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Original Article

Clinical Features Comparing Arterial Thrombosis and Venous Thromboembolism in Hospitalized Patients with COVID-19: Result from the CLOT-COVID Study

Michihisa Umetsu, MD,[1] Hajime Kanamori, MD,[1] Koji Murakami, MD,[1] Takuya Shiga, MD,[1] Sen Yachi, MD,[2] Makoto Takeyama, MD,[2] Yuji Nishimoto, MD,[3] Ichizo Tsujino, MD,[4] Junichi Nakamura, MD,[4] Naoto Yamamoto, MD,[5] Hiroko Nakata, MD,[6] Satoshi Ikeda, MD,[7] Shizu Aikawa, MD,[8] Hiroya Hayashi, MD,[9] Hirono Satokawa, MD,[10] Yoshinori Okuno, MD,[11] Eriko Iwata, MD,[12] Yoshito Ogihara, MD,[13] Nobutaka Ikeda, MD,[14] Akane Kondo, MD,[15] Takehisa Iwai, MD,[16] Norikazu Yamada, MD,[17] Tomohiro Ogawa, MD,[18] Takao Kobayashi, MD,[5] Makoto Mo, MD,[19] and Yugo Yamashita, MD,[11] on behalf of the CLOT-COVID Study Investigators

[1] *Tohoku University Hospital, Sendai, Miyagi, Japan*
[2] *Japan Community Health Care Organization Tokyo Shinjuku Medical Center, Tokyo, Japan*
[3] *Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Hyogo, Japan*
[4] *Hokkaido University Hospital, Sapporo, Hokkaido, Japan*
[5] *Hamamatsu Medical Center, Hamamatsu, Shizuoka, Japan*
[6] *Yokosuka General Hospital Uwamachi, Yokosuka, Kanagawa, Japan*
[7] *Nagasaki University Hospital, Nagasaki, Nagasaki, Japan*
[8] *Tsukuba Medical Center Hospital, Tsukuba, Ibaraki, Japan*
[9] *Osaka Metropolitan University Graduate School of Medicine, Osaka, Osaka, Japan*
[10] *Fukushima Medical University, School of Medicine, Fukushima, Fukushima, Japan*
[11] *Kyoto University Hospital, Kyoto, Kyoto, Japan*
[12] *Nankai Medical Center Japan Community Health Care Organization, Saiki, Osaka, Japan*
[13] *Mie University Hospital, Tsu, Mie, Japan*
[14] *Toho University Ohashi Medical Center, Tokyo, Japan*
[15] *Shikoku Medical Center for Children and Adults, Zentsuji, Kagawa, Japan*
[16] *Tsukuba Vascular Center, Tsukuba, Ibaraki, Japan*
[17] *Kuwana City Medical Center, Kuwana, Mie, Japan*
[18] *Fukushima Daiichi Hospital, Fukushima, Fukushima, Japan*
[19] *Yokohama Minami Kyosai Hospital, Yokohama, Kanagawa, Japan*

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Corresponding author: Michihisa Umetsu, MD. Tohoku University Hospital, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan
Tel: +81-22-717-7214, Fax: +81-22-717-7217
E-mail: mumetsu@med.tohoku.ac.jp

Objectives: This study aimed to investigate the clinical features of arterial thrombosis and venous thromboembolism (VTE) in coronavirus disease 2019 (COVID-19).
Methods: The CLOT-COVID Study was a retrospective, multicenter cohort study that enrolled 2,894 consecutively hospitalized patients with COVID-19 among 16 centers in Japan from April 2021 to September 2021. We compared the clinical features of arterial thrombosis and VTE.
Results: Thrombosis was observed in 55 patients (1.9%) during hospitalization. Arterial thrombosis and VTE occurred in 12 (0.4%) and 36 (1.2%) patients, respectively. Among the 12 patients with arterial thrombosis, 9 (75%), 2 (17%), and 1 developed ischemic cerebral infarction, myocardial infarction, and acute limb ischemia, respectively, and there were five patients (42%) without comorbidities. Among 36 patients with VTE, 19 (53%) and 17 (47%) developed pulmonary embolism (PE) and deep vein thrombosis (DVT), respectively. PE was common in the early stages of hospitalization; whereas, DVT was common beyond the early stages of hospitalization.
Conclusion: Among patients with COVID-19, arterial thrombosis was less common than VTE, although ischemic cerebral infarction seemed to be relatively common, and a certain number of patients developed arterial thrombosis even in the absence of known atherosclerosis risk factors.

Keywords: COVID-19, arterial thrombosis, venous thrombosis, VTE, Japan

Introduction

The coronavirus disease 2019 (COVID-19) is still spreading worldwide with variant mutations, and it has been widely associated with a coagulopathy risk, which can lead to thrombosis in both the vein and artery. The optimal management strategies for anticoagulation therapy,

including the appropriate dosage of anticoagulation therapy, are still being debated around the world.[1–4] Furthermore, the risk of thrombosis in patients with COVID-19 could widely vary according to ethnic differences and distinct resource availability. Recent studies from Japan reported that the number of patients diagnosed with thrombosis associated with COVID-19 could be small compared with reports from other countries,[5,6] although thrombosis was more common in patients with severe COVID-19 as well as those with several clinical features such as men and high D-dimer values on admission.[7,8] Obesity was not significantly associated with venous thromboembolism (VTE) during the hospitalization, but it was associated with the severity of COVID-19.[9] Thrombus development was associated with COVID-19 severity, and bleeding risk was related to COVID-19 severity and anticoagulation but not with age.[10–12]

In patients with COVID-19, VTE, particularly pulmonary embolism (PE), may be a major cause of thrombosis.[13–15] However, there has been limited data on the detailed types of thrombosis, which could be important for understanding thrombosis associated with COVID-19. Furthermore, there have been a number of reports for the alpha variant of COVID-19, but there is scarce data on other variants of COVID-19, including the delta variant.[16] Several studies for COVID-19-related thrombosis in Japan have been reported in the first and second waves, but after the third wave, there have been few large-scale studies.[17,18] Therefore, the present study aimed to investigate the clinical features of arterial thrombosis and VTE in COVID-19 using data from a large-scale multicenter observational study from Waves 4 and 5, when the medical care situation in Japan worsened.

Methods

Study population

The CLOT-COVID Study (Study of thrombosis and anticoagulation therapy in patients with COVID-19 in Japan: UMIN000045800) is a physician-initiated, retrospective, multicenter cohort study that enrolled consecutively hospitalized patients with COVID-19 among 16 centers in Japan from April 2021 to September 2021. We attempted to capture the status of patients affected by the fourth and fifth waves of COVID-19 infections in Japan. The present study was carried out in Japan by dedicated members of the Taskforce on VTE and COVID-19 in collaboration with the Japanese Society of Phlebology and the Japanese Society of Pulmonary Embolism Research.[5,19] Through hospital databases, we enrolled consecutive patients who were diagnosed with COVID-19 via a positive polymerase chain reaction test.

Ethics approval and participant consent

All the procedures were in accordance with the Declaration of Helsinki. The research protocol was approved by the relevant review boards or ethics committees of all participating centers. We waived written informed consent from each patient because we used clinical information obtained in routine clinical practices. This method is consistent with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare in Japan.

Data collection and definitions of patient characteristics

We used an electronic report form to collect data and follow-up information from patients. Data on the patient characteristics, pharmacological thromboprophylaxis managements, and clinical outcomes were collected from the hospital charts or hospital databases using prespecified definitions. Data entry into an electronic case report form was the responsibility of the physicians at each institution. At the general office, data were also manually checked for missing or contradictory input as well as for values outside of the expected range.

COVID-19 severity was classified as mild, moderate, or severe. Patients with mild COVID-19 were defined as those who did not require oxygen; those with moderate COVID-19 were defined as those who required oxygen; and those with severe COVID-19 were defined as those who required mechanical ventilation or extracorporeal membrane oxygenation (ECMO). **Supplementary Appendix 1** contains detailed definitions of the other patient characteristics.

Clinical outcomes

Thrombosis was assessed based on all events during hospitalization after patients tested positive for COVID-19, which was classified into arterial thrombosis, VTE, and other thromboses. Ischemic stroke, myocardial infarction, and other types of arterial thromboembolism were all examples of arterial thrombosis. Ischemic stroke was defined as a stroke that required prolonged hospitalization and had symptoms that lasted more than 24 h. Myocardial infarction was defined in accordance with the universal myocardial infarction guidelines.[20] The patients with arterial thrombosis and concomitant VTE were also included in the arterial thrombosis group. VTE was defined as either or both PE and deep vein thrombosis (DVT) objectively confirmed by imaging examinations (ultrasound, contrast-enhanced computed tomography, ventilation-perfusion lung scintigraphy, pulmonary angiography, or contrast venography) or by autopsy. Proximal DVT was defined as venous thrombosis located in the popliteal, femoral, or iliac veins. Distal DVT was defined as venous

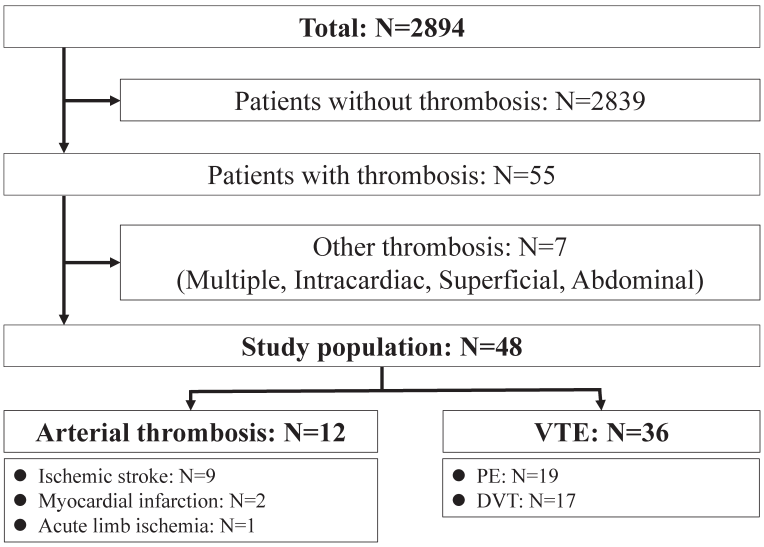

Fig. 1 Study flow chart.
VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis

thrombosis located in the calf veins below the knee, including the peroneal, posterior tibial, anterior tibial, and soleus muscle veins. PE was classified into five categories based on the most central pulmonary artery site where the thrombi were found: The main trunk pulmonary artery, the left or right main pulmonary artery, the lobar artery, the segmental artery, or the subsegmental artery. Other thrombosis types include intracardiac, portal, and superficial vein thromboses, as well as multiple thromboses.

Major bleeding was defined based on the International Society of Thrombosis and Hemostasis, which included a decrease in hemoglobin levels of at least 2 g/dL, the transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ.[21] Wave 4 included patients admitted in June 2021, and Wave 5 included patients admitted after July 2021 (**Supplementary Fig. 1**).

Statistical analysis

Categorical variables were presented as numbers and percentages. Based on their distributions, continuous variables were presented as the mean and standard deviation or the median and interquartile range (IQR). When applicable, categorical variables were compared using the chi-square test; otherwise, Fisher's exact test was used. Based on their distributions, continuous variables were compared using either the Student's t-test or the Wilcoxon rank sum test. All reported P-values were 2-tailed, and P-values less than 0.05 were considered statistically significant. JMP version 16.0.0 was used for all statistical analyses (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Thrombosis was observed in 55 of the 2,894 patients with COVID-19 (1.9%). Arterial thrombosis, VTE, and other thrombosis occurred in 12 (0.4%), 36 (1.2%), and 7 (0.2%) patients, respectively (**Fig. 1**). Two patients with arterial thrombosis had concurrent VTE.

The characteristics of patients with arterial thrombosis and VTE are shown in **Table 1**. There was no significant difference in baseline characteristics between patients with arterial thrombosis and those with VTE, including age, sex, and body weight (age: 63 vs. 56 years, P = 0.09; men: 92% vs. 83%, P = 0.48; body weight: 71.7 vs. 78.3 kg, P = 0.23). There was also no significant difference in D-dimer levels between the groups upon admission.

There was no significant difference in COVID-19 severity upon admission between patients with arterial thrombosis and those with VTE, whereas patients with arterial thrombosis showed less severe COVID-19 as the worst severity during hospitalization (mild: 8.3% vs. 0%; moderate: 50% vs. 22%; severe: 42% vs. 78%, P = 0.03) (**Table 1**).

Arterial thrombosis

Details of arterial thrombosis are shown in **Table 2**. There were 9 patients (75%) with ischemic cerebral infarction, 2 patients (17%) with myocardial infarction, and 1 patient (9.3%) with acute limb ischemia. Detailed individual cases of patients who developed arterial thrombosis during hospitalization are shown in **Table 3**. There were four patients who developed a concomitant ischemic cerebral infarction on admission, and one patient who was complicated with

Table 1 Comparison of the patient characteristics and pharmacological thromboprophylaxis management between patients with arterial thrombosis and those with VTE during hospitalization

	Patients with arterial thrombosis (N=12)	Patients with VTE (N=36)	P value
Baseline characteristics			
Age (years)	63±11	56±11	0.09
Men	11 (92%)	30 (83%)	0.48
Body weight (kg)	71.7±11.6	78.3±17.3	0.23
Body mass index (kg/m^2)	24.6±3.5	27.8±6.0	0.08
Body mass index >30 kg/m^2	2 (17%)	10 (28%)	0.44
D-dimer level upon admission (μg/mL)	1.9 (0.9–11.9)	2.5 (1.2–8.5)	0.67
Comorbidities			
Hypertension	5 (42%)	17 (47%)	0.74
Diabetes mellitus	3 (25%)	11 (31%)	0.71
Heart disease	1 (8.3%)	2 (5.6%)	0.73
Respiratory disease	2 (17%)	1 (2.8%)	0.09
Active cancer	0 (0%)	0 (0%)	—
History of major bleeding	0 (0%)	1 (2.8%)	1.00
History of VTE	1 (8.3%)	0 (0%)	0.08
Severity of COVID-19 on admission			
Mild	2 (17%)	3 (8.3%)	0.71
Moderate (Need oxygen)	6 (50%)	19 (53%)	
Severe (Need mechanical ventilation/ECMO)	4 (33%)	14 (39%)	
Worst severity of COVID-19 during hospitalization			
Mild	1 (8.3%)	0 (0%)	0.03
Moderate (Need oxygen)	6 (50%)	8 (22%)	
Severe (Need mechanical ventilation/ECMO)	5 (42%)	28 (78%)	
Pharmacological thromboprophylaxis managements			
Anticoagulants	11 (92%)	35 (97%)	0.40
Unfractionated heparin of a prophylactic dose	6/11 (55%)	15/35 (43%)	0.79
Unfractionated heparin of a therapeutic dose	3/11 (27%)	13/35 (37%)	
Low-molecular-weight heparin of a prophylactic dose	1/11 (9.1%)	5/35 (14%)	
Low-molecular-weight heparin of a therapeutic dose	0/11 (0%)	0/35 (0%)	
Direct oral anticoagulants	1/11 (9.1%)	1/35 (2.9%)	
Warfarin	0/11 (0%)	0/35 (0%)	
Others	0/11 (0%)	1/35 (2.9%)	
Characteristics in Wave 4 and Wave 5			
Wave 4 in Japan (June 2021)	4 (33%)	20 (56%)	0.18
Wave 5 in Japan (July 2021)	8 (66%)	16 (44%)	

VTE: venous thromboembolism; COVID-19: coronavirus disease 2019; ECMO: extracorporeal membrane oxygenation

atrial fibrillation during hospitalization.

The median duration between admission and diagnosis was 5.5 days (IQR: 1–11). Among the 12 cases, 4 were diagnosed on admission, all of which were cerebral infarction cases. Four cases experienced lacunar infarctions, two experienced infarctions in the middle cerebral artery lesion, and three cases were clinically diagnosed. Diagnostic imaging was not available in three cases; however, four cases were diagnosed with a single lesion and two cases with multiple lesions. These eight cases were conservatively treated; whereas, one case was treated by thrombolysis using tissue plasminogen activator. Following a stroke, two cases were discharged, five cases were transferred to rehabilitation, and two cases died. One patient with myocardial infarction underwent percutaneous coronary intervention, while the other received conservative treatment. The patients who underwent percutaneous coronary intervention were sent home; however, patients who were conservatively treated succumbed to COVID-19. The patient with acute limb ischemia had an acute thromboembolism of the superficial femoral artery, underwent thrombectomy and was discharged home.

Among 12 patients with arterial thrombosis, 8 received prophylactic anticoagulation therapy at the time of arte-

Table 2 Comparison of the detailed characteristics of thrombosis and clinical outcomes during hospitalization between patients with arterial thrombosis and those with VTE

	Patients with arterial thrombosis (N=12)	Patients with VTE (N=36)
Types of arterial thrombosis		
Ischemic cerebral infarction	9/12 (75%)	—
Myocardial infarction	2/12 (17%)	—
Acute limb ischemia	1/12 (8.3%)	—
Types of VTE		
PE with or without DVT	—	19/36 (53%)
Main trunk pulmonary artery	—	1/19 (5.3%)
Left or right main pulmonary artery	—	6/19 (32%)
Lobar artery	—	8/19 (42%)
Segmental artery	—	2/19 (11%)
Subsegmental artery	—	2/19 (11%)
DVT only	—	17/36 (47%)
Proximal DVT in the lower extremities	—	2/17 (12%)
Distal DVT in the lower extremities	—	6/17 (35%)
Veins in the upper extremities	—	6/17 (35%)
Others	—	3/17 (18%)
Major bleeding	1/12 (8.3% [0.0%–37.5%])	12/36 (33.3% [20.1%–49.7%])
All-cause death	3/12 (25.0% [8.3%–53.8%])	7/36 (19.4% [9.4%–35.3%])

VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis

rial thrombosis, including 4 with a prophylactic dose of unfractionated heparin (UFH), 2 patients with a therapeutic dose of UFH, 1 patient with a prophylactic dose of low-molecular-weight heparin, and 1 patient with direct oral anticoagulant due to concomitant atrial fibrillation. More than half of patients with arterial thrombosis had several comorbidities, such as hypertension and diabetes mellitus, while there were five patients (42%) without comorbidities.

VTE

Details of VTE are shown in **Table 2**. Among 36 patients with VTE, 19 (53%) had PE and 17 (47%) had DVT. The locations of the thrombus for PE were the main trunk pulmonary artery in 1 patient (5.3%), the left or right main pulmonary artery in 6 patients (32%), the lobar artery in 8 patients (42%), the segmental artery in 2 patients (11%), and the subsegmental artery in 2 patients (11%). The locations of the thrombus for DVT were proximal DVT in 2 patients (12%), distal DVT in 6 patients (35%), veins in the upper extremities in 6 patients (35%), and vena cava in 3 patients (18%). Among the 3 patients with vena cava thrombosis, 2 patients developed peri-catheter thrombosis related to ECMO. The timing of the onset of VTE is shown in **Fig. 2**. PE was more common in the early stages of hospitalization, whereas DVT was more common beyond the early stages of hospitalization.

Of the 36 VTE cases, severe COVID-19 cases were found in 28 cases. There was no correlation between COVID-19 severity and PE. Among these cases, 14 (50%) had PE, and 14 (50%) had DVT alone. Focusing on the 18 patients who developed VTE within 10 days of admission, 10 had severe COVID-19 with PE, and 2 cases had DVT alone, but there was no discernible difference between them ($P = 0.42$).

Bleeding complications and causes of death

Bleeding is one of the most crucial complications of anticoagulation therapy. One patient with arterial thromboembolism and 12 patients with VTE experienced bleeding problems. A patient with arterial thromboembolism and bleeding was due to an idiopathic arterial hemorrhage from a branch of the femoral artery; this patient required ECMO care and was treated with embolization. VTE cases included 6 cases of catheter or puncture site bleeding, 3 cases of gastrointestinal bleeding, 2 cases of airway bleeding, and 1 case of intramuscular bleeding. Eleven cases had severe COVID-19 infection that required ventilator treatment, except for one case of gastrointestinal bleeding. In addition, six cases required ECMO.

One case of stroke had been receiving therapeutic doses of anticoagulants since admission but was discontinued at the time of onset due to bleeding complications. Bleeding complications among patients with VTE occurred in four cases with prophylactic doses of anticoagulants and in eight cases with therapeutic doses.

There were ten deaths among the patients who developed thrombosis: 3 from arterial thromboembolism and 7 from VTE. All causes of death in arterial thromboembolism cases were related to COVID-19. The leading causes

Table 3 Details of individual cases who developed arterial thrombosis during hospitalization

	Types of thrombosis	Age (years)	Sex	Body weight (kg)	Body mass index (kg/m^2)	D-dimer level on admission (μg/mL)	Comorbidities	Anticoagulation therapy	Severity of COVID-19 on admission	Worst severity of COVID-19 during hospitalization	Prognosis at discharge
Patient 1	Ischemic cerebral infarction	61	Men	66.0	19.7	15.0	None	prophylactic	Mild	Mild	Alive
Patient 2	Ischemic cerebral infarction	55	Men	83.0	26.2	2.2	Hypertension, Diabetes mellitus, Respiratory disease	prophylactic	Moderate	Moderate	Alive
Patient 3	Ischemic cerebral infarction	72	Women	53.0	22.9	2.5	None	therapeutic	Moderate	Moderate	Alive
Patient 4	Ischemic cerebral infarction	57	Men	90.0	30.4	1.9	Hypertension	prophylactic	Mild	Moderate	Alive
Patient 5	Ischemic cerebral infarction	57	Men	72.0	22.7	1.7	None	therapeutic	Severe	Severe	Alive
Patient 6	Ischemic cerebral infarction	65	Men	77.8	25.4	28.5	Hypertension	discontinued due to bleeding (therapeutic)	Severe	Severe	Alive
Patient 7	Ischemic cerebral infarction	51	Men	67.2	24.7	140.2	Respiratory disease	prophylactic	Severe	Severe	Alive
Patient 8	Ischemic cerebral infarction	68	Men	67.1	23.9	1.8	Hypertension, Diabetes mellitus	prophylactic	Moderate	Severe	Dead COVID-19
Patient 9	Ischemic cerebral infarction	87	Men	61.7	23.7	1.5	Heart disease, History of VTE	prophylactic	Severe	Severe	Dead COVID-19
Patient 10	Myocardial infarction	48	Men	74.2	24.0	0.7	None	therapeutic	Moderate	Moderate	Alive
Patient 11	Myocardial infarction	59	Men	89.0	31.2	0.5	None	prophylactic	Moderate	Moderate	Dead COVID-19
Patient 12	Acute limb ischemia	70	Men	59.3	20.2	0.6	Hypertension, Diabetes mellitus	prophylactic	Moderate	Moderate	Alive

COVID-19: coronavirus disease 2019; VTE: venous thromboembolism

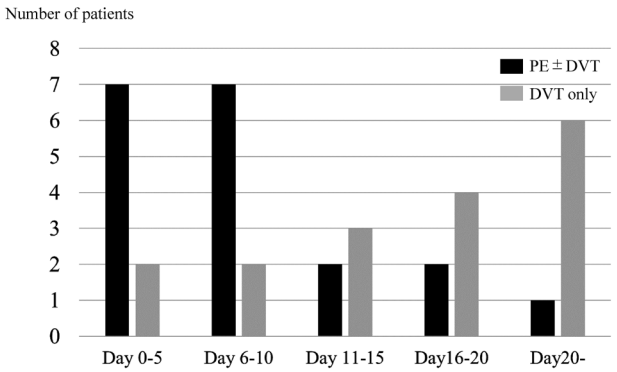

Fig. 2 The timing of onset for VTE.
VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis

of death in six patients with VTE were pneumonia and multiorgan failure linked to COVID-19 infection, and sepsis associated with catheter-related blood stream infection in one case.

Characteristics of patients with arterial thrombosis and VTE in Waves 4 and 5

The characteristics of VTE in Wave 4 of the predominantly alpha variant and Wave 5 of the predominantly delta variant in Japan are shown in **Supplementary Tables 1** and **2**. There were four patients with arterial thrombosis in Wave 4 and 8 patients in Wave 5. There was no significant difference in baseline characteristics, comorbidities, severity of COVID-19, or other factors between the waves. There were three deaths in arterial embolization cases, and all were in Wave 4 and related to COVID-19.

There were 20 patients with VTE in Wave 4 and 16 patients with VTE in Wave 5. There was no significant difference in COVID-19 severity at admission between Waves 4 and 5, whereas patients in Wave 5 more frequently received ECMO. Proximal DVT without PE was observed only in Wave 5 and mostly in ECMO cases.

Discussion

The present study detailed the clinical features of arterial thrombosis and VTE in Japan. Arterial thrombosis in patients with COVID-19 was less common compared with VTE, although ischemic cerebral infarction appeared to be relatively common in COVID-19 patients. There was no difference in the characteristics of patients with arterial thromboembolism or VTE except for the high severity of COVID-19 infection during hospitalization.

In the present study, the incidence of arterial thrombosis tends to be lower at 0.4% compared with 3.7%–4.4% in Europe.[22,23] Compared with patients with VTE, there were few cases of a high body mass index, and D-dimer values on admission were not relatively high. Notably, 42% of patients who developed arterial thrombosis had no comorbidities. This could imply that the development of COVID-19 could result in arterial thrombosis even in the absence of known atherosclerosis risk factors. Due to the systemic thrombotic tendency, thrombus in the thoracic aorta wall and coexistence with venous thrombosis were also experienced. Cerebral infarction was the most common cause of arterial thrombosis. Because symptoms appeared even in small thromboses, it is possible that they were detectable frequently. A thrombus formation in the aortic arch was detected in one case that could have potentially caused a cerebral infarction. Onset was bimodally distributed at the time of admission and for approximately 10 days, suggesting that attention should also be paid to impaired consciousness on admission and during the recovery phase of COVID-19.

PE is commonly thought to be a disease often attributed to embolism caused by DVT in the lower extremities, but COVID-19 has been noted to cause pulmonary thrombosis.[22] In the present study, PE was seen alone in 21% of cases. Furthermore, PE is frequently present alone in early-onset thrombosis, which may reflect thrombosis caused by COVID-19. PE occurred relatively early, within 10 days of admission, and is considered to be a COVID-19-related thrombosis. In addition, many of the patients with PE without DVT had emboli in relatively large pulmonary arteries.

Most of the bleeding complications occurred in patients with severe COVID-19. Half were severe enough to require ECMO, and bleeding at the puncture site and other procedure sites was common. Critically ill patients are at risk for bleeding regardless of a COVID-19 infection, and patients undergoing ECMO are especially at risk for bleeding.[24] Anticoagulation is mostly required in the treatment of VTE in critically ill patients, but its intensity must be carefully monitored. Few patients with DVT developed bleeding, forcing the discontinuation of anticoagulation therapy; similarly, stroke cases had atrial fibrillation but could not be treated with anticoagulants to avoid bleeding. In severe cases, prophylactic doses lead to fewer bleeding complications than therapeutic doses.[4] Independent factors for major bleeding have been reported, including a history of major bleeding, severe COVID-19 infection, and use of anticoagulants.[12] Anticoagulation in these patient groups requires more caution. When the risk of bleeding decreases, it may be necessary to consider the resumption of appropriate anticoagulation therapy.

This study was conducted during Waves 4 and 5, caused by the alpha and delta variants, respectively. There were almost no significant differences in the occurrence of arterial thrombosis, but more deaths occurred in Wave 4 than in Wave 5. The deaths were caused by COVID-19-related respiratory failure. In patients with VTE during Wave

5, proximal DVT without PE occurred more frequently. Based on the results of more ECMO procedures in Wave 5, it was thought that catheter-related thrombosis associated with ECMO increased along with the severity of COVID-19. Patients developed thrombosis during both waves, and a thrombotic tendency due to COVID-19 was observed. Attention should be continually paid to the possibility of thrombosis in patients with a severe COVID-19 infection.

Study limitations

The present study was a retrospective one, and not all patients received imaging examinations for determining the presence of thrombosis. Therefore, there might be undetected thrombosis. The data were obtained in the middle of the COVID-19 pandemic, which caused some difficulties in obtaining detailed clinical data, including vaccination status and treatment for COVID-19. Each institution had a unique method for preventing and diagnosing VTE, along with different circumstances that led to its diagnosis. As a result, data regarding VTE in patients with asymptomatic COVID-19 is incomplete, making it difficult to determine the prevalence of complications such as asymptomatic thrombosis.

Conclusion

Among patients with COVID-19, arterial thrombosis was less common compared with VTE, although ischemic cerebral infarction seemed to be relatively common, and a certain number of patients developed arterial thrombosis even in the absence of known atherosclerosis risk factors.

Acknowledgments

While the number of ECMO patients increased in Wave 5 in Japan, the reduction in mortality in patients with thrombosis may be due to the dedicated work of the medical professionals working on COVID-19 around the clock. We sincerely hope that our findings will be useful for the treatment of patients with COVID-19. Throughout the present study, we are grateful for the support and collaboration of the Japanese Society of Phlebology and the Japanese Society of Pulmonary Embolism Research. Ms. Emi Kuroki of the Japanese Society of Phlebology provided us with technical assistance.

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Conflict of Interest

All the authors have stated that they have no relevant relationships to disclose about the contents of this paper.

IRB Information

The research protocol was approved by the relevant review boards or ethics committees in all participating centers. Fukushima Daiichi Hospital was the primary institution for the ethics committee (Approval number: 2021-11-2).

Author Contributions

Study conception: all authors
Data collection: all authors
Analysis: MU, YY
Investigation: all authors
Writing: MU, YY
Critical review and revision: all authors
Final approval of the article: all authors
Accountability for all aspects of the work: all authors

Supplementary Materials

Supplementary materials are available at the online article sites on J-STAGE and PMC.

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