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Association between pre-admission anticoagulation and in-hospital death, venous thromboembolism, and major bleeding among hospitalized COVID-19 patients in Japan

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Abstract

Purpose: The coagulation activation leads to thrombotic complications such as venous thromboembolism (VTE) in patients with coronavirus disease-2019 (COVID-19). Prophylactic anticoagulation therapy has been recommended for hospitalized COVID-19 patients in clinical guidelines. This retrospective cohort study aimed to examine the association between pre-admission anticoagulation treatment and three outcomes: in-hospital death, VTE, and major bleeding among hospitalized COVID-19 patients in Japan.

Methods: Using a large-scale claims database built by the Medical Data Vision Co. in Japan, we identified patients hospitalized for COVID-19 who had outpatient prescription data at least once within 3 months before being hospitalized. Exposure was set as pre-admission anticoagulation treatment (direct oral anticoagulant or vitamin K antagonist), and outcomes were in-hospital death, VTE, and major bleeding. We conducted multivariable logistic regression analyses, adjusting for a single summarized score (a propensity score of receiving pre-admission anticoagulation) for VTE and major bleeding, due to the small number of outcomes.

Results: Among the 2612 analytic patients, 179 (6.9%) had pre-admission anticoagulation. Crude incidence proportions were 13.4% versus 8.5% for in-hospital

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death, 0.56% versus 0.58% for VTE, and 2.2% versus 1.1% for major bleeding among patients with and without pre-admission anticoagulation, respectively. Adjusted odds ratios (95% confidence intervals) were 1.25 (0.75–2.08) for in-hospital death, 0.21 (0.02–1.97) for VTE, and 2.63 (0.80–8.65) for major bleeding. Several sensitivity analyses did not change the results.

Conclusions: We found no evidence that pre-admission anticoagulation treatment was associated with in-hospital death. However, a larger sample size may be needed to conclude its effect on VTE and major bleeding.

KEYWORDS

administrative claims, anticoagulants, COVID-19, hemorrhage, venous thromboembolism

Key Points

- Coagulation activation leads to thrombotic events such as venous thromboembolism in patients with coronavirus disease-2019 (COVID-19).
- We used a large-scale claims database to compare outcomes among patients with and without pre-admission anticoagulation. Primary outcomes were in-hospital death, venous thromboembolism, and major bleeding.
- We found no association between pre-admission anticoagulation and the outcomes. The results from this study neither recommend nor discourage pre-admission anticoagulation among hospitalized COVID-19 patients.
- A larger sample size may be needed to conclude the effect of pre-admission anticoagulation on venous thromboembolism and major bleeding.

Plain Language Summary

Excessive activation of coagulation is well-known in patients with coronavirus disease-2019 (COVID-19) and it manifests as occlusion of blood vessels in the lower limb or lung. Blood thinners are the medication to prevent the formulation of blood clots and have been used for hospitalized COVID-19 patients. However, blood thinners sometimes cause bleeding in the digestive tract or brain and need careful monitoring. This study examined the effect of blood thinners, which were started before COVID-19 hospitalization, on in-hospital death, blood vessels occlusion, and bleeding. Statistical analyses found that pre-admission blood thinners intake was not associated with any of these events. The results suggest that blood thinners initiation before hospitalization neither benefit nor harm patients' survival. Because there were not enough patients who had blood vessels occlusion and bleeding in this study, a larger study is necessary.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, was first reported in Wuhan, China, in December 2019.[1] The global pandemic of COVID-19 has infected nearly 300 million people, with 5 million deaths up to early January 2022.[2] Previous studies have reported the occurrence of coagulopathies in patients with COVID-19,[3–5] leading to venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), which may precipitate critical conditions. Considering the physiological features, prophylactic anticoagulation, thromboprophylaxis with subcutaneous low-molecular-weight heparin, or unfractionated heparin has been suggested for use in patients hospitalized with COVID-19.[6–8]

The association between pre-admission anticoagulation treatment for a pre-existing condition (such as atrial fibrillation [AF] and deep vein thrombosis [DVT]) and patient outcomes of COVID-19 has been investigated.[9–20] These studies were conducted under the hypothesis that pre-admission anticoagulation therapy may mitigate the hypercoagulation physiology of COVID-19. However, as summarized in Table S1, conflicting results have been reported. About half the previous studies reported null results for the association between pre-admission anticoagulation with direct oral anticoagulant (DOAC) or vitamin K antagonist (VKA) and in-hospital mortality.[9,11,12,14,18–20] However, studies conducted by Rossi et al., Fröhlich et al., Harrison et al., and Chocron et al. reported that pre-admission anticoagulation was associated with lower risk of studied outcomes[10,15–17] and

Rivera-Caravaca et al. reported that pre-admission anticoagulation was associated with higher mortality.[13]

Although there are beneficial aspects of anticoagulation, concerns have arisen with regard to bleeding events with therapeutic anticoagulation. One study reported an increased odds ratio of major or clinically relevant nonmajor bleeding among patients with COVID-19 receiving therapeutic doses of anticoagulation treatment compared to those receiving prophylactic doses of anticoagulation treatment.[21] As shown in Table S2, several studies showed a higher incidence of bleeding events in patients with pre-admission anticoagulation treatment than in those without pre-treatment.[11,16,19,20] Given the conflicting data from previous studies, clinical practitioners need more information to decide whether pre-admission anticoagulation treatment should be maintained or terminated.

Herein, we examined this hypothesis among patients hospitalized with COVID-19 in Japan, in terms of three outcomes: in-hospital death, VTE, and major bleeding.

2 | METHODS

2.1 | Data sources

This study was a retrospective cohort study conducted using the insurance claims database of Medical Data Vision Co., Ltd. (MDV). The MDV database consists of inpatient, outpatient, and pharmacy claims from over 350 hospitals, including more than 30 million people, 23% of the total population in Japan.[22] We analyzed data obtained between January 1, 2020 and December 31, 2020. In the MDV database, identification numbers were assigned to each hospitalization episode, instead of to each patient. Because of the structure of this data, previous outpatient visits of hospitalized patients, the necessary information to measure the exposure, could only be identified if they visited the same hospital where they were hospitalized for COVID-19.

2.2 | Study population

Patients were included in this study if they met the following inclusion criteria: First, for data availability, patients were hospitalized with an admission diagnosis of COVID-19 and discharged by December 31, 2020; Second, the reimbursements of newly introduced financial incentives for COVID-19 were recorded for the patient. In April 2020, the Japanese government introduced incentives to make additional payments to hospitals if they treated hospitalized patients with COVID-19.[23] Since laboratory polymerase chain reaction (PCR) test results for COVID-19 were unavailable in the database, we used these incentives to narrow the study population to patients whose diagnosis of COVID-19 was plausible. Third, the patients' outpatient prescription data from the same hospital was identified within 3 months before admission. The 3-month look back period was adopted because a long-term prescription is usually limited to a maximum of 3 months for each outpatient visit in Japan. This period was long enough to measure and classify exposure status in the current Japanese healthcare system.

2.3 | Exposure and outcomes

Throughout the study, we set pre-admission anticoagulation treatment, a prescription of anticoagulants within 3 months before hospital admission due to COVID-19, as an exposure of interest. Anticoagulants were defined as one of the following DOACs or VKA, which are available in Japan: dabigatran, rivaroxaban, apixaban, edoxaban, and warfarin. The prescription of anticoagulants was identified using the Anatomical Therapeutic Chemical Classification System (ATC) codes corresponding to the drugs (dabigatran: B01AE07, rivaroxaban: B01AF01, apixaban: B01AF02, edoxaban: B01AF03, warfarin: B01AA03).[24]

We defined the outcomes in this study as in-hospital death, VTE, and major bleeding. VTE included DVT (ICD-10 codes: I80.1-I80.3, I82.2) and PE (I260, I269). Major bleeding included intracranial bleeding (ICD-10 codes:I60, I61, I62.0, I62.1, I62.9), upper gastrointestinal bleeding (ICD-10 codes:K92.0, K92.1, I85.0, I98.20, I98.3, K22.10, K22.12, K22.14, K22.16, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K63.80, K31.80), lower gastrointestinal bleeding (ICD-10 codes: K55.20, K62.5, K92.1, K92.2), and other bleeding (hematuria: N02.0-N02.9, R31.0, R31.1, R31.8, hemoperitoneum: K66.1, uterine and vaginal bleeding: N93.8, N93.9, N95.0, bleeding from throat: R04.1, hemoptysis: R04.2, bleeding from respiratory passages: R04.8, R04.9, retinal bleeding: H35.6, vitreous bleeding: H43.1, H45.0, hemarthrosis: M25.0).[25] In-hospital death was identified by hospital discharge outcome records, and the incidence of VTE and major bleeding were identified by diagnosis codes during hospitalization. The diagnosis codes of VTE and bleeding have been validated in the MDV database, with a positive predictive value (PPV) of 75% for VTE and 73% for major bleeding.[26] In-hospital death has also been validated with a PPV of 96% using the other claims database in Japan.[27]

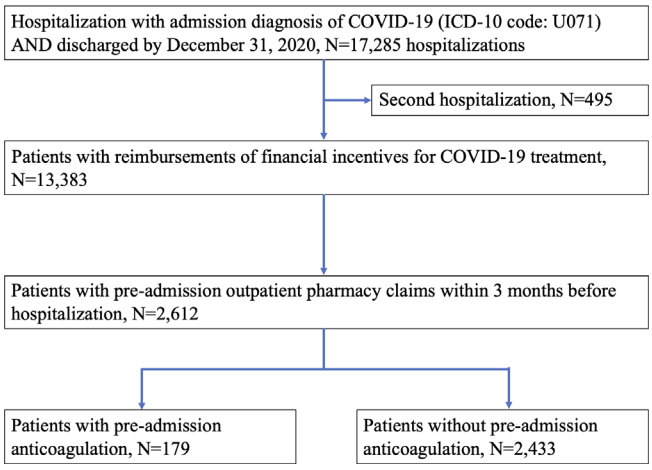

FIGURE 1 Flow of the population selection

2.4 | Covariates

We considered the following variables as potential confounders in this study: age, sex, body mass index (BMI), smoking history, comorbidities (cancer, hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, atrial fibrillation), immunosuppressant use, and history of VTE. We utilized the claims data until the first day of hospital admission for each patient to retrieve these covariates. Comorbidities and immunosuppressant use were identified using the corresponding ICD-10 codes (cancer: C00-C43, C45-C97, hypertension: I10-I13, I15, I67.4, dyslipidemia: E78, diabetes mellitus: E10-E14, chronic kidney disease: N18, atrial fibrillation: I48.0-I48.2, VTE: I80.1-I80.3, I82.2, I260, I269) or ATC codes (immunosuppressant: L04). Among the covariates, BMI information was missing for 279 patients (11%), and smoking history was missing for 417 patients (16%).

2.5 | Statistical analysis

We described the baseline characteristics of patients with and without pre-admission anticoagulation. The proportions of outcomes were crudely described by pre-admission anticoagulation status. We then conducted multivariable logistic regression analyses to compare patients with and without pre-admission anticoagulation treatment for the three outcomes. For in-hospital death, we adjusted for the aforementioned covariates. For VTE and major bleeding, because of the small number of outcomes, we adjusted for a single summarized score, namely, the propensity score of receiving pre-admission anticoagulation treatment. The propensity score was calculated using all the aforementioned covariates in a multivariable logistic regression model. For all statistical analyses, missing data on BMI and smoking history were imputed using multiple imputation by chained equations using all the variables, including the outcomes.[28]

Additionally, we conducted two sensitivity analyses for in-hospital death. First, we restricted the study population to individuals with cardiovascular disease (CVD) comorbidities, including atrial fibrillation/flutter (ICD-10 code: I48), ischemic heart disease (I20-I25), heart failure (I50, I11.0), cardiomyopathy (I13, I42, I43), stroke/transient ischemic attack/systemic thromboembolism (G45 except G45.4, I60-I63, I64.9, I69.0-I69.3, I74), and vascular disease (E10.5, E11.5, E12.5, E13.5, E14.5, I65, I66-I68 except I67.6, I69.4, I69.8, I70-I73, I75-I77, I79 except I79.8).[14] We performed this sensitivity

TABLE 1 Characteristics of hospitalized COVID-19 patients with and without pre-admission anticoagulation treatment

	Patients with pre-admission anticoagulation, *n* (%)	Patients without pre-admission anticoagulation, *n* (%)	*p*-value
Total	179 (DOAC: 134, VKA: 45)	2433	
Sex [Men, *n* (%)]	113 (63.1)	1528 (62.8)	0.931
Age, *n* (%)			<0.001
≦59	12 (6.7)	635 (26.1)	
60–74	38 (21.2)	606 (24.9)	
75≦	129 (72.1)	1192 (49.0)	
BMI, *n* (%)			0.242
≦24	109 (60.9)	1567 (64.4)	
25–29	40 (22.4)	502 (20.6)	
30≦	12 (6.7)	103 (4.2)	
Missing	18 (10.1)	261 (10.7)	
Smoking history, *n* (%)			0.916
Yes	63 (35.2)	838 (34.4)	
Missing	24 (13.4)	393 (16.2)	
Comorbidities, *n* (%)			
Cancer	69 (38.6)	888 (36.5)	0.583
Hypertension	147 (82.1)	1267 (52.1)	<0.001
Dyslipidemia	85 (47.5)	774 (31.8)	<0.001
Diabetes mellitus	97 (54.2)	943 (38.8)	<0.001
CKD	41 (22.9)	326 (13.4)	<0.001
Immunosuppressant use	13 (7.3)	121 (5.0)	0.180
Indication for anticoagulation			
History of AF	71 (39.7)	129 (5.3)	<0.001
History of VTE	25 (14.0)	60 (2.5)	<0.001

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist; VTE, venous thromboembolism.

analysis to increase the comparability of people who had received pre-admission anticoagulation treatment and those who did not. We identified the information on CVD using claims data until the first day of hospital admission. Second, we limited the study population to patients who did not change the anticoagulation strategy before and during hospitalization (i.e., patients with pre-admission anticoagulation and who continued anticoagulation during hospitalization, and patients without pre-admission anticoagulation and who did not initiate anticoagulation treatment during hospitalization), and conducted multivariable regression analysis for the association between pre-admission anticoagulation treatment and in-hospital death. This sensitivity analysis was conducted because in-hospital anticoagulation treatment may also affect patient outcomes.

All statistical analyses were conducted using Stata version 15 (StataCorp, Texas, USA). *p*-values and 95% confidence intervals (95% CIs) were calculated, and a two-sided *p*-value <0.05, was considered statistically significant. The authors followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

3 | RESULTS

Among 17 285 hospitalizations with admission diagnosis of COVID-19, 495 hospitalizations were excluded because they were second hospitalizations of the same patient. Of the remaining 16 790 hospitalizations, reimbursements of financial incentives for COVID-19 treatment were recorded among 13 383 hospitalizations. Finally, 2612 patients with pre-admission outpatient prescription data within 3 months before hospitalization, were included in the analysis (Figure 1). Of the 2612 patients, 179 (6.9%) had pre-admission anticoagulation treatment (DOAC, 134; VKA, 45), were indicated for atrial fibrillation (39.7%), a history of VTE (14.0%), or unknown indication. Patients with pre-admission anticoagulation treatment tended to be older and showed higher prevalence rates of hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, history of atrial fibrillation and VTE (Table 1). During hospitalization, 152 (84.9%) patients with pre-admission anticoagulation continued treatment, and 173 (7.1%) patients without pre-admission anticoagulation did not receive pre-admission anticoagulation treatment. Concerning steroids, 53 (29.6%) patients with pre-admission anticoagulation therapy and 681 (28.0%) patients without pre-admission anticoagulation received treatment with steroids.

In the whole cohort, 230 in-hospital deaths, 15 VTE (DVT, 10; PE, 9; both DVT and PE, 4), and 31 major bleeding events (intracranial bleeding, 3; upper gastrointestinal bleeding, 24; lower gastrointestinal bleeding, 13; other bleeding, 5; both upper and lower gastrointestinal bleeding, 13; both upper gastrointestinal bleeding and other bleeding, 1) were observed. Crude incidence proportions were in-hospital death: 13.4% versus 8.5%, VTE: 0.56% versus 0.58%, major bleeding: 2.2% versus 1.1% among patients with and without pre-admission anticoagulation treatment, respectively.

Multivariable logistic regression analysis showed that, for in-hospital death, fully adjusted odds ratio was 1.25 (95% CI: 0.75–2.08) when comparing patients with and without pre-admission

TABLE 2 Multivariable regression analyses for the association between pre-admission anticoagulation treatment and in-hospital death, VTE, and major bleeding

	In-hospital death			VTE			Major bleeding		
	Events, *n* (%)	Crude OR (95% CI)	aOR* (95% CI)	Events, *n* (%)	Crude OR (95% CI)	aOR** (95% CI)	Events, *n* (%)	Crude OR (95% CI)	aOR** (95% CI)
Nonuser: $N = 2433$	206 (8.5)	Ref.	Ref.	14 (0.58)	Ref.	Ref.	27 (1.1)	Ref.	Ref.
Pre-admission anticoagulation user: $N = 179$	24 (13.4)	1.67 (1.06–2.63)	1.25 (0.75–2.08)	1 (0.56)	0.97 (0.13–7.42)	0.21 (0.02–1.97)	4 (2.2)	2.04 (0.70–5.89)	2.63 (0.80–8.65)

Note: aOR*: fully adjusted for sex, age (three categories), body mass index (three categories), smoking history, cancer, hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, immunosuppressant use, history of atrial fibrillation and VTE. aOR**: adjusted for propensity score of receiving pre-admission anticoagulation.
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; VTE, venous thromboembolism; OR, odds ratio.

anticoagulation treatment (Table 2). After the adjustment with propensity scores, adjusted odds ratios was 0.21 (0.02–1.97) for VTE and 2.63 (0.80–8.65) for major bleeding.

In the first sensitivity analysis, 1605 patients with one of the CVD comorbidities were identified, and 163 in-hospital deaths were observed. Crude incidence proportion was 12.4% (21/170) versus 9.9% (142/1435), and fully adjusted odds ratio was 1.15 (0.70–1.90) comparing patients with and without pre-admission anticoagulation. In the second sensitivity analysis, 152 patients who continued pre-admission anticoagulation and 2260 patients without pre-admission anticoagulation treatment who did not initiate anticoagulation therapy during hospitalization, were included. Fully adjusted odds ratio was 0.95 (0.53–1.68), comparing patients with and without pre-admission anticoagulation treatment.

4 | DISCUSSION

4.1 | Statement of principal findings

In this retrospective cohort study, we examined the association between pre-admission anticoagulation therapy and three outcomes, among patients hospitalized with COVID-19. We did not find any statistically significant difference in the association between pre-admission anticoagulation treatment and in-hospital death. The point estimates of odds ratios for VTE and major bleeding were in line with the biological mechanisms (i.e., low for VTE and high for major bleeding); however, there was no statistical significance. The sensitivity analyses did not influence the conclusions.

4.2 | Comparison with previous studies

To our knowledge, this is the first study in Japan to examine the association between pre-admission anticoagulation treatment with in-hospital death, VTE, and major bleeding among hospitalized COVID-19 patients. The relative risk of in-hospital death found in this study (adjusted odds ratio: 1.25, 95% CI: 0.75–2.08) was consistent with some previous studies, which reported that there was no association between pre-admission anticoagulation therapy and mortality among patients hospitalized with COVID-19 shown in Table S1.[9,11,12,14,18–20] For example, a propensity score-matched cohort study in the Netherlands showed that the odds ratio for all-cause in-hospital mortality was 1.02 (95% CI: 0.80–1.30) among patients with and without pre-admission anticoagulation treatment.[18] Similarly, a propensity-score matched cohort study in New York City showed that the hazard ratio for all-cause mortality was 1.208 (95% CI: 0.750–1.946), comparing hospitalized and ambulatory patients with and without pre-admission anticoagulation treatment.[11] On the contrary, some studies showed that pre-admission anticoagulation treatment was associated with lower or higher probability of studied outcomes.[10,13,15–17] Some methodological limitations could be considered as an explanation. For example, several studies defined a composite outcome, not in-hospital mortality alone. A study by Fröhlich et al., which reported lower probability of the studied outcomes, defined the outcome as in-hospital all-cause mortality, need for invasive/noninvasive ventilation or ECMO implant.[15] Moreover, studies by Harrison et al. and Chocron et al. examined a composite outcome of in-hospital mortality or ICU admission.[16,17] Because not all patients admitted to the ICU result in in-hospital death, the results from these studies cannot be compared with those that defined in-hospital mortality as an outcome. In addition, a study by Rossi et al. reported lower in-hospital mortality among patients with pre-admission anticoagulation, but limited the analysis to the older population.[10] Furthermore, insufficient confounding adjustment could explain different results. A study by Rivera-Caravaca et al., which reported that pre-admission anticoagulation was associated with lower in-hospital mortality, did not include comorbidities in the regression model.[13]

It is noteworthy that the in-hospital mortality rate observed in our study (8.8%) was lower compared to the previous studies referred above, in which in-hospital mortality ranged from 15.0% to 43.8%. However, the in-hospital mortality in our study seems feasible when compared to a previous study in Japan reporting in-hospital mortality rates of 9.6%[29] and 7.5%.[30] One possible explanation is that in Japan, there were milder cases of patients hospitalized with COVID-19.

With regard to VTE, our results showed lower odds ratio of VTE among patients with pre-admission anticoagulation. Although this result did not reach statistical significance, the point estimate of odds ratio may indicate the protective effect of pre-admission anticoagulation. This result is in line with the result of some studies[18,20] but is contrary to that of another.[11] As we observed small number of VTE incidence in our study population, we should not reach conclusive answer from this result.

Notably, the incidence of VTE in this study was 0.4% (10/2612) for DVT and 0.3% (9/2612) for PE, and this is comparable to a previous study in Japan which reported an incidence proportion of 0.9% for DVT and 0.5% for PE.[30] On the other hand, the incidence proportion of VTE was lower compared to that of previous studies summarized in Table S2, which ranged from 1.2% to 6.8%.[11,18,20] This was also lower than that reported in a previous meta-analysis, which mainly included the studies from Western countries (the pooled incidence proportions of PE and DVT were 16.5% and 14.8%, respectively).[31] A possible explanation for the lower incidence of VTE in our study population is that the proportion of hospitalized patients with mild disease was higher in Japan. In addition, there are several known risk factors for VTE, such as obesity, diabetes mellitus, and smoking. We consider that the proportion of these risk factors (especially obesity) for VTE was smaller in Japanese patients compared to patients in western countries.[32]

With regard to major bleeding, our results showed a higher odds ratio for major bleeding among patients with pre-admission anticoagulation. Although this result did not reach statistical significance, the direction of the association between pre-admission anticoagulation and major bleeding is reasonable. This result is also in line with that of previous studies that reported a higher risk of bleeding in patients with pre-admission anticoagulation compared to those without (Table S2).[11,16,19,20] For example, one study in the United States

reported that the incidence proportion was 3 (1.2%) versus 20 (0.57%) among patients with and without pre-admission anticoagulation treatment, respectively.[11] Regarding the risk of major bleeding among hospitalized patients with COVID-19, one meta-analysis that included five studies reported that the pooled incidence proportion was 3.9% (95% CI, 1.2–7.9) for major bleeding.[33] The incidence proportion in our study (1.2%) was comparable to that reported in these studies.

4.3 | Possible explanations and implications

Previous studies have indicated that increased production of inflammatory cytokines and vascular endothelium damage causes coagulopathy in patients with COVID-19.[34,35] Accordingly, it is biologically plausible to hypothesize that anticoagulation during hospitalization may decrease the incidence rates of VTE or mitigate the severity of coagulopathy and lead to lower mortality among patients. Since coagulation activation may have occurred before hospitalization, it is conceivable that pre-admission anticoagulation treatment may confer lower mortality. However, the analyses showed no difference in VTE and in-hospital death among patients with and without pre-admission anticoagulation treatment.

Three explanations can be considered for our results of in-hospital death. First, the dose of pre-admission anticoagulant and the severity of COVID-19 may affect the observed association between pre-admission anticoagulation and in-hospital mortality. With regard to the anticoagulation during hospital admission, two RCTs reported that the therapeutic-dose anticoagulation with heparin decreased the in-hospital mortality among non-critically ill patients with COVID-19 compared to thromboprophylaxis, but did not decrease the in-hospital mortality among critically ill patients with COVID-19.[36,37] Identifying critically ill and non-critically ill patients in the analysis (although the severity was unmeasurable from our claims database), would help determine the different effects of pre-admission anticoagulation. Second, a lower incidence of VTE in this study compared to those in previous studies conducted in western countries may partly explain the result of in-hospital mortality. In-hospital mortality was reported to be 7.9%–15.6% in Japan[29,30] and 15.0%–43.8% in western countries.[9–20] A lower incidence of VTE has been reported in Japan,[30] which is in line with our result. The lower incidence of VTE may contribute to lower in-hospital mortality due to VTE. Third, residual confounding may have biased the observed associations. Although we adjusted for patient characteristics and comorbidities in the regression model, residual confounding inevitably remains in observational studies.

Because the effect of in-hospital anticoagulation treatment needs to be considered in our study, we conducted a sensitivity analysis comparing patients with pre-admission anticoagulation use who continued anticoagulation treatment after hospitalization, with patients without pre-admission anticoagulation who did not initiate anticoagulation therapy during hospitalization. The analysis showed that the observed association between pre-admission anticoagulation use and in-hospital death did not change, after considering in-hospital anticoagulation therapy.

The results of this study did not show improved outcomes among patients with pre-admission anticoagulation use compared to those without pre-admission anticoagulation use. The finding of no increased major bleeding events among patients with pre-admission anticoagulation therapy may indicate that clinical practitioners do not have to discontinue anticoagulation treatment during hospitalization, when clinically necessary.

4.4 | Strengths and weaknesses of the study

This study has several strengths. We utilized the claims data of hospitalized patients who were all discharged by the last day of the database, so there was no censoring in which we were unable to observe the outcomes. Additionally, we examined the incidence of major bleeding events that could be fatal, which has not been sufficiently investigated in previous studies. However, there are several limitations that should be acknowledged. First, as stated above, residual confounding may have biased the results. The possible residual confounding in this study, is the severity of comorbidities for which pre-admission anticoagulation treatment is necessary (e.g., history of atrial fibrillation or VTE). We conducted a sensitivity analysis limiting the study population to those with CVD comorbidities, for which pre-admission anticoagulation treatment may be necessary. This analysis aimed to increase comparability, but we could not account for the severity of CVD comorbidities. Second, we collected information on comorbidities from diagnosis codes recorded in outpatient and inpatient claims data. Since a limited number of studies have been conducted with regard to the validity of diagnosis in claims data in Japan, this may lead to misclassification of comorbidities and affect the results.[38] Third, misclassification of exposure may have occurred because previous outpatient visits could not be identified if individuals visited other hospitals than the ones they were hospitalized for COVID-19. To minimize bias, we included patients only if their outpatient prescription data, within 3 months before hospitalization, were identified. Fourth, adherence to prescribed anticoagulants before hospitalization could not be considered in the analyses because the prescriptions were identified by the available prescription data. If many patients with pre-admission anticoagulation prescriptions were not adherent to the drug, the results would most likely be diluted to the null association between pre-admission anticoagulation treatment and the studied outcomes. Finally, our results with relatively wide confidence intervals showed a less precise estimate compared to the estimate we would have obtained had we included all the patients in the analyses.

5 | CONCLUSION

In summary, using a large-scale claims database from Japan, we examined the association between pre-admission anticoagulation

treatment and in-hospital death, VTE, and major bleeding among hospitalized COVID-19 patients. No statistically significant differences were observed in the measured outcomes.

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CONFLICT OF INTEREST

Atsushi Miyawaki has a joint research project with MDV outside of this study and is receiving labor contributions. None of other authors declare any conflict of interest.

AUTHOR CONTRIBUTIONS

Motohiko Adomi designed this study, conducted data processing, analyzed the data, and wrote the manuscript. Masao Iwagami contributed to the acquisition of data, study design, and critical revision of the manuscript. Toshiki Kuno contributed to the conception and design of this study and the critical revision of the manuscript. Jun Komiyama and Yuta Taniguchi contributed to the design, data processing, and critical revision of the manuscript. Toshikazu Abe, Atsushi Miyawaki, Shinobu Imai, Kojiro Morita, Makoto Saito, Hiroyuki Ohbe, Tadashi Kamio, and Nanako Tamiya contributed to the design and critical revision of the manuscript. All authors read and approved the final manuscript.

ETHICAL STATEMENT

The ethics committee of The University of Tsukuba approved this study (approval number: 1624). Individual informed consent was waived because the claims data were deidentified using dummy identification numbers, before being made available to the researchers.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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