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MAIN TEXT

Risk factors for bleeding complications during venovenous extracorporeal membrane oxygenation as a bridge to recovery

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Abstract

Background: Bleeding complications during venovenous extracorporeal membrane oxygenation (V-V ECMO) can be critical. However, there is limited information on the associated risk factors. This study investigated the risk factors for bleeding complications during V-V ECMO as a bridge to recovery.

Methods: This single-center retrospective study enrolled 59 patients (bleeding and non-bleeding groups) who received V-V ECMO from 2012 to 2020, to evaluate whether peak activated partial thromboplastin time (APTT) value, lowest platelet count, and mobilization to sitting on the edge of the bed during V-V ECMO were risk factors for bleeding complications, defined according to the Extracorporeal Life Support Organization guidelines. Age, sex, body mass index, Sequential Organ Failure Assessment score, and ECMO duration before bleeding complications were covariates in the multivariate logistic regression analysis.

Results: Thirty-one (53%) participants experienced 36 bleeding complications; the ECMO cannulation site, gastrointestinal tract, and nasopharyngeal region were the most common bleeding sites. The use of transfusion products and length of ECMO and intensive care unit stay were significantly and medical costs were non-significantly increased in the bleeding group. Peak APTT (odds ratio [OR] 1.03, 95% confidence interval [CI] 1.01–1.05, $p < 0.01$) was significantly associated whereas the lowest platelet count (OR 0.96, 95% CI 0.82–1.13, $p = 0.66$) was unassociated with bleeding complications during ECMO. Achieving mobilization (OR 0.14, 95% CI 0.02–1.17, $p = 0.07$) decreased the trend of risk for bleeding complications.

Conclusions: Peak APTT might be an independent modifiable factor for bleeding complications during V-V ECMO. The protective effect of mobilization during V-V ECMO requires further investigation.

KEYWORDS

APTT, bleeding complication, mobilization, platelet count, V-V ECMO

[Correction added on 9 May 2022, after first online publication: CAUL funding statement has been added.]

1 | INTRODUCTION

With its proven efficacy as a bridge to recovery in the acute respiratory distress syndrome, venovenous extracorporeal membrane oxygenation (V-V ECMO) has been increasingly used for a rapidly widening range of indications.[1–3] However, various complications can occur during V-V ECMO; bleeding complications, which occur in 15%–50% of patients,[4–6] are among the most critical complications and result in a six-fold increase in the mortality risk.[5] Thus, to improve patient outcomes, intensive care unit (ICU) clinicians should essentially prevent bleeding during ECMO management.[7]

In most cases, anticoagulation with laboratory-based monitoring is used to prevent thrombosis in the ECMO circuit and membrane.[8] Although higher activated partial thromboplastin time (APTT) values and lower platelet counts are well-known risk factors for bleeding complications during ECMO,[8–11] the corresponding risk factors during V-V ECMO remain unclear. Mobilization, defined as rehabilitation to the level of sitting on the edge of the bed or higher during ECMO management, has recently been reported as a risk factor for iliopsoas hematoma.[12] Nonetheless, mobilization may improve patient outcomes, and the safety and feasibility of mobilization in ECMO patients have been reported in several studies.[13–16] However, few studies have undertaken a detailed investigation of specific hematological parameters and mobilization as risk factors for bleeding complications during V-V ECMO, especially among patients who are not on a long-term waiting list for transplantation. A better understanding of the coagulation state before hemorrhagic events and effective therapeutic management is necessary to reduce bleeding complications in critically ill patients with organ failure who require more intensive medical support, including V-V ECMO as a bridge to recovery.

We hypothesized that a higher APTT value, lower platelet count, and achieving mobilization during ECMO could be associated with bleeding complications. Therefore, in this study, we aimed to investigate the risk factors for bleeding complications during V-V ECMO, which is used as a bridge to recovery.

2 | METHODS

2.1 | Study design and patient selection

This single-center retrospective cohort study included all patients who received V-V ECMO as a bridge to recovery between December 2012 and March 2020 at the Japanese Red Cross Maebashi Hospital, a tertiary-care community care facility with 555 hospital beds and an 18-bed closed ICU (expanded from 12 to 18 beds in June 2018). On average, approximately 30 patients receive V-V or V-A ECMO annually at this hospital. The patients were divided into two groups: the bleeding group, which experienced bleeding complications at least once during ECMO management, and the non-bleeding group. In accordance with the guidelines of the Extracorporeal Life Support Organization (ELSO), bleeding complications were defined as a hemoglobin decrease of at least 2 g/dl in 24 h; transfusion of four or more units of red blood cell (RBC); retroperitoneal bleeding; clinically apparent airway or intracranial bleeding; or bleeding complications requiring surgical intervention; thrombotic complications were defined as clots requiring ECMO circuit replacement; deep venous thrombosis; systemic thromboembolism; cerebral infarction; or bowel ischemia.[8] Patients who were younger than 18 years, received V-V ECMO only during elective surgery, died within 24 h after ECMO cannulation, or were admitted to the ICU because of the coronavirus disease were excluded. This study was approved by the Ethics Committee of the Japanese Red Cross Maebashi Hospital.

2.2 | Patient management during V-V ECMO

Prior to ECMO initiation, a lung-protective ventilation strategy was adopted for all patients. Based on the indications for V-V ECMO in the ELSO guidelines,[7] patients with severe hypoxia, hypercapnia on unacceptable ventilator support, or immediate respiratory collapse (e.g., completely blocked airway) and without contraindications (e.g., severe intracranial hemorrhage or irrecoverable comorbidity) were considered eligible to receive V-V ECMO.[7,17] Immediately after initiating V-V ECMO, ventilatory protective lung-rest settings were enabled. According to the ventilation strategy shown in Table S1, the ECMO pump rotation was set to initially achieve a targeted flow of 60–80 ml/kg/min, and the flow and sweep gas flow were adjusted in accordance with the blood gas level.

If there were no contraindications (e.g., active bleeding or severe trauma), anticoagulation was initiated through a bolus infusion of unfractionated heparin (UFH; 40 units/kg) at the time of ECMO cannulation, followed by a continuous UFH infusion to achieve a target APTT of 40–60 s along with laboratory monitoring every 8 h. To prevent clots in the CRRT circuit or membrane when continuous renal replacement therapy (CRRT) was initiated during V-V ECMO, nafamostat was added within the non-heparinized CRRT circuit, but not systemically, with a target activated clotting time (ACT) of 150–200 s in the blood within the CRRT circuit.[18] For heparin-induced thrombocytopenia,

argatroban was titrated instead of UFH to achieve the same target APTT range. During all ECMO, blood transfusion was administered only to maintain a platelet count >50 000 cells/mm^3, fibrinogen level > 150 mg/dl, and hemoglobin level > 10 g/dl.[8] Proton-pump inhibitors were routinely administered to all patients receiving ECMO.

In case of bleeding complications, situational therapeutic management, including blood transfusions and surgical intervention, and interruption of continuous anticoagulation was immediately undertaken. For patients with uncontrollable bleeding complications, we specified a temporary transfusion target that included a platelet count >100 000 cells/mm^3 and a fibrinogen level > 200 mg/dl. Instead of monitoring the APTT value, a relatively higher ECMO flow rate (i.e., 4–5 L/min) was set to prevent clots in the ECMO circuits until we could resume anticoagulation. After confirming control of the bleeding and a stable circulatory state, without any blood transfusion requirement, the patient was observed for a few days before resuming anticoagulation.

A multidisciplinary team, comprising ICU physicians, nurses, medical engineers, and physiotherapists, was responsible for discussing the rehabilitation content in their daily rounds. Rehabilitation commenced with exercises in bed, then advanced to sitting in bed, sitting on the edge of the bed, standing, and, ultimately, ambulation, depending on the patient's condition. A multidisciplinary team performed rehabilitation therapy for 15–30 min per day. The ICU physicians were responsible for monitoring the vital signs and cannula sites of the patients during rehabilitation and for session cessation upon the occurrence of any adverse event.

2.3 | Data collection

Data on patient characteristics were retrospectively collected by two authors (K.L. and H.S.). One author extracted data from medical records, and the other confirmed the accuracy and validity of the extracted data, which included age, sex, body mass index (BMI), treatment history (steroid use, antiplatelets, and anticoagulation), comorbidities, the acute physiologic and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores, the presence of disseminated intravascular coagulation, and the disease or condition that necessitated ECMO.

Clinical treatment data, including the use of vasopressors, steroids, CRRT, neuromuscular blocking agents, anticoagulants, and antiplatelet therapy as well as daily laboratory monitoring data, including mean and peak APTT and mean and the lowest platelet values during ECMO, were collected. The transient excessive increase in the APTT value following a bolus injection of UFH during ECMO cannulation was excluded from the data collected because no bleeding complications associated with cannulation procedures were recorded.

Data on the highest ICU Mobility Scale (IMS) and the number of patients who achieved mobilization during ECMO were collected from the medical records. IMS is a numerical scale of rehabilitation intensity that is recorded daily by a physical therapist.[16] Mobilization during ECMO is defined as rehabilitation to the level of sitting on the edge of the bed or higher, which is equal to an IMS score of 3 or higher.[17,19] Furthermore, the duration from ECMO cannulation to the achievement of mobilization was determined for the patients who achieved mobilization during V-V ECMO.

We determined the period from ICU admission or intubation to ECMO cannulation, ECMO device-related information about cannula size, cannulation site, mean flow rate, mean pump rotation, the number of times that ECMO circuits and membranes were exchanged, and the number of times that the ECMO cannulation site was changed.

In the bleeding group, data on laboratory values (APTT and platelet count), rehabilitation, and ECMO device-related information were collected only for the duration from ECMO cannulation to the first bleeding complication because these data could be influenced by either the bleeding or the therapeutic interventions.

2.4 | Outcomes

The incidence and type of bleeding complications were described. The APTT value immediately preceding the bleeding event, duration from peak APTT value to the first bleeding event, and duration from ECMO cannulation to the first bleeding complication was ascertained. Besides the incidence and type of thrombotic complications, the quantities of blood transfusion products, including RBC, fresh frozen plasma (FFP), and platelet concentrate, that were used during ECMO, ECMO duration before the occurrence of the bleeding complication, total ECMO duration, length of ICU and hospital stay, in-hospital and 28-day mortality rates, and the total hospital costs (calculated at a 108 yen/USD exchange rate) were also investigated.

2.5 | Statistical analysis

Categorical data are summarized as numbers and percentages and compared using the chi-square or Fisher's exact test. The Shapiro–Wilk test was used to evaluate the

distribution of all continuous variables. Non-normally distributed continuous variables are described as the median and interquartile range and were tested using the Mann–Whitney *U* test.

To examine the study hypothesis, a multivariate logistic regression analysis was performed to investigate the association between bleeding complications and peak APTT, the lowest platelet count, and mobilization. Age, sex, BMI, SOFA score on ICU admission, and the ECMO duration prior to the occurrence of the bleeding complication were used as clinically important confounders in the analysis.[4,20,21] A history of antiplatelet and coagulant therapy was not included as confounders as they led to the creation of an unstable statistical model due to the significant distribution bias between the two groups (Figure S1).

Furthermore, we performed a post hoc analysis to investigate the association between the highest intensity level based on the IMS score or the duration from ECMO cannulation to the first mobilization and the occurrence of bleeding complications with the same covariates that were mentioned previously to evaluate the effects of rehabilitation intensity.[22]

All analyses were conducted using EZR software version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), based on the R Package (The R Foundation for Statistical Computing, Vienna, Austria). Statistical tests were two-sided, and significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Baseline patient characteristics

Among the 77 patients who received V-V ECMO as a bridge to recovery, 59 were enrolled in this study (Figure 1). Thirty-one patients met the ELSO bleeding criteria and were assigned to the bleeding group, and the remaining 28 were assigned to the non-bleeding group. Patient characteristics are shown in Table 1. The two groups did not differ significantly in age, sex, BMI, APACHE II score, SOFA score, and the causative disease for ECMO. The bleeding group had a significantly higher proportion of patients with a history of antiplatelet and anticoagulation n. In both groups, UFH was primarily used as the anticoagulant. No antiplatelet therapy was administered during ECMO in this entire study cohort. The frequency of APTT monitoring did not differ significantly between the two groups. The mean and peak APTT ($p = 0.05$ and 0.01, respectively) were significantly higher in the bleeding group, whereas there were no significant intergroup differences in the mean and the lowest platelet counts. Mobilization was frequently achieved in the non-bleeding group, with no significant difference. The duration from ECMO cannulation to the achievement of mobilization was similar in both groups.

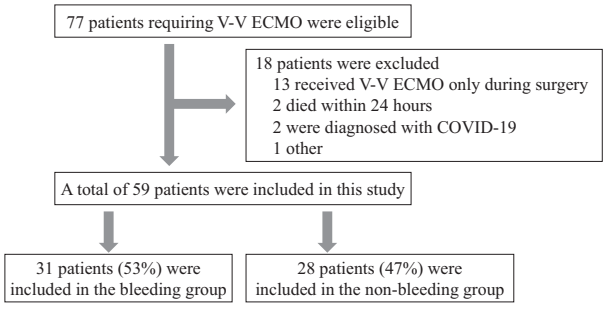

FIGURE 1 V-V ECMO, venovenous extracorporeal membrane oxygenation

Data on ECMO settings are shown in Table 2. The period from intubation or ICU admission to ECMO cannulation was comparable between the two groups. A 25-Fr-sized cannula for drainage was frequently inserted into the internal jugular vein, and a 19-Fr-sized cannula for the return was inserted into the femoral vein. ECMO blood flow and pump rates were similarly controlled. There was no intergroup difference in the number of patients who experienced ECMO circuits or membrane exchange or in the exchange times. Three patients experienced ECMO cannulation-site changes because of uncontrolled recirculation, insufficient drainage, and suspected infection. No cannulation-site changes resulted in bleeding complications.

3.2 | Bleeding complications

Altogether, 36 bleeding complications occurred in 31 patients (Table 3). The main sources of bleeding complications were ECMO cannulation sites, the gastrointestinal tract, and the nasal/oropharyngeal region in 10 (28%), 10 (28%), and 7 patients (19%), respectively. Among the 31 patients, 3 experienced two bleeding complication episodes, and 1 had three episodes during ECMO (Table S2). The median APTT immediately before the bleeding event was 53 s in patients with bleeding complications. The median duration from peak APTT to the first bleeding event was 3 days, and the median (IQR) time from ECMO cannulation to the first bleeding complication was 6 (3–9) days.

3.3 | Clinical outcomes

The bleeding group showed more frequent thrombotic complications (68% vs. 36%, $p < 0.01$), although the frequency of thrombotic events before the bleeding events was comparable (32% vs. 36%, $p = 0.79$; Table 4). The ECMO circuit and membrane exchange were the most dominant thrombotic complications (Table S3). In the bleeding group, a higher

TABLE 1 Patient characteristics

Variables	Bleeding group ($n = 31$)	Non-bleeding group ($n = 28$)	p value
Age (year)	70 [60–75]	69 [59–74]	0.79
Gender (male)	21 (68%)	19 (68%)	1
Body mass index (kg/m^2)	24 [23–27]	24 [21–26]	0.12
History of steroid use[a]	7 (23%)	3 (11%)	0.31
History of antiplatelet and anticoagulation	8 (26%)	1 (4%)	0.03
Comorbidities			
Chronic renal failure	1 (3%)	1 (4%)	1
Cirrhosis	0	1 (4%)	0.48
Immunosuppressed[b]	8 (26%)	3 (11%)	0.19
APACHE II score at ICU admission	26 [19–32]	26 [21–32]	0.49
SOFA score at ICU admission	10 [7–12]	8 [6–10]	0.12
SOFA score at ECMO cannulation	11 [7–13]	9 [7–12]	0.29
Presence of DIC according to the following criteria			
Japanese Society on Thrombosis and Hemostasis DIC criteria 2018	6 (19%)	3 (11%)	0.48
International Society on Thrombosis and Hemostasis overt DIC criteria	4 (13%)	1 (4%)	0.36
Causative disease for ECMO			
Pulmonary infection (bacterial, viral, fungal)	12 (39%)	5 (19%)	0.092
Non-infectious pulmonary disease[c]	19 (61%)	21 (75%)	0.28
Non-pulmonary disease[d]	0	2 (7%)	0.22
Patients receiving vasopressors during ECMO	10 (31%)	7 (25%)	0.58
Patients receiving steroids during ECMO	23 (74%)	15 (54%)	0.11
Patients receiving continuous renal replacement therapy during ECMO	18 (58%)	15 (54%)	0.80
Patients receiving neuromuscular blocking agents during ECMO	16 (52%)	11 (39%)	0.44
Anticoagulation during ECMO			
Unfractionated heparin	29 (94%)	25 (89%)	0.66
Nafamostat	4 (13%)	3 (11%)	1
Other anticoagulant agent[e]	4 (13%)	5 (18%)	1
Antiplatelet therapy during ECMO	0 (0%)	0 (0%)	
The times of APTT value measurement (per a day)	25 [12–38]	22 [17–29]	0.92
APTT value[f]			
Mean APTT value (s)	59 [49–76]	54 [45–64]	0.049
Peak APTT value (s)[g]	120 [76–180]	83 [62–102]	0.01
The number of Platelet count[g]			
Mean platelet count (×10 000/μl)	10 [7–13]	9 [6–15]	0.87
Lowest platelet count	5 [3–8]	6 [3–11]	0.61
Rehabilitation during ECMO[g]			
Highest ICU mobility scale[h]	0 [0–3]	0 [0–3]	0.62
Patients who achieved mobilization[i]	3 (10%)	9 (32%)	0.051

(Continues)

amount of RBC (24 units vs. 15 units; $p = 0.01$), FFP (16 units vs. 8 units; $p = 0.03$), and platelet concentrate transfusions (20 units vs. 10 units; $p = 0.06$); longer ECMO (21 days vs. 8 days; $p < 0.01$); and ICU stay (31 days vs. 18 days; $p = 0.02$)

TABLE 1 (Continued)

Variables	Bleeding group ($n = 31$)	Non-bleeding group ($n = 28$)	p value
Duration from ECMO cannulation to achievement of mobilization (days)	9 [5–14]	7 [7–9]	0.73

Note: Data in table are presented as median [interquartile range] or number (percentage).

Abbreviations: APACHE II, acute physiologic and chronic health evaluation II; APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; ECMO, extra corporeal membrane oxygenation; ICU, intensive care unit; SOFA, sequential organ failure assessment.

[a]Daily dose of more than 10 mg or cumulative dose of more than 700 mg prednisone.

[b]Immunosuppressed state comes from chemotherapy, radiation therapy, long-term or recent high-dose steroids, or immunodeficiency.

[c]Bleeding group comprises 10 patients with aspiration pneumonia, 5 patients with pulmonary edema, and 4 patients with interstitial pneumonia. The non-bleeding group comprises 7 patients with aspiration pneumonia, 6 patients with pulmonary edema, 3 patients with interstitial pneumonia, 2 patients with alveolar hemorrhages, pulmonary contusion, inhalation pneumonia, and chylothorax.

[d]That group comprises airway obstruction and abdominal compartment syndrome.

[e]Bleeding group comprises 3 patients treated with thrombomodulin and argatroban. The non-bleeding group comprises 3 patients treated with thrombomodulin and 2 patients treated with argatroban.

[f]Transient excessive increase in the APTT value at the time of ECMO cannulation were excluded.

[g]In the bleeding group, the data from ECMO cannulation to the first bleeding complication were analyzed.

[h]IMS is a numerical scale for measuring the maximum level of mobility of adult patients in the ICU (Hodgson C, et al. Heart and Lung. 2014; 43:19–24); IMS 0: Nothing (lying in bed, passive exercise), 1: sitting in bed, exercises in bed; 2: passively moved to a chair (no standing); 3: sitting over the edge of the bed; 4: standing; 5: transferring bed to chair; 6: marching in place (at bedside); 7: walking with the assistance of two or more people; 8: walking with the assistance of one person; 9: walking independently with a gait aid; 10: walking independently without a gait aid.[16]

[i]Mobilization was defined as rehabilitation at the level of sitting over the bed or higher, which is equal to an IMS score of 3 or higher.

were observed. There was no significant intergroup difference in the in-hospital (35% vs. 25%; $p = 0.41$) and 28-day (19% vs. 14%; $p = 0.73$) mortality rates. The total hospital costs tended to be higher in the bleeding group ($80 414 vs. $66 460; $p = 0.08$).

3.4 | Risk factors for bleeding complications

In multivariate logistic regression analysis (Figure 2), the peak APTT values (odds ratio [OR]:1.03, 95% confidence interval [CI]: 1.01–1.05, $p < 0.01$) were significantly associated with bleeding complications, whereas lowest platelet count (OR: 0.96, 95% CI: 0.82–1.13, $p = 0.66$) and mobilization during ECMO (OR: 0.14, 95% CI: 0.02–1.17, $p = 0.07$) were not.

In the post hoc analysis, the highest intensity of rehabilitation during ECMO was unassociated with bleeding complications (Figure S2).

4 | DISCUSSION

In this retrospective single-center study, the majority of patients who received V-V ECMO as a bridge to recovery experienced bleeding complications, as defined by the ELSO criteria. The most frequent bleeding complication site was the ECMO cannulation site, followed by the gastrointestinal tract. Unfavorable outcomes, including frequent thrombotic complications, increased use of transfusion products, longer ECMO duration, a longer length of ICU stay, and increased total hospital cost, were observed in the bleeding group. The peak APTT value was associated with an increased incidence of bleeding complications during ECMO while achieving mobilization, and the lowest platelet count was not an independent risk factor for bleeding complications.

4.1 | Comparison with previous studies

Studies based on data from large databases have identified several risk factors for bleeding complications.[6] However, most of these factors were determined before ECMO initiation, and the factors during treatment that we focused on have not been sufficiently examined due to the nature of the data in the database. Furthermore, to our best knowledge, this is the first study to investigate mobilization as a risk factor for all bleeding complications during V-V ECMO.

Some studies used the ACT as a faster investigation for ECMO monitoring. We used the APTT for daily ECMO management and ACT mainly for CRRT monitoring. Although there are few studies on bleeding complications associated with V-V ECMO as a bridge to recovery, our findings have high comparability to a previous study that followed the same ELSO criteria as was followed in our study.[11,25] Here, the dominant bleeding sites were the ECMO cannulation site and the gastrointestinal tract, followed by the nasal/oropharyngeal area. These findings are in line with those that were previously reported.[11,23–25]

TABLE 2 ECMO settings

Variables	Bleeding group ($n = 31$)	Non-bleeding group ($n = 28$)	p value
Days from ICU admission to ECMO cannulation (days)	0.1 [0–1.5]	0.1 [0–0.6]	0.70
Days from intubation to ECMO cannulation (days)	0.3 [0.1–0.9]	0.45 [0.2–1.5]	0.32
Drainage cannula at the time of first cannulation			
Cannula size (Fr)	25 [25–25]	25 [25–25]	0.74
Internal jugular vein	23 (74%)	17 (61%)	0.40
Femoral vein	8 (26%)	10 (36%)	0.57
Subclavian vein	0	1 (3%)	0.47
Return cannula at the time of first cannulation			
Cannula size (Fr)	19 [19–19]	19 [19–19]	0.83
Internal jugular vein	23 (74%)	17 (61%)	0.40
Femoral vein	8 (26%)	10 (36%)	0.57
Subclavian vein	0 (0%)	1 (3%)	0.39
Mean ECMO blood flow (L/min)	4.1 [3.8–4.3]	4.0 [3.6–4.2]	0.36
Mean ECMO pump rotation (rpm)	2900 [2700–3100]	2800 [2600–3000]	0.15
Patients experienced ECMO circuits or membrane exchange	19 (61%)	20 (71%)	0.58
ECMO circuits or membrane exchange for each patient (times)	0 [0–0]	0 [0–0]	0.21
The number of patients receiving ECMO cannulation site change[a]	2 (6%)	1 (4%)	0.63

Notes: Data are presented as median [interquartile range] or number (percentage). In the bleeding group, the data from ECMO cannulation to the first bleeding complication were analyzed.

Abbreviation: ECMO, extracorporeal membrane oxygenation; ICU: intensive care unit.

[a]No of patients who received cannulation site change because of bleeding.

However, our data showed no association between bleeding complications and ECMO duration, in contrast to the results of the previous study that focused on the association between ECMO duration and the incidence of intracranial hemorrhage.[26]

4.2 | Clinical impact due to bleeding complications

In this study, the bleeding group had more frequent thrombotic complications, requiring more transfusion products and a longer duration of ECMO and ICU stay. Although the mortality rate was similar, patients with bleeding complications tended to have higher hospital costs. Previous research, which focused on intracranial bleeding, reported a significant association between bleeding and mortality.[27] The low incidence of intracranial bleeding (6% of bleeding cases) might be the reason for the lack of association between bleeding and mortality in the present study.

Patients with bleeding complications had significantly more thrombotic complications during the total ECMO duration; however, the frequency was similar for the two groups prior to the onset of bleeding complications. The administration of transfusion products or discontinuation of anticoagulation may have contributed to consumptive coagulopathy and a resultant increase in thrombotic complications.[8]

APTT is a mainstay in anticoagulation monitoring and has a therapeutic target range of 1.5–2.5 times the APTT at the baseline.[8,9] The evidence shows that a higher APTT value is a risk factor for bleeding complications.[8,11] Although peak APTT was a risk factor in this study, the peak value was observed a few days before the bleeding event, and the APTT value immediately before the bleeding was within the therapeutic range. These data indicate that unexpected APTT elevation during ECMO could be an indicator of subsequent bleeding complications within a few days. To prevent subsequent bleeding complications,

TABLE 3 Bleeding complications

Variables	Total number of events ($n = 36$)
The number of bleeding complications, *n*	
ECMO cannulation site	10 (28%)
Gastrointestinal bleeding	10 (28%)
Nose/oropharynx region	7 (19%)
Hemothorax	3 (8%)
Intracranial bleeding	2 (6%)
Tracheal bleeding	2 (6%)
Surgical wound	1 (3%)
Intramuscular hematoma[a]	1 (3%)
The last APTT prior to bleeding event (s)	53 [46–69]
Duration from peak APTT to the first bleeding event (days)	3 [1–8]
Duration from ECMO cannulation to the first bleeding event (days)	6 [3–9]

Notes: Data in table are presented as median [interquartile range] or *n* (%). All bleeding complications met the definition of ELSO criteria. The number of patients experienced bleeding complications during ECMO was 31. Three patients experienced two times of bleeding complications and one patient three time (see Table S2).

Abbreviations: APTT, activated partial thromboplastin time; ECMO, extracorporeal membrane oxygenation.

[a]Left femur hematoma.

TABLE 4 Clinical outcomes

Variables	Bleeding group ($n = 31$)	Non-bleeding group ($n = 28$)	*p* value
Patients experienced thrombotic complication before the bleeding complication[a]	10 (32%)	10 (36%)	0.79
Patients experienced thrombotic complication during ECMO[b]	21 (68%)	10 (36%)	0.0069
Blood transfusion products use during ECMO			
Red blood cell[c] (units)	24 [13–58]	15 [8–23]	0.01
Fresh frozen plasma[d] (units)	16 [4–40]	8 [0–21]	0.03
Platelet concentrate[e] (units)	20 [8–85]	10 [0–33]	0.06
Length of ECMO (days)	21 [10–46]	8 [6–10]	<0.001
Length of ICU stay (days)	31 [16–65]	18 [11–27]	0.02
Length of hospital stay (days)	50 [33–81]	42 [23–85]	0.45
In-hospital mortality	11 (35%)	7 (25%)	0.41
28 days mortality	6 (19%)	4 (14%)	0.73
Total hospital costs[f] (US$)	80 414 [56 084–132 240]	66 460 [47 633–88 192]	0.08

Notes: Data are presented as median [interquartile range] or *n* (%). The definition of thrombotic complications is based on ELSO criteria: clots requiring ECMO circuit replacement, deep venous thrombosis (DVT), systemic thromboembolism, heparin-induced thrombocytopenia (HIT), cerebral infarction or bowel ischemia.

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

[a]Bleeding group comprises 10 clots requiring ECMO circuit replacement.

[b]Bleeding group comprises 21 clots requiring ECMO circuit replacement. The non-bleeding group comprises 8 clots requiring ECMO circuit replacement, DVT and HIT.

[c]One unit of this transfusion product is 140 ml in Japanese standard.

[d]One unit of this transfusion product is 120 ml in Japanese standard.

[e]Ten units of this transfusion product is 200 ml in Japanese standard.

[f]The exchange rate is 108 yen/dollar.

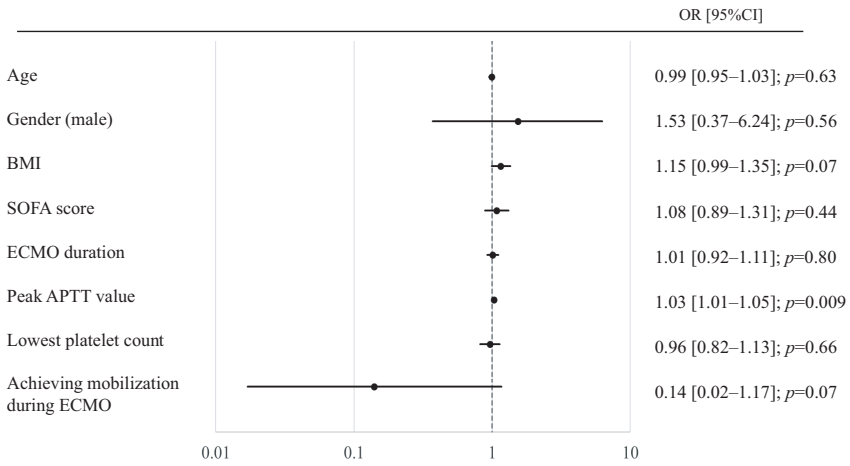

FIGURE 2 OR, odds ratio; CI, confidence interval

it might be necessary to closely monitor elevated APTT that is outside the normal range with reference to a strict target.[28] However, APTT is influenced by several factors besides heparin.[29–30] Furthermore, monitoring anticoagulant activity with anti-Xa and viscoelastic tests (TEG/ROTEM) might be an alternative strategy as these have greater validity than APTT in anticoagulant management.[31] Moreover, a low-dose anticoagulant or heparin-sparing strategy in ECMO could be a safe management option with fewer bleeding complications.[32–34]

Although the ELSO guidelines recommend maintaining a platelet count >100000/μl, the optimal threshold for platelet transfusion remains unclear.[8] In a previous report that identified the mean platelet count as an independent risk factor, the mean platelet count in patients with intracranial bleeding was 31000/μl, whereas the mean platelet count was 48000/μl in those without intracranial bleeding.[10] In our study, even the lowest platelet count exceeded 50000/μl. The target platelet count during ECMO should be further investigated and could be leveraged to prevent bleeding complications.

Our findings show that achieving mobilization is safe and is possibly associated with a lower risk for bleeding complications. This is consistent with the previous studies about the safety and efficacy of rehabilitation in critically ill and ECMO patients.[35–37]

Achieving mobilization during ECMO requires an experienced multidisciplinary collaborative team with diversified viewpoints, a goal-directed protocol, and adequate knowledge of ECMO management. Multi-professional assessments could lead to a solid and safe strategy with synergistic effects in patients who receive ECMO.[14] An inflammatory reaction is provoked by the interaction between blood and the ECMO membrane, which is crucial in coagulation activation.[38,39] Moderate activity can modulate the inflammatory response and induce the release of anti-inflammatory cytokines.[40] This process might stabilize the coagulation balance and result in fewer bleeding complications. Although the mechanism remains unclear, patients should not be immobilized even during ECMO if there is a risk of bleeding complications and their suitability for mobilization should be assessed appropriately by an experienced team.

Furthermore, the components of rehabilitation in critical care included frequency, configuration, and target, which were not sufficiently evaluated in our study.[13] Our analysis only focused on the intensity of rehabilitation; therefore, further multidisciplinary assessment is warranted to describe safe and optimal early mobilization during ECMO.

5 | LIMITATIONS

Our study has several limitations. First, it was a single-center, retrospective study with a small-sample analysis that limits the generalizability of the results to patients in other facilities and comprised unmeasured confounding factors. For example, anticoagulation before hospitalization[9,10] and fibrinogen levels[25] were not included in the analysis. The number of patients with renal failure or cirrhosis, which are generally considered risks, was not sufficiently included in our cohort.[40] Thus, further studies that specifically focus on these patients are necessary. Moreover, we could not analyze AT III, which is frequently monitored to control coagulation homeostasis in the current practice because the monitoring of AT III has been started recently,[7] and the patients in the first half of our cohort had been minimally monitored with AT III. Second, we could not evaluate the causal relationship between bleeding risk factors due to the retrospective study design. Third, patient selection bias, especially in mobilization, should be considered. We may have selectively performed aggressive rehabilitation in patients who were less likely to have bleeding complications. A randomized controlled study investigating the effect of implementing early mobilization on the incidence of bleeding complications during V-V ECMO is necessary. Fourth, advances in treatment strategies gradually emerged during the study period. Changes in the guidelines and emerging evidence for ECMO management

could have influenced our clinical practice. As some reports have indicated that the ACT is not a reliable marker of coagulation monitoring compared to the other makers,[8] we used ACT only when the patient was receiving CRRT and ECMO. Therefore, there were insufficient data on ACT for analysis. Furthermore, due to cost and facility-related limitations, we could not measure anti-Xa and conduct viscoelastic tests, such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM), which have drawn interest in establishing a better strategy for anticoagulation monitoring. Fifth, complications were retrospectively collected from medical records; this method could underestimate the clinical impact and overlook occurrences, particularly for minor intracranial bleeding and thrombotic complications. Finally, we could not perform a subgroup analysis to detect high-risk groups due to the small sample size. To overcome these limitations, a multicenter prospective study with more data or a randomized controlled trial is warranted to evaluate the causal relationship and the effect of rehabilitation.

6 | CONCLUSION

More than half of the patients who received V-V ECMO as a bridge to recovery experienced bleeding complications. The peak APTT value was a prognostic risk factor for bleeding complications, whereas the lowest platelet count and mobilization were not independent risk factors. Thus, the peak APTT should be targeted during V-V ECMO, and the protective impact of achieving mobilization on bleeding complications should be further investigated.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Study design, performed analysis, manuscript writing, data interpretation: Akira Kawauchi. *Study design, performed analysis, manuscript writing, data interpretation, data collection*: Keibun Liu. *Data interpretation*: Mitsunobu Nakamura. *Data interpretation, data collection*: Hiroyuki Suzuki. *Data interpretation, data collection*: Kenji Fujizuka. *Manuscript writing, data interpretation*: Minoru Nakano.

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SUPPORTING INFORMATION

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