0.48–11.92</td>
<td>0.284</td>
</tr>
</tbody>
</table>

Sedation Practice Before and After the Covid Pandemic

Finally, we explored the possibility that the COVID-19 pandemic may have changed our sedation practice in the ICU since our cohort comprised of patients from 2017 to 2022. March 2020 was considered as the beginning of the pandemic. No significant difference was found between the percentage of patients who achieved 24-hour off-sedation in VA-ECMO group (p = 0.72) or VV-ECMO group (p = 0.55) before and after the COVID-19 pandemic (Supplemental Fig. 3A-B).

Mortality and Withdrawal of Life-Sustaining Treatments (WLST)

The overall mortality for the VA-ECMO patients was 65.7% (94/143) and 48.3% (42/87) in the VV-ECMO patients. In the individual subgroups, the mortality was 88.5% (VA-ECMO coma\textsubscript{off}), 50.0% (VA-ECMO non-coma\textsubscript{off}), 83.7% (VA-ECMO coma\textsubscript{on}), 41.7% (VA-ECMO non-coma\textsubscript{on}), 75.0% (VV-ECMO coma\textsubscript{off}), 18.2% (VV-ECMO non-coma\textsubscript{off}), 63.6% (VV-ECMO coma\textsubscript{on}) and 45.3% (VV-ECMO non-coma\textsubscript{on}) (Supplementary Fig. 3C-D).

WLST contributed to 86.2% (81/94) of death in the VA-ECMO patients and 90.1% (38/42) in the VV-ECMO patients (Supplementary Fig. 3E).

Discussion
Our study is the first comprehensive analysis of prevalence, risk factors, and neurological outcomes of the comatose ECMO patients. We found that coma$_{off}$ was common in ECMO patients. The number of pRBC transfusion (aOR = 1.16), average lactate level (aOR = 1.91), and ABI (aOR = 6.41) during ECMO support were independent risk factors for coma$_{off}$. Coma$_{off}$ was strongly associated with unfavorable neurological outcomes at hospital discharge. There are multiple unique strengths of our study: 1) By implementing the institutional sedation cessation protocol, we minimized the confounding effect of sedation on the coma exams whenever feasible; 2) With the sedation cessation protocol in place, we were able to compare the patients on-sedation vs. those off-sedation; and 3) A standardized neuromonitoring protocol allowed for an early detection and prevention of ABIs in the ECMO patients.

Coma was commonly diagnosed when standardized sedation cessation and neuromonitoring protocols were implemented. In our cohort, the coma prevalence was: 56.6% in the VA-ECMO off-sedation group, 50.5% in the VA-ECMO on-sedation group, 52.2% in the VV-ECMO off-sedation group, and 17.2% in the VV-ECMO on-sedation group. The prevalence of coma varies in other ICU patient populations. Among out-of-hospital cardiac arrest survivors (unclear if off sedation), 56% remained in coma for > 24 hours after achieving return of spontaneous circulation, compared to 30% of in-hospital cardiac arrest survivors. Approximately 82% (however, < 1% off sedation) of the COVID-19 ICU patients remained comatose for a median of 10 days. Coma was also found in 16% of the patients (all off sedation) with severe sepsis. But none of those studies implemented a standardized sedation cessation protocol as the one used in our cohort.

Coma was associated with higher mortality and poor neurological outcomes. In our cohort, more patients died in the VA-ECMO coma$_{off}$ group than the non-coma$_{off}$ group (88.5% vs. 50.0%). Similar trend was also found in the VV-ECMO off-sedation patients (75.0% vs. 18.2%). The same pattern was observed in the neurological outcomes of those patients. It is surprising that no patient in the VA-ECMO coma$_{off}$ group and only 1 patient in the VV-ECMO coma$_{off}$ group had good outcomes upon discharge, which are striking numbers. Only 4 patients with coma$_{off}$ regained some consciousness (GCS $\geq$ 9) later in the hospital course, but they all had poor neurological outcomes at discharge, indicating that coma$_{off}$ may represent a surrogate marker for poor outcomes. The association of coma and mortality was also reported in other patient populations, e.g. post cardiac arrest (unclear if off sedation), ARDS related to COVID-19 (not off sedation), and severe sepsis (off sedation). Because of this significant association, being comatose while off sedation is commonly used to facilitate the decision to withdraw care in the real-world practice although it’s difficult to determine the “sufficient” off-sedation time. Also, it is important to remember that there is a high risk of bias from the self-fulfilling prophecy. In our cohort, WLST contributed to 86.2% of death in the VA-ECMO group and 90.1% in the entire VV-ECMO group.

Coma in the ICU setting is frequently multifactorial in nature, e.g., ABI, sedation/toxins, metabolic/electrolyte/endocrine derangement, nutrition, temperature, and infection. We included clinically relevant variables for coma$_{off}$ in our regression model and identified 3 independent risk factors: ABI, average whole blood lactate level, and the number of pRBC transfusions during ECMO support. ABI
was discovered in 31.7% of the ECMO patients in our study, which is likely due to our standardized neuromonitoring protocol. In our patient cohort, majority of our patients (58.3%) received RRT, which reduced confounding effects, although not completely, from metabolic imbalance as serum creatinine levels were normalized in most patients after RRT. The average levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) during the ECMO course were elevated. But their impact on the coma status was minimal if any with an unadjusted OR of only 1.00 and 1.01, respectively. Sedation frequently confounds coma exams, but proper sedation is often required to reduce ventilator desynchrony and to facilitate therapeutic interventions in the ICU. We implemented a sedation cessation protocol to all ECMO patients and minimized sedation when deemed safe. It is worth emphasizing that the median off-sedation duration was 2.5 days (IQR: 2.0–5.0) for the VA-ECMO off-sedation group, and 3.0 days (IQR: 2.0–9.0) for the VV-ECMO off-sedation group, which may be “sufficient” time to diagnose coma
d。“

Limitations

Our study also has several limitations. 1) It is a retrospective single-center study. The data may not be generalizable to other institutions and populations. 2) Although we have a total of 230 ECMO patients, the sample size in some subgroups is in the lower teens or even in single digits. Therefore, the study may not have enough power to detect contributions of various risk factors to the comatose status. In addition, due to missing data, many clinically important variables were not included in the analyses, such as sequential organ failure assessment (SOFA) and acute physiology and chronic health evaluation (APACHE) II scores. 3) Only a fraction of our patients achieved the coma\textsubscript{off} state, and the coma\textsubscript{on} state presented significant confounders for coma assessment. These may further limit the generalizability of our study across the ECCMO patients. But this study presents a viable method to further define the impact of coma on ECMO. 4) ABI was certainly under-diagnosed since most patients did not have MRI brain studies. In a recent autopsy study, 68% ECMO patients had ABI. Point-of-care MRI has been performed in selected ECMO patients in our institution which will significantly improve ABI detection. 5) We did not have enough data to explore the association between coma\textsubscript{off} and WLST and to investigate the possible self-fulfilling prophecy. Further studies are needed to answer this important question.

Conclusions

Our findings highlight the importance of understanding the impact of coma on the outcome of the ECMO patients. While proper sedation is crucial in the management of ECMO patients, our study underscores the necessity of implementing a standardized sedation weaning protocol. By doing so, we can more accurately assess the coma status, which may serve as a surrogate marker for poor outcomes upon hospital discharge.

Declarations
Acknowledgements


Details

1) The manuscript complies with all instructions to authors.

2) The authorship requirements have been met and the final manuscript was approved by all authors. Dr. Feng prepared the first draft and performed statistical analysis. Ms. Kolchinski and Mr. Kapoor collected the data. Dr. Khanduja collected the data and critically revised the manuscript. Drs. Hwang, Suarez, Geocadin, Kim, and Whitman provided critical revision. Dr. Cho provided study design, data analysis supervision, and finalizing the manuscript.

3) This manuscript has not been published elsewhere and is not under consideration by another journal.

4) The study is adhered to ethical guidelines and indicate ethical approvals (IRB) and use of informed consent, as appropriate. Retrospective studies require a statement regarding IRB approval (RB00216321).

5) Disclose Conflicts of Interest for all authors: none.

6) It is to confirm the use of reporting checklist (STROBE checklist: cohort studies).

7) List sources of funding for the study: none.

References


**Figures**
Figure 1

Flowchart of the study design.
Figure 2

Coma\textsubscript{off}, hospital discharge outcome, and acute brain injury (ABI) in the VA ECMO patients. A, the relationship between coma\textsubscript{off} and the outcomes at discharge. B, Kaplan Meier survival analysis comparing the probability of good outcome between the coma\textsubscript{off} and non-coma\textsubscript{off} subgroups at hospital discharge. Each solid dot represents a censored subject. C, the relationship between ABI and coma\textsubscript{off}. D, Different types of ABI in the coma\textsubscript{off} patients.
Figure 3

Coma\textsubscript{off}, hospital discharge outcome, and acute brain injury (ABI) in the VV ECMO patients. A, the relationship between coma\textsubscript{off} and the outcomes at discharge. B, Kaplan Meier survival analysis comparing the probability of good outcome between the coma\textsubscript{off} and non-coma\textsubscript{off} subgroups at hospital discharge. Each solid dot represents a censored subject. C, the relationship between ABI and coma\textsubscript{off}. D, Different types of ABI in the coma\textsubscript{off} patients.

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

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- ECMOcomapaperSupplementalmaterialsfinal.pdf