



Thrombotic and Cardiovascular Events and Treatment Patterns Among Patients Hospitalized with COVID-19 in Japan: An Analysis of a Nationwide Medical Claims Database

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ABSTRACT

Introduction: Limited data are available regarding the prevalence of thrombotic/cardiovascular disease and treatment patterns for patients with coronavirus disease 2019 (COVID-19) in Japan. In this study we describe patients hospitalized for COVID-19 in Japan.

Methods: This retrospective database study analyzed the Japan Medical Data Vision database (416 acute care hospitals) for patients hospitalized for COVID-19 during the identification period from 1 January 1 to 30 September 2020.

Results: Among 9282 eligible patients, 832 (9%) had developed thrombotic disease including myocardial infarction, ischemic stroke, deep vein thromboembolism and pulmonary embolism. Intriguingly, 171 (1.8%) had two thrombotic events and 25 (0.3%) had three or four thrombotic events at the same time. The data also showed that arterial thrombotic events accounted for 77% of total thrombotic events. Anticoagulant and/or antiplatelet medication was provided to 3312 patients. Even with antithrombotic medication, 21.2% of patients suffered from thrombotic diseases.

Conclusions: Patients with COVID-19 could experience thrombotic complications in every blood vessel. Further optimization of medication is crucial for preventing thrombotic complications and improving prognosis.

Keywords: COVID-19; Thrombosis; Japanese

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Key Summary Points

Why carry out this study?

Pre-existing cardiovascular disease appears to increase the chance of complications in COVID-19 patients; however, data in Japan are still limited to date.

This study used de-identified data from the Medical Data Vision database, which covers both general and cardiovascular hospitals, from 1 January 1 to 30 September 2020 to provide an up-to-date real-world characterization of treatment patterns and hospitalization outcomes of patients hospitalized for COVID-19 in Japan.

What was learned from the study?

Among 9282 eligible patients, 832 (9%) had developed thrombotic disease, including myocardial infarction, ischemic stroke, deep vein thromboembolism and pulmonary embolism, of which arterial thrombotic events accounted for 77% of total thrombotic events.

While anticoagulant and/or antiplatelet medication was provided to 3312 patients, 21.2% of patients suffered from thrombotic diseases.

Patients with COVID-19 could experience thrombotic complications in every blood vessel; thus, further optimization of medication is crucial for preventing thrombotic complications and improving prognosis

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has become a worldwide pandemic [1]. This disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which binds to and downregulates the angiotensin-converting

enzyme 2 (ACE2) receptor [2, 3]. COVID-19 primarily affects the respiratory tract by causing pneumonia and acute respiratory distress syndrome. Early observations showed that COVID-19 patients also experienced coagulopathy, resulting in the occurrence of thrombotic events [4, 5]. These studies reported high incidence rates of venous thromboembolism (VTE), including deep vein thromboembolism (DVT) and pulmonary embolism (PE), especially in patients with clinically severe disease. In addition, the rate of arterial thrombotic events, such as ischemic stroke, was reportedly also higher in this patient group [6, 7]. Furthermore, acute myocardial injury commonly complicates the clinical course of severe COVID-19. According to the Japanese Ministry of Health, Labor, and Welfare's guide for COVID-19 [8], patients aged > 65 years are more likely to develop severe symptoms when hospitalized, with high blood pressure, hyperlipidemia and diabetes the most common comorbidities in this patient group. Pre-existing cardiovascular disease appears to increase the chance of complications in COVID-19 patients; however, data in Japan are still limited to date. To address the prevalence of thrombotic/cardiovascular disease in patients hospitalized for COVID-19 in Japan, as well as their clinical characteristics and anticoagulant/antiplatelet medication usage, a retrospective observational study was conducted using nationwide health claims administrative data from diagnosis procedure combination (DPC) hospitals.

METHODS

Study Design and Data Source

This retrospective observational cohort study in Japan (ClinicalTrials.gov Identifier: NCT04828772) was performed utilizing data extracted from a hospital-based administrative claims database provided by Medical Data Vision Co., Ltd. (MDV, Tokyo, Japan). The database consists of healthcare claims data obtained from acute care hospitals using the DPC system. As of June 2020, the database comprised approximately 32 million inpatients

and outpatients in 416 acute care hospitals, covering 30% of Japanese hospitals that use the DPC system. Data recorded in the MDV database include International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes, disease names coded using Japanese-specific disease codes and procedures, and drug prescriptions and administration codes using Japanese-specific receipt codes. In-hospital mortality information is available in the electronic medical records (EMR) data [9]. The diagnoses and procedure records of this administrative database have been validated in terms of their accuracy as a substitute for clinical data [10].

Compliance with Ethics Guidelines

Data are de-identified and comply with the patient confidentiality requirements of the US Health Insurance Portability and Accountability Act. This study was approved by the Institutional Review Board at MINS (Tokyo, Japan; reference no. 200241).

Study population

Adult patient data from 1 January to 30 September 2020 were extracted from the MDV database. Eligible patients were those hospitalized for COVID-19 identified by ICD-10 codes for COVID-19. The month of the COVID-19 diagnosis (index date) on the in-hospital record was confirmed to be the same as the admission month. The follow-up period was defined as the time between the index date and one of the following: (1) death during the hospitalization, (2) discharge due to any reason except death or (3) 30 September if the patient had not been discharged. Patient characteristics, treatment patterns, severity of COVID-19 and thrombotic/cardiovascular outcomes were assessed for the follow-up period. To ascertain the history and comorbidities of patients, we applied a look-back period of 1 year prior to the index date.

Severity of COVID-19

The severity of COVID-19 was classified as severe or non-severe. Severe COVID-19 was defined as at least one record of extracorporeal membrane oxygenation (ECMO), mechanical ventilation or intensive care unit (ICU) admission during the follow-up period; otherwise, cases were classified as non-severe COVID-19.

Thrombotic/Cardiovascular Outcomes

The thrombotic/cardiovascular outcomes evaluated during the follow-up period included DVT, PE, systemic embolism, ischemic stroke, transient ischemic attack (TIA), myocardial infarction/acute coronary syndrome (ACS) and chronic ischemic heart disease. These outcomes were identified by ICD-10 codes.

Statistical Analysis

Demographic and clinical characteristics of cases were expressed as means and standard deviations for continuous variables and as counts and percentages for categorical variables. Continuous variables were evaluated with the two-sided *t*-test and categorical variables with the Chi-square test.

RESULTS

Patient Demography

In total, 9282 patients hospitalized for COVID-19 were identified between January 2020 and September 2020 (Fig. 1). The highest portions of target COVID-19 patients were in April ($n = 1882$; 20.3%) and August ($n = 2215$; 23.9%), which aligns with the two national COVID-19 peaks in Japan (Fig. 2a). Most of patients were > 60 years of age (54%), and 36% of patients were between 71 and 90 years of age (Fig. 2B). The mean age of the overall patients was 59 years, of which 57.1% were male (Table 1). Severe COVID-19 accounted for 22% of cases (Fig. 2c).

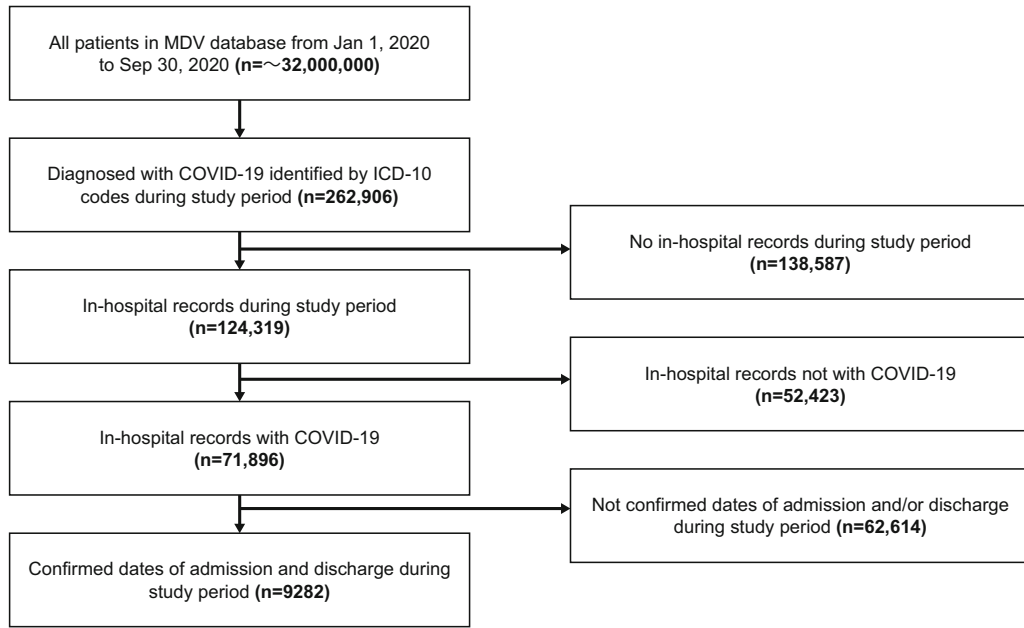


Fig. 1 Flow diagram of study population and patient identification. *COVID-19* Coronavirus disease 2019, *ICD-10* International Classification of Diseases, Tenth Revision, *MDV* Medical Data Vision Co., Ltd.

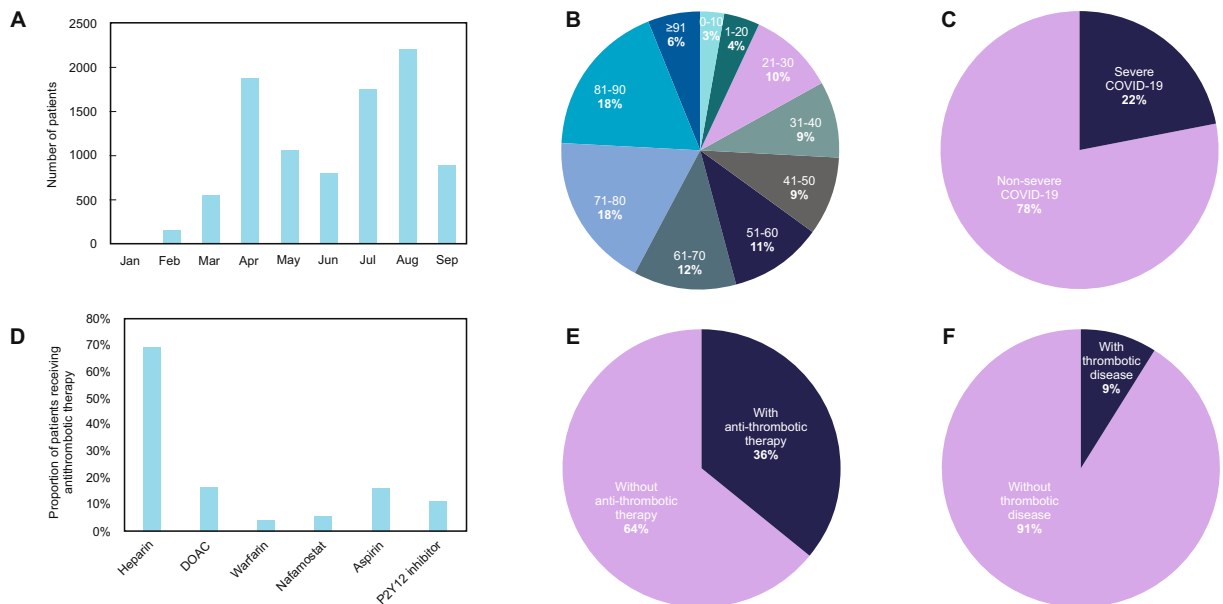


Fig. 2 Descriptive study results. **a** Number of patients hospitalized for COVID-19 between January 2020 and September 2020, **b** age distribution of patients hospitalized for COVID-19, **c** proportion of patients with severe or non-severe COVID-19 during hospitalization, **d** proportion of patients receiving antithrombotic therapy, **e** proportion of patients with or without antithrombotic therapy, **f** proportion of patients with or without thrombotic disease

Table 1 Characteristics of study patients with or without antithrombotic treatment

Characteristics	Overall study population (<i>n</i> = 9282)	With antithrombotic treatment (<i>n</i> = 3312)	Without antithrombotic treatment (<i>n</i> = 5970)	<i>P</i> value
Age (years), mean ± SD	59 ± 25	71 ± 19	53 ± 25	< 0.0001
Gender, male, <i>n</i> (%)	5296 (57.1)	2070 (62.5)	3226 (54.0)	< 0.0001
BMI (kg/m ²), <i>n</i> [mean ± SD]	7662 [22.5 ± 4.6]	2797 [22.4 ± 4.6]	4865 [22.5 ± 4.6]	0.4598
<i>Comorbidities, n</i> (%)				
Myocardial infarction	231 (2.5)	194 (5.9)	37 (0.62)	< 0.0001
Congestive heart failure	1279 (13.8)	845 (25.5)	434 (7.3)	< 0.0001
Hypertension	2618 (28.2)	1501 (45.3)	1117 (18.7)	< 0.0001
Peripheral vascular disease	337 (3.6)	226 (6.8)	111 (1.9)	< 0.0001
Stroke/TIA	530 (5.7)	422 (12.7)	108 (1.8)	< 0.0001
Chronic kidney disease	546 (5.9)	385 (11.6)	161 (2.7)	< 0.0001
Dyslipidemia	1389 (15.0)	821 (24.8)	568 (9.5)	< 0.0001
Diabetes mellitus	1294 (13.9)	812 (24.5)	482 (8.1)	< 0.0001
Cardiovascular disease	3769 (40.6)	2201 (66.5)	1568 (26.3)	< 0.0001
Chronic respiratory disease	1933 (20.8)	890 (26.9)	1043 (17.5)	< 0.0001
Any malignancy, including lymphoma and leukemia	1073 (11.6)	589 (17.8)	484 (8.1)	< 0.0001
Metastatic solid tumor	279 (3.0)	147 (4.4)	132 (2.2)	< 0.0001
Immunosuppressed condition	72 (0.8)	59 (1.8)	13 (0.2)	< 0.0001
HIV	31 (0.3)	18 (0.5)	13 (0.2)	0.0092
History of thrombosis	376 (4.1)	312 (9.4)	64 (1.1)	< 0.0001
Pregnancy	70 (0.8)	10 (0.3)	60 (1.0)	0.0002
<i>Charlson Comorbidity Index, n</i> (%)				
0	4491 (48.4)	823 (24.9)	3668 (61.4)	< 0.0001
1–2 (mild)	2796 (30.1)	1219 (36.8)	1577 (26.4)	
3–4 (moderate)	1080 (11.6)	667 (20.1)	413 (6.9)	
≥ 5 (severe)	915 (9.9)	603 (18.2)	312 (5.2)	
<i>Anticoagulant therapy during pre-index period, n</i> (%)				
Yes	781 (8.4)	689 (21.1)	92 (1.5)	< 0.0001
DOAC	211 (2.3)	185 (5.7)	26 (0.43)	
Warfarin	80 (0.86)	73 (2.2)	7 (0.12)	

Table 1 continued

Characteristics	Overall study population (<i>n</i> = 9282)	With antithrombotic treatment (<i>n</i> = 3312)	Without antithrombotic treatment (<i>n</i> = 5970)	<i>P</i> value
Antiplatelet/tes	490 (5.3)	431 (13.2)	59 (0.98)	

BMI Body mass index, *DOAC* direct oral anticoagulant, *HIV* human immunodeficiency virus, *n* number of patients, *SD* standard deviation; *TIA* transient ischemic attack

Patient Characteristics

Figure 2d and e show that antithrombotic therapy was provided to 3312 patients, with heparin (69.0%) the most frequently prescribed antithrombotic agent, followed by direct oral anticoagulants (DOAC) (16.8%), aspirin (16.3%), P2Y12 inhibitors (11.5%), nafamostat (5.6%) and warfarin (4.0%). The data showed that 832 of the 9282 patients (9.0%) had developed thrombotic disease (Fig. 2f) including DVT, PE, systemic embolism, ischemic stroke/TIA, myocardial infarction/ACS and chronic ischemic heart disease. The characteristics of patients treated with or without antithrombotic medication were also compared. The mean ages of the antithrombotic therapy group and the no therapy group were 71 and 53 years, respectively, of which 62.5% and 54.0% were male, respectively (Table 1). The mean body mass index was similar between the two groups (22.4–22.5 kg/m²).

In the antithrombotic therapy group, 66.5% of patients had cardiovascular disease, compared to 26.3% of the no therapy group (Table 1). Similarly, the prevalence of other disease complications (myocardial infarction, congestive heart failure, hypertension, peripheral vascular disease, cerebrovascular disease, stroke/TIA, chronic kidney disease, dyslipidemia and diabetes mellitus) in the antithrombotic therapy group was significantly higher in the antithrombotic therapy group than in the no therapy group. Other risk factors for aggravation of COVID-19 (i.e. chronic respiratory disease, malignancy, immunosuppressed condition, human immunodeficiency virus [HIV]) and higher Charlson Comorbidity Index (CCI) were more likely to affect patients in the

antithrombotic therapy group. The data also showed that 4.1% of the overall population had a history of thrombosis before COVID-19 diagnosis, with 9.4% in the antithrombotic therapy group and only 1.1% in the no therapy group. A total of 70 pregnant women were identified in the study population, of whom ten (0.3%) were in the antithrombotic therapy group and 60 (1.0%) were in the no therapy group.

Similarly, regarding the proportion of pre-existing cardiovascular disease, 21.1% of the antithrombotic therapy group had already received antithrombotic therapy during the pre-index period and only 1.5% of the no therapy group (Table 1).

Thrombotic Disease Development During Hospitalization for COVID-19

Deep venous thromboembolism, ischemic stroke and myocardial infarction/ACS were the three most frequent thrombotic/cardiovascular events in the overall study population and in the two subgroups (Table 2). The incidences of thrombotic/cardiovascular diseases were more than tenfold higher in the antithrombotic therapy group than in the no therapy group: DVT (6.8 vs. 0.4%), PE (1.8 vs. 0.1%), systemic embolism (2.3 vs. 0.2%), ischemic stroke/TIA (6.3 vs. 0.6%), myocardial infarction/ACS (5.4 vs. 0.5%) and chronic ischemic heart disease (5.0 vs. 0.4%). In addition, 15.8% of patients in the antithrombotic therapy group and 1.5% of those in the no therapy group had one complication, and 4.5% and 0.3% had two complications, respectively; 25 patients (0.75%) in the antithrombotic therapy group had three or four complications at the same time.

Table 2 COVID-19 severity and development of thrombotic/cardiovascular disease among study patients with or without antithrombotic treatment

Thrombotic/cardiovascular disease characteristics	Overall study population (<i>n</i> = 9282)	With antithrombotic treatment (<i>n</i> = 3312)	Without antithrombotic treatment (<i>n</i> = 5970)	<i>P</i> value
<i>Thrombotic/cardiovascular disease, n (%)</i>				
Deep venous thromboembolism	247 (2.7)	224 (6.8)	23 (0.4)	< 0.0001
Pulmonary embolism	64 (0.7)	58 (1.8)	6 (0.1)	< 0.0001
Systemic embolism	86 (0.9)	77 (2.3)	9 (0.2)	< 0.0001
Ischemic stroke/TIA	243 (2.6)	210 (6.3)	33 (0.6)	< 0.0001
Myocardial infarction/ACS	207 (2.2)	179 (5.4)	28 (0.5)	< .0001
Chronic ischemic heart disease	192 (2.1)	166 (5.0)	26 (0.4)	< 0.0001
<i>Duplication of outcome thrombotic/cardiovascular disease, n (%)</i>				< .0001
Patients with 1 event	612 (6.6)	524 (15.8)	88 (1.5)	
Patients with 2 events	171 (1.8)	152 (4.6)	19 (0.32)	
Patients with 3 events	21 (0.23)	21 (0.63)	0 (0)	
Patients with 4 events	4 (0.04)	4 (0.12)	0 (0)	
<i>COVID-19 severity, n (%)</i>				< 0.0001
Not severe	7278 (78.4)	2453 (74.1)	4825 (80.8)	
Severe	2004 (21.6)	859 (25.9)	1145 (19.2)	
<i>Procedure usage</i>				
Duration of hospitalization (days), mean ± SD	15 ± 14	20 ± 19	12 ± 10	< 0.0001
ECMO, <i>n</i> (%)	24 (0.26)	24 (0.73)	0 (0)	< 0.0001
Mechanical ventilation, <i>n</i> (%)	386 (4.2)	324 (9.8)	62 (1.0)	< 0.0001
Oxygen therapy, <i>n</i> (%)	3110 (33.5)	1762 (53.2)	1348 (22.6)	< 0.0001
ICU, <i>n</i> (%)	1792 (19.3)	695 (21.0)	1097 (18.4)	0.0023
Length of ICU stay (days), mean ± SD	6.6 ± 7.8	8.2 ± 9.0	3.7 ± 3.2	< 0.0001
In-hospital death, <i>n</i> (%)	505 (5.4)	300 (9.1)	205 (3.4)	< 0.0001

ASC Acute coronary syndrome, COVID-19 coronavirus disease 2019, ECMO extracorporeal membrane oxygenation, ICU intensive care unit, *n* number of patients, TIA transient ischemic attack

COVID-19 Severity of Patients With or Without Antithrombotic Treatment

The frequency of severe COVID-19 was 25.9% in the antithrombotic therapy group and 19.2% in the no therapy group (Table 2). Mean duration of hospitalization in the overall population and in the antithrombotic therapy and no therapy subgroups were 15, 20 and 12 days, respectively. The most frequently utilized procedure was oxygen therapy, followed in decreasing order of frequency by ICU admission, mechanical ventilation, and ECMO. The mean length of ICU stay was 8.2 days for the antithrombotic therapy group, which was longer than the 3.7 days for the no therapy group. In this study, 505 in-hospital deaths were registered, 300 in the antithrombotic therapy group and 205 in the no therapy group.

Non-Antithrombotic Cardiovascular Medication and Corticosteroid Use

During hospitalization for COVID-19, the prescription rates of antihypertensives (angiotensin II receptor blocker, ACE inhibitor,

beta blocker, calcium channel blocker and mineralocorticoid receptor antagonist) and statin were higher in the antithrombotic therapy group than in the no therapy group (Table 3). Calcium channel blockers were the most prescribed antihypertensive agent overall and in both patient subgroups, but they were prescribed more frequently to patients in the antithrombotic therapy group (36.6%) than to those in the no therapy group (14.1%). All three populations had similar portions of inhaled corticosteroid use (4.7, 5.0 and 4.6%, respectively). However, the antithrombotic therapy group had 22.9% of systemic corticosteroid, which was more than 8.0% for the no therapy group.

DISCUSSION

In this study, information on 9282 patients hospitalized for COVID-19 between January and September 2020 was collected from a large database of healthcare claims data compiled from approximately 30% of the DPC hospitals in Japan. We were therefore able to identify 832 patients with thrombotic events from this

Table 3 Non-antithrombotic cardiovascular medication and corticosteroid use

Medications	Overall study population (<i>n</i> = 9282)	With antithrombotic therapy (<i>n</i> = 3312)	Without antithrombotic therapy (<i>n</i> = 5970)
ARBs	1177 (12.7)	700 (21.1)	477 (8.0)
ACE inhibitors	219 (2.4)	153 (4.6)	66 (1.1)
Beta blocker	313 (3.4)	252 (7.6)	61 (1.0)
Calcium channel blocker	2056 (22.2)	1212 (36.6)	844 (14.1)
MRA	350 (3.8%)	248 (7.5)	102 (1.7)
Statin	1044 (11.3)	665 (20.1)	379 (6.4)
Inhaled corticosteroid	439 (4.7)	164 (5.0)	275 (4.6)
Systemic corticosteroid	1237 (13.3)	757 (22.9)	480 (8.0)

All values are presented as the number with the percentage in parentheses

ARB Angiotensin II receptor blockers, *ACE* angiotensin-converting enzyme, *MRA* mineralocorticoid receptor antagonist, *n* number of patients

patient sample. The joint team of the Japan Society of Thrombosis and Hemostasis (JSTH) and the Japanese Atherosclerosis Society (JAS) have previously reported the results of a questionnaire-based survey that described 108 Japanese COVID-19 patients who experienced thrombotic events [11]. Thus, the present study is the largest and the first nationwide database analysis of COVID-19-related thrombotic disease in Japan. In this study, we describe in detail how patients hospitalized for COVID-19 were managed during hospitalization, as well as the outcomes associated with different treatments in Japan.

Recent research has highlighted an apparent marked increase in the rates of VTE, including DVT and PE, in COVID-19 patients [4, 5]. In the present study, the incidence rate of DVT was 2.7% and accounted for 29.7% of all thrombotic events. The frequencies of DVT and PE were similar to those reported in the JSTH-JAS survey [11]. In comparison, a study in the Netherlands reported that the incidence of VTE was 49% among patients with severe COVID-19, with PE being the most common thrombotic complication [5]. In Western countries, PE is the third most common cardiovascular disease-related cause of death in the general population [12]. The prevalence of VTE in Japan is approximately one-eighth of that observed in the US general population, but similar to that among Asian Americans [13], suggesting racial influences. Indeed, genetic polymorphisms in the coagulation factor V (FV Leiden) and prothrombin (20210G>A) genes, common in populations of European ancestry, are associated with increased risk of VTE and account for 15–25% and 6–8% of patients with VTE, respectively [14]. These polymorphisms are present, respectively, in 2–15% and 1–6% of Caucasians, but have not been identified in Japanese populations. Thus, racial influences affecting VTE development could also pertain to COVID-19 patients. Several research groups have also reported rates of ischemic stroke of between 3% and 5% in patients admitted to the hospital with COVID-19 [6, 7]. The results of the present study show that the incidence of ischemic stroke was 2.5%, which is similar in magnitude to that reported in Western

countries. Unlike VTE, stroke risk is known to be significantly affected by lifestyle, rather than by genetic predisposition.

The findings of the present study also reveal that myocardial infarction/ACS and chronic ischemic heart disease occurred in COVID-19 patients at rates of 2.2% and 2.1%, respectively. These data are consistent with those reported in a recent study showing that COVID-19 is an independent risk factor for acute myocardial infarction and ischemic stroke [14, 15]. Notably, we found that arterial thrombotic events (stroke, myocardial infarction/ACS and chronic ischemic heart disease) accounted for 77% of total thrombotic events. Matsumoto et al. [16] recently reported an age-dependent increase of BNP/NT-proBNP levels in COVID-19 patients. It has been speculated that SARS-CoV-2 may directly cause myocardial tissue damage mediated by ACE-2 and modulated platelet activity, resulting in the formation of platelet thrombi [3]. ACE-2 is also expressed widely in extrapulmonary sites, including the blood vessels and heart [3]. Yamamoto et al. [17] reported that the anticoagulant nafamostat inhibits SARS-CoV-2 S protein-mediated fusion. Indeed, among the patients included in the present study, 182 received nafamostat, presumably for its direct inhibitory effects rather than for its action as an anticoagulant.

Several international societies propose thromboprophylaxis with unfractionated heparin or low-molecular-weight heparin in all COVID-19 patients requiring hospitalization [18, 19]. In the present study, 35.7% of patients received antithrombotic medications, including anticoagulants, with heparin being (24.6%) the most frequently prescribed, followed by DOAC (6.0%), antiplatelets, aspirin (5.1%), and P2Y12 inhibitors (4.1%). With regard to heparin, unfractionated heparin appeared to be used in most cases in this study, presumably due to the off-label use of low-molecular-weight heparin in Japan. Although heparin injection appears to have been used as thromboprophylaxis for VTE, oral antithrombotics were also provided to patients, including prior to their hospital admission. Importantly, even with antithrombotic medication, 21.6% of patients suffered from thrombotic disease. In addition, the mean

ICU stay of the antithrombotic therapy group was 8.2 days, which was longer than the 3.7 days for the no therapy group. Consistently, higher proportions of severe COVID-19 and procedure usages, such as oxygen therapy and mechanical ventilation, were identified in the antithrombotic therapy group. Notably, compared with the no therapy group, most of the antithrombotic therapy patients had multiple comorbidities, especially cardiovascular diseases (66.0 vs. 26.3%) and a history of thrombosis before COVID-19 diagnosis (9.4 vs. 1.1%). Indeed, a substantial number of patients in the antithrombotic therapy group had already received antithrombotic therapy at the time of hospital admission. Also, in comparison to patients in the no therapy group, more patients in the antithrombotic therapy group received antihypertensives (> 44 vs. ~ 17%) and statins (20.1 vs. 6.4%). Furthermore, there was a significant difference in mean age between patients in the antithrombotic therapy group and those in the no therapy group (71.3 vs. 52.5 years). The present study extends our knowledge of risk factors for COVID-19 severity by providing insights into thrombosis/cardiovascular disease.

The finding that 86 patients also had systemic embolisms suggests an association of COVID-19 with microvascular thrombosis in addition to macrovascular thrombosis. Intriguingly, 171(1.8%) patients had two thrombotic events and 25 patients (0.27%) had three or four thrombotic events at the same time. Taken together, these findings suggest that COVID-19 patients may experience thrombotic complications in every blood vessel, although the risk factors associated with arterial thrombosis are different from those for venous thromboembolism. To our best knowledge, clinical features of thrombotic complications in COVID-19 patients are similar to those observed in antiphospholipid antibody syndrome (APS) [20]. Thus, we speculate that a common pathophysiological mechanism contributes to both diseases. In patients with APS, moderate-intensity warfarin appears to be effective for preventing venous thrombosis as well as arterial thrombosis [21]; however, several international societies do not recommend the use of warfarin

for the management of coagulopathy in COVID-19 [18, 19].

Carvelli et al. [22] reported an association of COVID-19 inflammation with activation of complement C5a and its receptor axis. Complement activation is also linked to a range of thrombotic events. Patients with severe COVID-19 and those with APS have both been reported to have elevated blood C5a levels and extensive deposition of the terminal complement components [20, 23], suggesting a contribution to organ injury along with inflammation and thrombogenesis. In addition, the uptake of SARS-CoV-2 into cells is associated with the downregulation of ACE-2, which promotes a concomitant increase in levels of angiotensin II (AT-II) [3, 23]. AT-II has been implicated in promoting overexpression of tissue factor (TF) in platelets and macrophages, including in patients with APS [20, 23]. TF serves as a high-affinity receptor and cofactor for coagulation factors VII and VIIa. Thus, TF may be a critical mediator associated with the development of both arterial and venous thrombosis. Preliminary reports suggested that heparin treatment reduces mortality in COVID-19 patients [4, 18] and antiplatelet treatments, such as aspirin, might also be associated with better prognoses and the prevention of arterial thrombogenesis in these patients. Notably, at present it cannot be predicted if either venous or arterial thrombosis will occur in COVID-19 patients. Therefore, combination thromboprophylaxis with anticoagulant and antiplatelet agents may be considered for patients hospitalized with COVID-19 [20]. Finally, to better manage COVID-19-associated thrombotic complications, it is expected that new therapeutic agents will address the underlying molecular mechanisms of SARS-CoV-2 infection, as has been successful with anti-influenza or anti-HIV agents.

Limitations

First, the database covered claims data from Japanese DPC hospitals, and the study population may not represent the general patient population in Japan. Second, COVID-19

patients were defined based on ICD-10 codes, but we were not able to validate those diagnoses against medical records. Because the database is hospital-based, the past medical history of patients prior to the study period was not obtained. Third, regarding initiation date of antithrombotic medication, we could not distinguish initiation prior to hospitalization from initiation prior to COVID-19 diagnosis; in some cases, medications may have been initiated before the definitive diagnosis was established. Fourth, we could not determine whether the timing of antithrombotic therapy was before or after the presentation of in hospital thrombotic events; in some cases, medications may have been received to prevent for recurrent thrombotic events.

CONCLUSIONS

Patients with COVID-19 may experience thrombotic complications in every blood vessel. Further optimization of medication is crucial for preventing thrombotic complications and improving prognosis.

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interpretation. Yasuhiko Miyata: concept and design, data interpretation. Yoshio Anazawa: concept and design, data analysis, data interpretation.

Disclosures. Naoki Terasaka, Yukako Matsuo, Hirohide Kataoka, Yasuhiko Miyata and Yoshio Anazawa are Bristol Myers Squibb K.K. employees.

Compliance with Ethics Guidelines. Data are de-identified and comply with the patient confidentiality requirements of the US Health Insurance Portability and Accountability Act. This study was approved by the Institutional Review Board at MINS (Tokyo, Japan; reference no. 200241).

Data Availability. The datasets analyzed during the current study are not publicly available due to licensing agreement with Medical Data Vision Co., Ltd.

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