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ORIGINAL ARTICLE
Epidemiology

D-Dimer Values and Venous Thromboembolism in Patients With COVID-19 in Japan

— From the CLOT-COVID Study —

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Background: To date, there are no large-scale data on the association between D-dimer levels at admission and the occurrence of venous thromboembolism (VTE) in Japanese patients with coronavirus disease 2019 (COVID-19).

Methods and Results: The CLOT-COVID study was a retrospective, multicenter cohort study enrolling consecutive hospitalized patients with COVID-19 across 16 centers in Japan from April 2021 to September 2021. Among 2,894 enrolled patients, 2,771 (96%) had D-dimer levels measured at admission. Patients were divided into 3 groups based on tertiles of D-dimer levels at admission (1st tertile, D-dimer ≤0.5 μg/mL, n=949; 2nd tertile, D-dimer 0.51–1.09 μg/mL, n=894; 3rd tertile, D-dimer ≥1.1 μg/mL, n=928). The higher the tertile group, the more severe the COVID-19 status at admission. The incidence of VTE during hospitalization was highest in the 3rd tertile group (1st tertile, 0.3%; 2nd tertile, 0.3%; 3rd tertile, 3.6%; P<0.001). Even after adjusting for confounders in the multivariable logistic regression model, the higher D-dimer levels in the 3rd tertile (≥1.1 μg/mL) were independently associated with a higher risk of VTE during hospitalization (adjusted odds ratio 4.83 [95% confidence interval 1.93–12.11; P<0.001]; reference=1st tertile).

Conclusions: Higher D-dimer levels at admission were associated with a higher risk of VTE events during hospitalization in Japanese patients with COVID-19. This could be helpful in determining patient-specific anticoagulation management strategies for COVID-19 in Japan.

Key Words: COVID-19; D-dimer; Venous thromboembolism

The association between coronavirus disease 2019 (COVID-19) infection and arterial and venous thrombosis, including venous thromboembolism (VTE), has been reported worldwide.[1–10] In Western countries, anticoagulation therapy has been recommended for all hospitalized COVID-19 patients due to the high risk of thrombosis and the potential benefit for improvement of the survival rate by the primary prevention of thrombosis, but this remains controversial, especially with regard to the optimal intensity of anticoagulation therapy.[11] In contrast, previous studies have suggested that the risk of thrombosis in Japanese patients with COVID-19 may be relatively

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low, and racial differences may have to be considered when deciding anticoagulation management strategies.[12,13]

The International Society of Thrombosis and Haemostasis (ISTH) interim guidance on the recognition and management of coagulopathy in COVID-19 recommends measuring coagulation markers in all patients with COVID-19.[14] D-Dimer, thought to be one of the most important coagulation markers for the risk assessment of COVID-19-related thrombosis, could be helpful in determining more suitable patients for anticoagulation therapy. In fact, D-dimer levels have been one of the major inclusion criteria in several previous randomized clinical trials investigating optimal anticoagulation therapy for COVID-19.[14–17] However, to date, there limited data are available regarding the relationship between the occurrence of VTE and D-dimer levels in COVID-19 patients in Japan.[18] Therefore, the aim of this study was to assess the association between D-dimer levels at admission and VTE events during hospitalization in patients with COVID-19, using the database of a large-scale, multicenter observational study for COVID-19.

Methods

Study Population

The CLOT-COVID study (Thrombosis and Anticoagulation Therapy in patients with COVID-19 in Japan Study; University Hospital Medical Information Network [UMIN] Clinical Trials Registry ID: UMIN45800) is a retrospective, physician-initiated, multicenter cohort study that enrolled consecutive hospitalized patients with COVID-19 across 16 centers in Japan from April 2021 to September 2021 (the fourth and fifth waves of COVID-19 infections in Japan). This study was conducted by dedicated members of the Taskforce of VTE and COVID-19 in Japan in collaboration with the Japanese Society of Phlebology and the Japan Pulmonary Embolism Study Group.[13] Patients with a positive polymerase chain reaction test and a diagnosis of COVID-19 were consecutively enrolled from the hospital databases.

In all, 2,894 patients were enrolled into the CLOT-COVID study. After excluding 123 patients without D-dimer levels at admission, the present study population consisted of 2,771 (96%) patients who had D-dimer levels measured at admission. The study population was divided into 3 groups based on tertiles of D-dimer levels at admission: 1st tertile, D-dimer ≤0.5 μg/mL; 2nd tertile, D-dimer 0.51–1.09 μg/mL; 3rd tertile, D-dimer ≥1.1 μg/mL.

Ethics Approval and Consent to Participate

All procedures in this study were performed in accordance with the Declaration of Helsinki. The relevant review boards or ethics committees of all participating institutions approved the study protocol. Because clinical information obtained in routine clinical practice was used, the requirement for written informed consent from each patient was waived. This method is consistent with the Japanese Ministry of Health, Labor and Welfare's guidelines for epidemiological studies.

Data Collection

Electronic reports were used to collect patient data and follow-up information. Data on patient characteristics, pharmacological thromboprophylaxis management, and clinical outcomes were collected from hospital medical records or hospital databases according to prespecified definitions. The physicians at each institution were responsible for data entry into an electronic case report form. Furthermore, general office staff manually checked the data for omissions, inconsistencies, and values outside the expected range.

Definitions for Patient Characteristics

Hypertension was diagnosed if the peripheral blood pressure was 140/90 mmHg or higher or if the patient was taking medication for hypertension. Diabetes was diagnosed based on HbA1c levels (National Glycohemoglobin Standardization Program [NGSP], 6.5%) and was assumed if the patient was taking medication for diabetes. Heart disease was defined as any heart disease, including heart failure, angina pectoris, and previous myocardial infarction. Heart failure was diagnosed if a patient had a history of hospitalization for heart failure, symptoms due to heart failure (New York Heart Association [NYHA] functional class ≥2), or a left ventricular ejection fraction <40%. Respiratory diseases were defined as persistent lung diseases such as asthma, chronic obstructive pulmonary disease, and restrictive pulmonary disease. Patients with active cancer were defined as those undergoing cancer treatment, such as chemotherapy or radiotherapy, those scheduled for cancer surgery, those with metastasis to other organs, and/or those with end-stage cancer.[19] A history of major bleeding was diagnosed if the patient had an ISTH history of major bleeding, consisting of a decrease in hemoglobin levels of at least 2 g/dL, the transfusion of at least 2 units of blood, and symptomatic bleeding in a critical site or organ.[20] The severity of the COVID-19 was classified as mild, moderate, or severe; patients who did not require oxygen were defined as having mild COVID-19, those who required oxygen were defined as having moderate COVID-19, and those who required mechanical ventilation or extracorporeal membrane oxygenation were defined as having severe COVID-19.

The unfractionated heparin therapeutic dose was defined as unfractionated heparin administration targeting the therapeutic range with reference to the activated partial thromboplastin time (APTT). The unfractionated heparin prophylactic dose was defined as a fixed dose of unfractionated heparin and was not based on the APTT.

Clinical Outcomes

The primary outcome measure in the present study was VTE during the hospitalization. VTE was defined as pulmonary embolism (PE) and deep vein thrombosis (DVT) that was objectively confirmed by imaging studies (ultrasound, contrast-enhanced computed tomography, ventilation-perfusion lung scintigraphy, pulmonary angiography, contrast-enhanced venography) or autopsy. PE was classified into 5 categories according to the most central pulmonary artery site where the thrombi were located, namely the main trunk pulmonary artery, the left or right main pulmonary artery, the lobar artery, the segmental artery, or the subsegmental artery. Proximal DVT was defined as venous thrombosis occurring in the popliteal, femoral, or iliac veins. Distal DVT was defined as venous thrombosis located in the calf veins, including the peroneal, posterior tibial, anterior tibial, and soleus muscle veins below the knee.

Secondary outcome measures in the present study were major bleeding and all-cause death during hospitalization. Major bleeding was diagnosed as ISTH major bleeding, which consisted of a reduction in the hemoglobin level by

Table 1. Patient Characteristics, Pharmacological Thromboprophylaxis Management, and Imaging Examinations During Hospitalization

	Total (n=2,771)	D-dimer tertiles			P value
		1st (n=949; D-dimer ≤0.5 μg/mL)	2nd (n=894; D-dimer 0.51–1.09 μg/mL)	3rd (n=928; D-dimer ≥1.1 μg/mL)	
Baseline characteristics					
Age (years)	53.4±17.0	47.7±17.0	52.5±15.3	60.0±16.2	<0.001
Men	1,820 (65.7)	611 (64.4)	592 (66.2)	617 (66.5)	0.58
Body weight (kg)	69.7±17.7	68.6±17.1	72.4±18.8	68.7±17.7	<0.001
Height (cm)	165.1±10.1	165.3±10.5	165.7±10.1	164.4±9.6	0.020
Body mass index (kg/m^2)	25.4±5.3	25.0±5.2	26.2±5.6	25.2±5.2	<0.001
Body mass index >30 kg/m^2	449 (16.2)	139 (14.6)	173 (19.4)	137 (14.8)	0.008
D-dimer at admission (μg/mL)	0.80 [0.50–1.30]	0.50 [0.50–0.50]	0.77 [0.62–0.90]	1.63 [1.30–2.87]	<0.001
Comorbidities					
Hypertension	842 (30.4)	207 (21.8)	295 (33.0)	340 (36.6)	<0.001
Diabetes	582 (21.0)	125 (13.2)	206 (23.0)	251 (27.0)	<0.001
Heart disease	244 (8.8)	60 (6.3)	70 (7.8)	114 (12.3)	<0.001
Respiratory disease	289 (10.4)	88 (9.3)	95 (10.6)	106 (11.4)	0.31
Active cancer	55 (2.0)	7 (0.7)	13 (1.5)	35 (3.8)	<0.001
History of major bleeding	25 (0.9)	4 (0.4)	6 (0.7)	15 (1.6)	0.014
History of VTE	13 (0.5)	4 (0.4)	2 (0.2)	7 (0.8)	0.23
Severity of COVID-19 at admission					
Mild	1,643 (59.3)	791 (83.4)	540 (60.4)	312 (33.6)	
Moderate (needing oxygen)	913 (32.9)	148 (15.6)	316 (35.3)	449 (48.4)	<0.001
Severe (mechanical ventilation)	215 (7.8)	10 (1.1)	38 (4.3)	167 (18.0)	
Pharmacological thromboprophylaxis					
Anticoagulants	1,218 (44.0)	198 (20.9)	384 (43.0)	636 (68.5)	<0.001
Unfractionated heparin of prophylactic dose	680/1,218 (55.8)	88/198 (44.4)	229/384 (59.6)	363/636 (57.1)	
Unfractionated heparin of therapeutic dose	154/1,218 (12.6)	4/198 (2.0)	28/384 (7.3)	122/636 (19.2)	
Low-molecular-weight heparin of prophylactic dose	192/1,218 (15.8)	58/198 (29.3)	64/384 (16.7)	70/636 (11.0)	
Low-molecular-weight heparin of therapeutic dose	0/1,218 (0.0)	0/198 (0.0)	0/384 (0.0)	0/636 (0.0)	
Direct oral anticoagulants	161/1,218 (13.2)	39/198 (19.7)	52/384 (13.5)	70/636 (11.0)	
Warfarin	19/1,218 (1.6)	7/198 (3.5)	6/384 (1.6)	6/636 (0.9)	
Imaging examinations during hospitalization					
Any imaging examination	145/2,771 (5.2)	12/949 (1.3)	23/894 (2.6)	110/928 (11.9)	<0.001
Ultrasound examination of the lower extremities	38/2,771 (1.4)	5/949 (0.5)	5/894 (0.6)	28/928 (3.0)	<0.001
Contrast-enhanced CT examination	120/2,771 (4.3)	9/949 (0.9)	20/894 (2.2)	91/928 (9.8)	<0.001
Reasons for performing contrast-enhanced CT					
Suspicion of VTE	58/120 (48.3)	7/9 (77.8)	5/20 (25.0)	46/91 (50.5)	
Other reasons	62/120 (51.7)	2/9 (22.2)	15/20 (75.0)	45/91 (49.5)	

Unless indicated otherwise, data are given as the mean±SD, median [interquartile range], or n (%). Unfractionated heparin of therapeutic dose was defined as administration of unfractionated heparin targeting the therapeutic range with a reference to the activated partial thromboplastin time (APTT). Unfractionated heparin of prophylactic dose was defined as administration of a fixed dose of unfractionated heparin without reference to the APTT. CT, computed tomography; VTE, venous thromboembolism.

at least 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ.[20]

Statistical Analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as the mean±SD or the median and interquartile range (IQR) based on their distributions. Categorical variables were compared with the Chi-squared test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using analysis of variance (ANOVA) or the Kruskal-Wallis test depending on their distributions. Clinical outcomes are presented as numbers of events and percentages. To adjust for clinically relevant variables, we constructed a multivariable logistic regression model to estimate the adjusted odds ratio (OR) and its 95% confidence interval (CI) of the 3rd tertile of D-dimer levels at admission, using the 1st tertile as the reference, for VTE events during hospitalization. Consistent with previous reports,[10,21,22] and in consideration of clinical relevance, 4 risk-adjusting variables of patient characteristics at admission (age, sex, body mass index >30 kg/m^2, and severity of COVID-19 at admission)

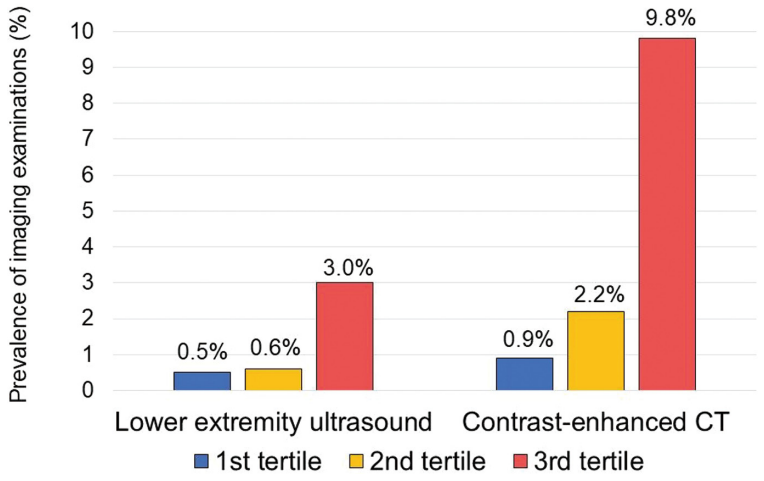

Figure 1. Prevalence of imaging examinations during hospitalization according to tertiles of D-dimer levels at admission. CT, computed tomography.

Table 2. Clinical Outcomes During Hospitalization

	Total (n=2,771)	D-dimer tertiles			P value
		1st (n=949; D-dimer ≤0.5 μg/mL)	2nd (n=894; D-dimer 0.51–1.09 μg/mL)	3rd (n=928; D-dimer ≥1.1 μg/mL)	
VTE	39/2,771 (1.4)	3/949 (0.3)	3/894 (0.3)	33/928 (3.6)	<0.001
Day from admission to VTE event (days)	11 [4–19]	9 [8–25]	17 [10–19]	10 [3–19]	
VTE types					
PE with DVT	13/39 (33.3)	1/3 (33.3)	1/3 (33.3)	11/33 (33.3)	
PE only	8/39 (20.5)	1/3 (33.3)	1/3 (33.3)	6/33 (18.2)	
DVT only	18/39 (46.2)	1/3 (33.3)	1/3 (33.3)	16/33 (48.5)	
Location of thrombi in PE (n=21)					
Main trunk pulmonary artery	2/21 (9.5)	1/2 (50.0)	0/2 (0.0)	1/17 (5.9)	
Left or right main pulmonary artery	6/21 (28.6)	0/2 (0.0)	1/2 (50.0)	5/17 (29.4)	
Lobar artery	9/21 (43)	0/2 (0.0)	1/2 (50.0)	8/17 (47.1)	
Segmental artery	2/21 (9.5)	0/2 (0.0)	0/2 (0.0)	2/17 (11.8)	
Subsegmental artery	2/21 (9.5)	1/2 (50.0)	0/2 (0.0)	1/17 (5.9)	
Location of thrombi in DVT (n=31)					
Proximal DVT	8/31 (25.8)	1/2 (50.0)	1/2 (50.0)	6/27 (22.2)	
Distal DVT	12/31 (38.7)	0/2 (0.0)	1/2 (50.0)	11/27 (40.7)	
Veins in the upper extremities	7/31 (22.6)	0/2 (0.0)	0/2 (0.0)	7/27 (25.9)	
Others	4/31 (12.9)	1/2 (50.0)	0/2 (0.0)	3/27 (11.1)	
Major bleeding	55/2,771 (2.0)	6/949 (0.6)	12/894 (1.3)	37/928 (4.0)	<0.001
All-cause death	149/2,771 (5.4)	11/949 (1.2)	22/894 (2.5)	116/928 (12.5)	<0.001

Unless indicated otherwise, data are given as the median [interquartile range] or n (%). Pulmonary embolism (PE) was classified into 5 categories according to the most central pulmonary artery site where the thrombi were located: the main trunk pulmonary artery, left or right main pulmonary artery, the lobar artery, the segmental artery, or the subsegmental artery. Proximal deep vein thrombosis (DVT) was defined as venous thrombosis that was located in the popliteal, femoral, or iliac veins. Distal DVT was defined as venous thrombosis located in calf veins including the peroneal, posterior tibial, anterior tibial, and soleus muscle veins below the knee. VTE, venous thromboembolism.

were selected, in addition to pharmacological thromboprophylaxis. All statistical analyses were performed using SPSS version 23. All reported P values are 2-tailed, and P<0.05 was considered statistically significant.

Results

Patient Characteristics at Admission

The median D-dimer level at admission in the entire cohort was 0.8 μg/mL (IR 0.5–1.3 μg/mL). Based on D-dimer levels, patients were divided into three groups (1st tertile, n=949; 2nd tertile, n=894; 3rd tertile, n=928), with median (IQR) D-dimer levels in the 1st, 2nd, and 3rd tertiles being 0.50 (0.50–0.50), 0.77 (0.62–0.90), and 1.63 (1.30–2.87) μg/mL, respectively. Patient characteristics differed in several aspects; the higher the D-dimer tertile, the older patients were, and the more prevalent hypertension, diabetes, heart disease, active cancer, and a history of major bleeding were (**Table 1**). The higher the tertile group, the more severe the COVID-19 status at admission, with 83.4%, 60.4%, and 33.6% of

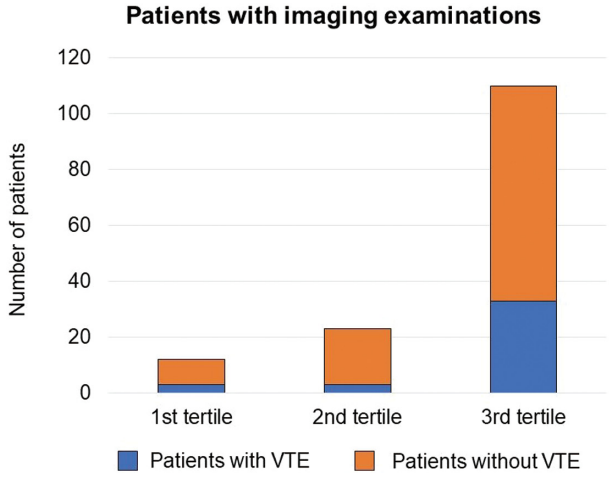

Figure 2. Patients with and without venous thromboembolism (VTE) among those with imaging examinations according to tertiles of D-dimer levels at admission. The incidence rates of VTE among patients with imaging examinations were 25.0% in the 1st tertile, 13.1% in the 2nd tertile, and 30.0% in the 3rd tertile.

patients in the 1st, 2nd, and 3rd tertiles, respectively, having mild COVID-19, 15.6%, 35.3%, and 48.4% of patients having moderate COVID-19, and 1.1%, 4.3%, and 18.0% of patients having severe COVID-19 (P<0.001).

Pharmacological Thromboprophylaxis Management and Imaging Examinations During Hospitalization

The higher the tertile group, the more frequent the pharmacological thromboprophylaxis (20.9%, 43.0%, and 68.5% of patients in the 1st, 2nd, and 3rd tertiles, respectively; P<0.001; **Table 1**). Patients in the 3rd tertile received anticoagulants, with prophylactic-dose heparin being the most common type of anticoagulation (57.1%; 363/636), followed by therapeutic-dose heparin (19.2%; 122/636).

During hospitalization, contrast-enhanced CT and ultrasound examinations of the lower extremities were performed in 4.3% (120/2,771) and 1.4% (38/2,771) of patients in the entire study population, respectively (**Table 1**). Patients in the 3rd tertile more frequently underwent both contrast-enhanced CT and ultrasound examinations of the lower extremities (contrast-enhanced CT: 0.9%, 2.2%, and 9.8% of patients in the 1st, 2nd, and 3rd tertiles, respectively [P<0.001]; lower extremity ultrasound: 0.5%, 0.6%, and 3.0% of patients in the 1st, 2nd, and 3rd tertiles, respectively [P<0.001]; **Figure 1**).

Clinical Outcomes

The incidence of VTE during hospitalization was highest in the 3rd tertile (0.3%, 0.3%, and 3.6% in the 1st, 2nd, and 3rd tertiles, respectively; P<0.001; **Table 2**). Even after adjusting for confounders in the multivariable logistic regression model, the higher D-dimer levels in the 3rd tertile (≥1.1 μg/mL) were independently associated with a higher risk of VTE during hospitalization (adjusted OR 4.83; 95% CI 1.93–12.11; P<0.001; reference=1st tertile; **Supplementary Table**). The incidence rates of VTE among patients with imaging examinations (VTE-positive rates) were 25.0% in the 1st tertile, 13.1% in the 2nd tertile, and 30.0% in the 3rd tertile (**Figure 2**).

Similarly, the incidence of major bleeding and all-cause death during hospitalization was highest in the 3rd tertile (major bleeding: 0.6%, 1.3%, and 4.0% of patients in the 1st, 2nd, and 3rd tertiles, respectively [P<0.001]; all-cause death: 1.2%, 2.5%, and 12.5% of patients in the 1st, 2nd, and 3rd tertiles, respectively [P<0.001]; **Table 2**).

Discussion

The main findings of the present study are that: (1) patient characteristics differ in several aspects according to D-dimer levels at admission, including a more severe COVID-19 status of admission in the higher D-dimer tertiles with a higher prevalence of pharmacological thromboprophylaxis; and (2) patients in higher D-dimer tertiles more frequently underwent imaging examinations, and had a higher risk of the occurrence of VTE.

There are several points to keep in mind when interpreting the results of the present study. The incidence of VTE in the present study was lower than that in previous studies from outside Japan.[1–10] However, it is unclear whether this is due to racial differences or the lower prevalence of imaging examinations. The possibility that the incidence of VTE events was underestimated due to a lower prevalence of imaging examinations needs to be considered. Conversely, the incidence of VTE may not necessarily be low, considering that many patients received pharmacological thromboprophylaxis.

The present study showed an association between the D-dimer level at admission and the severity of COVID-19 infection. Previous reports have shown an association between the severity of COVID-19 infection and the incidence of thrombotic events.[12] Even for diseases other than COVID-19, the frequency of thrombosis increases in severely ill patients, including those with longer bed rest and complications of disseminated intravascular coagulation. However, in a previous report, the incidence of VTE was higher in patients admitted to the intensive care unit (ICU) with COVID-19 than in patients admitted to the ICU with other diseases or other viral infections.[9] This suggests that COVID-19 itself may be associated with the higher risk of thrombosis, independent of the severity of a patient's general condition, and that it is important to strive to prevent thrombosis.

It has been shown that D-dimer levels are associated with the development of thrombosis and the mortality of COVID-19 patients.[23–26] For this reason, some guidance

recommends that coagulation markers, including D-dimer levels, should be evaluated first in the treatment of patients with COVID-19 and that low-molecular-weight heparin should be administered to all patients who require hospitalization unless there are contraindications.[14] However, there are still insufficient data in Japan. The present study revealed the usefulness of D-dimer measurements in predicting the development of VTE in Japanese patients with COVID-19.

In the present study we divided D-dimer levels into tertiles, and approximated the cut-off values frequently used in clinical practice (0.5 and 1.0), which may be applicable to clinical practice. As in previous reports, the prevalence of imaging examinations including contrast-enhanced CT examinations and ultrasound examination of the lower extremities during hospitalization seemed to be low in the present study. The prevalence of imaging examinations was significantly higher for patients in the 3rd tertile than in the other tertiles, but was still only 11.9%. This may be due to the possibility that the respiratory symptoms of COVID-19 could have obscured the onset of PE, and so not enough imaging examinations were performed, or trying to avoid contact between COVID-19-positive patients and technicians, or problems in the hospital's conduits. However, the VTE-positive rate was higher in the 3rd tertile group than in the other 2 groups. In addition, even after adjusting for confounders, the adjusted risk of VTE in the 3rd tertile group was significantly higher, with an adjusted OR of 4.83, which seemed to have a major impact on the occurrence of VTE. In this sense, D-dimer levels at admission could be a very important biomarker for stratifying the risk of VTE in Japanese patients with COVID-19. More aggressive imaging examinations may be reasonable for patients with high D-dimer levels at admission, especially when VTE is suspected.

Study Limitations

The present study has several limitations. First, the CLOT-COVID study was based on observational cohort data from 16 selected institutions in Japan, and the clinical decisions regarding the management and examination strategies were at the discretion of the attending physicians. In actual clinical practice for COVID-19, the rate of imaging tests was very low in terms of in-hospital conduits and contact avoidance. Therefore, the 145 cases examined by imaging studies represent a very limited cohort. To minimize the effect of this selection bias as much as possible, the D-dimer values of all 2,771 patients were assessed. Second, D-dimer testing methods and detection thresholds may differ among institutions. Third, these data were from patients hospitalized with COVID-19 in Japan from April 2021 to September 2021. Since new variants of COVID-19 have been emerging, application of the present results to all COVID-19 patients should be done with caution.

Conclusions

Higher D-dimer levels at admission were associated with a higher risk of VTE during hospitalization in Japanese patients with COVID-19, which could be helpful in determining patient-specific anticoagulation management strategies for COVID-19 in Japan.

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Disclosures

None of the authors have any relationships to disclose that are relevant to the contents of this paper.

IRB Information

The relevant review boards or ethics committees of all participating centers approved the research protocol. The ethics committee of the primary institution was the Ethics Committee of Fukushima Daiichi Hospital (Approval no. 2021-11-2).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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