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ORIGINAL ARTICLE

Association Between the Development of Thrombosis and Worsening of Disease Severity in Patients With Moderate COVID-19 on Admission

— From the CLOT-COVID Study —

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Background: The worsening of coronavirus disease 2019 (COVID-19) severity is a critical issue in current clinical settings and may be associated with the development of thrombosis.

Methods and Results: This study used patient data obtained in the CLOT-COVID study, a retrospective multicenter cohort study. The demographics of patients with moderate COVID-19 on admission with and without worsened severity during hospitalization were compared and predictors were identified. Of 927 patients with moderate COVID-19 on admission, 182 (19.6%) had worsened severity during hospitalization. Patients with worsening of severity were older, more likely to have hypertension, diabetes, heart disease, and active cancer, and more likely to use pharmacological thromboprophylaxis. Patients with worsening of severity had higher D-dimer levels on admission and were more likely to develop thrombosis and major bleeding during hospitalization than those without worsening. Increased age (odds ratio [OR]: 1.02, 95% confidence interval [CI]: 1.01–1.03, P=0.005), diabetes (OR: 1.63, 95% CI: 1.11–2.33, P=0.012), D-dimer levels >1.0 μg/mL on admission (OR: 2.10, 95% CI: 1.45–3.03, P<0.001), and thrombosis (OR: 6.28, 95% CI: 2.72–14.53, P<0.001) were independently associated with worsening of COVID-19 severity.

Conclusions: Approximately 20% of patients with moderate COVID-19 had worsened severity during hospitalization. Increased age, diabetes, D-dimer levels >1.0 μg/mL on admission, and the development of thrombosis during hospitalization were significantly associated with worsened COVID-19 severity.

Key Words: COVID-19; D-dimer; Thrombosis; Worsening of the severity

Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the severity of COVID-19 infections ranges from asymptomatic to severe respiratory disease.[1] Although most of patients with COVID-19 do not have severe symptoms at diagnosis,[2] some patients, especially moderately ill patients, experience worsening of the severity of COVID-19, which may require admission to intensive care units (ICUs) for critical care including mechanical ventilation support and extracorporeal membrane oxygenation (ECMO).[2] Therefore, the worsening of COVID-19 severity during hospitalization is a clinically

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relevant issue, and identifying risk factors for worsening of COVID-19 severity is critical.

Previous studies have reported that advanced age, male gender, and several comorbidities are associated with severity and mortality in COVID-19.[1,3] Hypoxemic respiratory failure is the most common cause of clinical deterioration in hospitalized patients with COVID-19[4] and pulmonary endothelial injury and microvascular thrombosis contribute to respiratory compromise.[5] The coagulation cascade can be disrupted with systemic inflammation, resulting in the development of thrombosis.[6] Previous reports describing the complications of COVID-19 identified increased coagulation activation as an important marker of disease severity and mortality risk.[7,8] Several recent studies have reported a high prevalence of venous thromboembolism (VTE) in more severe cases of COVID-19, suggesting that VTE is associated with COVID-19 severity.[9–13] Therefore, the development of thrombosis may be associated with the worsening COVID-19 severity. However, their association has not been fully elucidated. In this study, the demographics of patients with and without worsening of the severity of COVID-19 during hospitalization were compared and the risk factors for worsening of COVID-19 severity in patients who were moderately ill on admission were investigated.

Methods

Study Population

The CLOT-COVID Study (Thrombosis and AntiCoaguLatiOn Therapy in patients with COVID-19 in Japan Study: UMIN000045800) is a physician-initiated, retrospective, multicenter, cohort study that enrolled all consecutive hospitalized patients with COVID-19 at 16 centers in Japan from April 2021 to September 2021. This study aimed to investigate the incidence of thrombosis and the real-world management strategies for anticoagulation therapy in patients with COVID-19 during the fourth and fifth waves of the COVID-19 pandemic,[14] which were predominantly caused by the α and δ variants of SARS-CoV-2, respectively, in Japan.

The present study was conducted by the dedicated members of the Taskforce of VTE and COVID-19 in Japan in a collaborative effort with the Japanese Society of Phlebology and Japanese Society of Pulmonary Embolism Research.[15] Consecutive patients who were diagnosed with COVID-19 with a positive polymerase chain reaction (PCR) test were enrolled through the hospital databases.

In this study, the data of 927 moderately-ill patients who had COVID-19 on hospital admission were evaluated. Worsening of severity was defined as the progression of patients with COVID-19 to a severe status or all-cause death during hospitalization. Regarding the severity of COVID-19, patients with mild COVID-19 were defined as those who did not require oxygen supplementation, patients with moderate COVID-19 were defined as those who required oxygen supplementation, and patients with severe COVID-19 were defined as those requiring mechanical ventilation or ECMO.

This study was conducted in accordance with the Declaration of Helsinki. The relevant review boards or ethics committees at all participating centers approved the research protocol. The requirement of written informed consent was waived due to the use of clinical information obtained during routine clinical practices. This study is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare in Japan.

Data Collection

Patient data and follow-up information were recorded using an electronic report form. Patient characteristics, pharmacological thromboprophylaxis management, and clinical outcomes were obtained from the hospital charts or hospital databases according to pre-specified definitions. The physicians at each institution entered the patient data into an electronic case report form. The data were manually checked at the general office for missing or contradictory input and values out of the expected range.

Definitions of Patient Characteristics

Hypertension was diagnosed if peripheral blood pressure was >140/90 mmHg or if the patient was prescribed medication for hypertension. Diabetes was diagnosed if the hemoglobin A1c was >6.5% or was assumed if the patient was prescribed medication for the treatment of diabetes. Heart disease was defined as heart failure, angina pectoris, or a history of myocardial infarction. Heart failure was diagnosed if the patient had a history of a hospitalization for heart failure, symptoms due to heart failure (New York Heart Association functional class ≥2), or a left ventricular ejection fraction <40%. Respiratory disease was defined as persistent lung disorders such as asthma, chronic obstructive pulmonary disease, or restrictive lung diseases. Patients with active cancer were defined as those receiving treatment for cancer, such as chemotherapy or radiotherapy, scheduled to undergo cancer surgery, or those with metastasis to other organs and/or terminal cancer.[16] A history of major bleeding was defined using the International Society of Thrombosis and Hemostasis (ISTH) major bleeding definition, which includes a ≥2 g/dL reduction in hemoglobin, the transfusion of ≥2 units of blood, or symptomatic bleeding in a critical area or organ.[17]

A therapeutic dose of unfractionated heparin was defined as the administration of unfractionated heparin targeting the therapeutic range using a referenced activated partial thromboplastin time (APTT). A prophylactic dose of unfractionated heparin was defined as the administration of unfractionated heparin in a fixed dose without referring to the patient's APTT.

Clinical Outcomes

The primary outcome of this study was thrombosis during hospitalization after patients were diagnosed with COVID-19 via a positive PCR test. Thrombosis included VTE, ischemic stroke, myocardial infarction, and systemic arterial thromboembolism during the hospitalization. VTE was defined as pulmonary embolism (PE) and/or deep vein thrombosis (DVT) objectively confirmed by imaging examinations (ultrasound, contrast-enhanced computed tomography [CT],

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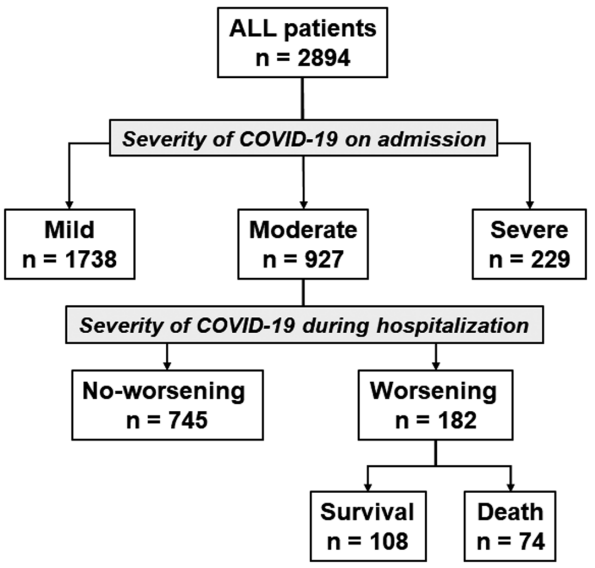

Figure 1. Flow chart of the Thrombosis and AntiCoaguLatiOn Therapy in patients with COVID-19 in Japan Study (CLOT-COVID) study, which enrolled 2,894 patients with COVID-19, including 927 patients with moderate COVID-19 who were evaluated in the present study. Of these patients, 182 (19.6%) had worsened COVID-19 severity during hospitalization, including 108 (59.3%) who survived and 74 (40.7%) who died during hospitalization. COVID-19, coronavirus disease 2019.

ventilation-perfusion lung scintigraphy, pulmonary angiography, or contrast venography) or by autopsy. Ischemic stroke was defined as stroke either requiring or prolonging hospitalization with symptoms lasting for >24 h. Myocardial infarction was defined in accordance with the universal myocardial infarction guidelines.[18] The secondary outcome was major bleeding episodes during hospitalization, defined using the ISTH major bleeding definition.[17]

Statistical Analysis

Continuous values were tested for normal distribution using the Kolmogorov-Smirnov test and are presented as the mean and standard deviation (SD) for parametric data or as the median and interquartile range (IQR) for non-parametric data. Categorical variables are presented as numbers and percentages. The unpaired t-test or Mann-Whitney U-test were used to compare continuous variables, and the Chi-squared test or Fisher's exact test were used to compare categorical variables. A multivariable logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence interval (CI) of risk factors for the worsening of COVID-19 severity during hospitalization. Potential variables were selected based on previous reports[2,19,20] and also included the development of thrombosis and major bleeding. Variables with P values <0.05 on univariate logistic analysis were included in the multivariate logistic regression analysis. All statistical analyses were performed using SPSS (version 23.0; SPSS, Inc., Chicago, IL, USA). All reported P values were 2-tailed, and statistical significance was set at P<0.05.

Results

Among 2,894 patients admitted to the participating hospitals with COVID-19, 927 (32.0%) had moderate COVID-19. Overall, the condition of 182 COVID-19 patients (19.6%) had worsened during hospitalization, including 108 (59.3%) who survived and 74 (40.7%) who died during hospitalization (**Figure 1**).

Patient Characteristics and Management Strategies

COVID-19 patients with worsening of severity during hospitalization were older (P<0.001), had a significantly higher prevalence of comorbidities, including hypertension (P<0.001), diabetes (P<0.001), heart disease (P=0.002), and active cancer (P=0.017), and had a higher D-dimer level on admission (P<0.001) compared to patients without worsened COVID-19 severity during hospitalization (**Table 1**). Furthermore, patients with worsening of severity during hospitalization had more comorbidities (**Supplementary Figure**). Pharmacological thromboprophylaxis was more likely to be administered to patients with worsening of COVID-19 severity (88.5%) than those without (71.4%, P<0.001) (**Table 1**). Contrast-enhanced CT examinations were performed more often in patients with worsened severity (22.5%) than in those without (3.4%; P<0.001).

Incidences of Thrombosis and Major Bleeding

Patients who had worsened COVID-19 severity were more likely to develop thrombosis during hospitalization than those without worsened COVID-19 severity (9.3% vs. 1.5%, P<0.001) (**Table 2**). Patients with the worsening of COVID-19 severity were more likely to develop VTE during hospitalization than those without (7.7% vs. 0.7%, P<0.001), whereas there was no significant difference in the incidence of arterial thrombotic events between the 2 groups (1.6% vs. 0.8%, P=0.711). Thrombosis occurred more frequently in patients with worsening of COVID-19 severity regardless of prophylactic anticoagulant use (**Figure 2**). Patients with worsened COVID-19 severity were more likely to develop major bleeding during hospitalization than those without worsened severity (5.5% vs. 1.5%, P=0.001).

Risk Factors of Worsening COVID-19 Severity After Admission

The univariate logistic regression analysis revealed that increased age, hypertension, diabetes, heart disease, active cancer, D-dimer level >1.0 μg/mL on admission, development of thrombosis, and development of major bleeding were significantly associated with worsening of COVID-19 severity (**Table 3**). Interestingly, in the multivariate logistic regression analysis, only increased age (adjusted OR: 1.02, 95% CI: 1.01–1.03, P<0.001), diabetes (adjusted OR: 1.63, 95% CI: 1.11–2.33, P=0.012), D-dimer >1.0 μg/mL on admission (adjusted OR: 2.10, 95% CI: 1.45–3.03, P<0.001), and development of thrombosis (adjusted OR: 6.28, 95% CI: 2.72–14.53, P<0.001) were independently associated with the worsening of the severity of COVID-19. The development of thrombosis showed the strongest association with the worsening of COVID-19 severity.

Discussion

This study revealed that patients who had worsening of the severity of COVID-19 during hospitalization were older, had a significantly higher prevalence of several comorbidi-

Table 1. Patient Characteristics and Management Strategies During Hospitalization

	Patients with moderate COVID-19 on admission (N=927)	Worsening of severity during hospitalization (N=182)	No worsening of severity during hospitalization (N=745)	P value
Baseline characteristics				
Age (years)	57.9±14.7	63.9±14.2	57.2±14.9	<0.001
Sex (male)	638 (68.8)	132 (72.5)	506 (67.9)	0.229
Body weight (kg)	70.0 (60.0–80.0)	70.0 (60.3–81.3)	70.0 (60.0–80.0)	0.636
BMI (kg/m^2)	25.2 (22.6–28.7)	25.7 (23.1–29.5)	25.0 (22.5–28.6)	0.195
>30	163 (17.6)	38 (20.9)	125 (16.9)	0.193
D-dimer level on admission (μg/mL) (N=913)	1.03 (0.70–1.60)	1.40 (0.90–2.52)	1.00 (0.70–1.50)	<0.001
Comorbidities				
Hypertension	353 (38.1)	93 (51.1)	260 (34.9)	<0.001
Diabetes	241 (26.0)	66 (36.3)	175 (23.5)	<0.001
Heart disease	98 (10.6)	31 (17.0)	67 (9.0)	0.002
Respiratory disease	103 (11.1)	19 (10.4)	84 (11.3)	0.748
Active cancer	23 (2.5)	9 (4.9)	14 (1.9)	0.017
History of major bleeding	9 (1.0)	2 (1.1)	7 (0.9)	0.844
History of VTE	4 (0.4)	0 (0.0)	4 (0.5)	0.322
Pharmacological thromboprophylaxis managements				
Anticoagulants	693 (74.8)	161 (88.5)	532 (71.4)	<0.001
Unfractionated heparin of a prophylactic dose	446 (48.1)	86 (47.3)	360 (48.3)	
Unfractionated heparin of a therapeutic dose	72 (7.8)	43 (23.6)	29 (3.9)	
Low molecular-weight heparin of a prophylactic dose	60 (7.0)	8 (4.4)	52 (7.0)	
Low molecular-weight heparin of a therapeutic dose	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
Direct oral anticoagulants	101 (10.9)	22 (12.1)	79 (10.6)	
Warfarin	9 (1.0)	1 (0.5)	8 (1.1)	
Others	3 (0.3)	0 (0.0)	3 (0.4)	
Imaging examinations during hospitalization				
Ultrasound examination of the lower extremities	23 (2.5)	3 (1.6)	20 (2.7)	0.420
Contrast-enhanced CT examination	66 (7.1)	41 (22.5)	25 (3.4)	<0.001
Reasons for performing contrast-enhanced CT				
Suspicion of VTE	29 (3.1)	18 (9.9)	11 (1.5)	<0.001
Other reasons	37 (4.0)	23 (12.6)	14 (1.9)	
Hospitalized period (days)	12.0 (9.0–18.0)	17.0 (10.0–26.0)	11.0 (8.0–16.0)	<0.001

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean and standard deviation or the median and interquartile range based on their distributions. Unfractionated heparin of a therapeutic dose was defined as the administration of unfractionated heparin targeting a therapeutic range referencing the APTT. Unfractionated heparin of a prophylactic dose was defined as the administration of unfractionated heparin of a fixed dose without referencing the APTT. APTT, activated partial thromboplastin time; BMI, body mass index; CT, computed tomography; COVID-19, coronavirus disease 2019; VTE, venous thromboembolism.

ties, had higher D-dimer levels on admission, and were more likely to receive pharmacological thromboprophylaxis than patients without worsened COVID-19. Patients with worsened severity of COVID-19 were more likely to develop thrombosis during hospitalization, regardless of prophylactic anticoagulant use, and the development of thrombosis was independently associated with worsened COVID-19 severity after admission.

Severe COVID-19 occurs in 15–30% of hospitalized individuals and results in in-hospital death in 30–70% of patients, depending on patient age and comorbidities.[2,21] A previous study undertaken in the United States reported that 302/787 patients (38%) admitted with mild to moderate COVID-19 progressed to more severe status or death.[22] A previous Chinese study reported that 19.6% of patients with moderate COVID-19, 27.8% of patients with severe COVID-19, and 66.7% of patients with critical COVID-19 experienced disease progression during a median follow up time of 24 days.[23] A recent Japanese study reported that 49/210 patients (23%) exhibiting no or mild COVID-19 symptoms on admission required oxygen supplementation during hospitalization.[24] The nationwide COVID-19 Registry in Japan (COVIREGI-JP) study reported that mechanical ventilation or ECMO was required during hospitalization in 2.0% of patients with non-severe and 26.4% of patients with severe COVID-19.[25] In this study, 19.6% of patients with moderate COVID-19 upon admission had worsening of COVID-19 severity, which is consistent with previous reports.

COVID-19 has been associated with the disruption of the coagulation cascade that results in pulmonary microthrombi and arterial and/or venous thrombotic-related events.[6] VTE has been reported as the most common thrombosis, as its incidence in patients with COVID-19 is

Table 2. Clinical Outcomes During Hospitalization

	Patients with moderate COVID-19 on admission (N=927)	Worsening of severity during hospitalization (N=182)	No worsening of severity during hospitalization (N=745)	P value
Thrombosis	28 (3.0)	17 (9.3)	11 (1.5)	<0.001
VTE	19 (2.0)	14 (7.7)	5 (0.7)	<0.001
PE with or without DVT	8 (0.9)	5 (2.7)	3 (0.4)	
DVT only	11 (1.2)	9 (4.9)	2 (0.3)	
Arterial thrombotic events	9 (1.0)	3 (1.6)	6 (0.8)	0.711
Ischemic stroke	3 (0.3)	1 (0.5)	2 (0.3)	
Myocardial infarction	2 (0.2)	1 (0.5)	1 (0.1)	
Systemic arterial thromboembolism	1 (0.1)	0 (0.0)	1 (0.1)	
Other thrombosis	3 (0.3)	1 (0.5)	2 (0.3)	
Major bleeding	21 (2.3)	10 (5.5)	11 (1.5)	0.001

The clinical outcomes are presented as numbers of events and percentages. DVT, deep vein thrombosis; PE, pulmonary embolism. Other abbreviations as in Table 1.

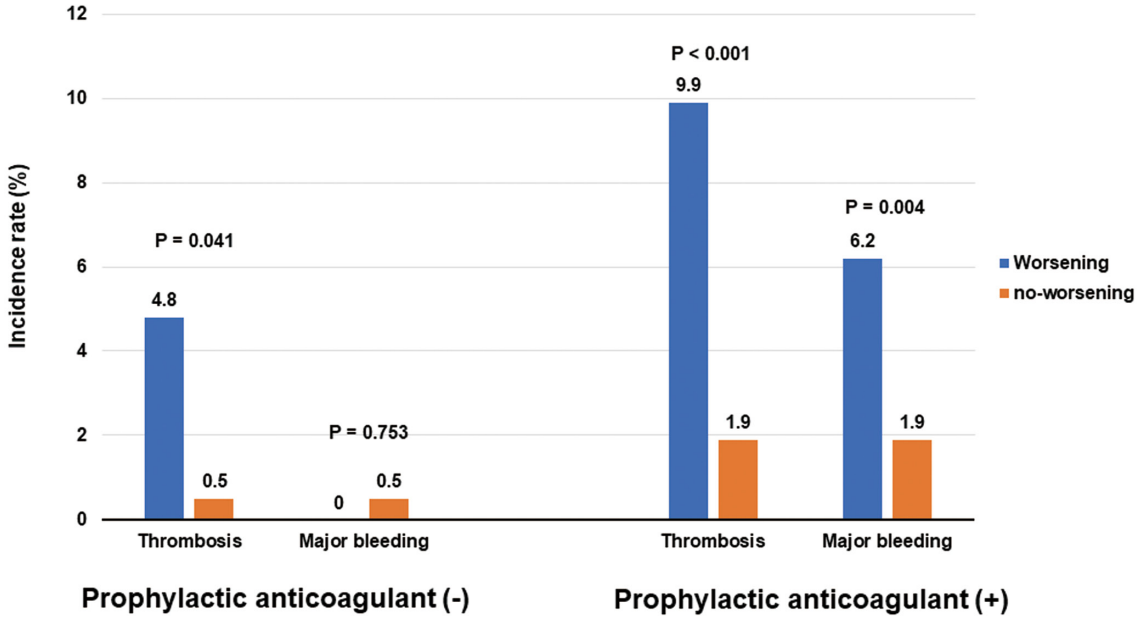

Figure 2. Incidence of thrombosis and major bleeding in patients with and without worsening of the severity of coronavirus disease 2019 (COVID-19) stratified by the presence or absence of prophylactic anticoagulant administration. Thrombosis occurred more frequently in patients with worsened COVID-19 severity regardless of the administration of prophylactic anticoagulants.

20–43%, typically in the form of PE.[26] Recent systematic reviews and metanalyses reported that VTEs were present in 13–17% of patients hospitalized with COVID-19.[9,27] The incidence of VTE in patients with COVID-19 vary greatly depending on COVID-19 severity and the VTE screening strategy; the incidence may be higher in patients with more severe COVID-19 and when imaging examinations are conducted more frequently.[9,27] In this study, patients with worsened COVID-19 severity underwent contrast-enhanced CT examinations more frequently, which may have influenced the detection of thrombosis. Among moderately ill patients with COVID-19, the incidence of VTE ranged from 0.9 to 2.5% in the previous landmark randomized clinical trials investigating the efficacy and safety of therapeutic or prophylactic doses of anticoagulants.[5,28] Consistent with these studies, the incidence of VTE was 2.0% in patients with moderate COVID-19 in this study. In a previous study, clot-fibrinolysis waveform analysis revealed that the coagulation-fibrinolysis balance was maintained in patients with mild COVID-19, but tended towards coagulation-dominant in patients with moderate to severe COVID-19, most notably in moderate patients.[29] Plasma thrombin generation and tissue plasminogen activator, a marker of endothelial damage, is increased in patients with moderate COVID-19 compared to a matched control group of hospitalized patients without COVID-19 despite

Table 3. Risk Factors of Worsening of COVID-19 Severity After Hospital Admission

Variables	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age (years)	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.03)	0.005
Sex	0.80 (0.56–1.15)	0.230	–	
BMI >30	1.31 (0.87–1.96)	0.194	–	
Hypertension	1.95 (1.41–2.70)	<0.001	1.34 (0.99–1.95)	0.125
Diabetes	1.85 (1.31–2.62)	<0.001	1.63 (1.11–2.33)	0.012
Heart diseases	2.08 (1.31–3.29)	0.002	1.50 (0.90–2.50)	0.112
Lung diseases	0.92 (0.54–1.55)	0.748	–	
Active cancer	2.72 (1.16–6.38)	0.022	1.96 (0.74–5.20)	0.175
D-dimer level >1.0 μg/mL on admission	2.44 (1.73–3.45)	<0.001	2.10 (1.45–3.03)	<0.001
Development of thrombosis	6.88 (3.16–14.95)	<0.001	6.28 (2.72–14.53)	<0.001
Development of major bleeding	3.88 (1.62–9.28)	0.002	1.92 (0.72–5.14)	0.193

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

the use of pharmacological thromboprophylaxis.[30] These studies suggest that the hemostatic balance between coagulation and bleeding leans toward coagulation in patients with moderate COVID-19, even when anticoagulants are administered. Therapeutic-dose anticoagulation with heparin has been reported to be more effective than usual-care thromboprophylaxis in patients with moderate COVID-19.[28]

In this study, several risk factors of worsening of the severity of COVID-19 were identified. A meta-analysis of 13 studies including 1,807 patients with COVID-19 reported that serum D-dimer levels in patients with severe COVID-19 were significantly higher than those in patients with milder severity.[31] Another meta-analysis reported a strong relationship between higher D-dimers levels and overall disease progression, which may be useful to predict overall disease progression, severity, and mortality.[32] These results are consistent with those of the current study. Increased age has also been associated with disease progression and mortality in patients with COVID-19. The proportion of patients who progress to severe and critical disease or death increases with age, especially among patients aged ≥50 years.[33,34] Compared to patients aged 30–59 years, those aged <30 years and >59 years were 0.6- and 5.1-fold more likely to die after developing symptoms of COVID-19, respectively.[35] Patients with COVID-19 aged >70 years have a higher risk of severe disease, intensive care requirements, and death.[36] Diabetes has also been reported as a risk factor for adverse outcomes of COVID-19.[37–39] A Japanese study reported that diabetes is an independent risk factor of disease progression in patients with COVID-19 with no or mild symptoms who do not require oxygen administration.[24] These factors can attenuate the immune response, leading to increased susceptibility to viral infections, and exacerbating the infection. In addition to these potential baseline risk factors, comorbidities, and biomarkers, the development of thrombosis was found to be independently and strongly associated with worsening COVID-19 severity in this study, suggesting that more aggressive pharmacological thromboprophylaxis may be helpful for the prevention of worsening COVID-19 severity.

Study Limitations

This study has several limitations. First, the present study was based on an observational study, and can show only association, not causality. The causal relationship between the development of thrombosis and the worsening of the severity of COVID-19 is unclear as the timing of the worsening of the severity and the development of thrombosis was not evaluated. In addition, the use of pharmacological thromboprophylaxis was determined by the attending physicians, which may have influenced the clinical outcomes. Moreover, the precise dose of anticoagulants used for thromboprophylaxis was not recorded; however, unfractionated heparin was administered in prophylactic and therapeutic doses. Second, data regarding respiratory symptoms, inflammatory markers, medications administered for COVID-19, and the amount of inhaled oxygen were not available in this study. Third, the worsening of the severity of COVID-19 in patients with mild COVID-19 on admission was not analyzed in this study, as many patients with mild COVID-19 are treated without hospitalization in Japan; therefore, the study population would not be representative of all patients with mild COVID-19. Fourth, contrast-enhanced CT examination was performed more frequently in this study than in a previous Japanese report,[12] though it was infrequent, which may have resulted in the underdiagnosis of thrombosis. Regarding the diagnosis of thrombosis based on imaging findings, the rate of detection on contrast-enhanced CT scans was approximately 30% in patients with and without worsening severity (**Supplementary Table**). Finally, the present study investigated risk factors associated with the worsening of the severity during hospitalization and did not include data from after hospital discharge.

Conclusions

In the current real-world Japanese COVID-19 registry, approximately 20% of patients with moderate COVID-19 had worsened COVID-19 severity during hospitalization. The development of thrombosis during hospitalization was significantly associated with worsening of the severity of COVID-19.

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Disclosures

The authors declare that there are no conflicts of interest. K.M. is a member of *Circulation Journal*'s Editorial Team.

IRB Information

The relevant review boards or ethics committees at all participating centers approved the research protocol. The primary ethics committee was that of Fukushima Daiichi Hospital (approval number: 2021-11-2).

Data Availability

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. However, if the relevant review board or ethics committee approve the data sharing and all investigators of the CLOT-COVID Study give their consent, the deidentified participant data will be shared on a request basis through the principal investigator. Study protocol and statistical analysis plan will also be available. The data will be shared as Microsoft Excel files via email during the proposed investigation period.

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Supplementary Files

Please find supplementary file(s);
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