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Original Article

# The current status of thrombosis and anticoagulation therapy in patients with COVID-19 in Japan: From the CLOT-COVID study

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ABSTRACT

*Background:* Data on thrombosis and current real-world management strategies for anticoagulation therapy are scarce but important for understanding current issues and unmet needs of an optimal management of patients with coronavirus disease 2019 (COVID-19).
*Method:* The CLOT-COVID Study (thrombosis and antiCoaguLatiOn Therapy in patients with COVID-19 in Japan Study: UMIN000045800) was a retrospective, multicenter cohort study enrolling consecutive hospitalized patients with COVID-19 among 16 centers in Japan from April 2021 to September 2021, and we tried to capture the status of the patients in the fourth and fifth waves of the COVID-19 infections in Japan. We enrolled consecutive hospitalized patients who were diagnosed with COVID-19 and had a positive polymerase chain reaction test obtained from the hospital databases.
*Results:* Among 2894 patients with COVID-19, 1245 (43%) received pharmacological thromboprophylaxis. The proportion of pharmacological thromboprophylaxis increased according to the severity of the COVID-19 in 9.8% with mild COVID-19, 61% with moderate COVID-19, and 97% with severe COVID-19. The types and doses of anticoagulants varied widely across the participating centers. During the hospitalization, 38 patients (1.3%) and 126 (4.4%) underwent ultrasound examinations for the lower extremities and contrast-enhanced computed tomography examinations, respectively, and 55 (1.9%) developed thrombosis, mostly venous thromboembolism

*Abbreviations:* APTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CI, confidence interval; CT, computed tomography; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; ISTH, International Society of Thrombosis and Hemostasis; LMWH, low-molecular-weight heparin; PCR, polymerase chain reaction; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

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(71%). The incidence of thrombosis increased according to the severity of the COVID-19 in 0.2% with mild COVID-19, 1.4% with moderate COVID-19, and 9.5% with severe COVID-19. Major bleeding occurred in 57 patients (2.0%) and 158 (5.5%) died, and 81% of them were due to respiratory failure from COVID-19 pneumonia.
*Conclusions:* In the present large-scale observational study, pharmacological thromboprophylaxis for hospitalized patients with COVID-19 was common especially in patients with severe COVID-19, and management strategies varied widely across the participating centers. The overall incidence of thrombosis was substantially low with an increased incidence according to the severity of the COVID-19.


## Introduction

The coronavirus disease 2019 (COVID-19) has become a huge threat all over the world as a pandemic [1,2], which has also been reported to cause arterial and venous thrombotic complications including a high prevalence of venous thromboembolism (VTE) [3–13]. Based on the concept that patients with COVID-19 are at a high risk of developing thrombosis leading to a worse mortality, the potential benefit of anticoagulation therapy for primary prevention of thrombosis and an improvement in the survival has been reported [14]. Several current international guidelines for COVID-19 recommend a pharmacological thromboprophylaxis for all hospitalized patients with COVID-19 [15]. However, the risk of thrombosis and bleeding adverse events with anticoagulation therapy in patients with COVID-19 could widely vary according to the ethnic differences and distinct resource availability [16], which should be taken into consideration when deciding the management strategies of anticoagulation therapy for patients with COVID-19. Actually, several previous studies have reported that the number of patients diagnosed with thrombosis associated with COVID-19 in Japan could be small as compared to the reports from other countries [17,18], which could lead to widely varying management strategies in daily clinical practice. Data on thrombosis and the current real-world management strategies of anticoagulation therapy are important for understanding the current issues and unmet needs of optimal management of patients with COVID-19. However, there is a scarcity of data on these issues in Japan. Thus, we conducted a large-scale multicenter observational study to reveal the current status of thrombosis and anticoagulation therapy in hospitalized patients with COVID-19 in Japan.

## Methods

### *Study population*

The CLOT-COVID Study (thrombosis and antiCoaguLatiOn Therapy in patients with COVID-19 in Japan Study: UMIN000045800) was a physician-initiated, retrospective, multicenter cohort study enrolling consecutive hospitalized patients with COVID-19 among 16 centers in Japan from April 2021 to September 2021, and we tried to capture the status of the patients in the fourth and fifth waves of the COVID-19 infections in Japan. The current study was conducted by 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 [19]. We enrolled consecutive hospitalized patients who were diagnosed with COVID-19 and had a positive polymerase chain reaction (PCR) test obtained from the hospital databases.

### *Ethics approval and consent to participate*

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

### *Data collection*

We collected the patient data and follow-up information using an electronic report form. Data on the patient characteristics, pharmacological thromboprophylaxis managements, and clinical outcomes were collected from the hospital charts or hospital databases according to the pre-specified definitions. The physicians at each institution were responsible for the data entry into an electronic case report form. In addition, data were manually checked for missing or contradictory input and values out of the expected range at the general office.

### *Definitions for the patient characteristics*

Hypertension was diagnosed if the peripheral blood pressure was >140/90 mmHg or if the patient was taking medication for hypertension. The presence of diabetes was diagnosed using the hemoglobin A1c (National Glycohemoglobin Standardization Program, 6.5%) as the standard or was assumed if the patient was taking medication for the treatment of diabetes. Heart disease was defined as heart disorders such as heart failure, angina pectoris, and a history of myocardial infarction. Heart failure was diagnosed if the patient had a history of a hospitalization for heart failure, the patient had symptoms due to heart failure (New York Heart Association functional class ≥2), or the left ventricular ejection fraction was <40%. Respiratory disease was defined as a persistent lung disorder such as asthma, chronic obstructive pulmonary disease, or restrictive lung disease. Patients with active cancer were defined as those on treatment for cancer, such as chemotherapy or radiotherapy, those scheduled to undergo cancer surgery, those with metastasis to other organs, and/or those with terminal cancer [20]. A history of major bleeding was diagnosed if the patient had a history of International Society of Thrombosis and Hemostasis (ISTH) major bleeding, which consisted of a reduction in the hemoglobin level by at least 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ [21].

The severity of the COVID-19 was classified as mild, moderate, or severe COVID-19. Patients with mild COVID-19 were defined as those who did not require oxygen, patients with moderate COVID-19 were defined as those who required oxygen, and patients with severe COVID-19 were defined as those who required mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Pharmacological thromboprophylaxis management was evaluated by the usage of anticoagulants during the hospitalization except for their usage for the treatment of thrombosis, which were divided into the following 7 groups according to the types and doses of the anticoagulants; unfractionated heparin (UFH) of a prophylactic dose, UFH of a therapeutic dose, low-molecular-weight heparin (LMWH) of a prophylactic dose, LMWH of a therapeutic dose, direct oral anticoagulants (DOACs), warfarin, and others. UFH of a therapeutic dose was defined as the administration of UFH targeting a therapeutic range referencing the activated partial thromboplastin time (APTT). UFH

of a prophylactic dose was defined as the administration of UFH of a fixed dose without referencing the APTT.

### *Clinical outcomes*

The outcome measures in the present study were thrombosis, major bleeding, and all-cause death during the hospitalization after the patients were diagnosed with COVID-19 and had a positive PCR test. The 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), ventilation-perfusion lung scintigraphy, pulmonary angiography, or contrast venography] or by autopsy. PE was classified into the following five categories according to the most central pulmonary artery site where the thrombi were located: main trunk pulmonary artery, left or right main pulmonary artery, lobar artery, segmental artery, or subsegmental artery. Proximal DVT was defined as venous thrombosis that was located in the popliteal, femoral, or iliac veins. Distal DVT was defined as venous thrombosis that was located in calf veins including the peroneal, posterior tibial, anterior tibial, gastrocnemius muscle veins, and soleus muscle veins below the knee. Veins in upper extremities included thrombosis in brachial, axillary, subclavian, internal jugular, and brachiocephalic veins [22]. Ischemic stroke was defined as stroke either requiring or prolonging the hospitalization with symptoms lasting more than 24 h. Myocardial infarction was defined in accordance with the universal myocardial infarction guidelines [23]. Major bleeding was diagnosed as ISTH major bleeding, which consisted of a reduction in the hemoglobin level by at least 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ [21]. We classified the causes of death as due to respiratory failure from COVID-19 pneumonia, due to PE, due to thrombosis other than PE, or due to other causes. Death was judged to be due to PE (fatal PE) or thrombosis if it was confirmed by autopsy or if death followed a clinically severe PE or thrombosis without a specific cause of death.

### *Statistical analysis*

Categorical variables were presented as numbers and percentages. Continuous variables were presented as the mean and standard deviation (SD) or the median and interquartile range (IQR) based on their distributions. In this primary report from the CLOT-COVID study, we tried to perform an overview of the current status of the patient characteristics, management strategies, and clinical outcomes through descriptive statistics. The clinical outcomes during the hospitalization are presented as numbers of events and percentages with the 95% confidence intervals (CI). As a sensitivity analysis, we also described the patient characteristics, pharmacological thromboprophylaxis strategies, and clinical outcomes only in patients who underwent imaging examinations. All statistical analyses were performed with JMP version 14.0.0 software (SAS Institute Inc., Cary, NC, USA).

## Results

### *Patient characteristics*

During the study period, we identified 2894 consecutive hospitalized patients with COVID-19. The mean age was 53 years and 65% were men (Table 1). The mean body weight and body mass index were 68.9 kg and 25.3 kg/m$^2$, respectively. The proportion of a body mass index of >30 kg/m$^2$ was 16%. The median D-dimer level upon admission was 0.8 μg/mL. The severity of the COVID-19 upon admission was mild, moderate, or severe in 60%, 32%, and 7.9% of patients, respectively. The worst severity of the COVID-19 during the hospitalization was mild, moderate, and severe in 44%, 43%, and 13% of patients, respectively.

**Table 1**
Patient characteristics, pharmacological thromboprophylaxis management, and imaging examinations during the hospitalization.

| | Total ($N$ = 2894) |
|---|---|
| Baseline characteristics | |
| Age (years) | 53 ± 18 |
| Men | 1885 (65%) |
| Body weight (kg) | 68.9 ± 18.5 |
| Height (cm) | 164.4 ± 12.4 |
| Body mass index (kg/m$^2$) | 25.3 ± 5.4 |
| Body mass index >30 kg/m$^2$ | 459 (16%) |
| D-dimer level upon admission (μg/mL) ($N$ = 2771) | 0.8 (0.5–1.3) |
| Comorbidities | |
| Hypertension | 874 (30%) |
| Diabetes mellitus | 597 (21%) |
| Heart disease | 255 (8.8%) |
| Respiratory disease | 298 (10%) |
| Active cancer | 60 (2.1%) |
| History of major bleeding | 28 (1.0%) |
| History of VTE | 15 (0.5%) |
| Severity of COVID-19 upon admission | |
| Mild | 1738 (60%) |
| Moderate (Need oxygen) | 927 (32%) |
| Severe (Need mechanical ventilation/ECMO) | 229 (7.9%) |
| Worst severity of COVID-19 during hospitalization | |
| Mild | 1283 (44%) |
| Moderate (Need oxygen) | 1230 (43%) |
| Severe (Need mechanical ventilation/ECMO) | 381 (13%) |
| Pharmacological thromboprophylaxis managements | |
| Anticoagulants | 1245 (43%) |
| Unfractionated heparin of a prophylactic dose | 685/1245 (55%) |
| Unfractionated heparin of a therapeutic dose | 161/1245 (13%) |
| Low-molecular-weight heparin of a prophylactic dose | 204/1245 (16%) |
| Low-molecular-weight heparin of a therapeutic dose | 0/1245 (0%) |
| Direct oral anticoagulants | 164/1245 (13%) |
| Warfarin | 19/1245 (1.5%) |
| Others | 12/1245 (1.0%) |
| Imaging examinations during hospitalization | |
| Ultrasound examination of the lower extremities | 38 (1.3%) |
| Contrast-enhanced CT examination | 126 (4.4%) |
| Reasons for performing contrast-enhanced CT examination | |
| Suspicion of VTE | 59/126 (47%) |
| Other reasons | 67/126 (53%) |

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.
VTE, venous thromboembolism; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; APTT, activated partial thromboplastin time; CT, computed tomography.

### *Pharmacological thromboprophylaxis management and imaging examinations*

During the hospitalization, 1245 patients (43%) received anticoagulants (Table 1). Among the patients with anticoagulants, 55% received UFH of a prophylactic dose, 13% received UFH of a therapeutic dose, 16% received LMWH of a prophylactic dose, and 13% received DOACs. The proportion of pharmacological thromboprophylaxis increased dramatically according to the worst severity of the COVID-19 during the hospitalization in 9.8% with mild COVID-19, 61% with moderate COVID-19, and 97% with severe COVID-19 (Fig. 1). The distribution of a detailed pharmacological thromboprophylaxis varied widely across the participating centers (Fig. 2).

During the hospitalization, 38 patients (1.3%) and 126 (4.4%) underwent ultrasound examinations for the lower extremities and contrast-enhanced CT examinations, respectively (Table 1). Among the patients with contrast-enhanced CT examinations, more than half of them received contrast-enhanced CT examinations due to other reasons than the suspicion of VTE.

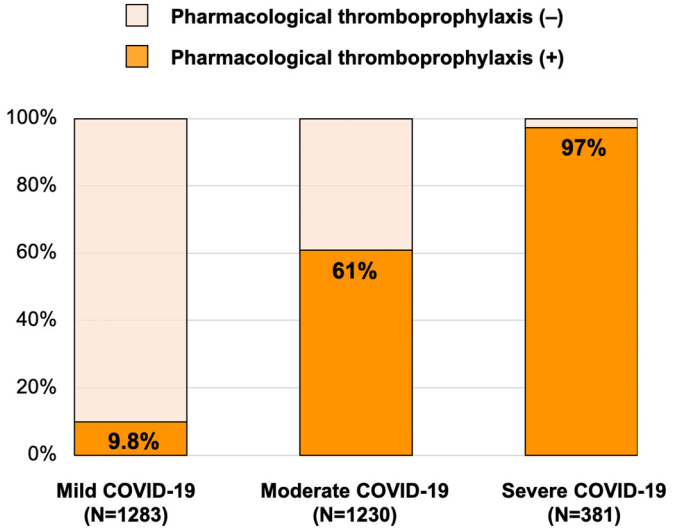


**Fig. 1.** Proportion of pharmacological thromboprophylaxis according to the worst severity of COVID-19 during the hospitalization. Patients with mild COVID-19 were defined as those who did not require oxygen, patients with moderate COVID-19 were defined as those who required oxygen, and patients with severe COVID-19 were defined as those who required mechanical ventilation or extracorporeal membrane oxygenation.
COVID-19, coronavirus disease 2019.

*Clinical outcomes during the hospitalization*

During the hospitalization, 55 patients [1.9% (95% CI, 1.5–2.5%)] developed thrombosis (Table 2). The incidence of thrombosis increased sequentially according to the worst severity of the COVID-19 during the hospitalization in 0.2% with mild COVID-19, 1.4% with moderate COVID-19, and 9.5% with severe COVID-19 (Fig. 3). As for the types of thrombosis, 39 patients [1.3% (95% CI, 1.0–1.8%)], 9 [0.3% (95% CI, 0.2–0.6%)], 2 [0.07% (95% CI, 0.00–0.27%)], and 1 [0.04% (95% CI, 0.00–0.22%)] developed VTE, ischemic stroke, myocardial infarction, and systemic arterial thromboembolism, respectively (Table 2). Among the 39 patients with VTE, 21 (54%) and 18 (46%) developed PE and DVT, respectively. Most sites of the thrombi associated with the PE were more proximal than the lobar artery, whereas the major sites of the thrombi associated with the DVT were distal veins in the lower extremities and veins in the upper extremities.

Major bleeding occurred in 57 patients [2.0% (95% CI, 1.5–2.5%)]. The most frequent site of the major bleeding was gastrointestinal (44%), followed by surgery-related/iatrogenic (19%). During the hospitalization, 158 patients [5.5% (95% CI, 4.7–6.3%)] died, and 81% of them were due to respiratory failure from COVID-19 pneumonia.

*Anticoagulation strategies and clinical outcomes after developing VTE*

Among 39 patients with VTE, 38 (97%) received pharmacological thromboprophylaxis before the VTE diagnosis (Table 3). After the VTE diagnosis, 83% of the patients with anticoagulants received UFH as an anticoagulation therapy. However, at the time of discharge, 80% of the patients with anticoagulants received DOACs as an anticoagulation therapy. Among the 39 patients with VTE, 8 (21%) died during the hospitalization, however, no patients died due to PE.

*Sensitivity analysis*

Among 151 patients who underwent imaging examinations, the median D-dimer level upon admission was higher in the patients with VTE than those without VTE [2.8 (1.3–11) μg/mL vs. 1.6 (1.0–2.9) μg/mL, $p = 0.03$). And, the cut-off value to predict the development of VTE was 2.8 μg/mL by receiver-operating characteristic curve analysis. The proportion of pharmacological thromboprophylaxis increased according to the severity of the COVID-19 in 33% with mild COVID-19, 88% with moderate COVID-19, and 96% with severe COVID-19 (Online Fig. 1). The incidence of thrombosis also increased according to the severity of the COVID-19 in 11% with mild COVID-19, 24% with moderate COVID-19, and 32% with severe COVID-19 (Online Fig. 2).

## Discussion

The main findings of the present study were as follows: 1) nearly half of the hospitalized patients with COVID-19 received a pharmacological thromboprophylaxis with an increased proportion according to the severity of the COVID-19, 2) the pharmacological thromboprophylaxis strategies including the types and doses of the anticoagulants varied widely across the participating centers, and 3) the overall incidence of thrombosis, mostly VTE, was substantially low with a small number of patients with imaging examinations, however, the incidence of thrombosis increased according to the severity of the COVID-19.

The proportion of hospitalized patients with COVID-19 who received a pharmacological thromboprophylaxis, mostly UFH of a prophylactic dose, was substantially higher in the present study than in the previous studies with a targeted population from the first and second waves of COVID-19 infections in Japan (43% vs. up to 25%) [17,19,24,25]. This change may

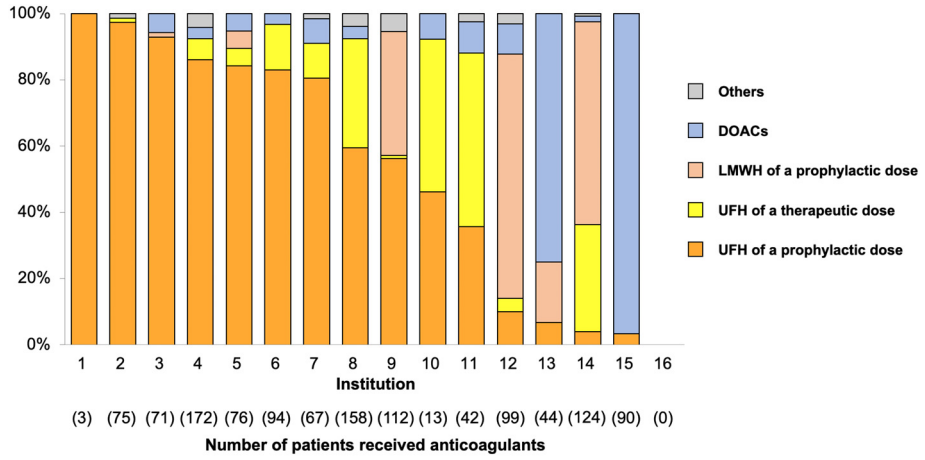


**Fig. 2.** Distribution of the detailed pharmacological thromboprophylaxis according to the participating centers. Pharmacological thromboprophylaxis was classified as UFH of a prophylactic dose, UFH of a therapeutic dose, LMWH of a prophylactic dose, DOACs, and others.
LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; DOAC, direct oral anticoagulant.

**Table 2**
Clinical outcomes during hospitalization.

| | |
|---|---|
| Thrombosis | $N = 55/2894$ (1.9% [1.5–2.5%]) |
| VTE | 39/2894 (1.3% [1.0–1.8%]) |
| Days from admission to the VTE event (days) | 11 (4–19) |
| D-dimer level upon the VTE diagnosis (μg/mL) ($N = 37$) | 18.1 (6.6–36.5) |
| VTE types | |
| PE with or without DVT | 21/39 (54%) |
| Main trunk pulmonary artery | 2/21 (9.5%) |
| Left or right main pulmonary artery | 6/21 (29%) |
| Lobar artery | 9/21 (43%) |
| Segmental artery | 2/21 (9.5%) |
| Subsegmental artery | 2/21 (9.5%) |
| DVT only | 18/39 (46%) |
| Proximal DVT in the lower extremities | 3/18 (17%) |
| Distal DVT in the lower extremities | 6/18 (33%) |
| Veins in the upper extremities | 6/18 (33%) |
| Others | 3/18 (17%) |
| Arterial thrombotic events | 12/2894 (0.4% [0.2–0.7%]) |
| Ischemic stroke | 9/2894 (0.3% [0.2–0.6%]) |
| Myocardial infarction | 2/2894 (0.07% [0.00–0.27%]) |
| Systemic arterial thromboembolism | 1/2894 (0.04% [0.00–0.22%]) |
| Others | 7/2894 (0.2% [0.1–0.5%]) |
| Major bleeding | $N = 57/2894$ (2.0% [1.5–2.5%]) |
| Site of bleeding | |
| Intracranial | 4/57 (7.0%) |
| Respiratory | 2/57 (3.5%) |
| Gastrointestinal | 25/57 (44%) |
| Urinary | 1/57 (1.8%) |
| Intrathoracic/Intra-abdominal | 2/57 (3.5%) |
| Surgery-related/Iatrogenic | 11/57 (19%) |
| Subcutaneous | 1/57 (1.8%) |
| Others | 11/57 (19%) |
| All-cause death | $N = 158/2894$ (5.5% [4.7–6.3%]) |
| Cause of death | |
| Due to respiratory failure from COVID-19 pneumonia | 128/158 (81%) |
| Due to PE (fatal PE) | 0/158 (0%) |
| Due to thrombosis other than PE | 0/158 (0%) |
| Due to other causes | 30/158 (19%) |

The clinical outcomes during hospitalization are presented as numbers of events and percentages with the 95% CI. PE was classified into the following five categories according to the most central pulmonary artery site where the thrombi were located: main trunk pulmonary artery, left or right main pulmonary artery, lobar artery, segmental artery, or subsegmental artery. Proximal DVT was defined as venous thrombosis that was located in the popliteal, femoral, or iliac veins. Distal DVT was defined as venous thrombosis that was located in the calf veins including the peroneal, posterior tibial, anterior tibial, and soleus muscle veins below the knee.
VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; CI, confidence interval; COVID-19, coronavirus disease 2019.

have been affected by the COVID-19 Clinical Practice Guidelines version 5.0 issued by the Japanese Ministry of Health, Labour and Welfare on May 26, 2021, which recommended prophylactic-dose heparin for hospitalized patients with moderate or severe COVID-19. However, the proportion of a pharmacological thromboprophylaxis had not yet reached the "universal" pharmacological thromboprophylaxis for all hospitalized patients with COVID-19, as recommended by several current international guidelines in other countries [15]. In addition, the pharmacological thromboprophylaxis strategies varied widely across the participating centers, suggesting that the current management strategies might have been based on individual decisions and the distinct resource availability at each institution.

In line with the previous studies [17,19,24,25], the present study from Japan showed a lower incidence of VTE in hospitalized patients with COVID-19 than that in the studies from Western countries [7,9,10]. The interpretation of the present results should be taken with caution because

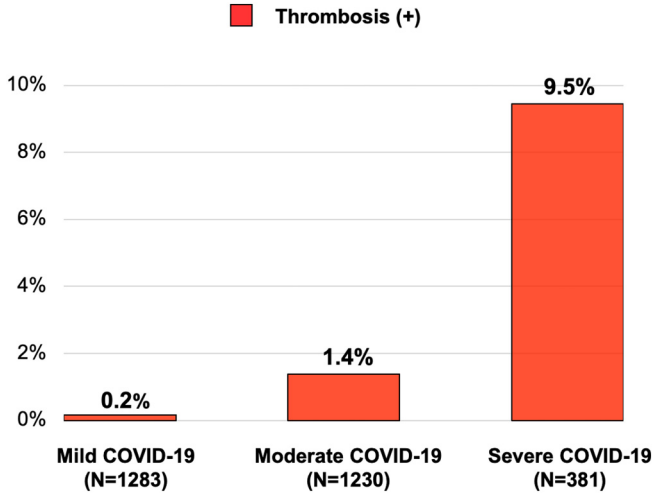


**Fig. 3.** Incidences of thrombosis according to the worst severity of COVID-19 during the hospitalization. Patients with mild COVID-19 were defined as those who did not require oxygen, patients with moderate COVID-19 were defined as those who required oxygen, and patients with severe COVID-19 were defined as those who required mechanical ventilation or extracorporeal membrane oxygenation.
COVID-19, coronavirus disease 2019.

the number of patients that underwent imaging examinations was small, which may have been partly due to the difficulty in diagnosing VTE in patients with COVID-19 from the following perspectives: 1) the symptoms of COVID-19, such as fever, dyspnea, and tachypnea, mimic those of PE [26], 2) a major influence of COVID-19 on the hemodynamic status and oxygenation could mask the suspicion of VTE leading to imaging examinations,

**Table 3**
Anticoagulation strategies and clinical outcomes among patients with VTE.

| | Patients with VTE ($N = 39$) |
|---|---|
| Pharmacological thromboprophylaxis before the VTE diagnosis | |
| Anticoagulants | 38 (97%) |
| Unfractionated heparin of a prophylactic dose | 16/38 (42%) |
| Unfractionated heparin of a therapeutic dose | 15/38 (39%) |
| Low-molecular-weight heparin of a prophylactic dose | 3/38 (7.9%) |
| Low-molecular-weight heparin of a therapeutic dose | 0/38 (0%) |
| Direct oral anticoagulants | 1/38 (2.6%) |
| Warfarin | 0/38 (0%) |
| Others | 3/38 (7.9%) |
| Anticoagulation therapy after the VTE diagnosis | |
| Anticoagulants | 35 (90%) |
| Unfractionated heparin | 29/35 (83%) |
| Low-molecular-weight heparin | 0/35 (0%) |
| Direct oral anticoagulants | 5/35 (14%) |
| Edoxaban | 1/5 (20%) |
| Rivaroxaban | 2/5 (40%) |
| Apixaban | 2/5 (40%) |
| Others | 1/35 (2.9%) |
| Anticoagulation therapy at the time of discharge | |
| Anticoagulants | 30 (77%) |
| Unfractionated heparin | 5/30 (17%) |
| Low-molecular-weight heparin | 0/30 (0%) |
| Direct oral anticoagulants | 24/30 (80%) |
| Edoxaban | 17/24 (71%) |
| Rivaroxaban | 3/24 (13%) |
| Apixaban | 4/24 (16%) |
| Others | 1/30 (3.3%) |
| All-cause death during hospitalization | 8/39 (21%) |
| Cause of death | |
| Due to respiratory failure from COVID-19 pneumonia | 5/8 (63%) |
| Due to PE (fatal PE) | 0/8 (0%) |
| Due to other causes | 3/8 (38%) |

VTE, venous thromboembolism; PE, pulmonary embolism; COVID-19, coronavirus disease 2019.

and 3) a high threshold for imaging examinations due to isolation [27]. On the other hand, the incidence of VTE in patients with severe COVID-19 was relatively high despite a quite high prevalence of a pharmacological thromboprophylaxis, which was consistent with the previous reports [7,8,18]. Given a high risk of developing VTE in patients with severe COVID-19 [28,29], clinicians might need to conduct imaging examinations without delay when patients are suspected of developing VTE.

In addition to who should receive anticoagulation therapy among patients with COVID-19, it could also be important to know what is the optimal type and dose of anticoagulants. The latest updated international guidelines from the US National Institutes of Health recommend therapeutic-dose heparin, especially LWMH, for hospitalized patients who require low-flow oxygen but do not require intensive care [30]. That recommendation is based on recent randomized clinical trials that showed that therapeutic-dose heparin increased the probability of survival to hospital discharge with a reduced use of cardiovascular or respiratory organ support as compared to prophylactic-dose heparin [31–33]. Notably, LMWH is preferable to UFH in terms of bleeding, however, LMWH for thromboprophylaxis in patients with COVID-19 is not covered by the Japanese national insurance. Furthermore, given the concern that anticoagulation therapy might be associated with a higher risk of bleeding, especially in Asians as compared to Caucasians [34,35], it could be important to achieve a good balance between the thrombotic and bleeding risks with an appropriate type and dose of anticoagulants in Japan. Considering the uncertainty and varieties of the anticoagulation strategies in the real world, further investigations are warranted to clarify the optimal pharmacological thromboprophylaxis strategies for patients with COVID-19 in Japan, including the indications, types, and doses of anticoagulants.

### *Study limitations*

The present study had several limitations. First, the present study was based on observational cohort data and the decisions regarding the management strategies were at the discretion of the attending physicians. In particular, the number of patients who underwent imaging examinations was considerably small. Therefore, we could not deny the potential for selection bias and an under-diagnosis of thrombosis, which should be cautious when interpreting the present results. Second, patients with moderate I COVID-19, defined in the COVID-19 Clinical Practice Guidelines as patients with dyspnea or pneumonia but not requiring oxygen, were classified as patients with mid COVID-19 in the present study from the clinical point of view. Finally, the demographics and practice patterns as well as the clinical outcomes in the patients at the present participating centers may differ from those at other centers. Thus, it should be interpreted with caution whether the present results could be extrapolated to patients at all institutions in Japan.

## Conclusions

In the present large observational study, pharmacological thromboprophylaxis for hospitalized patients with COVID-19 was common especially in patients with severe COVID-19, and the management strategies varied widely across the participating centers. The overall incidence of thrombosis was substantially low with an increased incidence according to the severity of the COVID-19.

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## Declaration of competing interest

The authors declare that there is no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2022.03.015.

## References

[1] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20. https://doi.org/10.1056/NEJMoa2002032.
[2] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.
[3] Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9–14. https://doi.org/10.1016/j.thromres.2020.04.024.
[4] Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalized patients with COVID-19 in a new York City health system. JAMA 2020;324:799–801. https://doi.org/10.1001/jama.2020.13372.
[5] Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46:1089–98. https://doi.org/10.1007/s00134-020-06062-x.
[6] Fraissé M, Logre E, Pajot O, Mentec H, Plantefève G, Contou D. Thrombotic and hemorrhagic events in critically ill COVID-19 patients: a French monocenter retrospective study. Crit Care 2020;24:275. https://doi.org/10.1186/s13054-020-03025-y.
[7] Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 2020;191:148–50. https://doi.org/10.1016/j.thromres.2020.04.041.
[8] Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020;18:1421–4. https://doi.org/10.1111/jth.14830.
[9] Llitjos J-F, Leclerc M, Chochois C, Monsallier J-M, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020;18:1743–6. https://doi.org/10.1111/jth.14869.
[10] Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, et al. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. Circulation 2020;142:184–6. https://doi.org/10.1161/CIRCULATIONAHA.120.047430.
[11] Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, et al. Deep vein thrombosis in hospitalized patients with COVID-19 in Wuhan, China: prevalence, risk factors, and outcome. Circulation 2020;142:114–28. https://doi.org/10.1161/CIRCULATIONAHA.120.046702.
[12] Cohen SL, Gianos E, Barish MA, Chatterjee S, Kohn N, Lesser M, et al. Prevalence and predictors of venous thromboembolism or mortality in hospitalized COVID-19 patients. Thromb Haemost 2021;121:1043–53. https://doi.org/10.1055/a-1366-9656.
[13] Li J-Y, Wang H-F, Yin P, Li D, Wang D-L, Peng P, et al. Clinical characteristics and risk factors for symptomatic venous thromboembolism in hospitalized COVID-19 patients: a multicenter retrospective study. J Thromb Haemost 2021;19:1038–48. https://doi.org/10.1111/jth.15261.
[14] Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020;75:2950–73. https://doi.org/10.1016/j.jacc.2020.04.031.
[15] Kaptein FHJ, Stals MAM, Huisman MV, Klok FA. Prophylaxis and treatment of COVID-19 related venous thromboembolism. Postgrad Med 2021;133:27–35. https://doi.org/10.1080/00325481.2021.1891788.
[16] Iba T, Connors JM, Spyropoulos AC, Wada H, Levy JH. Ethnic differences in thromboprophylaxis for COVID-19 patients: should they be considered? Int J Hematol 2021;113:330–6. https://doi.org/10.1007/s12185-021-03078-x.
[17] Horiuchi H, Morishita E, Urano T, Yokoyama K. Questionnaire-survey joint team on the COVID-19-related thrombosis. COVID-19-related thrombosis in Japan: final report of a questionnaire-based survey in 2020. J Atheroscler Thromb 2021;28:406–16. https://doi.org/10.5551/jat.RPT001.
[18] Yamashita Y, Maruyama Y, Satokawa H, Nishimoto Y, Tsujino I, Sakashita H, et al. Incidence and clinical features of venous thromboembolism in hospitalized patients

with coronavirus disease 2019 (COVID-19) in Japan. Circ J 2021;85:2208–14. https://doi.org/10.1253/circj.CJ-21-0169.

[19] Yamashita Y, Yamada N, Mo M. The primary prevention of venous thromboembolism in patients with COVID-19 in Japan: current status and future perspective. Ann Vasc Dis 2021;14:1–4. https://doi.org/10.3400/avd.ra.20-00145.

[20] Sakamoto J, Yamashita Y, Morimoto T, Amano H, Takase T, Hiramori S, et al. Cancer-associated venous thromboembolism in the real world - from the COMMAND VTE registry. Circ J 2019;83:2271–81. https://doi.org/10.1253/circj.CJ-19-0515.

[21] Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692–4. https://doi.org/10.1111/j.1538-7836.2005.01204.x.

[22] Mai C, Hunt D. Upper-extremity deep venous thrombosis: a review. Am J Med 2011;124:402–7. https://doi.org/10.1016/j.amjmed.2010.11.022.

[23] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35. https://doi.org/10.1161/CIR.0b013e31826e1058.

[24] Fujiwara S, Nakajima M, Kaszynski RH, Fukushima K, Tanaka M, Yajima K, et al. Prevalence of thromboembolic events and status of prophylactic anticoagulant therapy in hospitalized patients with COVID-19 in Japan. J Infect Chemother 2021;27:869–75. https://doi.org/10.1016/j.jiac.2021.02.019.

[25] Oba S, Hosoya T, Amamiya M, Mitsumura T, Kawata D, Sasaki H, et al. Arterial and venous thrombosis complicated in COVID-19: a retrospective single center analysis in Japan. Front Cardiovasc Med 2021;8:767074. https://doi.org/10.3389/fcvm.2021.767074.

[26] Bozorgmehr R, Pishgahi M, Tajabadi Z, Aryafar M. Pulmonary thromboembolism and infarction mimicking COVID-19 symptoms; report of three cases. Arch Acad Emerg Med 2020;8:e88.

[27] Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–7. https://doi.org/10.1016/j.thromres.2020.04.013.

[28] Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. Res Pract Thromb Haemost 2020;4:1178–91. https://doi.org/10.1002/rth2.12439.

[29] Jiménez D, García-Sanchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, et al. Incidence of VTE and bleeding among hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. Chest 2021;159:1182–96. https://doi.org/10.1016/j.chest.2020.11.005.

[30] COVID-19 treatment guidelines panel. Statement on anticoagulation in hospitalized patients. National Institutes of Health. Available at: a]https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-anticoagulation-in-hospitalized-patients/ (accessed January 20, 2022).

[31] REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, Goligher EC, Bradbury CA, McVerry BJ, et al. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med 2021;385:777–89. https://doi.org/10.1056/NEJMoa2103417.

[32] Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, Áinle FN, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. BMJ 2021;375:n2400. https://doi.org/10.1136/bmj.n2400.

[33] Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. JAMA Intern Med 2021;181:1612–20. https://doi.org/10.1001/jamainternmed.2021.6203.

[34] Chiang C-E, Wang K-L, Lip GYH. Stroke prevention in atrial fibrillation: an Asian perspective. Thromb Haemost 2014;111:789–97. https://doi.org/10.1160/TH13-11-0948.

[35] Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, et al. Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY atrial fibrillation registry. Circulation 2014;129:1568–76. https://doi.org/10.1161/CIRCULATIONAHA.113.005451.