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ORIGINAL RESEARCH

Risk Factors for Bleeding in Coronavirus Disease 2019 Patients on Extracorporeal Membrane Oxygenation and Effects of Transcatheter Arterial Embolization for Hemostasis

Kazuki Goto[1)], Yukihisa Takayama[1)], Gaku Honda[1)], Kazuaki Fujita[1)], Akinobu Osame[1)], Hiroshi Urakawa[1)], Kota Hoshino[2)3)], Yoshihiko Nakamura[2)3)], Hiroyasu Ishikura[2)3)] and Kengo Yoshimitsu[1)]

1) Department of Radiology, Faculty of Medicine, Fukuoka University, Japan
2) Department of Emergency and Critical Care Medicine, Faculty of Medicine, Fukuoka University, Japan
3) ECMO Center, Fukuoka University Hospital, Japan

Abstract:
Purpose: To evaluate risk factors for bleeding events in coronavirus disease 2019 (COVID-19) patients on extracorporeal membrane oxygenation (ECMO) and to share the initial results of transcatheter arterial embolization (TAE) for hemostasis.
Material and Methods: Forty-three COVID-19 patients who received ECMO from May 2020 to September 2021 were enrolled in this study. Patients with sudden onset anemia immediately underwent computed tomography to assess bleeding. We compared laboratory data, duration of ECMO, hospitalization period, and fatality of patients' groups with and without significant hemorrhagic events using the chi-square test and Mann-Whitney *U* test. We also assessed the results of TAE in patients who received hemostasis.
Results: A total of 25 bleeding events occurred in 24 of the 43 patients. Age was a risk factor for bleeding events and fatality. The average duration of ECMO and hospitalization period were significantly longer in those with bleeding events (42.9 and 54.3 days) than in those without bleeding events (16.2 and 25.0 days) ($p < 0.05$). In addition, those with bleeding had higher fatality (45.8%) than those without (15.8%) ($p < 0.05$). Active extravasation was confirmed for 5 events in 4 of 24 patients. TAE was attempted and performed successfully in all but one of these four cases, in whom bleeding ceased spontaneously.
Conclusions: Elderly COVID-19 patients on ECMO had a greater risk of bleeding complications and fatal outcomes. TAE was effective in providing prompt hemostasis for patients who have the treatment indication.

Keywords:
coronavirus disease 2019 (COVID-19), extracorporeal membrane oxygenation (ECMO), bleeding, extravasation, transcatheter arterial embolization (TAE)

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Introduction

After its emergence in late 2019, coronavirus disease 2019 (COVID-19) rapidly developed into a global pandemic [1] causing mild to moderate respiratory symptoms in most patients and respiratory failure requiring intubation and mechanical ventilation in some [2, 3]. Not surprisingly, higher mortality has been reported for those COVID-19 patients requiring mechanical ventilation [3, 4]. To supplement or supplant mechanical ventilation, veno-venous extracorporeal membrane oxygenation (V-V ECMO) and veno-arterial ECMO (V-A ECMO) have been life-supporting technologies used in intensive care units (ICUs), especially in COVID-19 patients with severe respiratory or circulatory failure [5, 6].

Although V-V ECMO and V-A ECMO can be used as rescue therapy for patients with severe respiratory failure, complications such as bleeding, thromboembolism, and intubation problems have been reported in COVID-19 patients on ECMO [7]. Prolonged heparinization or heparin overdose, coagulopathy, thrombocytopenia, platelet dysfunction,

Corresponding author: Yukihisa Takayama, ytakayama@fukuoka-u.ac.jp
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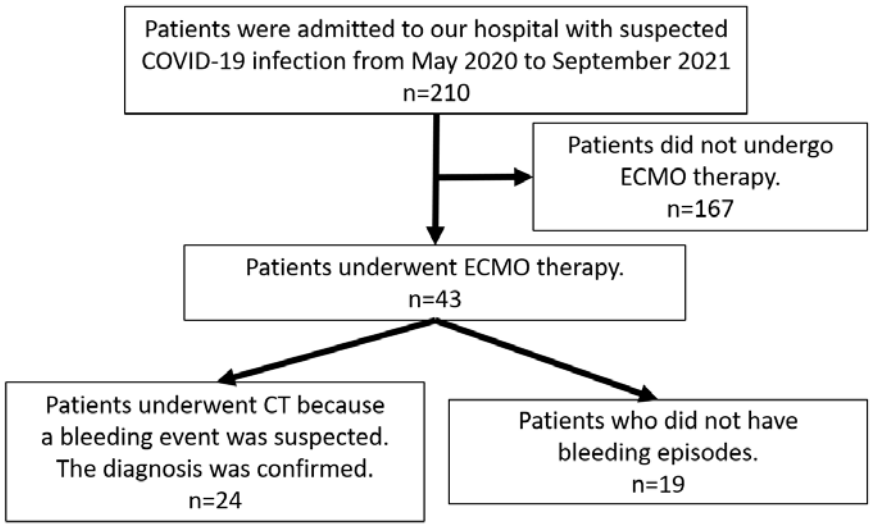

Figure 1. A summary flowchart of patient selection.

acquired von Willebrand syndrome, and hyperfibrinolysis have all been suggested as the causes of bleeding complications during ECMO [8]. The critical balance between adequate anticoagulation and prevention of bleeding or thrombosis can be difficult for physicians to obtain in COVID-19 patients on ECMO [8]. Internal bleeding can lead to life-threatening complications such as organ failure and death, and immediate treatment is required upon detection [9]. Even if a bleeding event is successfully controlled, the patient's stay in the ICU is likely prolonged and their risk of other complications increases.

Transcatheter arterial embolization (TAE) is one of the effective treatments for patients with massive hemorrhage. Several reports have described successful TAE for active arterial bleeding in COVID-19 patients without ECMO support [10-12]. However, there are few reports regarding TAE for bleeding complications in COVID-19 patients on ECMO. We performed this study in part to determine which patient characteristics, if any, were associated with bleeding and fatal outcomes of bleeding in COVID-19 patients on ECMO. The two purposes of the present study are to evaluate the risk factors for bleeding in COVID-19 patients under ECMO support and to share our experience using TAE for hemostasis.

Material and Methods

Patients

Our institutional review board approved this study and waived the requirement to obtain written informed consent from each patient because of its retrospective nature. From May 2020 to September 2021, a total of 210 patients were admitted to our hospital with suspected COVID-19 infection. The inclusion criteria were (1) the confirmation of the COVID-19 diagnosis by a real-time reverse transcription-polymerase chain reaction test or an antigen test and (2) the administration of ECMO support due to severe respiratory failure. Finally, a total of 43 patients [6 females and 37 males; median (range) age, 59.0 (30-74) years] were found and enrolled in this study. They were divided into bleeding and nonbleeding groups. The "bleeding group" comprised 24 patients exhibiting sudden onset of anemia based on blood tests and/or a sudden decrease in blood pressure. The criteria of anemia of our institute were as follows: low red blood cell count of $<3.86 \times 10^4/\mu L$, low hemoglobin of <11.6 g/dL, low hematocrit of <35.1%, and low mean corpuscular volume of <83.6 fL. Their massive hemorrhages were confirmed by an unenhanced computed tomography (CT) or contrast-enhanced CT (CECT). In a subanalysis, the bleeding group was divided into fatal and nonfatal cases. The "nonbleeding group" comprised the remaining 19 patients without apparent bleeding events. Patients with hemorrhages at cannula insertion sites, surgical incisions, and dermal or mucosal regions were included in the nonbleeding group because those bleeding sites could be treated by pausing anticoagulant administration and astriction without a blood transfusion [13]. ICU physicians decided to perform CT examination when they suspected a progression of anemia based on blood tests, sudden or continuous decrease in blood pressure, or lack of response to blood transfusions. A flowchart of patient selection is shown in **Fig. 1**.

Image acquisition of CT

CT examinations were performed using an 80-row 160-slice helical CT (Aquilion Lightning, Canon Medical Systems, Tokyo, Japan). The scanning parameters were as follows: 0.5 mm × 80-row, 120 kVp, three-dimensional auto-exposure control, 0.5 s/rotation, 0.813 beam pitch, 512 × 512 matrix, 320-500 mm field-of-view, and slice thickness of 5 mm. In addition, 0.5 mm (for head and neck) or 1.0 mm (for chest and body) slice thickness volume data were also used for developing multiplanar reconstruction images. For obtaining CECT, 600 mgI/kg iodine contrast medium (Iopamiron 370, Bayer Health Care, Osaka, Japan, or Optiray 350, Guerbet Japan, Tokyo, Japan) was injected for 30 s

Table 1. Comparisons of Analyzed Characteristics between Two Groups.

	Unit	Bleeding group (n = 24)	Nonbleeding group (n = 19)	Univariable analysis	Multivariable analysis	
				P value	Odds ratio (95% CI)	P value
Age, median (range)	years	62.5 (40–74)	51.0 (30–69)	0.002*	1.10 (1.01–1.20)	0.028*
Gender, Female/Male		3/21	3/16	0.76		
BMI > 30, n (%)		6 (25.0%)	7 (36.8%)	0.40		
Comorbidities, n (%)						
Hypertension		9 (37.5%)	7 (36.8%)	0.97		
Diabetes mellitus		2 (8.0%)	1 (5.3%)	0.70		
Cardiovascular disease		6 (25.0%)	4 (21.1%)	0.76		
COPD		1 (4.0%)	0	0.37		
Chronic kidney disease		2 (8.0%)	3 (15.8%)	0.45		
Anticoagulant agent prior to ECMO		4 (16.0%)	0	0.06		
ECMO indications, n (%)						
Cardiogenic shock		0 (0%)	2 (10.5%)	0.10		
Respiratory failure		24 (100%)	17 (89.5%)	0.10		
ECMO modalities, n (%)						
V-V		0 (0%)	2 (10.5%)	0.10		
V-A		24 (100%)	17 (89.5%)	0.10		
Serum blood test prior to ECMO						
Platelet, median (range)	$\times 10^4/\mu L$	17.5 (8.7–37.3)	22.9 (3.5–35.3)	0.33		
APTT, average ± SD	sec	42.1 ± 26.6	41.7 ± 18.4	0.43		
D-dimer, average ± SD	μg/mL	12.3 ± 24.1	15.5 ± 30.5	0.26		
FDP, average ± SD	μg/mL	41.4 ± 88.7	39.3 ± 73.8	0.18		
Fibrinogen, median (range)	mg/dL	636.0 (210–904)	617.0 (186–1188)	0.91		
PIC, average ± SD	μg/mL	4.6 ± 8.6	7.1 ± 14.5	0.6		
Duration of ECMO, average ± SD	day	42.9 ± 40.6	16.2 ± 15.2	0.04*	1.04 (0.96–1.13)	0.33
Hospitalization period, average ± SD	day	54.3 ± 47.1	25.0 ± 22.3	0.08*	0.99 (0.93–1.05)	0.80
Duration of the initiation of ECMO to the bleeding event, average ± SD	day	20.7 ± 28.3	n/a	n/a		
Mortality, n (%)		11 (45.8%)	3 (15.8%)	0.04**		

CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; V-V, veno-venous; V-A, veno-arterial; APTT, activated partial thromboplastin time; FDP, fibrinogen/fibrin degradation products; PIC, plasmin-alpha2-plasmin inhibitor-complex; SD, standard deviation; n/a, not available

* The Mann–Whitney U test and multiple logistic regression analysis show a significant difference.

** The chi-square test shows a significant difference.

at a variable injection rate. Arterial-phase images were obtained using a bolus tracking method, and delayed-phase images were captured at 180 s after the commencement of contrast medium injection. Breath-hold techniques could not be used because patients were sedated. Non-contrast-enhanced and arterial-phase scans were obtained from the head to the pelvic floor, and delayed-phase scans were obtained from the chest to the lower limbs. In 15 of the 24 patients, both unenhanced and dual-contrast-enhanced images were obtained. In the remaining nine patients, only unenhanced images were obtained because of intracranial, airway, or lung parenchymal hemorrhage. When ICU physicians suspected sites of bleeding from neurological examinations or detection of blood in endotracheal or chest tubes, CECT was not performed.

Assessment of patient characteristics immediately prior to ECMO

The clinical characteristics of the groups with and without bleeding events are shown in **Table 1**. In this study, body mass index (BMI) of 30 kg/m^2 or greater was used as a cut-off value for high vs. normal weight because moderate or severe obesity (BMI greater than or equal to 30 kg/m^2) has been reported as a risk factor for severe COVID-19 infection [14, 15]. Hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, and chronic kidney disease were evaluated as comorbidities because they are also known as risk factors [14, 16]. The hospitalization period was defined as the duration from the date of admission to that of discharge, but all enrolled patients were transferred to other hospitals to continue their treatment after completing ECMO therapy because our hospital is a tertiary referral center. Therefore, in this study, the hospitalization period can be considered the length of the patient's stay in the ICU. The completion of ECMO therapy was decided after an ECMO weaning test showed stable carbon dioxide levels. In addition, improvements of pneumonia on chest radiographs, tidal volume, and the ratio of arterial oxygen par-

tial pressure to fractional inspired oxygen were used as guides to the timing of weaning from ECMO.

Assessment of CT

Two radiologists (KG and YT, with 5 and 23 years of experience in CT interpretation of emergency radiology, respectively) reviewed the CECT images and obtained consensus regarding bleeding sites and the presence of active arterial bleeding. Active arterial bleeding was defined when radiologists found a classic pattern of active extravasation on CECT [17]. The classic pattern of active extravasation means that the administered contrast medium has escaped from injured arteries, resulting in a jet or focal area of hyperattenuation within a hematoma on arterial-phase imaging, becoming enlarged or fading into the hematoma on delayed-phase imaging [17]. In this study, no patient showed a pseudoaneurysm on CECT.

TAE procedure

Angiography was performed if radiologists diagnosed that hemorrhages were promptly treatable by TAE based on CECT. The criteria of CECT findings for indication of TAE were as follows: the presence of active extravasation; hemorrhages located in the retroperitoneal space, muscle, or gastrointestinal tract; and accessible bleeding sites by a catheter. In addition, the indication of TAE was evaluated if patients showed a progression of anemia based on blood tests and patient's vital signs regardless of prior conservative therapies, such as anticoagulant cessation, astriction and blood transfusions, or endoscopic intervention. However, we did not use quantitative indices, such as the size of hemorrhage and blood transfusion volume, to determine the indication of TAE.

Angiography was performed using a combined CT and angiography system, the so-called IVR-CT (Artis Zee Ceiling and Somatom Emotion 16; Siemens, Erlangen, Germany). This system consists of flat-panel angiography equipment and a 16-row multidetector CT scanner. Active extravasation and its sites were judged by interventional radiologists by referring to a two-dimensional digital subtraction angiography (2D-DSA) image. The evaluation of hemostasis was also judged by 2D-DSA after embolization. The choice of embolic agents was made by the operator. During angiography, interventional radiologists and nurses were required to wear appropriate personal protective equipment to ensure adequate personal protection and infection control in the context of COVID-19 [18]. The operator wore an N95 mask, shoe covers, a cap, protective goggles, a 0.35-mPb X-ray protection apron, an additional sterile gown, and an extra set of gloves during the procedure.

Statistical analysis

First, the patient backgrounds of the two groups were compared using the chi-square test. The results of serum blood tests, duration of ECMO, and hospitalization period of the two groups were compared using the Mann-Whitney *U* test. Regarding the bleeding group, we also compared hospitalization periods between patients who underwent TAE and those who did not using the Mann-Whitney *U* test. After univariable analyses, multiple logistic regression analysis was performed to identify factors that differentiated the bleeding group from the nonbleeding group. Additional analyses were performed to identify factors differentiating fatal bleeding cases from nonfatal bleeding cases. Statistical analyses were performed using IBM SPSS Statistics 25.0 (IBM Japan, Tokyo). P-values < 0.05 were considered significant for each analysis.

Second, the number, frequency, and site of bleeding events and the number of active extravasation findings in the bleeding group were evaluated by referring to CT. Third, the characteristics of patients who underwent angiography were assessed. In addition to patient characteristics, bleeding sites detected on CT, the responsible and embolized arteries of bleeding detected on 2D-DSA, chosen embolic agents for TAE, technical success, complications of TAE, and patients' outcome after TAE were reviewed.

Results

Comparison of patient characteristics between two groups

The patients with bleeding events were significantly older and were associated with a longer duration of ECMO, longer hospitalization period, and higher fatality compared with the nonbleeding group ($p < 0.05$). Conversely, there were no significant differences between two groups regarding any other patient characteristics. Multiple logistic regression analysis showed that age was a significant factor contributing to bleeding events in our ECMO-treated COVID-19 patients ($p < 0.05$). The details of the results of the comparison between the two groups are shown in **Table 1**.

In addition, when the patients of the bleeding group were divided into those who died and those who did not, patients with a fatal outcome were significantly older and were associated with a longer duration of ECMO ($p < 0.05$). Multiple logistic regression analysis showed that age was a significant factor contributing to fatal outcomes in our ECMO-treated COVID-19 patients with bleeding events ($p < 0.05$). The details of the comparison in the bleeding group between fatal and non-fatal cases are shown in **Table 2**.

Details of bleeding events in 24 patients on ECMO

A total of 25 massive hemorrhages occurred in 24 patients on ECMO. One patient had two metachronous bleeding events. The details of the 25 massive hemorrhages in 24 patients on ECMO are shown in **Table 3**. The most common sites of bleeding were the muscles and the gastrointestinal tract.

Nine patients with massive hemorrhages at intracranial, airway, lung parenchymal and thoracic sites could be treated by pausing anticoagulant administration, with or without blood transfusions. No exacerbation of anemia was observed in those patients based on follow-up blood tests and a follow-up unenhanced CT. Six of 10 patients with intramus-

Table 2. Comparisons of Analyzed Characteristics in the Bleeding Group between Fatal and Nonfatal Cases.

	Unit	Fetal cases (n = 11)	Nonfatal cases (n = 13)	Univariable analysis	Multivariable analysis	
				P value	Odds ratio (95% CI)	P value
Age, median (range)	years	67.0 (54–72)	59.0 (40–74)	0.02*	1.18 (1.00–1.39)	0.048*
Gender, Female/Male		2/9	1/12	0.43		
BMI > 30, n (%)		2 (18.2%)	4 (30.8%)	0.48		
Comorbidities, n (%)						
Hypertension		5 (45.5%)	4 (30.8%)	0.46		
Diabetes mellitus		1 (9.1%)	1 (7.7%)	0.90		
Cardiovascular disease		2 (18.2%)	4 (30.8%)	0.48		
COPD		1 (9.1%)	0	0.46		
Chronic kidney disease		1 (9.1%)	1 (7.7%)	0.90		
Anticoagulant agent prior to ECMO		3 (27.3%)	1 (7.7%)	0.20		
Serum blood test prior to ECMO						
Platelet, median (range)	$\times 10^4/\mu L$	16.2 (8.7–32.9)	20.8 (9.8–37.2)	0.18		
APTT, average ± SD	sec	47.2 ± 35.1	37.8 ± 16.9	0.45		
D-dimer, average ± SD	μg/mL	9.9 ± 15.7	14.3 ± 30.0	0.73		
FDP, average ± SD	μg/mL	39.6 ± 89.8	43.0 ± 91.4	0.49		
Fibrinogen, median (range)	mg/dL	572.0 (210–777)	676.0 (251–904)	0.12		
PIC, average ± SD	μg/mL	2.4 ± 2.0	6.5 ± 11.4	0.30		
Duration of ECMO, average ± SD	day	52.6 ± 24.3	34.8 ± 50.1	0.02*	1.01 (0.99–1.04)	0.29
Hospitalization period, average ± SD	day	55.3 ± 27.3	53.5 ± 60.3	0.36		
Duration of the initiation of ECMO to the bleeding event, average ± SD	day	22.1 ± 20.4	19.5 ± 34.5 (1–132)	0.25		

CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; APTT, activated partial thromboplastin time; FDP, fibrinogen/fibrin degradation products; PIC, plasmin-alpha2-plasmin inhibitor-complex; SD, standard deviation

* The Mann–Whitney U test and multiple logistic regression analysis show a significant difference.

Table 3. The Details of 25 Massive Hemorrhages in 24 Patients on ECMO.

Bleeding sites	Number of bleeding events (%)	Number of active arterial extravasation findings on CECT	Median (range) of duration from the initiation of ECMO to the bleeding event (days)
Intracranial	4 (16.0%)	0	2.5 (2–6)
Airway or lung parenchyma	3 (12.0%)	0	24.0 (1–132)
Thorax	2 (8.0%)	0	26.0 (13–49)
Intramuscular	10 (40.0%)	10	11.5 (6–21)
Right psoas muscle	1 (4.0%)	1	11
Left psoas muscle	2 (8.0%)*	2	13.5 (11–16)
Bilateral psoas muscles	2 (8.0%)	2	13.0 (12–14)
Left iliacus muscle	1 (4.0%)	1	12
Left iliacus and gluteus maximus muscles	1 (4.0%)	1	9
Left rectus abdominis muscle	1 (4.0%)	1	6
Right subscapularis muscle	1 (4.0%)	1	9
Right adductor magnus muscle	1 (4.0%)	1	21
Gastrointestinal	6 (24.0%)	3	26.0 (1–66)
Upper gastrointestinal	2 (8.0%)	0	17.5 (1–34)
Lower gastrointestinal	4 (16.0%)*	3	26.0 (17–66)

ECMO, extracorporeal membrane oxygenation; CECT, contrast-enhanced computed tomography

* One patient had two metachronous bleeding events.

cular hemorrhages could be treated by pausing anticoagulant administration, astriction and blood transfusions. Five of 6 patients with gastrointestinal hemorrhage were treated by both anticoagulant cessation and endoscopic intervention. No exacerbation of anemia was observed in those patients based on follow-up blood tests. Two patients (one intramuscular and one gastrointestinal hemorrhages) underwent a follow-up CECT, but no exacerbation of hemorrhage was observed.

Angiography was performed for 4 intramuscular hemor-

Table 4. Characteristics of Patients in Whom TAE Was Performed.

Case	Reference value	Unit	Case 1 (1st event)	Case 1 (2nd event)	Case 2	Case 3
Age/gender			73/M		63/M	48/M
Comorbidity			Hypertension Hyperlipidemia		Hypertension Intracranial hemorrhage	No
Anticoagulant agent			Argatroban	Not used	Heparin	Heparin
Serum blood test at the beginning of TAE						
Platelet	15.8–34.8	$\times 10^4/\mu L$	12.6	11.0	21.7	13.7
APTT	28–45	sec	35.4	36.7	35.5	57.5
D-dimer	<1.0	μg/mL	4.8	20.5	12.0	1.2
FDP	<5	μg/mL	11	65	28	4
Fibrinogen	180–320	mg/dL	374	286	383	320
PIC	<0.8	μg/mL	0.3	8.9	3.6	0.3
Duration from the initiation of ECMO to the bleeding event		day	16	35	6	9
Active extravasation on CECT			+	+	+	+
Bleeding sites on CECT			Left psoas muscle	Ileum	Left rectus abdominis muscle	Right subscapularis muscle
The responsible and embolized artery on 2D-DSA			Left iliolumbar artery	Ileal artery	Left inferior epigastric artery	Right lateral thoracic artery
Embolic agents			NBCA	Metallic microcoil	GS	GS
Technical success			Success	Success	Success	Success
Complication of TAE			None	None	None	None
Hospitalization period		day	50		8	100
Outcome			Death		Alive	Alive

TAE, transcatheter arterial embolization; APTT, activated partial thromboplastin time; FDP, fibrinogen/fibrin degradation products; PIC, plasmin-alpha2-plasmin inhibitor-complex; ECMO, extracorporeal membrane oxygenation; CECT, contrast-enhanced computed tomography; 2D-DSA, two-dimensional digital subtraction angiography; NBCA, N-butyl-2-cyanoacrylate; GS, gelatin sponge; TAE, transcatheter arterial embolization

rhages and one gastrointestinal massive hemorrhage in 4 patients because interventional radiologists predicted that their bleeding would be promptly treatable by TAE based on CECT. They underwent angiography and CECT on the same day. One patient (Case 1 in **Table 4**) had two metachronous bleeding events at 16 and 35 days after the initiation of ECMO and underwent CECT and TAE twice. One patient had bleeding in the right adductor magnus muscle and underwent CECT twice within 3 days before angiography. Although a follow-up CECT showing an increase in the size of the hematoma was performed, along with angiography, no active extravasation was seen on 2D-DSA. His case was evaluated as spontaneous cessation of bleeding, and TAE was not performed. Three other patients also underwent TAE. The characteristics and details of patients who underwent angiography are shown in **Table 4**.

The hospitalization period of the 3 patients in the bleeding group who underwent TAE [median (range), 50.0 (8-100) days] was not significantly different from that of 21 patients who did not undergo TAE [40.0 (10-225) days] ($p = 0.95$). Details of angiography in 3 bleeding events of 2 patients are shown in **Fig. 2**-**6**.

Details of fatal cases

Fourteen patients (11 in the bleeding group and 3 in the non-bleeding group) had fatal outcomes. Ten patients died of respiratory failure directly due to COVID-19 pneumonia. Two patients, including one patient who underwent TAE twice (Case 1 in **Table 4**), died of acute respiratory distress syndrome without weaning from ECMO. The cause of death in the remaining two patients was a combination of bacterial infection with COVID-19 pneumonia and multiple organ failure. However, no patients in this cohort died of bleeding.

Discussion

The present study revealed that age was a significant factor associated with COVID-19 patients on ECMO with bleeding events. The age was also significantly associated with a fatal outcome in the bleeding group. More than half of the COVID-19 patients on ECMO experienced massive hemorrhage, the most common sites being the muscles and the gastrointestinal tract. TAE could provide prompt hemostasis when COVID-19 patients on ECMO with bleeding events have an indication of TAE.

Several possible causes of a bleeding tendency in COVID-19 patients under ECMO have been suggested. First, anticoagulation management during ECMO support by continuous administration of anticoagulant agents such as heparin is essential [19]; however, well-known adverse effects of heparin are bleeding and heparin-induced thrombocytopenia [20]. Second, COVID-19 infection tends to show

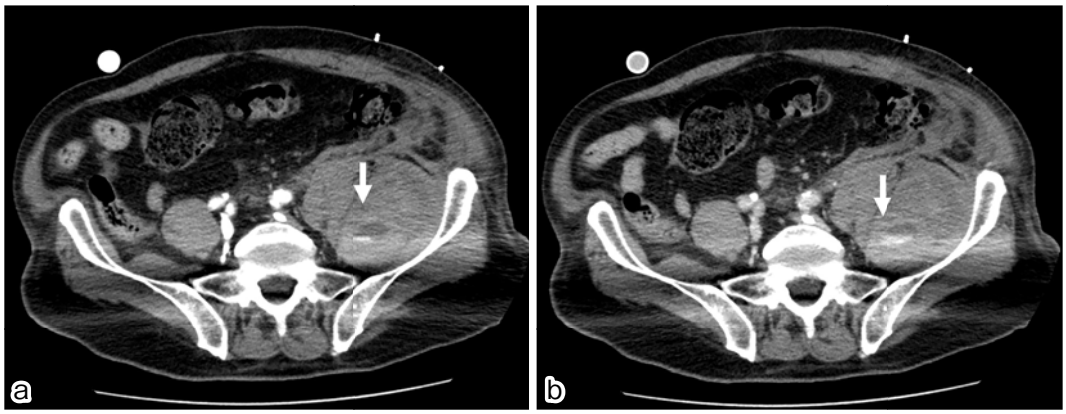

Figure 2. CECT of Case 1 at the first bleeding event. (a) The arterial-phase CECT image shows a jet of contrast medium within the hematoma of the left psoas muscle (arrow). (b) The jet of contrast medium is enlarged on the delayed-phase image (arrow). This is the classic pattern of active extravasation.

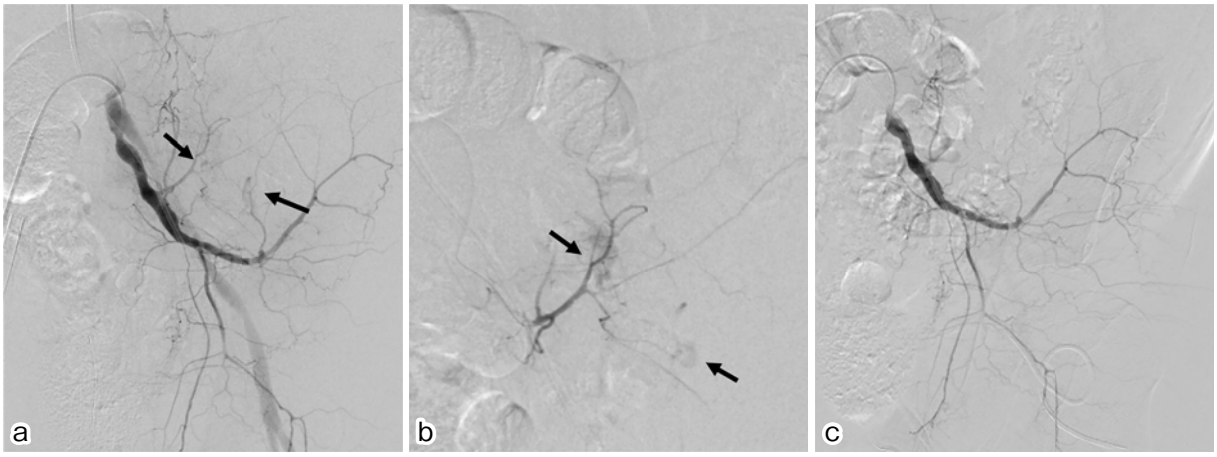

Figure 3. Angiography of Case 1 at the first bleeding event. (a) 2D-DSA of the left internal iliac artery (IIA) was obtained after a 5.0-French catheter (Twist B, Medikit Co., Ltd., Tokyo, Japan) was advanced into the left IIA. 2D-DSA shows active extravasations from the branch of the left iliolumbar artery (arrows). (b) The 2D-DSA image of the branch of the left iliolumbar artery was obtained after a 1.9-French microcatheter (Nadeshiko Akane, JMS Co., Ltd., Hiroshima, Japan) navigated by a 0.014-inch guidewire (Transend, Boston Scientific Japan, Tokyo, Japan) was coaxially advanced. 2D-DSA shows active extravasations from the branch of the left iliolumbar artery (arrows). (c) The 2D-DSA image of the left IIA after TAE shows the disappearance of active extravasation. TAE was performed using a mixture of N-butyl-2-cyanoacrylate and lipiodol at a volume ratio of 1:3 after the microcatheter was advanced as close as possible to the bleeding points.

a transition from suppressed fibrinolysis to hyperfibrinolysis as the disease progresses [21]. Third, it has been reported that COVID-19 infection may be associated with immune thrombocytopenia, a rare autoimmune disease [22].

Our study showed that the muscles and gastrointestinal tract were high-frequency sites of massive hemorrhage during ECMO support. Intramuscular and gastrointestinal hemorrhages occurred at an average of 12.1 days (range 6-12) of ECMO treatment, which was consistent with previous reports [23, 24]. One possible mechanism of intramuscular hemorrhage is the long-term confinement to the supine position of COVID-19 patients on ECMO because they are generally sedated to prevent cannula dislodgement [24, 25]. This physical position may cause blood vessel ruptures due to compression of dorsal-side muscles [25]. Another possible mechanism is supposed to be external forces associated with positional changes and daily care by nursing care staff [25]. These may cause muscle strain and lead to blood vessel rupture [25].

Ischemia-reperfusion-related damage is thought to be the main cause of gastrointestinal hemorrhage during ECMO support [13, 26]. When patients are in the state of ischemia and hypoxia, the blood redistributes and stress ulcers occur in the gastrointestinal tract due to the insufficient blood supply, decreased mucosal blood flow, ischemia, and reperfusion injury [13]. This stress ulceration can progress and erode larger vessels, resulting in gastrointestinal bleeding [13]. Anticoagulation also increases the risk of gastrointestinal bleeding [27]. It is difficult to prevent bleeding complications during ECMO support, even though medical staff are aware of the risk.

Overall, patients with bleeding events and fatal outcomes

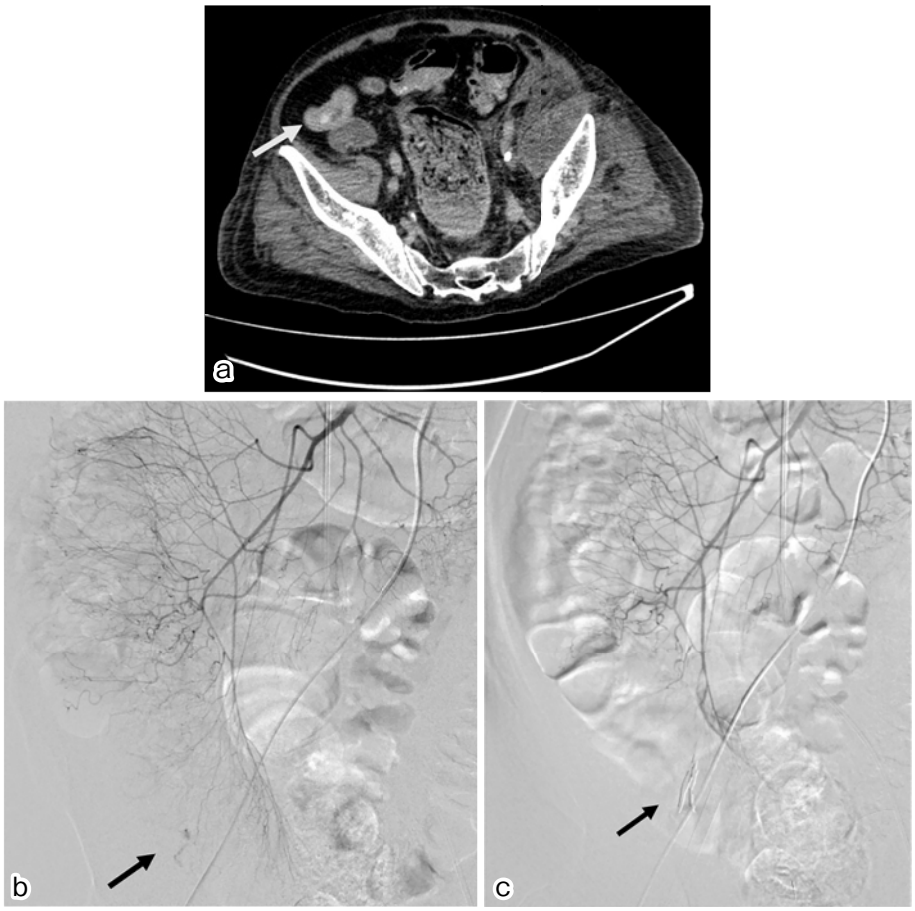

Figure 4. CT and angiography of Case 1 at the second bleeding event. (a) The delayed-phase image of CECT shows the active extravasation of contrast medium in the ileal lumen (arrow). (b) 2D-DSA of the superior mesenteric artery (SMA) was obtained after a 5.0-French catheter (Twist B) was advanced into the SMA. 2D-DSA shows the active extravasation of contrast medium from the limbs of the vasa recta of the ileal artery (arrow). (c) The 2D-DSA image of SMA after TAE shows the disappearance of active extravasation (arrow). TAE was performed using two pushable metallic microcoils after a 1.9-French microcatheter (Nadeshiko Akane) navigated by a 0.014-inch guidewire (Transend) was coaxially advanced as close as possible to the bleeding points.

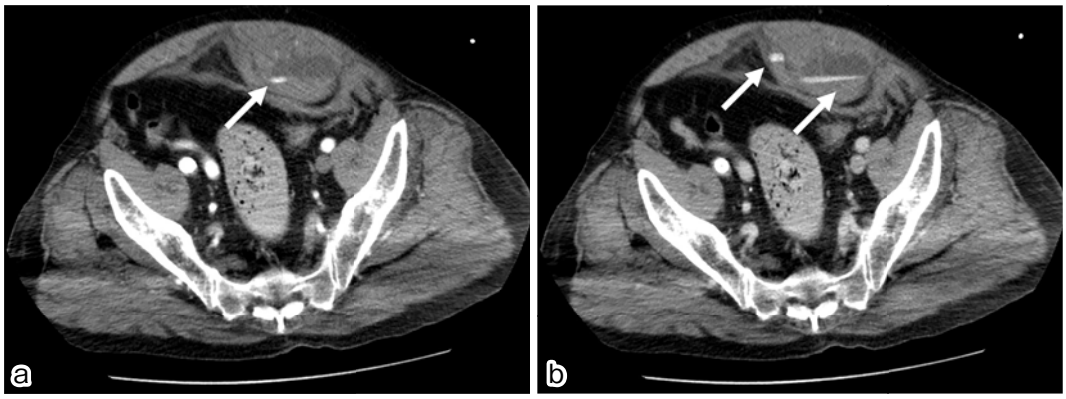

Figure 5. CECT of Case 2. (a) The arterial-phase CECT image shows a jet of contrast medium within the hematoma of the left rectus abdominis muscle (arrow). (b) The jet of contrast medium is enlarged on the delayed-phase image (arrows). This is the classic pattern of active extravasation.

were significantly older than those without. This result was consistent with that of a previous study [10]. The reason is unclear, but we speculate that aging processes, such as atherosclerotic changes and weakening of connective tissues, might make older patients more vulnerable to hemorrhage during ECMO support. Although the bleeding group showed

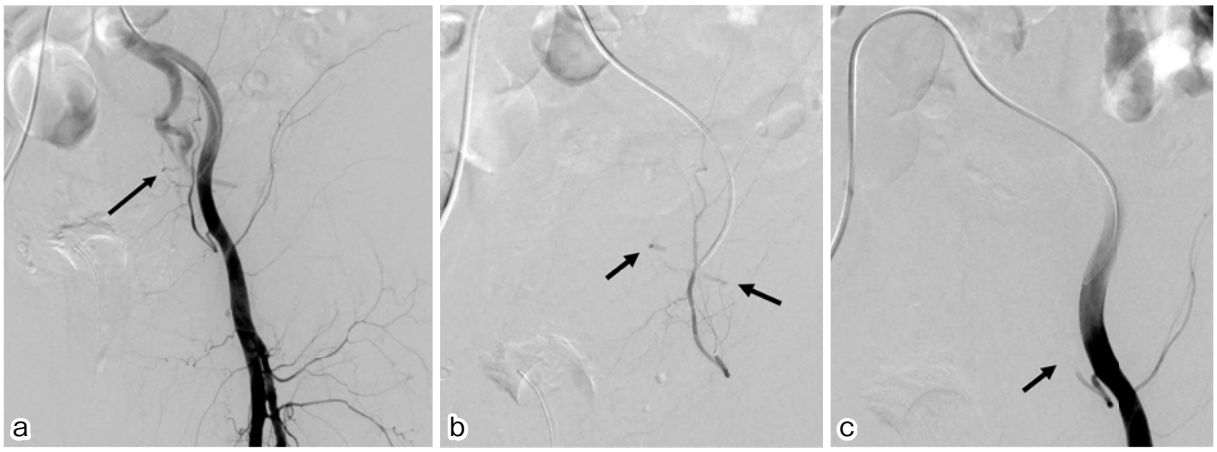

Figure 6. Angiography of Case 2. (a) 2D-DSA of the left external iliac artery (EIA) was obtained after a 5.0-French catheter (Twist B) was advanced into the left EIA. 2D-DSA shows active extravasations from the branch of the inferior epigastric artery (arrow). (b) 2D-DSA of the branch of the inferior epigastric artery was obtained after a 1.9-French microcatheter (Nadeshiko Akane) navigated by a 0.014-inch guidewire (Transend) was coaxially advanced. (c) 2D-DSA of the left EIA after TAE shows the disappearance of active extravasation (arrows). TAE was performed using gelatin sponge particles after the microcatheter was advanced as close as possible to the bleeding point.

a significantly longer duration of ECMO, Dreier et al. have suggested that bleeding episodes are not directly related to the duration of ECMO [28]. However, it is certain that the longer duration of ECMO necessarily prolonged the duration of anticoagulation. This would result in an increased risk of bleeding complications. In addition, COVID-19 patents who need a longer duration of ECMO and hospitalization period likely have worse pulmonary function to start with [5, 6]. As our results showed, elderly COVID-19 patients on ECMO with bleeding events might have a greater risk of fatality.

Bleeding complications in our series were first treated by pausing anticoagulant administration, astriction, endoscopic intervention, and/or blood transfusion. However, if interventional radiologists determine the indication of TAE for bleeding events, the results showed that TAE would be an effective and curative method of treatment. After hemostasis was obtained by TAE, ICU physicians could promptly restart ECMO if needed. However, it was still difficult to conclude whether or not TAE affected the hospitalization period or patient's prognosis from the present study because of a small number of patients who underwent TAE. In the currently available COVID-19 treatment guidelines, there is also no clear description of using TAE for bleeding complications in COVID-19 patients on ECMO [29].

Our study has some limitations. First, we analyzed a small number of patients at a single center. It might be difficult to avoid biases in our results and speculations. Our retrospective design was also a potential source of bias. In particular, we did not have sufficient patient data to evaluate whether TAE could contribute to improving patients' fatality. Further studies using larger numbers of patients might be able to compare TAE with other therapies in ECMO-treated COVID-19 patients who experience bleeding. Second, we calculated the durations of hospitalization from the date of admission to that of discharge. Apart from those patients who succumbed to death, all enrolled patients were transferred to other hospitals to continue their treatment after they completed ECMO therapy. We could not evaluate the detailed outcomes of patients after discharge from our hospital. This might affect the calculation of hospitalization duration and its relationship to patient outcomes.

In conclusion, elderly COVID-19 patients on ECMO had a greater risk of bleeding complications and fatal outcomes. TAE was effective in providing prompt hemostasis for patients who have the treatment indication.

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Author Contribution: Conceptualization: Kazuki Goto, Yukihisa Takayama, and Akinobu Osame

Formal analysis: Kazuki Goto and Yukihisa Takayama

Investigation: Gaku Honda, Kazuaki Fujita, Akinobu Osame, Hiroshi Urakawa, Kota Hoshino, Yoshihiko Nakamura, and Hiroyasu Ishikura

Methodology: Yukihisa Takayama and Kengo Yoshimitsu

Writing - original draft: Kazuki Goto and Yukihisa Takayama

Writing - review & editing and supervision: Kengo Yoshimitsu

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