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Original Article

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Significant Impact of Age on Mortality and Non-significant Impact of Age on Thrombosis and Major Bleeding in Patients with COVID-19: From the CLOT-COVID Study

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Aim: There is scarce data on the impact of age on clinical outcomes in patients with coronavirus disease 2019 (COVID-19).

Method: 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 five groups according to age strata; -19, 20–39, 40–59, 60–79, and 80- years.

Results: Most patients under 19 had mild COVID-19 on admission (99%), while older patients had more severe COVID-19. The incidence rates of clinical outcomes during hospitalization in patients aged ≤ 19, 20–39, 40–59, 60–79, and 80 ≥ years were 0.0%, 0.5%, 2.2%, 2.7%, and 1.5% for thrombosis; 0.0%, 1.2%, 1.5%, 3.4%, and 2.0% for major bleeding; and 0.0%, 0.4%, 2.0%, 12.1%, and 16.8% for all-cause death, respectively. In the stratified analysis according to COVID-19 severity on admission, the incidences of thrombosis were generally higher among patients with more severe status, although those were not significantly different among age strata in all sub-types of COVID-19 severity. However, the incidences of all-cause death were significantly higher with increasing age in all sub-types of COVID-19 severity.

Conclusions: In the current large observational study of patients with COVID-19, the risk of mortality became markedly higher with increased age. However, the risks of thrombosis and major bleeding did not necessarily increase as age increases, which seemed to be consistent irrespective of COVID-19 severity on admission.

Key words: COVID-19, Age, Thrombosis, Bleeding, Mortality

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Introduction

Coronavirus disease 2019 (COVID-19) is a viral illness caused by the severe acute respiratory syndrome coronavirus 2. It has become a major health problem worldwide as a pandemic[1, 2]. Clinical presentations of COVID-19 reportedly vary widely across patients, ranging from asymptomatic to fatal COVID-19 [3]. Previous studies reported that several patient characteristics, including old age, male sex, obesity, and presence of comorbidities, were risk factors for mortality, and old age was a strong risk factor of mortality[3-6].

The main pathophysiology of COVID-19 is a respiratory infectious disease, and the main treatment strategies for COVID-19 are treatments for respiratory viral infection. COVID-19 reportedly causes thrombosis[7, 8], which could be related to worsening disease severity. Thus, several current guidelines recommend that hospitalized patients with COVID-19 should receive anticoagulation therapy to prevent thrombosis, leading to improved clinical outcomes[9, 10]. Although the risk of thrombosis in patients with COVID-19 seemed to be greatly influenced by COVID-19 severity[11], the impact of age on thrombosis in patients with COVID-19 has not been fully evaluated. Furthermore, the risk of bleeding might also be clinically relevant in determining more suitable patients for anticoagulation therapy and the intensity of anticoagulation therapy. Thus, the current study aimed to evaluate the impact of age on thrombosis, major bleeding, and mortality using a large-scale multicenter observational database of 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. It enrolled 2894 consecutive hospitalized patients diagnosed with COVID-19 infection by a positive polymerase chain reaction test among 16 centers in Japan from April 2021 to September 2021. The design of the study was previously reported in detail[12, 13]. All participating centers' relevant review boards or ethics committees (Supplementary Appendix 1) approved the research protocol. All procedures complied 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.

In the current study, we divided the entire cohort into five groups according to age strata; -19 years, 20–39 years, 40–59 years, 60–79 years, and 80- years, and compared patient characteristics and clinical characteristics outcomes among the five groups.

Data Collection and Definitions for Patient Characteristics

Data on the patient characteristics, management strategies, and clinical outcomes were collected from the hospital charts or hospital databases according to the prespecified definitions. The physicians at each institution were responsible for the data entered into an electronic case report form. Data were manually checked for missing or contradictory input and values out of the expected range at the general office.

The severity of COVID-19 was classified as mild, moderate, or severe COVID-19. Patients with mild COVID-19 were those who did not require oxygen. Those with moderate COVID-19 required oxygen, and those with severe COVID-19 required mechanical ventilation or extracorporeal membrane oxygenation (ECMO)[14, 15]. The usage of anticoagulants evaluated pharmacological thromboprophylaxis management during the hospitalization except for their usage for the treatment of thrombosis. The detailed definitions of other patient characteristics are described in Supplementary Appendix 2.

Clinical Outcomes

The outcome measured in the current study was thrombosis, major bleeding, and all-cause death during hospitalization. The thrombosis included venous thromboembolism (VTE), ischemic stroke, myocardial infarction, and systemic arterial thromboembolism, which were newly diagnosed after the patients were diagnosed with COVID-19. VTE was defined as pulmonary embolism and/or deep vein thrombosis objectively confirmed by imaging examinations (ultrasound, contrast-enhanced computed tomography, ventilation-perfusion lung scintigraphy, pulmonary angiography, or contrast

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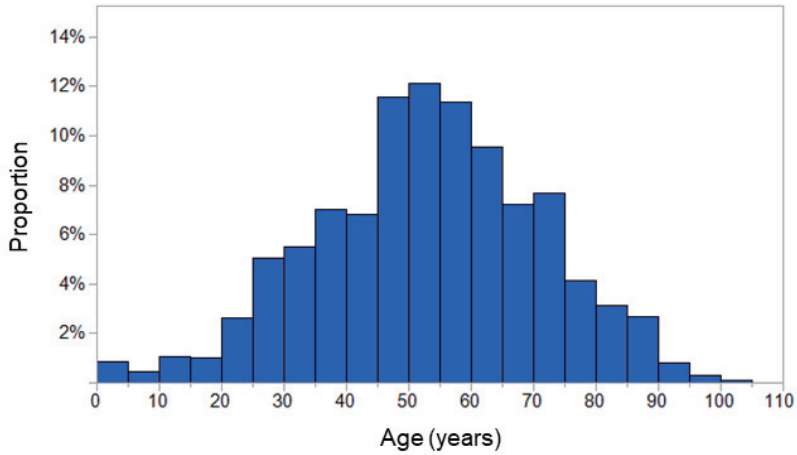

Fig. 1. Distribution of age on admission

The mean age was 52.7 ± 17.9 years old, and patients aged -19, 20–39, 40–59, 60–79, and 80- years were accounted for 93 (3.2%), 579 (20%), 1205 (42%), 821 (28%), and 196 (6.8%), respectively.

venography) or by autopsy. Ischemic stroke was defined as a stroke either requiring or prolonging the hospitalization with symptoms lasting more than 24 hours. Myocardial infarction was defined per universal myocardial infarction guidelines[16]. 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[17].

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 a one-way analysis of variance or the Kruskal–Wallis test based on their distributions. The clinical outcomes are presented as numbers of events and percentages, which were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used. We also conducted a stratified analysis according to the severity of COVID-19 on admission. 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.

Results

Patient Characteristics

The mean age was 52.7 ± 17.9 years old, and patients aged -19, 20–39, 40–59, 60–79, and 80- years were accounted for 93 (3.2%), 579 (20%), 1205 (42%), 821 (28%), and 196 (6.8%), respectively **(Fig. 1)**. The patient characteristics according to age strata were different in several aspects across five groups **(Table 1)**. The median D-dimer levels at admission became higher as increasing age (0.5, 0.5, 0.8, 1.0, and 1.2 μg/mL, $P<0.001$). As for the severity of COVID-19 on admission, the vast majority of patients under 19 had a mild COVID-19 (99%), while older patients showed a more severe status of COVID-19 compared with younger patients **(Table 1)**. Similarly, older patients showed more severe status of the worst severity of COVID-19 during hospitalization compared with younger patients **(Fig. 2)**. Older patients more frequently received pharmacological thromboprophylaxis compared with younger patients, and unfractionated heparin of a therapeutic dose were less common in younger patients **(Table 1)**.

Clinical Outcomes during the Hospitalization

The incidences of thrombosis during hospitalization were 0.0%, 0.5%, 2.2%, 2.7%, and 1.5% in patients aged -19, 20–39, 40–59, 60–79, and 80- years, respectively **(Fig. 3)**. The incidences of VTE during hospitalization were 0.0%, 0.5%, 1.7%, 1.8%, and 0.5% in patients aged -19, 20–39, 40–59, 60–79, and 80- years, respectively **(Table 2)**. The mortality rates in patients with thrombosis were 0.0%, 22.2%,

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Table 1. Patient characteristics according to age strata

	-19 years (N=93)	20-39 years (N=579)	40-59 years (N=1205)	60-79 years (N=821)	80- years (N=196)	*P*-value
Baseline characteristics						
Age (years)	10.3±6.4	31.3±5.4	50.4±5.4	68.1±5.6	85.4±4.3	<0.001
Men	46 (49%)	357 (62%)	856 (71%)	538 (66%)	88 (45%)	<0.001
Body weight (kg)	37.8±23.0	74.1±20.4	74.2±16.6	64.5±12.9	52.3±11.8	<0.001
Body mass index (kg/m^2)	19.3±4.5	26.3±6.4	26.4±5.2	24.2±4.2	21.7±4.3	<0.001
Body mass index >30 kg/m^2	4 (4.3%)	138 (24%)	242 (20%)	66 (8.0%)	9 (4.6%)	<0.001
D-dimer level on admission (μg/mL) (N=2771)	0.5 (0.5-0.8)	0.5 (0.5-0.9)	0.8 (0.5-1.1)	1.0 (0.6-1.7)	1.2 (0.6-2.9)	<0.001
Comorbidities						
Hypertension	0 (0%)	28 (4.8%)	332 (28%)	408 (50%)	106 (54%)	<0.001
Diabetes mellitus	0 (0%)	41 (7.1%)	266 (22%)	240 (29%)	50 (26%)	<0.001
Heart disease	3 (3.2%)	7 (1.2%)	58 (4.8%)	130 (16%)	57 (29%)	<0.001
Respiratory disease	11 (12%)	50 (8.6%)	106 (8.8%)	103 (13%)	28 (14%)	0.01
Active cancer	0 (0%)	2 (0.4%)	16 (1.3%)	32 (3.9%)	10 (5.1%)	<0.001
History of major bleeding	0 (0%)	1 (0.2%)	8 (0.7%)	16 (2.0%)	3 (1.5%)	0.005
History of VTE	0 (0%)	1 (0.2%)	3 (0.3%)	7 (0.9%)	4 (2.0%)	0.007
Severity of COVID-19 on admission						
Mild	92 (99%)	463 (80%)	696 (58%)	385 (47%)	102 (52%)	<0.001
Moderate (Need oxygen)	1 (1.1%)	98 (17%)	405 (34%)	336 (41%)	87 (44%)	
Severe (Need mechanical ventilation/ECMO)	0 (0%)	18 (3.1%)	104 (8.6%)	100 (12%)	7 (3.6%)	
Pharmacological thromboprophylaxis	0 (0%)	133 (23%)	539 (45%)	480 (58%)	93 (47%)	<0.001
Unfractionated heparin of a prophylactic dose	-	80/133 (60%)	295/539 (55%)	269/480 (56%)	41/93 (44%)	-
Unfractionated heparin of a therapeutic dose	-	4/133 (3.0%)	58/539 (11%)	86/480 (18%)	13/93 (14%)	-
Length of hospitalization (days)	6 (4-9)	7 (5-9)	9 (6-13)	12 (8-19)	13 (9-19)	<0.001

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean and standard deviation or the median and interquartile range based on their distributions. Categorical variables were compared using the chi-square test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using 1-way analysis of variance or Kruskal-Wallis test based on their distributions.Unfractionated heparin of a prophylactic dose was defined as the administration of a fixed dose without reference to the APTT, while unfractionated heparin of a therapeutic dose was defined as administration of a therapeutic dose with reference to the APTT.
VTE, venous thromboembolism; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; APTT, activated partial thromboplastin time.

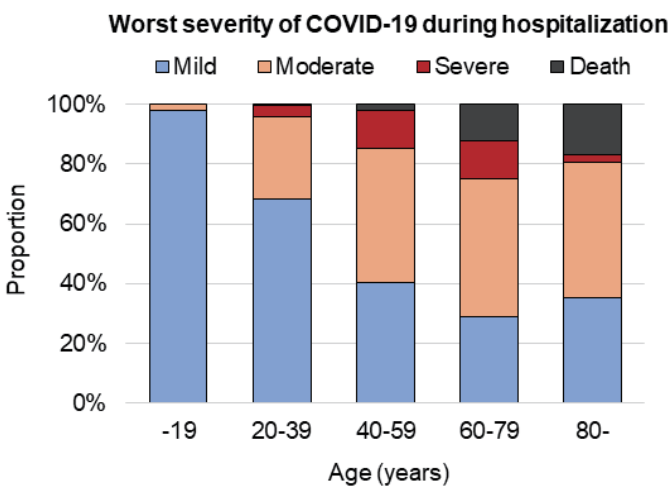

Fig. 2. Distribution of worst severity of COVID-19 during hospitalization according to age strata

The worst severity of COVID-19 during hospitalization was classified as mild, moderate, severe, and death. Patients with mild COVID-19 did not require oxygen. Those with moderate COVID-19 w required oxygen, and those with severe COVID-19 required mechanical ventilation or extracorporeal membrane oxygenation.
COVID-19, coronavirus disease 2019.

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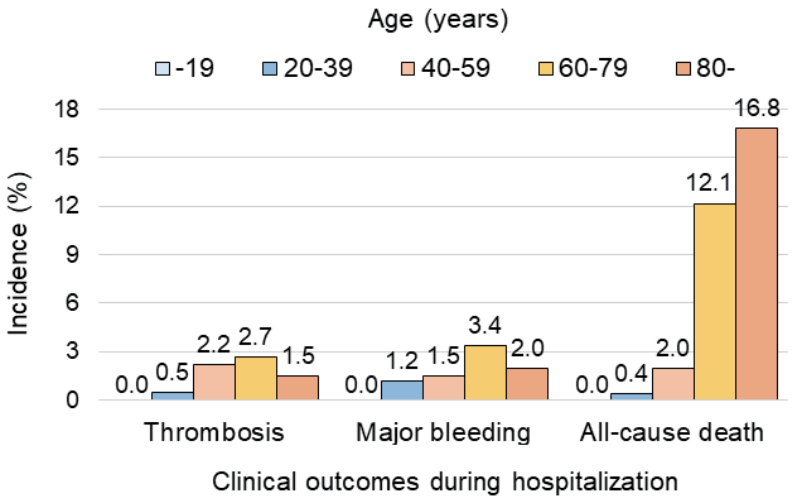

Fig. 3. Incidences of thrombosis, major bleeding, and all-cause death during hospitalization according to age strata

Table 2. Clinical outcomes during hospitalization according to age strata

	-19 years (N=93)	20-39 years (N=579)	40-59 years (N=1205)	60-79 years (N=821)	80- years (N=196)	*P*-value
Thrombosis	0 (0%)	3 (0.5%)	27 (2.2%)	22 (2.7%)	3 (1.5%)	0.02
VTE	-	3 (0.5%)	20 (1.7%)	15 (1.8%)	1 (0.5%)	0.11
PE with or without DVT	-	3/3 (100%)	12/20 (60%)	5/15 (33%)	1/1 (100%)	-
DVT only	-	0/3 (0%)	8/20 (40%)	10/15 (67%)	0/1 (0%)	-
Arterial thrombotic events	-	0 (0%)	6 (0.5%)	5 (0.6%)	1 (0.5%)	0.34
Ischemic stroke	-	-	4/6 (67%)	4/5 (80%)	1/1 (100%)	-
Myocardial infarction	-	-	2/6 (33%)	0/5 (0%)	0/1 (0%)	-
Systemic arterial thromboembolism	-	-	0/6 (0%)	1/5 (20%)	0/1 (0%)	-
Other thrombosis	-	0 (0%)	2 (0.2%)	3 (0.4%)	2 (1.0%)	0.14
Major bleeding	0 (0%)	7 (1.2%)	18 (1.5%)	28 (3.4%)	4 (2.0%)	0.008
Site of bleeding						
Intracranial	-	1/7 (14%)	1/18 (5.6%)	2/28 (7.1%)	0/4 (0%)	-
Respiratory	-	0/7 (14%)	1/18 (5.6%)	1/28 (3.6%)	0/4 (0%)	-
Gastrointestinal	-	1/7 (14%)	8/18 (44%)	15/28 (54%)	1/4 (25%)	-
Urinary	-	0/7 (0%)	1/18 (5.6%)	0/28 (0%)	0/4 (0%)	-
Intrathoracic/Intra-abdominal	-	0/7 (0%)	0/18 (0%)	1/28 (3.6%)	1/4 (25%)	-
Surgery-related/Iatrogenic	-	2/7 (29%)	5/18 (28%)	3/28 (11%)	1/4 (25%)	-
Subcutaneous	-	0/7 (0%)	0/18 (0%)	1/28 (3.6%)	0/4 (0%)	-
Others	-	3/7 (43%)	2/18 (11%)	5/28 (18%)	1/4 (25%)	-
All-cause death	0 (0%)	2 (0.4%)	24 (2.0%)	99 (12.1%)	33 (16.8%)	<0.001

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

22.7%, and 66.7% in patients aged 20–39, 40–59, 60–79, and 80- years, respectively.

The incidences of major bleeding during hospitalization were 0.0%, 1.2%, 1.5%, 3.4%, and 2.0% in patients aged -19, 20–39, 40–59, 60–79, and 80- years, respectively **(Fig. 3)**. The most common site of bleeding was gastrointestinal bleeding, followed by surgery-related/iatrogenic bleeding **(Table 2)**. Major bleeding according to age strata stratified by the usage of ECMO is shown in **Supplementary Table 1**. The incidences of all-cause death during hospitalization became markedly higher as increasing age, and those

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were 0.0%, 0.4%, 2.0%, 12.1%, and 16.8% in patients aged -19, 20–39, 40–59, 60–79, and 80- years, respectively **(Fig. 3)**.

Clinical Outcomes Stratified by the Severity of COVID-19 on Admission

In the stratified analysis according to the severity of COVID-19 on admission, the incidences of thrombosis were generally higher among patients with a more severe status. However, those were not significantly different among age strata in all sub-types of COVID-19 severity **(Fig. 4A)**. Similarly, the incidences of major bleeding were generally higher among patients with more severe status. However, those were not significantly different among age strata in all subtypes of COVID-19 severity **(Fig. 4B)**.

The incidences of all-cause death were generally markedly higher among patients with more severe status, and those were significantly higher with increasing age in all sub-types of COVID-19 severity **(Fig. 4C)**.

Clinical outcomes comparing patients with and without pharmacological thromboprophylaxis stratified by the severity of COVID-19 on admission are shown in **Supplementary Table 2**. Patients with pharmacological thromboprophylaxis generally showed higher incidences of thrombosis, while they showed higher incidences of major bleeding except for patients with severe COVID-19 on admission.

Discussion

The main findings of the current study were as follows: 1) Older patients had more severe COVID-19 on admission and the worst severity of COVID-19 during hospitalization, while most younger patients had mild COVID-19 throughout hospitalization; 2) Although the risk of all-cause death became markedly higher as increasing age, the risks of thrombosis and major bleeding did not necessarily become higher as increasing age; 3) Although old age showed a significantly higher risk of all-cause death irrespective of COVID-19 severity on admission, the risks of thrombosis and major bleeding were not significantly different according to age strata in all sub-types of COVID-19 severity on admission.

Previous studies reported that old age was associated with a more severe status of COVID-19 and a higher risk of mortality[3-6]. Consistent with the previous reports, the current study showed that older patients showed a more severe status of COVID-19 on admission and the worst severity of COVID-19 during hospitalization. Notably, although the prevalence of patients with severe COVID-19 on admission who required mechanical ventilation/ECMO was a relatively low rate of 3.6% among patients over 80, the in-hospital mortality rate was the highest at 16.8%. This might suggest aggressive treatment strategies, including mechanical ventilation/ECMO, for patients over 80. Most patients under 19 had mild COVID-19 on admission, and none of those died during hospitalization. Considering a wide-varying severity of COVID-19 and in-hospital mortality according to age strata, different medical management strategies according to different ages would be important.

COVID-19-associated thrombosis could be important because it might be related to worsening disease severity. Historically, acutely ill hospitalized patients are at a high risk of VTE, and previous studies reported that old age was a risk factor for VTE in these patients[18, 19]. However, the impact of age on thrombosis in patients with COVID-19 has not been fully evaluated. The current study showed that the risk of thrombosis did not necessarily become higher as increasing age. The incidence rates of thrombosis were low in patients under 39, and those seemed to be plateau in patients over 40. In line with the current study, a previous study from Japan reported that incidence rates of deep vein thrombosis (DVT) and PE were 0.1% and 0.1% in patients aged under 50, while those ranged 0.7%–1.7% and 0.2%–0.4% in patients aged over 50 [20]. Unlike mortality risk, old age might have a minor impact on the risk of thrombosis in patients with COVID-19.

A previous study showed that the COVID-19 severity on admission had a major influence on clinical outcomes, although Japanese patients with COVID-19 demonstrated fewer comorbidities and a trend toward lower mortality[21, 22]. Another study evaluating patients with severe COVID-19 requiring mechanical ventilation reported that older patients showed a high mortality rate of 49.7% in the 80s and 83.3% in the 90s[23]. In line with the previous report, the current study revealed that old age showed a significantly higher risk of all-cause death irrespective of COVID-19 severity on admission, and patients with severe COVID-19 over 80 showed a quite high mortality rate of 85.7%. These results suggest preventing progression to severe COVID-19 in elderly patients might be a major public health care problem. Regarding medical resource availability, appropriate hospital admission criteria might be a clinically relevant issue, especially for old patients. Whereas the current study also showed that the risk of thrombosis was not significantly different according to age strata in all sub-types of COVID-19 severity on admission. Although the severity of COVID-19 could

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Figure 4A

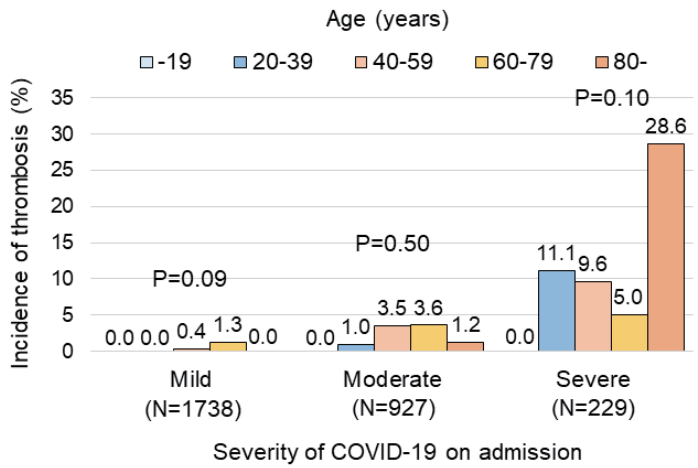

Figure 4B

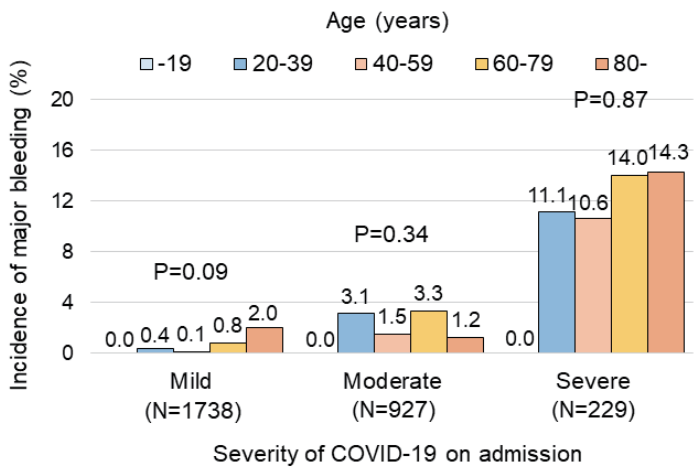

Figure 4C

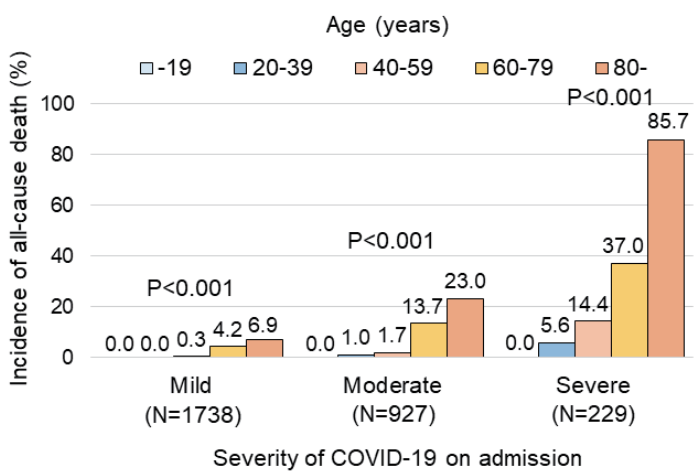

Fig. 4. Incidences of thrombosis (A), major bleeding (B), and all-cause death (C) during hospitalization according to age strata, stratified by the severity of COVID-19 on admission

COVID-19, coronavirus disease 2019.

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significantly influence the development of thrombosis, old age might have a minor influence on the development of thrombosis beyond the severity of COVID-19. Considering the quite high incidence rate of mortality in elderly patients with a more severe status of COVID-19 compared with the incidence rate of thrombosis, the optimal treatment for viral infection of COVID-19 seems to be a major issue. Furthermore, there might be a dilemma whether elderly patients should be treated aggressively, including mechanical ventilation and ECMO, in terms of medical resource availability.

Study Limitations

The current study had several limitations. First, the current study was observational, which can be subject to various biases inherent to the observational study design. Especially, the therapeutic decision-making, including thromboprophylaxis, mechanical ventilation, and ECMO, was left to the attending physician's discretion, which could influence the current results. In addition, the criteria of admission to the hospital was left to the discretion of each hospital depending on patient characteristics including age and COVID-19 severity, which should be cautious for the interpretation of the current results. Second, the diagnosis of thrombosis could be influenced by the availability of imaging examinations at each institution. There could be some under-diagnosis of thrombosis, especially in elderly patients. Third, the current study evaluated only clinical outcomes during hospitalization. Thus, we could not discuss the risk of clinical outcomes after discharge. Fourth, the absolute number of patients diagnosed with thrombosis seemed to be small in the current study compared to the reports from other countries11, which was in line with other previous reports in Japan[14, 22]. This could be partly due to different races, practices, medical resource availability, and screening of imaging examinations. However, because the current study was conducted in Japan, we could not evaluate the influence of racial differences on clinical outcomes.

Conclusions

In the current large observational study of patients with COVID-19, although the risk of mortality became markedly higher as increasing age, the risks of thrombosis and major bleeding did not necessarily become higher as increasing age, which seemed to be consistent irrespective of COVID-19 severity on admission.

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Supplementary Appendix 1: List of Participating Centers and Investigators

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Toho University Ohashi Medical Center: Nobutaka Ikeda (Toho University Ohashi Medical Center Ethics Committee: the approval number H21083)

Shikoku Medical Center for Children and Adults: Akane Kondo (Shikoku Medical Center for Children and Adults Ethics Committee: the approval number R03-31)

Yokohama Minami Kyosai Hospital: Makoto MO (Yokohama Minami Kyosai Hospital Ethics Committee: the approval number 1-21-11-1)

Supplementary Appendix 2: Definitions for Patient Characteristics

Hypertension was diagnosed if the peripheral blood pressure was >140/90mmHg or if the patient was taking medication for hypertension. The presence of diabetes was diagnosed using the hemoglobin A1c (HbA1c) [National Glycohemoglobin Standardization Program (NGSP), 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 [NYHA] 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[1]. 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[2].

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Supplementary Table 1. Major bleeding during hospitalization according to age strata stratified by usage of ECMO

	-19 years (N = 93)	20-39 years (N = 579)	40-59 years (N = 1205)	60-79 years (N = 821)	80- years (N = 196)
Patients with ECMO	0	5	18	12	0
Major bleeding	-	1 (20%)	6 (33%)	6 (50%)	-
Intracranial	-	1/1 (100%)	1/6 (17%)	0/6 (0%)	-
Respiratory	-	0/1 (0%)	0/6 (0%)	0/6 (0%)	-
Gastrointestinal	-	0/1 (0%)	0/6 (0%)	3/6 (50%)	-
Urinary	-	0/1 (0%)	0/6 (0%)	0/6 (0%)	-
Intrathoracic/Intra-abdominal	-	0/1 (0%)	0/6 (0%)	0/6 (0%)	-
Surgery-related/Iatrogenic	-	0/1 (0%)	5/6 (83%)	2/6 (33%)	-
Subcutaneous	-	0/1 (0%)	0/6 (0%)	0/6 (0%)	-
Others	-	0/1 (0%)	0/6 (0%)	1/6 (17%)	-
Patients without ECMO	93	574	1187	809	196
Major bleeding	0 (0%)	6 (1.1%)	12 (1.0%)	22 (2.7%)	4 (2.0%)
Intracranial	-	0/6 (0%)	1/12 (8.3%)	2/22 (9.1%)	0/4 (0%)
Respiratory	-	0/6 (0%)	0/12 (0%)	1/22 (4.6%)	0/4 (0%)
Gastrointestinal	-	1/6 (17%)	8/12 (67%)	12/22 (55%)	1/4 (25%)
Urinary	-	0/6 (0%)	1/12 (8.3%)	0/22 (0%)	0/4 (0%)
Intrathoracic/Intra-abdominal	-	0/6 (0%)	0/12 (0%)	1/22 (4.6%)	1/4 (25%)
Surgery-related/Iatrogenic	-	2/6 (33%)	0/12 (0%)	1/22 (4.6%)	1/4 (25%)
Subcutaneous	-	0/6 (0%)	0/12 (0%)	1/22 (4.6%)	0/4 (0%)
Others	-	3/6 (50%)	2/12 (17%)	4/22 (18%)	1/4 (25%)

The clinical outcomes are presented as numbers of events and percentages. ECMO, extracorporeal membrane oxygenation.

Supplementary Table 2. Clinical outcomes comparing patients with and without pharmacological thromboprophylaxis stratified by the severity of COVID-19 on admission

	Pharmacological thromboprophylaxis (+)	Pharmacological thromboprophylaxis (-)	*P* value
Severity of COVID-19 on admission			
Mild (N = 1738)	(N = 326)	(N = 1412)	
Thrombosis	8 (2.5%)	0 (0%)	< 0.001
Major Bleeding	4 (1.2%)	4 (0.3%)	0.02
Moderate (N = 927)	(N = 693)	(N = 234)	
Thrombosis	26 (3.8%)	2 (0.9%)	0.03
Major Bleeding	20 (2.9%)	1 (0.4%)	0.03
Severe (N = 229)	(N = 226)	(N = 3)	
Thrombosis	19 (8.4%)	0 (0%)	1.00
Major Bleeding	27 (12.0%)	1 (33.3%)	0.33

The clinical outcomes are presented as numbers of events and percentages, which were compared using the chi-squared test when appropriate; otherwise, Fisher's exact test was used.