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Original Article

Risk Factors and Impact on Outcomes of Thrombosis in Patients with COVID-19 in Japan: From the CLOT-COVID Study

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Objectives: The relationship between the thrombotic event and prognosis in patients with coronavirus disease 2019 (COVID-19) has not yet been fully investigated in Japan. Our study aimed to investigate the clinical outcomes and risk factors for thrombosis in hospitalized patients with COVID-19 in Japan.

Materials and Methods: We compared the patient characteristics and clinical outcomes among patients with thrombosis (N=55) and those without thrombosis (N=2839) by using a large-scale data of CLOT-COVID study (thrombosis and antiCoaguLatiOn Therapy in patients with COVID-19 in Japan Study: UMIN000045800). Thrombosis included venous thromboembolism, ischemic stroke, myocardial infarction, and systemic arterial thromboembolism.

Results: Higher rates of mortality and bleeding events were shown in hospitalized patients with COVID-19 with thrombosis compared to those without thrombosis (all-cause mortality, 23.6% vs. 5.1%, P<0.001; major bleeding, 23.6% vs. 1.6%, P<0.001). Multivariable analysis revealed that the independent risk factors of thrombosis were male sex, D-dimer level on admission>1.0 μg/mL, and moderate and severe COVID-19 status on admission.

Conclusions: The development of thrombosis in hospitalized patients with COVID-19 was related to higher mortality and major bleeding, and several independent risk factors for thrombosis could help determine the patient-appropriate treatment for COVID-19.

Keywords: COVID-19, thrombosis, risk factors, clinical outcomes

Introduction

Coronavirus disease 2019 (COVID-19) has high complication rates of thrombosis, including venous and arterial thrombosis.[1–7] The thrombosis with COVID-19 has been reported in 20%–30% hospitalized patients in Western

countries.[1,2,4] However, previous studies have shown that COVID-19-related thrombosis in Japanese hospitalized patients was considerately lower than that in other countries,[8–10] which could be related to the relatively low mortality rate of COVID-19 in Japan.[11] The risk factors of thrombosis due to COVID-19 could differ depending on racial differences, patient clinical background, and local medical resource availability. In addition to an increased risk of thrombosis, patients with COVID-19 might be exposed to the risk of excessive bleeding due to factors such as coagulation factor consumption in severe inflammation, disproportion in platelet production and destruction, and the use of anticoagulant agents.[12] Therefore, the risk assessment for thrombosis could be clinically crucial to determine the optimized anticoagulation treatment for COVID-19. However, there is little data on the clinical features and outcomes involved in the development of thrombosis in patients with COVID-19 in Japan. Therefore, we conducted a survey on risk factors and outcomes for thrombosis in patients with COVID-19 using a large observation database in Japan.

Materials and Methods

Study population and data collection

We conducted the CLOT-COVID study (thrombosis and antiCoaguLatiOn Therapy in patients with COVID-19 in Japan Study: UMIN000045800), which is a physician-driven, multicenter, retrospective cohort study in Japan.[13] Consecutive patients with COVID-19 who were hospitalized in 16 institutions were registered from April to September 2021. We divided the patients across the cohort into those with thrombosis and those without. Thrombosis included venous thromboembolism, ischemic stroke, myocardial infarction, and systemic arterial thromboembolism. Patient background data and progress information were collected from medical records or databases of each facility using electronic reports, according to predefined definitions. Physicians in each facility performed data entry into the electronic reports, and the central office reviewed the collected data for missing, contradictory, and outlier values.

All procedures in the present study were implemented in accordance with the Helsinki Declaration. The study protocol was authorized by the ethics committees of each participating institutions. Due to the use of clinical information derived during daily clinical practices, the requirement of written informed consent was exempted. This study is consistent with the epidemiological research guidelines by the Ministry of Health, Labour and Welfare. The ethics committee of Fukushima Daiichi Hospital was the primary institution (IRB Approval number: 2021-11-2).

Definitions

The detailed definitions of thrombosis and other patient characteristics in the CLOT-COVID study have been previously reported.[13] The severity of COVID-19 was defined as "mild" if the patient did not need oxygen, "moderate" if the patient needed oxygen, and "severe" if the patient needed mechanical ventilation or extracorporeal membrane oxygenation. Pharmacological thromboprophylaxis was defined as follows: the therapeutic dose of heparin was defined upon administration, targeting the therapeutic range with reference to the activated partial thromboplastin time. The prophylactic dose of heparin was defined upon administration at a fixed dose without reference to the activated partial thromboplastin time. Direct oral anticoagulants and warfarin were administered to patients who had been taking anticoagulants prior to hospitalization, as well as to those who had received them after hospitalization. Direct oral anticoagulants were provided based on the patient's body weight or renal function. The use of thromboprophylaxis was determined by the attending physician at each institution without a defined regimen.

The clinical outcomes included all-cause death and major bleeding during hospitalization. The causes of death were categorized as respiratory failure due to COVID-19 pneumonia, pulmonary thromboembolism (PE), thrombosis other than PE, and other causes. The death due to PE or thrombosis was defined if the patient died after the onset of clinically serious PE or thrombotic event without other cause of death, or if diagnosed via autopsy. Major bleeding was diagnosed in accordance with the definition of International Society of Thrombosis and Hemostasis.[14]

Statistical analysis

Categorical variables were shown as numbers and percentages and compared using the chi-square test or Fisher's exact test. Continuous variables were shown as mean and standard deviation or median and interquartile range, and compared using Student's t-test or Wilcoxon's rank-sum test. The clinical outcomes were shown as the number of events and percentages. To estimate the odds ratio (OR) and 95% confidence interval (CI) of the risk factors for thrombosis, we conducted the multivariable regression model. We chose five variables of patient characteristics [age, sex, body mass index (BMI) >30 kg/m^2, D-dimer level on admission >1.0 μg/mL, and severity of COVID-19 on admission] in consistent with previous reports[15] and in considering clinical propriety. The patients whose D-dimer data was missing on admission were excluded. The cutoff value of D-dimer level >1.0 μg/mL was determined based on the clinical cutoff value for thrombosis in daily clinical practice. We analyzed the data using R (version 4.0.2, R Core Team). All P-values were reported as two-tailed, and $P<0.05$ was considered statistically significant.

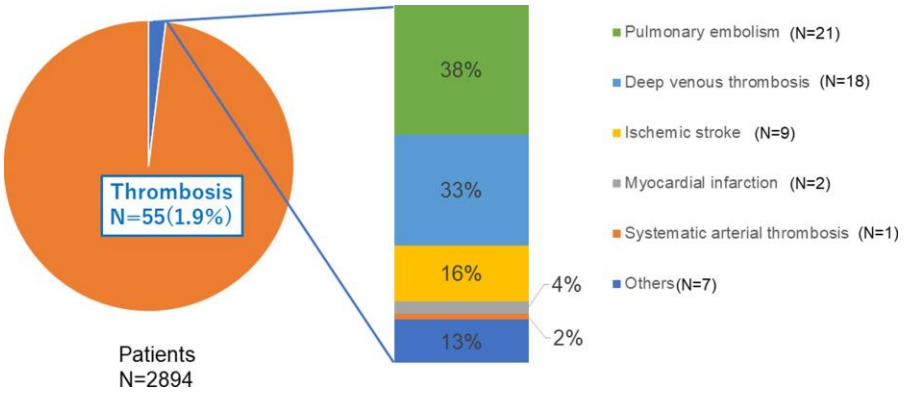

Fig. 1 Sites of thrombosis development in hospitalized patients with COVID-19. Three patients developed thrombosis at two or more sites.

Results

A total of 2894 patients with COVID-19 were enrolled in this study. Fifty-five patients (1.9%) developed thrombosis. Of those, 39 (71%) developed venous thromboembolism, including 21 (38%) PE and 18 (33%) deep venous thrombosis cases. Twelve patients (22%) developed arterial thrombosis including nine (16%) ischemic stroke, two (4%) myocardial infarction, and one (2%) systemic thromboembolism cases. Three patients developed thrombosis at two or more sites (**Fig. 1**). The average time of the thrombotic events from admission was 14.1 days (4–19 days).

Patient characteristics and pharmacological thromboprophylaxis

The mean age, male gender, mean body weight, and mean height were higher in patients with thrombosis (59 vs. 53 years old, P=0.006; 85.5% vs. 64.7%, P=0.001; 74.5 vs. 68.8 kg, P=0.02; and 167.9 vs. 164.3 cm, P=0.03, respectively) (**Table 1**). The median length of hospitalization was longer in patients with thrombosis than in those without thrombosis (33 vs. 9 days, P<0.001). The rate of hypertension (47.3% vs. 29.9%, P= 0.007) and the median D-dimer level on admission (2.3 vs. 0.8 μg/mL, P<0.001) were significantly higher in patients with thrombosis. Patients with thrombosis showed higher severity of COVID-19 on admission compared to those without thrombosis (severe, 34.5% vs. 7.4%; moderate, 51.0% vs. 31.7%; and mild, 14.5% vs. 60.9%, P<0.001). The similar tendency was found for the worst severity during hospitalization (severe: 65.5% vs. 12.2%, moderate: 30.9% vs. 42.7%, and mild: 3.6% vs. 45.1%, P<0.001). Among 55 patients with thrombosis, 53 patients (96.3%) had received anticoagulation therapy prior to thrombosis diagnosis. The rate of administration of pharmacological thromboprophylaxis was higher in patients with thrombosis than in those without (96.4% vs. 42.0%, P<0.001) (**Table 1**). Among 39 patients with venous thromboembolism, anticoagulation therapy was provided after making a diagnosis of thrombosis. Twenty-nine, five, and one patient received low-molecular-weight heparin, direct oral anticoagulants, and other anticoagulants, respectively, while four patients did not receive anticoagulation therapy.

Clinical outcomes

All-cause mortality was 5.5% and significantly higher in patients with thrombosis (23.6% vs. 5.1%; P<0.001) (**Table 2**). The vast majority of causes of death were respiratory failure due to COVID-19 pneumonia, which showed the same trend in both groups. There was no event ascertained as death due to fatal PE. Among the patients with arterial thrombosis, 2/9 patients with ischemic stroke and 1/2 patients with myocardial infarction died from respiratory failure due to COVID-19 pneumonia. The rate of major bleeding events was 2.0% and significantly higher in patients with thrombosis (23.6% vs. 1.6%; P<0.001). Of the 57 patients with major bleeding, the site with the most bleeding was gastrointestinal in 25 (43.9%) patients, followed by surgery related or iatrogenic in 11 (19.3%), intracranial in four (7.0%), respiratory in two (3.5%), intrathoracic or intraabdominal in two (3.5%), urinary in one (1.8%) and subcutaneous in one (1.8%) (**Table 2**).

Risk factors of thrombosis

After multivariate logistic regression analysis, male sex (OR 2.75; 95%CI, 1.28–5.93; P=0.01), D-dimer level on admission>1.0 μg/mL (OR 5.22; 95%CI, 2.40–11.30; P<0.001), moderate (OR 3.52; 95%CI, 1.55–8.01; P=0.003) and severe (OR 7.50; 95%CI, 3.07–18.30; P=0.03) COVID-19 on admission were independently associated with thrombosis during hospitalization (**Table 3**).

Table 1 Patient characteristics and pharmacological thromboprophylaxis

	Total (N=2894)	Patients with thrombosis (N=55)	Patients without thrombosis (N=2839)	P value
Baseline characteristics				
Age (years)	53±18	59±13	53±18	0.006
Men	1885 (65.1%)	47 (85.5%)	1838 (64.7%)	0.001
Body weight (kg)	68.9±18.5	74.5±16.5	68.8±18.5	0.02
Height (cm)	164.4±12.4	167.9±7.8	164.3±12.4	0.03
Body mass index (kg/m^2)	25.3±5.4	26.5±5.5	25.2±5.4	0.09
Body mass index >30 kg/m^2	459 (15.9%)	12 (21.8%)	447 (15.7%)	0.26
D-dimer level on admission* (μg/mL)	0.8 (0.5–1.3)	2.3 (1.4–5.9)	0.8 (0.5–1.2)	<0.001
D-dimer level on admission>1.0 μg/mL*	974 (33.7%)	46 (83.6%)	928 (32.7%)	<0.001
Length of hospitalization (days)	9 (6–14)	33 (20–49)	9 (6–14)	<0.001
Comorbidities				
Hypertension	874 (30.2%)	26 (47.3%)	848 (29.9%)	0.007
Diabetes mellitus	597 (20.6%)	16 (29.1%)	581 (20.5%)	0.13
Heart disease	255 (8.8%)	6 (10.9%)	249 (8.8%)	0.63
Respiratory disease	298 (10.3%)	3 (5.5%)	295 (10.4%)	0.37
Active cancer	60 (2.1%)	0 (0.0%)	60 (2.1%)	0.63
History of major bleeding	28 (1.0%)	1 (1.8%)	27 (1.0%)	0.42
History of venous thromboembolism	15 (0.5%)	1 (1.8%)	14 (0.5%)	0.25
Severity of COVID-19 on admission				
Mild	1738 (60.1%)	8 (14.5%)	1730 (60.9%)	<0.001
Moderate	927 (32.0%)	28 (51.0%)	899 (31.7%)	
Severe	229 (7.9%)	19 (34.5%)	210 (7.4%)	
Worst severity of COVID-19 during hospitalization				
Mild	1283 (44.3%)	2 (3.6%)	1281 (45.1%)	<0.001
Moderate	1230 (42.5%)	17 (30.9%)	1213 (42.7%)	
Severe	381 (13.2%)	36 (65.5%)	345 (12.2%)	
Pharmacological thromboprophylaxis	1245 (43.0%)	53 (96.4%)	1192 (42.0%)	<0.001
Prophylactic dose of unfractionated heparin	685 (55.0%)	24 (45.3%)	661 (55.5%)	
Therapeutic dose unfractionated heparin	161 (12.9%)	18 (34.0%)	143 (12.0%)	
Prophylactic dose of low-molecular-weight heparin	204 (16.4%)	7 (13.2%)	197 (16.5%)	
Therapeutic dose of low-molecular-weight heparin	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Direct oral anticoagulants	164 (13.2%)	3 (5.7%)	161 (13.5%)	
Warfarin	19 (1.5%)	0 (0.0%)	19 (1.6%)	
Others	12 (1.0%)	1 (1.9%)	11 (0.9%)	

*The patients whose D-dimer data was missing on admission were excluded (N=2771).

Discussion

The major findings of the present study are as follows: (i) the development of thrombosis in patients with COVID-19 was associated with higher mortality and bleeding risk during hospitalization, (ii) patient characteristics differed in several aspects comparing patients with thrombosis and those without, and (iii) independent risk factors of thrombosis during hospitalization in patients with COVID-19 were male sex, D-dimer level >1.0 μg/mL on admission, and moderate to severe status of COVID-19 on admission.

The increased incidence of thrombosis is known to be related with COVID-19. A number of mechanisms are thought to be contributed to elevated thrombosis in COVID-19. Primarily, COVID-19 affects the not only the respiratory system but also the vascular system, which could contribute to elevated thrombosis risk, including elevated levels of inflammatory cytokines and increased systematic inflammation with endothelial injury.[16] Moreover, immobility under ventilator and using of central venous catheters in intensive care unit become contributing factors to a prothrombotic status in COVID-19. A previous meta-analysis including 42 studies enrolling 8271 patients reported that COVID-19 thrombosis is associated with a greater mortality. In this study, overall mortality was 23% among patients with thrombosis and 13% among those without thrombosis.[17] The present study showed

Table 2 Clinical outcomes

	Total (N=2894)	Patients with thrombosis (N=55)	Patients without thrombosis (N=2839)	P value
All-cause death	158 (5.5%)	13 (23.6%)	145 (5.1%)	<0.001
Causes of death				
Respiratory failure due to COVID-19 pneumonia	128 (81.0%)	10 (76.9%)	118 (81.4%)	
Pulmonary thromboembolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Thrombosis other than pulmonary thromboembolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Other causes	30 (19.0%)	3 (23.1%)	27 (18.6%)	
Major bleeding	57 (2.0%)	13 (23.6%)	44 (1.6%)	<0.001
Bleeding sites				
Intracranial	4 (7.0%)	0 (0.0%)	4 (9.1%)	
Respiratory	2 (3.5%)	2 (15.4%)	0 (0.0%)	
Gastrointestinal	25 (43.9%)	3 (23.1%)	22 (50.0%)	
Urinary	1 (1.8%)	0 (0.0%)	1 (2.3%)	
Intrathoracic or Intraabdominal	2 (3.5%)	0 (0.0%)	2 (4.5%)	
Surgery related or Iatrogenic	11 (19.3%)	7 (53.8%)	4 (9.1%)	
Subcutaneous	1 (1.8%)	0 (0.0%)	1 (2.3%)	
Others	11 (19.3%)	1 (7.7%)	10 (22.7%)	

Table 3 Multivariable analysis for the risk factors for thrombosis during hospitalization

	Univariate		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per 1 year)	1.02 (1.01–1.04)	0.006	1.01 (0.99–1.03)	0.43
Men	3.20 (1.51–6.80)	0.002	2.75 (1.28–5.93)	0.01
Body mass index >30 kg/m^2	1.49 (0.78–2.85)	0.23	1.65 (0.81–3.36)	0.17
D-dimer level on admission>1.0 μg/mL	10.00 (4.88–20.50)	<0.001	5.22 (2.40–11.30)	<0.001
Severity of COVID-19 on admission				
Mild	—	—	—	—
Moderate (versus mild)	6.74 (3.06–14.80)	<0.001	3.52 (1.55–8.01)	0.003
Severe (versus mild)	19.60 (8.46–45.20)	<0.001	7.50 (3.07–18.30)	0.03

OR: odds ratio

considerably higher mortality in patients with thrombosis (23.6%), compared to those without thrombosis (5.1%). The overall mortality of COVID-19 is relatively lower in Japan than that in Western countries[11]; however, the present study revealed that the mortality among hospitalized patients with COVID-19 with thrombosis is as high as that in Western countries. Overall mortality (5.5%) in the present study showed a similar tendency as that in the previous Japanese registry in a different study period.[10]

Interestingly, despite the higher mortality among patients with thrombosis in the present study, no patients died from PE or arterial thrombosis, and the major cause of death was COVID-19 pneumonia. That is, thrombosis associated with COVID-19 could be involved in pathogenesis indirectly exacerbating mortality. The immunothrombosis and prothrombotic conditions with COVID-19 are related to the development of thrombosis, which could contribute to exacerbation of patient condition. The explanation leads to the fact that the present study showed moderate to severe condition of COVID-19 as the independent risk factor for thrombosis. Since developing pulmonary embolism worsens oxygenation and the severity of COVID-19, it might be better to consider these patients separately when analyzing the severity during hospitalization. Of the 21 patients who developed pulmonary embolism during hospitalization, COVID-19 worsened in seven patients, 2/2 patients with mild COVID-19 worsened to moderate, and 5/8 patients with moderate COVID-19 worsened to severe COVID-19. In a subgroup analysis with respect to the categories that exclude the seven patients who developed pulmonary embolism that worsened the severity of COVID-19 during hospitalization, the analysis for patient characteristics, clinical outcomes, and multivariable analysis for the risk factors for thrombosis showed similar tendencies to the main analysis, except for mean body weight (**Supplemental Tables 1**–**3**).

In a previous multicenter trial, independent factors for venous thromboembolism were advancing age, cancer, longer interval from symptom onset, and higher D-dimer level on admission.[7] In concordance with the study, higher D-dimer level on admission was an independent risk factor for thrombosis in the present study. Active cancer was not found to be a risk factor for thrombosis, but this might be due to a relatively lower rate in the present study. In the present study, most patients with thrombosis had been received anticoagulation therapy prior to the diagnosis of thrombosis. It could thus be considered that thromboprophylaxis might have been used for patients who were suspected of having thrombosis, such as those with elevated D-dimer levels, decreased oxygenation, or severe status of COVID-19. It should be noted that a severe status, such as immobility under ventilator and use of central venous catheters in the intensive care unit, may contribute to the development of a prothrombotic status in COVID-19 cases.

A previous study showed that patients with COVID-19 were at a relatively high risk of bleeding with anticoagulation therapy.[18] In line with the previous study, the present study revealed that patients with thrombosis had a higher risk of bleeding and high rate of pharmacological thromboprophylaxis therapies, and the opposite was true for patients with major bleeding. Patients with major bleeding were administered pharmacological thromboprophylaxis (51/57 patients; 89.5%), while 13 of 57 (22.8%) patients developed thrombosis. This issue could be more important, particularly in Asians, because Asians have a higher bleeding risk related to anticoagulation agents compared to Caucasians.[19] Therefore, it is important to consider the balance between thrombotic events and bleeding risks in patients those with different ethnic backgrounds when administrating pharmacological thromboprophylaxis agents. Previous studies have shown a high incidence of venous thromboembolism in intensive care units despite pharmacological thromboprophylaxis,[3,4] which implied that patients are at high risk of thrombosis despite anticoagulation therapy, especially those with more severe COVID-19. Recently, a large-scale study integrating randomized control trials reported that therapeutic dose anticoagulation in non-severe patients could have benefit compared to prophylactic dose anticoagulation.[20] In contrast, another study showed no benefit of therapeutic dose anticoagulation for critically ill patients admitted to intensive care units.[21] Two other randomized control trials in patients with moderate and with increased D-dimer levels reported that therapeutic dose anticoagulation was shown to reduce mortality.[22,23] However, only a small number of Asians were enrolled in all these studies. Although the doses and types of anticoagulation therapy are still controversial, the independent risk factors and outcomes for thrombosis in the present study could be valuable for clinicians when determining more suitable anticoagulation treatment in patients with COVID-19. Further studies are needed to confirm the association of various thrombotic events and establish treatment to improve outcomes of patients with COVID-19.

The present study has some limitations. First, this observational study could be affected by various biases constituent in the study design particularly the course of the treatment, including the administration and intensity of anticoagulation therapy or oxygen prescription, since it was at the discretion of the attending physician of each facility. Second, the definitions of severity in the present study have a minor difference from those in the COVID-19 Clinical Practice Guidelines issued by the Japanese Ministry of Health, Labour and Welfare. Third, there was no data on kidney disease and the number of patients who were originally administered anticoagulants or antithrombotic drugs before hospitalization, which might have some impact on the clinical outcomes. Fourth, there were several missing data on the D-dimer levels on admission and at the time of the thrombotic events. Furthermore, the screening of thrombosis had not been performed in all patients, which could lead to the underdiagnosis of thrombosis. Multivariate analysis with many variables could not be performed because the total number of outcomes was quite small.

Conclusions

Development of thrombosis in hospitalized patients with COVID-19 was associated with higher mortality and bleeding risk. Several independent risk factors for thrombosis could help to determine the optimal treatment strategies for patients with COVID-19.

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Disclosure Statement (COI)

All authors declare no conflict of interest.

Author Contributions

Study conception: YY, MM
Data collection: SY, MT, YN, IT, JN, NY, HN, SI, MU, SA, HH, HS, YO, EI, YO, NI, AK, TI, MM, YY
Analysis and Investigation: SY, MT, YY
Manuscript preparation: SY
Funding acquisition: YY
Critical review and revision: all authors
Final approval of the article: all authors
Accountability for all aspects of the work: all authors

Supplementary Information

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

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