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Characteristics of bleeding complications in patients with severe COVID19 requiring veno-venous extracorporeal membrane oxygenation in Japan

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Abstract:
Background: Complications during veno-venous extracorporeal membrane oxygenation (VV-ECMO) are associated with in-hospital mortality. Asian patients on extracorporeal membrane oxygenation (ECMO) have a higher risk of bleeding and in-hospital mortality than Caucasian patients. This study aimed to characterise and identify bleeding complications and their associated factors related to in-hospital mortality in patients with severe COVID-19 requiring VV-ECMO in Japan.
Methods: In this retrospective observational analysis, the prospective nationwide multicentre registry was used to track real-time information from intensive care units throughout Japan during the COVID-19 pandemic. VV-ECMO patients' registry data between February 1, 2020, and October 31, 2022, were used.
Results: This study included a total of 441 patients; 178 (40%) had bleeding complications in the following sites: 20% at the cannulation site, 16% in the gastrointestinal tract, 16% in the ear-nose-throat, 13% at the tracheostomy site, 9% intrathoracic, 6% intracranial, and 5%, in the iliopsoas. Anticoagulation was discontinued in >50% of patients with intracranial, iliopsoas, and gastrointestinal tract bleeding. ECMO was discontinued in one-third of patients with intracranial, intramuscular, and iliopsoas haemorrhages. Multivariable logistic regression analysis revealed that only gastrointestinal tract bleeding was associated with in-hospital mortality (odds ratio: 2.49; 95% confidence interval: 1.11–5.60; P=0.03).
Conclusions: Bleeding complication incidence was 40% in the Japanese population. Gastrointestinal tract bleeding emerged as a significant predictor of adverse outcomes, necessitating further research into preventive strategies and optimised care protocols. The study findings can help inform the management of VV-ECMO patients with COVID-19.

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Extra Table

What is known on this topic?

- Asian patients on extracorporeal membrane oxygenation (ECMO) have a higher risk of bleeding and in-hospital mortality than Caucasian patients.

What does this paper add?

- The incidence of all bleeding complications was 40% in Japanese patients with severe COVID-19 requiring VV-ECMO.
- The most common bleeding complication was cannulation site bleeding, followed by gastrointestinal tract bleeding.
- Gastrointestinal tract bleeding was the only bleeding complication associated with in-hospital mortality.
- The characteristics of bleeding complications during ECMO may vary across countries.

Characteristics of bleeding complications in patients with severe COVID-19 requiring veno-venous extracorporeal membrane oxygenation in Japan

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Abstract

Background: Complications during veno-venous extracorporeal membrane oxygenation (VV-ECMO) are associated with in-hospital mortality. Asian patients on extracorporeal membrane oxygenation (ECMO) have higher risks of bleeding and in-hospital mortality than Caucasian patients. This study aimed to characterise and identify bleeding complications and their associated factors related to in-hospital mortality in patients with severe coronavirus disease 2019 (COVID-19) requiring VV-ECMO in Japan.

Methods: In this retrospective observational analysis, the prospective nationwide multicentre registry was used to track real-time information from intensive care units throughout Japan during the COVID-19 pandemic. VV-ECMO patients' registry data between 1 February 2020 and 31 October 2022 were used.

Results: This study included 441 patients; 178 (40%) had bleeding complications in the following sites: 20% at the cannulation site, 16% in the gastrointestinal tract, 16% in the ear-nose-throat, 13% at the tracheostomy site, 9% intrathoracic, 6% intracranial, and 5% in the iliopsoas. Anticoagulation was discontinued in >50% of patients with intracranial, iliopsoas, and gastrointestinal tract bleeding. ECMO was discontinued in one-third of patients with intracranial, intramuscular, and iliopsoas haemorrhages. Multivariable logistic regression analysis revealed that only gastrointestinal tract bleeding was associated with in-hospital mortality (odds ratio: 2.49; 95% confidence interval: 1.11–5.60; *P*=0.03).

Conclusions: Incidence of bleeding complications was 40% in the Japanese population. Gastrointestinal tract bleeding emerged as a significant predictor of adverse outcomes, necessitating further research into preventive strategies and optimised care protocols. These findings can guide the management of VV-ECMO patients with COVID-19.

Keywords

Bleeding; Coronavirus Disease 2019; Gastrointestinal Tract; Respiratory Distress Syndrome; Mortality

Introduction

The number of patients requiring veno-venous extracorporeal membrane oxygenation (VV-ECMO) for the management of refractory acute respiratory distress syndrome has increased, especially during the coronavirus disease 2019 (COVID-19) pandemic.[1-5]

Bleeding complications associated with VV-ECMO are common and potentially lethal.[6] In particular, intracranial haemorrhage is reported in many countries as a bleeding complication associated with in-hospital mortality.[7] Although the incidence of bleeding complications in patients requiring VV-ECMO is >30% in European countries,[8] the incidence in patients with COVID-19 requiring VV-ECMO is reportedly higher than that in patients with non-COVID-19 acute respiratory distress syndrome. This is attributed to higher doses of anticoagulation regimens, severe acute respiratory distress syndrome coronavirus 2-associated vasculitis, microbleeds associated with critical illness, and other COVID-19-specific factors.[9,10]

Bleeding complications during VV-ECMO have been reported to be associated with

in-hospital mortality and the need for renal replacement therapy for acute kidney injury, infection, and poor neurological outcomes.[11] Additionally, Asian patients—including those who are Japanese—on extracorporeal membrane oxygenation (ECMO) have a higher risk of bleeding and in-hospital mortality than Caucasian patients.[12,13] However, no study has evaluated the characteristics of bleeding complications during COVID-19-related VV-ECMO in the Japanese population using nationwide cohort data.

Therefore, this study aimed to characterise the bleeding complications in Japanese patients with severe COVID-19 requiring VV-ECMO and identify their associated factors.

Methods

Study design and patients

In this retrospective analysis, a prospective nationwide multicentre registry, the Cross Intensive Care Unit Searchable Information System (CRISIS) database, was used to track real-time information from intensive care units throughout Japan during the COVID-19 pandemic. The CRISIS collects data from 738 of 1223 Japanese facilities, including intensive care units, cardiac care units, and tertiary emergency medical and critical care centres in Japan. Although there is no officially approved ECMO centre in Japan, participating facilities were registered at certified institutions by the Japanese Society of Intensive Care Medicine, the Japanese Association for Acute Medicine, and the Japanese Society of Respiratory Care Medicine. These facilities are staffed by board-certified doctors of emergency and critical care medicine, anaesthesiology, and intensive care medicine.

Data from patients registered in CRISIS who met the following inclusion criteria were analysed: age ≥ 18 years, laboratory-confirmed diagnosis of COVID-19 (using real-time polymerase chain reaction/next-generation sequencing), and undergone VV-ECMO for refractory acute respiratory distress syndrome. Patients with missing information on study

variables (characteristics of bleeding complications and in-hospital mortality) were excluded. The registry data between 1 February 2020 and 31 October 2022 were used in the analysis.

CRISIS was approved by the Institutional Review Board of Hiroshima University (approval number: E-1965) and each participating institute. In addition, this study was approved by the Institutional Review Board of Yokohama City University (approval number: B200700034), and the need for informed consent was waived due to its retrospective nature. Instead, an opt-out statement was posted on the website. The study was conducted according to the principles of the Declaration of Helsinki.

Data collection and definitions

The following patient data were collected from the CRISIS database: age, sex, body mass index, pre-ECMO ratio of arterial oxygen partial pressure to fractional inspired oxygen, pre-ECMO positive end-expiratory pressure, number of ventilatory days before ECMO, outcome of ECMO (weaning success or deceased while on ECMO), duration of ECMO, duration of ventilator use, and in-hospital mortality.

Additionally, the following data were retrospectively collected using a pre-designed standardised case record form for this study linked with the CRISIS database (Figure S1): ethnicity, preexisting coagulation disorder, anticoagulant drugs administered during ECMO (unfractionated heparin, argatroban, or nafamostat mesylate [NM]), anticoagulation management index, bleeding complications: anatomical sites (vascular access, gastrointestinal, ear-nose-throat, tracheostomy site, intrathoracic, intracranial, iliopsoas, intramuscular, intraabdominal, and others), onset time, diagnostic procedures, and haemostatic intervention types.

Bleeding complications were defined as instances in which bleeding required a clinical intervention such as transfusion. Physicians at each facility determined bleeding complications based on the information from electronic medical records.

Statistical analysis

First, we described the incidence (n, %), onset timing (median, interquartile range), diagnostic procedures (n, %), and intervention types (n, %) for each bleeding complication. The onset timing was compared among the bleeding complications using the Kruskal–Wallis test, and Steel–Dwass analysis was added to examine the onset timing.

The factors associated with each bleeding complication were also examined. The chi-square test or Fisher's exact test was used to compare categorical variables, and the Mann–Whitney U test was used to compare continuous variables between the groups.

Finally, to identify factors associated with in-hospital mortality, a multivariable logistic regression analysis was performed using independent variables with *P*-values of <0.05 in univariate comparisons and variables reported in previous studies. The variation inflation factor was checked to avoid multi-collinearity (variance inflation factor >10 as a violation). Moreover, a sensitivity analysis was performed, excluding variables with >5% missing study variables. The association of haemostatic interventions (Surgical, Endoscopic, or Transcatheter Arterial Embolization) with in-hospital mortality was also examined in the bleeding complications group.

All statistical tests were two-tailed, and statistical significance was set at a *P*-value of <0.05. All statistical analyses were performed using JMP® 17 (SAS Institute, Inc., Cary, NC, USA).

Results

Study participants

In total, 643 patients were enrolled in this study, among whom 202 were excluded owing to missing information on study variables, resulting in a final sample size of 441 patients from 57 facilities (Figure 1, Figure S2).

Characteristics of each bleeding complication

In total, 178 (40%) patients had bleeding complications (Table 1). Their incidences were as follows: cannulation site bleeding, 22%; gastrointestinal tract bleeding, 16%; ear-nose-throat bleeding, 16%; tracheostomy site bleeding, 13%; intrathoracic haemorrhage, 9%; intracranial haemorrhage, 6%; and iliopsoas haemorrhage, 5%. Anticoagulation was discontinued in more than half of the patients with intramuscular, iliopsoas, gastrointestinal tract, intrathoracic, and intracranial bleeding. Twelve of the 49 patients with gastrointestinal tract bleeding required endoscopic haemostasis, and 8 of the 16 patients with iliopsoas haemorrhage required transcatheter arterial embolisation. ECMO was discontinued in one-third of the patients with intracranial, intramuscular, and iliopsoas haemorrhages for haemostasis. Cannulation site, ear-nose-throat, and tracheostomy site bleeding were treated surgically in most patients.

Onset timing of each bleeding complication

A significant difference was observed in onset timing among the bleeding complications ($P<0.001$) (Figure 2). Cannulation site bleeding was more common immediately after ECMO introduction than other complications. Gastrointestinal tract bleeding and intracranial and intramuscular haemorrhage occurred later than catheter site complications. These sites of haemorrhage were observed to extend beyond 3 weeks from the initiation of ECMO (Table S1).

Factors associated with bleeding complications

Table 2 shows the factors associated with each bleeding complication. No differences were observed in patient characteristics. Unfractionated heparin was the most commonly used anticoagulant, and an activated partial thromboplastin time (APTT) of 40–60 s was commonly achieved. Although awake ECMO was more common for iliopsoas and tracheostomy site bleeding (P=0.02), no differences in rehabilitation or prone position rates were found between the different bleeding complications.

Factors associated with in-hospital mortality

The in-hospital mortality rate was 32.2% for all patients, 60.0% for those with bleeding complications, and 40.1% for those with non-bleeding complications (P<0.001). Table 3 shows the characteristics of the survivors and non-survivors at the time of hospital discharge. The following variables were used for multivariable logistic regression analysis: age, body mass index, duration of ECMO, duration of ventilator use, NM use, and incidence of gastrointestinal tract, ear-nose-throat or intrathoracic bleeding. Age (odds ratio: 1.04; 95% confidence interval: 1.01–1.07; P=0.004), duration of ECMO (1.03; 1.01–1.05; P<0.001), and incidence of gastrointestinal tract bleeding (2.49; 1.11–5.60; P=0.03) were significantly associated with in-hospital mortality.

Sensitivity analysis of the factors associated with in-hospital mortality, excluding variables with >5% missing study variables, showed similar results as the main analysis (Table S2).

The performance of haemostatic interventions for bleeding complications during ECMO was not associated with in-hospital mortality (50.3% vs. 49.7%, P=0.09).

Discussion

In this study, the incidence of all bleeding complications was 40% in Japanese patients with severe COVID-19 requiring VV-ECMO, and the most common bleeding complication was cannulation site bleeding, followed by gastrointestinal tract bleeding, ear-nose-throat bleeding, and tracheostomy site bleeding. Gastrointestinal tract bleeding was the only bleeding complication associated with in-hospital mortality. Additionally, the performance of haemostatic interventions for bleeding complications was not associated with in-hospital mortality.

In a review of the current literature on patients with COVID-19 on ECMO, the incidence of bleeding complications ranged from 27% to 42%.[9,10,14] In France, the incidence of overall bleeding complications was 49%, cannulation site bleeding was 18%, ear-nose-throat bleeding was 12%, intrathoracic haemorrhage was 6%, intracranial haemorrhage was 8%, and gastrointestinal tract bleeding was 7.6%.[15] In the United States, the overall incidence was 28%, and the incidence of intracranial haemorrhage was 4.6%.[16] In the United Kingdom, the overall incidence was 31%, intracranial haemorrhage was 10.5%, intrathoracic haemorrhage was 7.8%, and gastrointestinal tract bleeding was 3.8%.[17] These results were different in each country; however, intracranial haemorrhage was commonly associated with in-hospital mortality.[10,14-17] On the other hand, ECMO registry data from the same Asian country, China, showed an 18% incidence of bleeding complications, cannulation site bleeding of 7.1%, intracranial haemorrhage of 2.8%, intrathoracic bleeding of 1.5%, and gastrointestinal tract bleeding of 3.5%. Intracranial haemorrhage was not documented to be associated with in-hospital mortality, as in Japan.[18] The characteristics of bleeding complications during ECMO may vary across countries.

This study showed that gastrointestinal tract bleeding was a common bleeding complication in Japan. Gastrointestinal tract bleeding was associated with in-hospital

mortality, tended to develop later than other bleeding complications, and was more common in patients who received prolonged ECMO management (>21 days) (Figure 2, Table S1). Previous studies have suggested that prolonged ECMO management can lead to multiple organ failure, which is associated with in-hospital mortality.[19,20] Multi-organ failure is followed by gastrointestinal mucosal damage, leading to gastrointestinal tract bleeding.[21] Therefore, gastrointestinal tract bleeding was assumed to be the most common complication associated with in-hospital mortality in Japan.

The reasons why gastrointestinal tract bleeding is more common in Japan than in other countries remain unclear. There was no clear difference in the duration of ECMO between Japan and other countries,[10,14-17] suggesting that the duration of ECMO could not be the reason for the high incidence of gastrointestinal tract bleeding. Unfractionated heparin was commonly used, and there was no difference in APTT management (40–60 s) between Japan and other countries.[9] However, NM, which is infrequently used in other countries,[9] was prescribed in Japan for thromboprophylaxis in ECMO and continuous renal replacement therapy[22] or as a treatment for COVID-19 to prevent viral entry into cells.[23]

NM is a broad-spectrum, synthetic serine protease inhibitor used in Japan and Korea. The dosing for DIC, a continuous infusion of 0.06–0.20 mg/kg/h, is used.[24] The indicated dose to prevent blood coagulation is a continuous infusion at 20–50 mg/h.[22] Compared with unfractionated heparin, NM reduces the risk of thrombosis, with no significant difference in bleeding risk.[24] However, in patients with COVID-19, some studies have reported an association between bleeding complications and NM use for thromboprophylaxis in ECMO or as a treatment for COVID-19,[25-27] necessitating further studies.

Conversely, intracranial haemorrhage was not associated with in-hospital mortality in Japan; this may be due to the few cases of early intracranial haemorrhage. Intracranial haemorrhage usually occurs within 4 days of ECMO initiation,[28] leads to treatment

discontinuation, and is associated with early mortality.[29-31] However, in the present study, two-thirds of the cases of intracranial haemorrhage occurred >10 days after ECMO initiation. Differences in management practices and ethics may contribute to differences in the risk of in-hospital mortality from intracranial haemorrhage in Europe, the USA, and Asia;[14-18] this aspect warrants further research. On the other hand, as previously reported, the present study showed a higher incidence of iliopsoas haemorrhage than that in other countries.[32,33] Awake ECMO management was also associated with iliopsoas haemorrhage.[33]

This study has some limitations. First, there may have been a selection bias owing to the voluntary registration system. Second, detailed clinical information on individual patients was unavailable. Therefore, we could not assess the severity of each bleeding complication. Information on various potential confounders, such as the use of oral anticoagulants, antiplatelet medications, and anti-ulcer drugs before ECMO induction, was lacking. Lastly, the decision to initiate or terminate ECMO or discharge from the intensive care unit was left to the judgement of the attending physician, and no standardised protocols were used.

In conclusion, the incidence of bleeding complications was 40% in the Japanese population, according to the nationwide cohort data used in this study. Gastrointestinal tract bleeding was the only bleeding complication associated with in-hospital mortality, and the performance of haemostatic interventions for bleeding complications was not associated with in-hospital mortality. The characteristics of bleeding complications during ECMO may vary across countries. Therefore, individualised management strategies should be developed to prevent bleeding complications.

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Ethical approval statement

This study was approved by the Institutional Review Board of Yokohama City University (approval number: B200700034), and the need for informed consent was waived owing to its retrospective nature. Instead, an opt-out statement was posted on the website. The study was conducted according to the principles of the Declaration of Helsinki.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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Figure 1: Flowchart of patients on VV-ECMO included in this study.
VV-ECMO, veno-venous extracorporeal membrane oxygenation.

Figure 2: Onset timing of each bleeding complication
This figure compares the timing of the onset of each bleeding complication.
GI, gastrointestinal

Figure S1: Examining the characteristics of bleeding complications during COVID-19-related VV-ECMO.
A standardised case record form specifically designed for this study, linked with the CRISIS database.

COVID-19, coronavirus disease 2019; VV-ECMO, veno-venous extracorporeal membrane oxygenation.

Figure S2: Number of ECMOs performed in each facility.

Table 1. Characteristics of each bleeding complication

Variable [frequency (%)/median (IQR)]	Cannulation site		GI tract		Ear-nose-throat		Tracheostomy site		Intrathoracic		Intracranial		Iliopsoas		Intramuscular		Intra-abdominal		Other	
Incidence	69	[22%]	49	[16%]	49	[16%]	40	[13%]	29	[9%]	18	[6%]	16	[5%]	13	[4%]	3	[1%]	22	[7%]
Diagnostic procedures																				
Physical examination	65	[94%]	47	[96%]	49	[100%]	39	[98%]	19	[65%]	8	[44%]	5	[31%]	9	[69%]	2	[67%]	17	[77%]
Laboratory	14	[20%]	20	[41%]	3	[6%]	3	[7%]	5	[17%]	0	[0%]	8	[50%]	6	[46%]	1	[33%]	6	[27%]
CT	0	[0%]	0	[0%]	2	[4%]	1	[3%]	13	[45%]	17	[94%]	14	[88%]	9	[69%]	2	[66%]	1	[5%]
Others	0	[0%]	0	[0%]	0	[0%]	0	[0%]	4	[14%]	0	[0%]	1	[6%]	1	[7%]	0	[0%]	0	[0%]
Intervention types																				
Surgical intervention‡	53	[77%]	0	[0%]	35	[71%]	38	[95%]	1	[4%]	0	0%]	0	0%]	5	[38%]	1	[33%]	6	[27%]
Discontinuation	9	[13%]	30	[61%]	8	[16%]	14	[35%]	16	[55%]	9	[50%]	10	[63%]	10	[77%]	1	[33%]	5	[22%]

of. anticoagulant																			
Endoscopic haemostasis	0	[0%]	12	[24%]	0	[0%]	0	[0%]	1	[3%]	0	[0%]	0	[0%]	0	[0%]	0	[0%]	0	[0%]
TAE	0	[0%]	6	[12%]	2	[4%]	1	[3%]	2	[7%]	0	[0%]	8	[50%]	4	[31%]	2	[66%]	1	[5%]
Discontinuation of ECMO	1	[1%]	1	[2%]	0	0%]	1	[3%]	2	[7%]	3	[17%]	3	[19%]	4	[30%]	0	0%]	2	[9%]
Others	2	[3%]	6	[12%]	6	[13%]	1	[3%]	4	[14%]	1	[6%]	0	[0%]	0	[0%]	0	[0%]	1	[5%]

CT: computed tomography. ECMO: extracorporeal membrane oxygenation. ENT: ear, nose, and throat

GI: gastrointestinal. TAE: transcatheter arterial embolisation

* Bleeding from a peripheral cannulation site such as the neck, groin, or axilla.

† Bleeding not only from tracheostomy site but also from oral and airway after tracheostomy.

‡ Including compression haemostasis and skintight sutures.

§ Incidence was calculated as each bleeding complication/all bleeding complications

Table 2. Factors associated with each bleeding complication

Variable [frequency (%)/ median (IQR)]	No bleeding complication (n=263)		Cannulation site (n=69)		GI tract (n=49)		Ear-nose-throat (n=49)		Tracheostomy site (n=40)		Intrathoracic (n=29)		Intracranial (n=18)		Iliopsoas (n=16)		Intramuscular (n=13)		Intra abdominal (n=3)		Other (n=23)		*P* value
Patient's character																							
Age (years)	56	[48-64]	56	[48-63]	64	[55-70]	60	[51-66]	57	[49-64]	59	[50-67]	61	[55-68]	64	[52-70]	56	[49-64]	66	[58-73]	57	[53-63]	0.11
Male	213	[81]	60	[87]	41	[85]	41	[82]	33	[79]	20	[83]	13	[72]	13	[81]	11	[92]	1	[33]	19	[83]	0.58
Ethnic, Japanese	194	[95]	63	[93]	42	[91]	46	[92]	40	[100]	29	[100]	18	[100]	16	[100]	13	[100]	3	[100]	18	[78]	0.55
Body Mass index(kg/m^2)	28	[25-33]	28	[24-31]	27	[25-29]	27	[25-30]	28	[25-31]	27	[23-29]	26	[24-31]	28	[23-32]	27	[24-33]	28	[26-29]	28	[25-29]	0.84
HFNC before ventilator	98	[41]	30	[43]	16	[32]	18	[37]	13	[33]	9	[39]	4	[22]	5	[31]	4	[31]	3	[100]	8	[35]	0.74
Time to ECMO from ventilator use (days)	1	[0-4]	2	[1-6]	3	[0-6]	1	[1-6]	4	[1-7]	3	[0-9]	4	[2-8]	6	[2-10]	7	[2-10]	1	[0-1]	6	[1-11]	0.66
ECMO Management																							
APTT management 40-60 sec	114	[57]	53	[78]	29	[62]	36	[72]	36	[90]	14	[51]	14	[77]	10	[63]	8	[62]	1	[33]	13	[57]	0.22
APTT management 60-80 sec	48	[24]	17	[25]	13	[27]	9	[18]	3	[8]	7	[24]	2	[11]	3	[19]	2	[16]	0	[0]	5	[22]	0.34
ACT management 160-200 sec	54	[27]	10	[14]	9	[18]	9	[18]	2	[4]	5	[13]	3	[10]	3	[17]	2	[15]	1	[33]	3	[13]	0.65
ACT management 180-220 sec	23	[11]	8	[12]	6	[12]	6	[12]	3	[8]	5	[17]	2	[11]	2	[12]	1	[8]	0	[0]	2	[9]	0.95
TEG management	1	[0.5]	3	[4]	3	[6]	1	[2]	2	[5]	4	[14]	0	[0]	0	[0]	0	[0]	0	[0]	1	[5]	0.26

ACT: activated

clotting time. APTT: activated partial thromboplastin time. ECMO: extracorporeal membrane oxygenation. HFNC: high-flow nasal cannula

GI: gastrointestinal. TEG: thromboelastography.

*Rehabilitation means sitting on the edge of the bed during ECMO.

**Awake ECMO is a state of consciousness and spontaneous breathing.

Table 3. Factors associated with in-hospital mortality

Variable [frequency (%)/median (IQR)]	Non-survival (n=142)		Survival (n=299)		Univariate analysis	Multivariable analysis		
					P value	Odds	95% CI	*P* value
Patients' characteristics								
Age (years)	62	[55-69]	55	[48-63]	<0.001	1.04	[1.01-1.07]	0.004
Male	117	[82.4]	247	[82.]	0.96			
Ethnicity, Japanese	122	[95.3]	239	[95.2]	0.97			
Body mass index (kg/m^2)	27	[24-30]	29	[25-33]	0.008	1.00	[0.96-1.05]	0.89
History of coagulation disorder	1	[0.7]	4	[1.4]	0.50			
HFNC before ventilator	58	[47.2]	100	[37.0]	0.06			
Time to ECMO from ventilator use (days)	3	[0-7]	1	[0-4]	0.17			
ECMO management characteristics								
Prone position during ECMO	86	[60.1]	193	[64.6]	0.66			
Rehabilitation	26	[20.1]	65	[25.6]	0.23			
Awake ECMO								
Management index of anticoagulated therapy								
APTT management 40-60 s	77	[61.1]	163	[64.4]	0.53			
APTT management 60-80 s	33	[26.2]	54	[21.3]	0.29			
ACT management 160-200 s	25	[19.8]	56	[22.3]	0.61			
ACT management 180-220 s	19	[15.1]	26	[10.3]	0.17			
TEG management	3	[2.4]	4	[1.6]	0.69			
UFH use	100	[100]	100	[100]				

Argatroban use	6	[4.3]	8	[2.8]	0.41			
Nafamostat mesylate use	19	[13.6]	21	[7.3]	0.04	1.19	[0.49-2.87]	0.70
Outcomes								
Duration of ECMO (days)	22	[7-39]	9	[5-15]	<0.001	1.03	[1.01-1.05]	<0.001
Duration of ventilator (days)	37	[23-58]	20	[12-36]	<0.001	0.99	[0.98-1.00]	0.16
Type of bleeding complications								
Cannulation site	25	[17.6]	36	[12.4]	0.12			
GI tract	30	[21.3]	17	[5.7]	<0.001	2.49	[1.11-5.60]	0.03
Ear-nose-throat	23	[16.2]	24	[8.0]	0.01	1.56	[0.71-3.38]	0.26
Tracheostomy site	17	[12.0]	22	[7.4]	0.12			
Intrathoracic	17	[12.0]	11	[4.0]	0.001	2.27	[0.87-5.93]	0.09
Intracranial	9	[6.3]	9	[3.0]	0.11			
Iliopsoas	7	[4.9]	9	[3.0]	0.41			
Intramuscular	5	[3.5]	8	[2.7]	0.76			
Intraabdominal	1	[0.7]	2	[0.7]	0.96			
Others	10	[7.0]	12	[4.0]	0.18			

ACT: activated clotting time. APTT: activated partial thromboplastin time. BMI: body mass index. CI: confidence interval. ECMO: extracorporeal membrane oxygenation. GI: gastrointestinal. HFNC: high-flow nasal cannula. IQR: interquartile range. NIV: non-invasive positive pressure ventilation. P/F: PaO_2/FIO_2 ratio. UFH: Unfractionated heparin. s: seconds

Table S1 Time of onset and number of patients with each bleeding complication

	Time of onset				
Bleeding complication	0–5 days	6–10 days	11–15 days	16–20 days	Over 21 days
Cannulation site	43	13	3	4	1
	(67%)	(20%)	(5%)	(6%)	(2%)
GI tract	10	8	4	6	17
	(22%)	(17%)	(9%)	(13%)	(38%)
Ear-nose-throat	17	10	10	6	3
	(50%)	(29%)	(29%)	(18%)	(3%)
Tracheostomy site	7	9	8	3	7
	(21%)	(26%)	(24%)	(4%)	(21%)
Intrathoracic	6	9	2	3	5
	(24%)	(36%)	(12%)	(12%)	(20%)
Intracranial	2	3	4	2	6
	(13%)	(20%)	(27%)	(13%)	(40%)
Iliopsoas	0	4	4	3	0
	(0%)	(37%)	(37%)	(27%)	(0%)
Intramuscular	3	2	3	1	4
	(23%)	(16%)	(23%)	(8%)	(31%)
Intraabdominal	0	1	0	1	0
	(0%)	(50%)	(0%)	(50%)	(0%)

GI: gastrointestinal. TAE: transcatheter arterial embolisation

Table S2 Sensitivity analysis for identifying factors associated with in-hospital mortality

Variable [frequency (%)/median (IQR)]	Univariate analysis	Multivariable analysis*		
	P value	Odds ratio	95% CI	*P* value
Age	<.001	1.04	(1.01–1.07)	0.007
Duration of ECMO	<.001	1.03	(1.01–1.05)	<0.001
Incidence of GI bleeding	<.001	2.38	(1.06–5.34)	0.04

BMI: body mass index. CI: confidence interval. ECMO: extracorporeal membrane oxygenation. GI: gastrointestinal. IQR: interquartile range

*: The following variables were used in the multivariate analysis: age, BMI, duration of ECMO, duration of ventilator use, nafamostat mesylate use, and incidence of GI, ear-nose-throat, or intrathoracic bleeding.

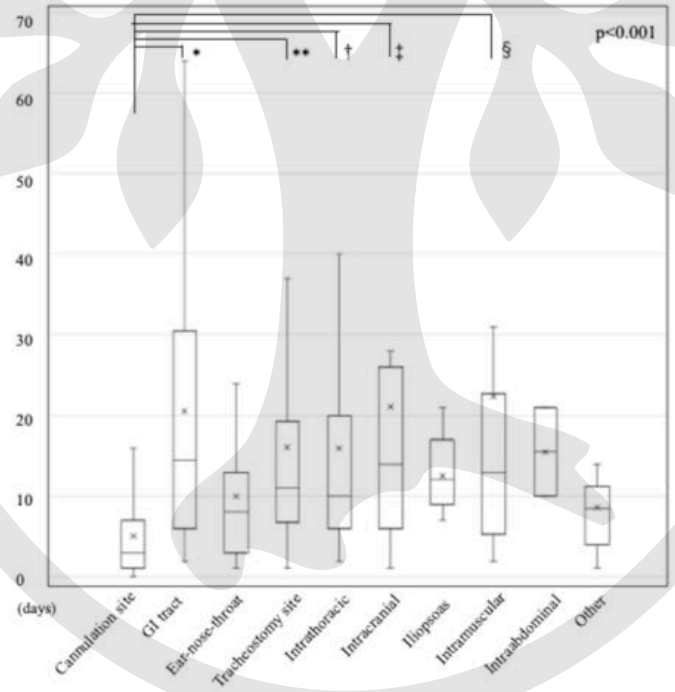
643 ECMO patients enrolled in the CRISIS registry at the time of database lock (October 31, 2022)

Excluded
202 patients with missing study variables (clinical characteristics of bleeding complications or factors associated with in-hospital mortality)

Patients included in the analysis ($n = 441$)

Patients with bleeding complications ($n = 178$)

Patients without bleeding complications ($n = 263$)



Examining the characteristics of bleeding complications during COVID-19-related VV-ECMO

Name of facility: Back to list

Case No: ← Previous case Next case →

Ethnicity
☐ Japanese ☐ Black ☐ Caucasian
☐ Asian ☐ Hispanic ☐ Others

History of coagulation disorder
○No ○Yes

☐Leukaemia ☐ Multiple myeloma
☐Thrombocytopenia ☐ Myelodysplastic syndrome
☐Haemophilia type A/B ☐ Lymphoma
☐von Willebrand disease ☐Others

Anticoagulation management targets
○No ○Yes

☐ APTT 40-60sec ☐ ACT 160-200sec
☐ APTT 60-80sec ☐ ACT 180-220sec
☐ APTT over80sec ☐ ACT over220

Anticoagulation drugs
○No ○Yes

Select drugs
Select drugs

Presence of bleeding complications
○No ○Yes

Select bleeding complications

Onset timing Days

Diagnostic procedures
☐Physical examination
☐CT
☐Laboratory
☐ Others

Intervention types ○No ○Yes
☐Discontinuation of anticoagulant ☐Surgical intervention
☐Endoscopic haemostasis
☐Discontinued ECMO ☐TAE ☐Others

Age Height
Sex Weight
BMI

Start of ECMO DD/MM/YY

P/F ratio at introduction of ECMO

PEEP at introduction of ECMO

Weaning off ECMO DD/MM/YY

Outcome

Prone position
○No ○Yes

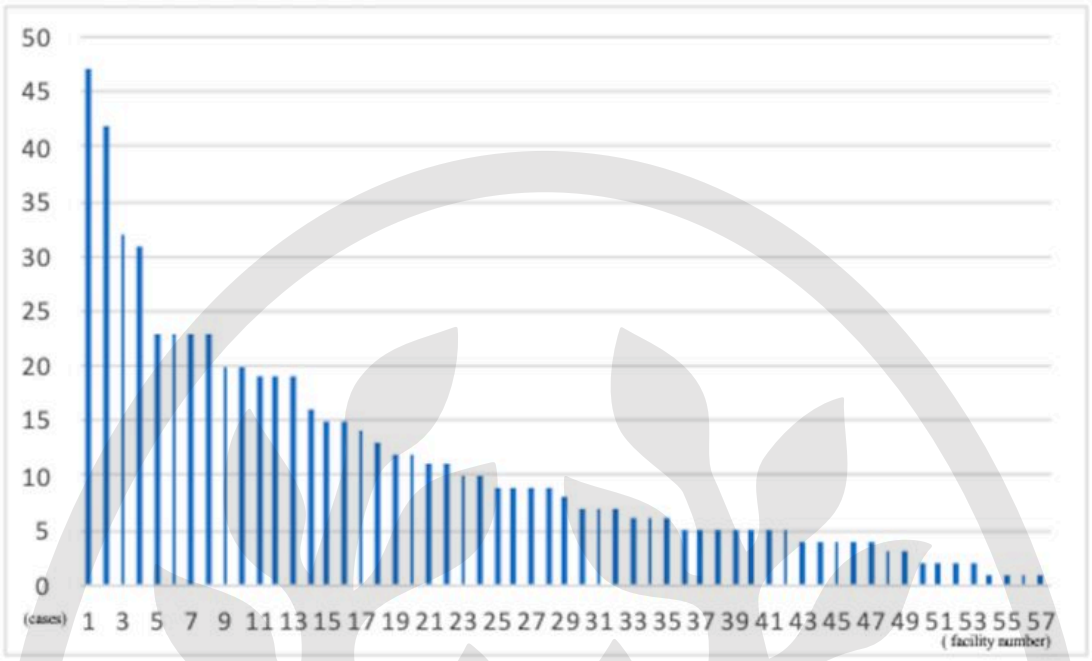
Re-intubation
○No ○Yes

Oxygenation therapy before ventilator use

Start of ventilator support DD/MM/YY

End of ventilator support DD/MM/YY

History of present illnesses



Characteristics of bleeding complications in patients with severe coronavirus disease 2019 requiring veno-venous extracorporeal membrane oxygenation in Japan: A nationwide multicentre observational study

Figure1:Characteristics of each bleeding complication

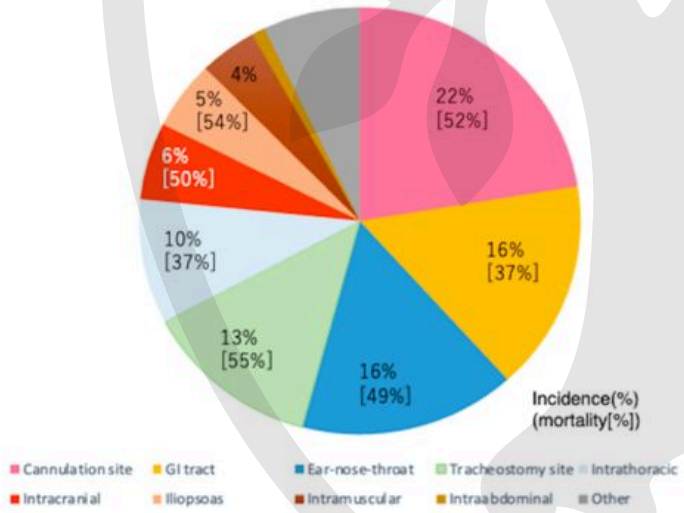
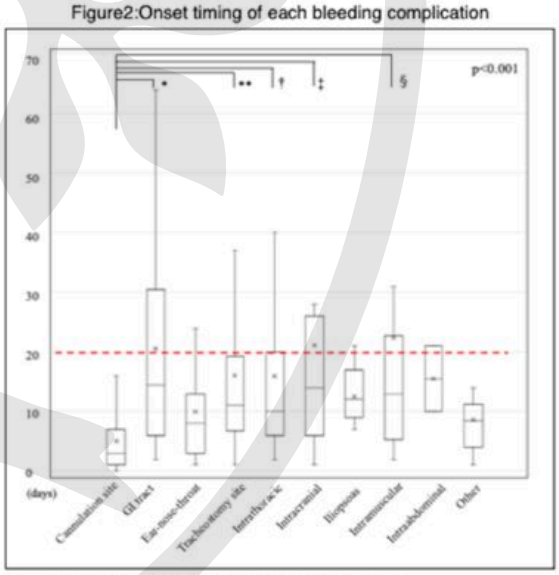


Figure2:Onset timing of each bleeding complication



Visual summary

Asian patients, including Japanese patients, on ECMO have been reported a higher risk of bleeding and in-hospital mortality than Caucasian patients. However, to the best of our knowledge, no study has evaluated the characteristics of bleeding complications during COVID-19-related VV-ECMO in the Japanese population. The study revealed that the incidence of bleeding complications was 40% in the Japanese population. Gastrointestinal tract bleeding was the only bleeding complication associated with in-hospital mortality. In this study, GI bleeding was more common around 21 days after induction and was complicated by other mucosal bleeding, e.g. nasopharynx, which may have associated with multiple organ failure bleeding.