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Influence of sex on development of thrombosis in patients with COVID-19: From the CLOT-COVID study

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ABSTRACT

Introduction: There has been limited data on the influence of sex on development of thrombosis in patients with coronavirus disease 2019 (COVID-19).

Materials and methods: The CLOT-COVID Study was a retrospective, multicenter cohort study enrolling 2894 consecutive hospitalized patients with COVID-19 among 16 centers in Japan from April 2021 to September 2021. We divided the entire cohort into the men ($N = 1885$) and women ($N = 1009$) groups.

Results: There were no significant differences in D-dimer levels at admission between men and women. Men had more severe status of the COVID-19 at admission compared with women (Mild: 57% versus 66%, Moderate: 34% versus 29%, and Severe: 9.1% versus 5.7%, $P < 0.001$). Men more often received pharmacological thromboprophylaxis than women (47% versus 35%, $P < 0.001$). During the hospitalization, men more often developed thrombosis than women (2.5% [95%CI, 1.9–3.3%] versus 0.8% [95%CI, 0.4–1.6%], $P = 0.001$). Men had numerically higher incidences of thrombosis than women in all subgroups of the worst severity of COVID-19 during the hospitalization (Mild: 0.3% versus 0.0%, Moderate: 1.6% versus 1.0%, and Severe: 11.1% versus 4.3%). Even after adjusting confounders in the multivariable logistic regression model, the excess risk of men relative to women remained significant for thrombosis (adjusted OR, 2.51; 95%CI, 1.16–5.43, $P = 0.02$).

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; CI, confidence interval; CT, computed tomography; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; OR, odds ratio; PCR, polymerase chain reaction; PE, pulmonary embolism; VTE, venous thromboembolism.

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Conclusions: In the current large observational study of patients with COVID-19, men had more severe status of the COVID-19 than women, and the risk of development of thrombosis was higher in men compared with women, which could be helpful in determining the patient-specific optimal management strategies for COVID-19.

1. Introduction

The coronavirus disease 2019 (COVID-19) has become a huge threat as a pandemic [1,2], which has been reported to cause cardiovascular complications including a high prevalence of thrombosis [3–5]. Based on the potential benefit of anticoagulation therapy for primary prevention of thrombosis leading to improved survival, several current guidelines recommend a pharmacological thromboprophylaxis for all hospitalized patients with COVID-19 [6,7]. However, the risk of thrombosis in patients with COVID-19 could widely vary according to patient characteristics, and optimal pharmacological thromboprophylaxis strategies for patients with COVID-19 could be still a matter of debate [8]. Thus, risk assessment for development of thrombosis might be clinically relevant in determining more suitable patients for anticoagulation therapy as well as intensity of anticoagulation therapy.

A previous study reported that men might be at higher risk for venous thromboembolism (VTE) compared with women in general population [9], and another previous study reported that men had a higher risk of recurrence than women in patients with VTE [10], which might suggest a different influence of sex on development of thrombosis. Although previous studies reported several potential risk factors of thrombosis in patients with COVID-19 [5,11], the influence of sex on development of thrombosis in patients with COVID-19 have not been fully evaluated. Thus, the current study aimed to evaluate clinical characteristics and outcomes between men and women and assess the influence of sex on development of thrombosis, using a large-scale multicenter observational database of patients with COVID-19 in Japan.

2. Materials and methods

2.1. 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. We enrolled consecutive patients who were diagnosed as COVID-19 infection by a positive polymerase chain reaction (PCR) test, and a total of 2894 hospitalized patients with COVID-19 were included into the CLOT-COVID Study. In the current study, we divided the entire cohort into the men and women groups.

The relevant review boards or ethics committees in all participating centers approved the research protocol. All procedures followed were in accordance with the Declaration of Helsinki. 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.

2.2. Data collection and definitions for patient characteristics

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, and data were manually checked for missing or contradictory input and values out of the expected range at the general office.

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) [12,13]. Pharmacological thromboprophylaxis management was evaluated by the usage of anticoagulants during the hospitalization except for their usage for the treatment of thrombosis. The detailed definitions of other patient characteristics are described in Supplementary Appendix 1.

2.3. Clinical outcomes

The primary outcome measure in the current study was thrombosis during the hospitalization after the patients were diagnosed as COVID-19 infection by a positive PCR test. The thrombosis included VTE, ischemic stroke, myocardial infarction, and systemic arterial thromboembolism. 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. 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 [14].

The secondary outcome measures in the current study were major bleeding and all-cause death during the hospitalization. Major bleeding was diagnosed as 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 [15].

2.4. Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables were presented as the mean and standard deviation or the median and interquartile range based on their distributions. Categorical variables were compared with the chi-square test when appropriate; otherwise, a Fisher's exact test was used. Continuous variables were compared using Student's *t*-test or Wilcoxon's rank sum test based on their distributions. The clinical outcomes are presented as numbers of events and percentages with the 95% confidence intervals (CI). We further evaluated clinical outcomes by stratified analysis according to the worst severity of COVID-19 during the hospitalization. In addition, to adjust for the clinically relevant variables, we constructed the multivariable logistic regression model to estimate the odds ratio (OR) and their 95% CI of men relative to women for development of thrombosis. Consistent with previous reports [5,11,16] and consideration of clinical relevance, we selected 4 risk-adjusting variables of baseline characteristics (age, body mass index [BMI] >30 kg/m^2, D-dimer levels at admission >1.0 μg/mL, and severity of COVID-19 at admission) and pharmacological thromboprophylaxis. All statistical analyses were performed with JMP version 14.0.0 software (SAS Institute Inc., Cary, NC, USA). All reported *P*-values were 2-tailed, and P-values <0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

Among the 2894 patients, men accounted for 1885 (65%) and

women 1009 (35%). Men had a higher body weight and BMI than women (73.9 kg versus 59.4 kg, $P < 0.001$ and 25.7 kg/m^2 versus 24.4 kg/m^2, P < 0.001), while there were no significant differences in age and D-dimer levels at admission between men and women (Table 1). As for comorbidities, men more often had hypertension and diabetes mellitus than women, while there were no significant differences in active cancer and a history of VTE between men and women.

Men had more severe status of the COVID-19 at admission compared with women (Mild: 57% versus 66%, Moderate: 34% versus 29%, and Severe: 9.1% versus 5.7%, $P < 0.001$) (Table 1). Similarly, men had more severe status of the worst severity of COVID-19 during hospitalization compared with women (Mild: 40% versus 52%, Moderate: 44% versus 39%, and Severe: 15% versus 9.2%, P < 0.001).

3.2. Pharmacological thromboprophylaxis management and imaging examinations

Men more often received pharmacological thromboprophylaxis than women (47% versus 35%, $P < 0.001$) (Table 1). There was no significant difference in ultrasound examinations of the lower extremities during the hospitalization between men and women, whereas men more often received contrast-enhanced CT examinations during the hospitalization than women (5.3% versus 2.6%, P < 0.001).

3.3. Clinical outcomes during the hospitalization

During the hospitalization, men more often developed thrombosis than women (2.5% [95% CI, 1.9–3.3%] versus 0.8% [95% CI, 0.4–1.6%], $P = 0.001$) (Table 2). Men had numerically higher incidences of thrombosis than women in all subgroups of the worst severity of COVID-19 during the hospitalization (Mild: 0.3% versus 0.0%, Moderate: 1.6% versus 1.0%, and Severe: 11.1% versus 4.3%) (Fig. 1A). Even after adjusting confounders in the multivariable logistic regression model, the excess risk of men relative to women remained significant for thrombosis (adjusted OR, 2.51; 95% CI, 1.16–5.43, $P = 0.02$). The most frequent thrombosis during the hospitalization was VTE (71%), and men more often developed VTE than women (1.8% [95% CI, 1.2–2.5%] versus 0.6% [95% CI, 0.2–1.3%], $P = 0.01$).

There were no significant differences in major bleeding and all-cause death during the hospitalization between men and women (Major bleeding: 2.2% [95% CI, 1.6–3.0%] versus 1.5% [95% CI, 0.9–2.5%], $P = 0.17$; All-cause death: 5.8% [95% CI, 4.8–6.9%] versus 4.9% [95% CI, 3.7–6.4%], $P = 0.30$) (Table 2). The incidences of major bleeding and all-cause death comparing men and women according to the worst severity of COVID-19 during the hospitalization are shown in Fig. 1B and Fig. 1C.

4. Discussion

The main findings of the current study were as follows: 1) Men had more severe status of the COVID-19 than women with a higher proportion of pharmacological thromboprophylaxis; 2) Although there was no significant difference in D-dimer levels at admission between men and women, the risk of development of thrombosis was higher in men compared with women.

Previous studies reported a similar prevalence of COVID-19 infection between men and women but a more severe status of COVID-19 with a worse outcome in men compared with women [17–21], which was also confirmed at all age groups. The sex-related difference in the severity and outcome in patients with COVID-19 could be partly explained by mechanisms of virus infection, immune response to the virus, development of hyperinflammation and hypercoagulability, systemic inflammation, as well as thrombosis [22]. Consistent with these previous reports, the current study showed that men had more severe status of the COVID-19 than women. The current study also showed that men more often received pharmacological thromboprophylaxis, which could be

Table 1
Patient characteristics and management strategies during hospitalization.

	Men N = 1885	Women N = 1009	P-value
Baseline characteristics			
Age (years)	52 ± 16	53 ± 20	0.17
Body weight (kg)	73.9 ± 17.5	59.4 ± 16.6	<0.001
Body mass index (kg/m^2)	25.7 ± 5.1	24.4 ± 5.8	<0.001
Body mass index >30 kg/m^2	305 (16%)	154 (15%)	0.52
D-dimer level at admission (μg/mL) (*N* = 2771)	0.8 (0.5–1.3)	0.7 (0.5–1.3)	0.17
Comorbidities			
Hypertension	616 (33%)	258 (26%)	<0.001
Diabetes mellitus	429 (23%)	168 (17%)	<0.001
Heart disease	187 (9.9%)	68 (6.7%)	0.004
Respiratory disease	187 (10%)	111 (11%)	0.36
Active cancer	44 (2.3%)	16 (1.6%)	0.18
History of major bleeding	16 (0.9%)	12 (1.2%)	0.37
History of VTE	11 (0.6%)	4 (0.4%)	0.50
Severity of COVID-19 at admission			
Mild	1075 (57%)	663 (66%)	<0.001
Moderate (Need oxygen)	638 (34%)	289 (29%)	
Severe (Need mechanical ventilation/ ECMO)	172 (9.1%)	57 (5.7%)	
Worst severity of COVID-19 during hospitalization			
Mild	763 (40%)	520 (52%)	<0.001
Moderate (Need oxygen)	834 (44%)	396 (39%)	
Severe (Need mechanical ventilation/ ECMO)	288 (15%)	93 (9.2%)	
Pharmacological thromboprophylaxis managements			
Anticoagulants	894 (47%)	351 (35%)	<0.001
Unfractionated heparin of a prophylactic dose	477/894 (54%)	208/351 (59%)	0.003
Unfractionated heparin of a therapeutic dose	123/894 (14%)	38/351 (11%)	
Low-molecular-weight heparin of a prophylactic dose	166/894 (19%)	38/351 (11%)	
Low-molecular-weight heparin of a therapeutic dose	0/894 (0%)	0/351 (0%)	
Direct oral anticoagulants	105/894 (12%)	59/351 (17%)	
Warfarin	15/894 (1.7%)	4/351 (1.1%)	
Others	8/894 (0.9%)	4/351 (1.1%)	
Imaging examinations during hospitalization			
Ultrasound examination of the lower extremities	23 (1.2%)	15 (1.5%)	0.55
Contrast-enhanced CT examination	100 (5.3%)	26 (2.6%)	<0.001
Reasons for performing contrast-enhanced CT examination			
Suspicion of VTE	48/100 (48%)	11/26 (42%)	0.60
Other reasons	52/100 (52%)	15/26 (58%)	

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. Categorical variables were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using the Student's t-test or Wilcoxon's rank sum test based on distribution. 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 a referencing the APTT.
VTE, venous thromboembolism; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; APTT, activated partial thromboplastin time; CT, computed tomography.

Table 2
Clinical outcomes during hospitalization.

	Men $N = 1885$	Women $N = 1009$	P-value
Thrombosis	47 (2.5% [1.9–3.3%])	8 (0.8% [0.4–1.6%])	0.001
VTE	33 (1.8% [1.2–2.5%])	6 (0.6% [0.2–1.3%])	0.01
PE with or without DVT	19/33 (58%)	2/6 (33%)	–
DVT only	14/33 (42%)	4/6 (67%)	–
Arterial thrombotic events	11 (0.6% [0.3–1.1%])	1 (0.1% [0.0–0.6%])	0.053
Ischemic stroke	8/11 (73%)	1/1 (100%)	–
Myocardial infarction	2/11 (18%)	0/1 (0%)	–
Systemic arterial thromboembolism	1/11 (9.1%)	0/1 (0%)	–
Other thrombosis	6 (0.3% [0.1–0.7%])	1 (0.1% [0.0–0.6%])	0.25
Major bleeding	42 (2.2% [1.6–3.0%])	15 (1.5% [0.9–2.5%])	0.17
All-cause death	109 (5.8% [4.8–6.9%])	49 (4.9% [3.7–6.4%])	0.30

The clinical outcomes are presented as numbers of events and percentages with the 95% confidence intervals, which were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used as categorial variables. VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; CI, confidence intervals.

partly due to a higher proportion of more severe status of COVID-19 in men. This could be partly because some clinicians felt that some of patients especially with mild COVID-19 should not necessarily receive pharmacological thromboprophylaxis based on thrombotic and bleeding risk although several current guidelines recommend a pharmacological thromboprophylaxis for all hospitalized patients with COVID-19.

Although sex could have a different influence on thrombosis in patients with COVID-19, little has been reported about a potential influence of sex on thrombosis in patients with COVID-19. In addition, race differences and distinct resource availability in each country may have notable implications in the presentation and diagnosis of thrombosis [12,13]. A recent study from U.S.A. reported that men hospitalized with COVID-19 were more likely to have venous and arterial thromboembolic events [23]. Another study also reported that men hospitalized with COVID-19 had a greater risk of thrombosis than women focusing on different age groups [24]. Consistent with the previous report, the current study from Japan also showed a higher risk of thrombosis in men compared with women, which seemed to be consistent even after stratifying the severity of COVID-19 or adjusting clinically relevant confounders including pharmacological thromboprophylaxis. The established mechanisms for the influence of sex on thrombosis in patients with COVID-19 remain unclear. Theoretically, COVID-19 is thought to develop thrombosis through an activation of coagulation-related factors due to a cytokine storm [8]. The activation of coagulation might be recognized as increased D-dimer levels, elevated prothrombin time, and activated partial thromboplastin time [25]. A previous study reported that sex had different immunity response with more cytokine production in men, which was suggested by higher levels of CRP, D-dimer, interleukin-6, interleukin-8, and interleukin-18 in men compared with women in patients with COVID-19 [26]. However, the current study showed comparable D-dimer levels at admission between men and women, which could suggest potential benefit of different risk management for thrombosis according to sex beyond D-dimer levels at admission.

Anticoagulation therapy could reduce thrombosis, but could be likely to increase bleeding events. Thus, an attention should be paid to take a good balance between thrombotic and bleeding risks. The current study also showed no large sex-related difference in the risk for major bleeding. The current results could suggest the utility of different pharmacological thromboprophylaxis strategies between men and

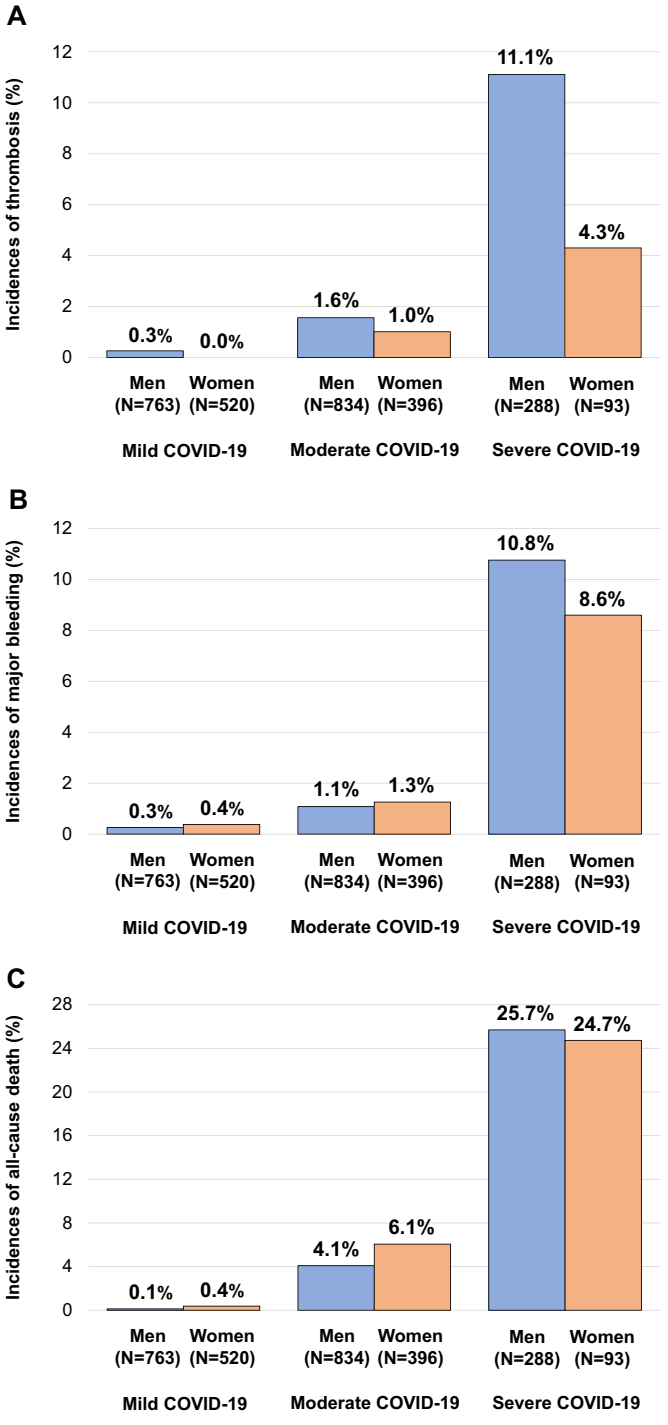

Fig. 1. Incidences of thrombosis (A), major bleeding (B) and all-cause death (C) comparing men and women according to the worst severity of COVID-19 during the hospitalization.
Patients with mild COVID-19 were defined as those who did not require oxygen, patients with moderate COVID-19 were defined as 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.

women in hospitalized patients with COVID-19. In addition to who should receive pharmacological thromboprophylaxis, it could also be important to know what is the optimal intensity of anticoagulants. Currently, there seemed to be conflicting results for the optimal intensity of anticoagulation therapy [27–30], which could be partly due to

different study population with heterogeneity-risk of thrombosis. Considering the potential higher risk of thrombosis in men than women, future clinical studies might have to consider incorporating the influence of sex when determining patient-specific pharmacological thromboprophylaxis strategies for patients with COVID-19. There may be possibility that more intensive pharmacological thromboprophylaxis in very high-risk patients among men has potential benefit for mortality.

4.1. Study limitations

The current study had several limitations. First, the current study was an observational study, which can be subject to various biases inherent to observational study design. Especially, the therapeutic decision-making including pharmacological thromboprophylaxis was left to the discretion of the attending physicians, which could have some influence on clinical outcomes. Second, the absolute number of clinical outcomes was relatively small, although it was derived from a large observational database of patients with COVID-19. Thus, we could not conduct the multivariable analysis with comprehensive variables, which could cause residual confounding. Especially, different critical status of patients including mechanical support in intensive care unit setting could have a certain influence on the current results. Third, because the current study was conducted in Japan, we could not evaluate the influence of racial differences on clinical outcomes. Finally, the current study evaluated only clinical outcomes during the hospitalization. Thus, we could not discuss the risk of thrombosis after discharge.

5. Conclusions

In the current large observational study of patients with COVID-19, men had more severe status of the COVID-19 than women, and the risk of development of thrombosis was higher in men compared with women, which could be helpful in determining the patient-specific optimal management strategies for COVID-19.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2022.03.023.

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