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Original Article

The influence of pre-admission antiplatelet and anticoagulation therapy on the illness severity in hospitalized patients with COVID-19 in Japan

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ARTICLE INFO

Keywords:
COVID-19
Anticoagulants
Antiplatelet therapy
Japan

ABSTRACT

Introduction: Many articles have reported that the coronavirus disease 2019 (COVID-19) causes coagulation abnormalities and pulmonary thrombosis, contributing to a poorer prognosis. The study aimed to evaluate whether pre-admission anticoagulation and antiplatelet therapy prevented severe COVID-19 illness or not. Materials and methods: We conducted a study to determine whether taking antiplatelet or anticoagulation agents before admission affected the severity on admission using a large nationwide cohort of hospitalized COVID-19 patients in Japan. We analyzed a large nationwide cohort of hospitalized COVID-19 patients in Japan from February 9 to July 31, 2020. Results and conclusion: A total of 4265 patients from 342 facilities in Japan were included. Their use was associated with a slight reduction in the disease severity on admission in a propensity score-matched analysis which controlled for underlying diseases. However, this difference was not statistically significant.

1. Introduction

Coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China, in December 2019 and subsequently spread globally [1]. Many articles have reported that it causes coagulation abnormalities and pulmonary thrombosis, contributing to a poorer prognosis [2,3]. The prognosis of COVID-19 is improved by the use of anticoagulant agents during hospitalization [4]. In contrast, there is still very limited knowledge on whether antiplatelet drugs might have a similar effect [5]. We previously reported that disease severity on admission strongly affects illness severity and mortality during hospitalization [6]. Some patients take anticoagulants and antiplatelet drugs for their underlying disease before experiencing COVID-19. There are some reports of whether anticoagulants or antiplatelet agent prevents coagulation abnormalities at admission. Russo et al. reported no differences in the risk of acute respiratory distress syndrome (ARDS) at admission or death during hospitalization treated with anticoagulant and antiplatelet drugs [7]. Additionally, another paper reported no difference in survival and time to mechanical ventilation between the two groups [8,9]. Furthermore, a meta-analysis from a total of 9 articles revealed that antiplatelet therapies were not associated with an increased risk of mortality [10]. We conducted a study to determine whether taking antiplatelet or anticoagulation agents before hospital admission affected the severity on admission using a large nationwide cohort of hospitalized COVID-19 patients in Japan.

2. Methods

2.1. Study design

This was an observational study and used data collected from February 9, 2020 to July 31, 2020 of the COVIREGI-JP cohort, the

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https://doi.org/10.1016/j.jiac.2021.07.016
Received 23 April 2021; Received in revised form 24 June 2021; Accepted 15 July 2021
Available online 24 July 2021
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### Table 1
Comparison of the characteristics of patients with and without anticoagulant/antiplatelet drugs.

| Baseline parameter | No treatment group (n = 3921), n(%) | Anticoagulant group (n = 105), n(%) | Antplatelet group (n = 218), n(%) | Comparison of the characteristics of patients with and without anticoagulant agents | OR (95% CI) | p value<sup>a</sup> | Adjusted OR (95% CI) | p value<sup>b</sup> | Comparison of the characteristics of patients with and without antiplatelet agents | OR (95% CI) | p value<sup>a</sup> | Adjusted OR (95% CI) | p value<sup>b</sup> |
|-------------------|------------------------------------|------------------------------------|----------------------------------|-----------------------------------|----------|----------|-------------------|----------|-----------------------------------|----------|----------|-------------------|----------|
| Age, median (IQR) | 49 (33, 65)                        | 81 (71, 85)                        | 76 (68, 82)                      | 1.08                              | .0001   | 1.06     | <.0001            | 1.07     | .0001                            | 1.04     | .0001                            |
| Male sex          | 2332 (59.5%)                       | 62 (59%)                           | 148 (67.9%)                      | 0.96                              | .0578   | 1.36     | .2225             | 1.44     | .0139                            | 1.95     | 0.0014                           |
| BMI (<25)         | 995 (25.4%)                        | 16 (15.2%)                         | 45 (20.6%)                       | 0.55                              | .0027   | 0.88     | 0.6742            | 0.78     | .0011                            | 0.79 (0.5-1.23) | 0.29                             |
| Current or past smoking history | 1469 (37.5%)                       | 41 (39%)                           | 106 (48.6%)                      | 1.02                              | .0387   | 1.15     | 0.5932            | 1.58     | .0156                            | 1.4 (0.96-2.04) | 0.08                             |
| Daily or occasional alcohol intake | 2794 (71.3%)                       | 64 (61%)                           | 138 (63.3%)                      | 0.64                              | .0293   | 0.91     | 0.6828            | 0.74     | 0.0156                            | 1.07     | 0.71                             |
| Myocardial infarction/Congestive heart failure | 62 (1.6%)                           | 35 (33.3%)                         | 49 (22.5%)                       | 18.14                              | <.0001  | 0.05     | <.0001            | 11.74    | <.0001                            | 3.05 (1.9-4.89) | <.0001                           |
| Peripheral vascular disease | 24 (0.6%)                           | 5 (4.8%)                           | 19 (8.7%)                        | 4.76                              | 0.0012  | 1.41     | 0.52              | 13.16    | <.0001                            | 4.21 (9.11-6.4) | 0.0001                           |
| Cerebrovascular disease | 112 (2.9%)                         | 22 (21%)                           | 80 (36.7%)                       | 5.45                              | <.0001  | 1.43     | 0.24              | 16.84    | <.0001                            | 6.81     | <.0001                           |
| Paralysis         | 28 (0.7%)                          | 6 (5.7%)                           | 11 (5%)                          | 1.09                              | .0001   | 0.07     | <.0001            | 3.56     | 0.0001                            | 2.37 (1.87-3.49) | 0.0001                           |
| Dementia          | 159 (4.1%)                         | 22 (21%)                           | 46 (21.1%)                       | 5.09                              | <.0001  | 0.85     | 0.60              | 5.23     | <.0001                            | 1.28     | 0.36                             |
| COPD/Chronic lung disease/Bronchial asthma | 295 (7.5%)                          | 14 (13.3%)                         | 34 (15.6%)                       | 1.78                              | <.0001  | 0.93     | 0.8372            | 2.22     | <.0001                            | 1.31     | 0.26                             |
| Liver dysfunction | 78 (2%)                            | 4 (3.8%)                           | 7 (3.2%)                         | 1.89                              | 0.028   | 1.15     | 0.803             | 1.6 (0.73-3.5) | 0.243                             | 0.92     | 0.85                             |
| Peptic ulcer disease | 21 (0.5%)                          | 0 (0.0%)                           | 4 (1.8%)                         | NA                                | .73     | 1.09     | 0.73              | 3.56     | 0.0028                            | 2.37     | 0.18                             |
| Hypertension      | 633 (16.1%)                        | 42 (40%)                           | 131 (60.1%)                      | 2.95                              | <.0001  | 0.87     | 0.73              | 3.56     | <.0001                            | 2.37     | 0.18                             |
| Hyperlipidemia    | 341 (8.7%)                         | 12 (11.4%)                         | 81 (37.2%)                       | 1.14                              | <.0001  | 0.55     | 0.09              | 6.15     | <.0001                            | 2.65 (1.83-9.11) | <.0001                          |
| Diabetes          | 478 (12.2%)                        | 28 (26.7%)                         | 95 (43.6%)                       | 2.26                              | 0.0003  | 1.11     | 0.7088            | 5.37     | <.0001                            | 2.34     | <.0001                           |
| Obesity           | 180 (4.6%)                         | 3 (2.9%)                           | 13 (6%)                          | 1.46                              | 0.39    | 0.81     | 0.75              | 1.33     | <.0001                            | 0.93     | 0.84                             |
| Moderate to severe renal dysfunction/Hemodialysis before admission | 27 (0.7%)                          | 1 (1%)                             | 13 (6%)                          | 0.99                              | <.0001  | 1.01     | 0.12              | 9.06     | <.0001                            | 3.1 (1.3-7.38) | 0.0106                          |
| Solid tumor/Metastatic solid tumor | 141 (3.6%)                          | 8 (7.6%)                           | 9 (4.1%)                         | 0.98                              | 0.88    | 0.47     | 0.749             | 1.12     | 0.75                             | 0.43 (0.19-0.95) | 0.04                             |
| Leukemia/Lymphoma | 38 (1%)                            | 2 (1.9%)                           | 8 (3.7%)                         | 1.73                              | 0.4533  | 0.67     | 0.63              | 3.8      | 0.0007                            | 2.76     | 0.098                            |
| Collagen disease  | 36 (0.9%)                          | 2 (1.9%)                           | 8 (3.7%)                         | 1.37                              | 0.4174  | 0.97     | 0.13-3.49         | 3.8      | 0.0047                            | 4.1 (1.44-11.07) | 0.008                           |
| Immunosuppression | 92 (2.3%)                          | 5 (4.8%)                           | 10 (4.6%)                        | 1.98                              | 0.1454  | 1.75     | 0.92              | 9.87     | <.0001                            | 4 (2.07-7.75) | <.0001                           |
| ACEI              | 38 (1%)                            | 5 (4.8%)                           | 21 (9.6%)                        | 3.46                              | 0.092   | 0.95     | 0.92              | 4.96     | <.0001                            | 1.53     | 0.0333                           |
| ARB               | 343 (8.7%)                         | 28 (26.7%)                         | 73 (33.5%)                       | 3.25                              | <.0001  | 1.61     | 0.07              | 1.53     | <.0001                            | 1.03 (1.25) | 0.0333                           |

Abbreviations. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II Receptor Blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; OR, odds ratio.

<sup>a</sup> Definitions are as described previously.

<sup>b</sup> chi-squared test between treatment and no treatment.
2.2. Definitions

“Severe disease on admission” was defined as the fulfillment of one or more of the following criteria: requiring invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, \( \text{SpO}_2 \geq 94\% \) on room air, or tachypnea (respiratory rate \( \geq 24 \) breaths per minute) [11]. “Anticoagulant agents” included warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban. “Antiplatelet agents” included aspirin, clopidogrel, ticlodipine, cilostazol, ticagrelor, or prasugrel. “No treatment” was defined as patients who had not taken anticoagulant or antiplatelet agents. “Elevated D-dimer” was defined as patients whose D-dimer was \( \geq 1 \) mg/ml.

2.3. Statistical analysis

We used propensity score (PS) matching to adjust for confounders. PS was defined as the probability of receiving an anticoagulant or antiplatelet drug, estimated using multivariable logistic regression models. The baseline variables included in the models, including risk factors for severity on admission, are listed in Table 1. As clinically presumed baseline characteristics for the use of anticoagulant and antiplatelet agents overlapped, the same variables were used in multivariable logistic regression models to calculate the PS, except for “peptic ulcer disease,” as none of the patients were taking anticoagulants on admission. Patients were matched with a fixed ratio of 1:2 using the optimal matching method, which selects all matches simultaneously, without replacement, to minimize the total absolute difference in the PS across all matches. Missing values were imputed using the mean value for continuous variables and the modal value for categorical variables. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

2.4. Ethics

This study was approved by the National Center for Global Health and Medicine ethics review committee (NCGM-G-003494-0). Additionally, the requirement for consent was waived because the study was retrospective.

3. Results

3.1. Cohort characteristics

A total of 4265 patients from 342 facilities in Japan were included. Their median age was 52.0 years (interquartile range [IQR]: 34–69 years); 59.8% were male; 68.5% of those with data had a body mass index (BMI) > 25 kg/m\(^2\); 4.6% were obese (based on a physician’s diagnosis); and 45.6% were current or previous smokers. In the whole cohort, 8.1% (344/4265) patients were on anticoagulants, antiplatelet agents, or both, before admission, including 105 (2.46%) on anticoagulants, 218 (5.11%) on antiplatelet agents, and 21 (0.49%) on both agents.

3.2. Comparison of the characteristics of patients with respect to anticoagulant/antiplatelet agent use

Patient characteristics according to anticoagulant and antiplatelet agent use, are summarized in Table 1. Anticoagulant users were older, and were more likely than non-users to be non-drinkers of alcohol, to have underlying medical conditions, and to be taking angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). Patients on anticoagulants were less likely than non-users to have a BMI \( < 25 \) kg/m\(^2\).

Similarly, patients taking antiplatelet agents were older, and were more likely than non-users to be non-drinkers of alcohol, to have underlying medical conditions, and to be ACEI or ARB users. Patients on antiplatelet agents were less likely than non-users to have a BMI \( > 25 \) kg/m\(^2\). In contrast to the anticoagulant users, the antiplatelet agent users were significantly more likely than non-users to be male, past or present smokers, have peptic ulcer disease, hyperlipidemia, renal disease, lymphoma/leukemia, collagen disease, and immunosuppressive therapy. Twenty-one patients were taking both agents. Their median age was 75 years (IQR: 69–79 years), and 12/21 (57.1%) had a severe illness on admission. The major predisposing factors were old myocardial infarction (52.4%), congestive heart failure (47.6%), diabetes mellitus without complications (42.9%), hypertension (38.1%), and cerebrovascular disease (28.6%). The number of patients in this group was too small to perform further analysis.

3.3. Effect of anticoagulant agents on disease severity on admission and elevated D-dimer

The prevalence of severe disease on admission was 27.9% (1184/
4244) in the whole cohort, 25.8% (1011/3921) in the no treatment group, 50.5% (53/105) in anticoagulant users, and 49.5% (108/218) in antiplatelet agent users. The number of patients with available D-dimer on admission was 2625 (including 733 with severe disease on admission), and the number of patients with missing D-dimer was 1619 (including 439 with severe disease on admission). Of the 2625 patients with available D-dimer, 222/733 (30.3%) had severe disease and elevated D-dimer on admission, while 133/1892 (7.0%) did not have severe disease but had elevated D-dimer on admission. The effect of anticoagulant agents on disease severity on admission and elevated D-dimer are summarized in Table 2.

In the crude analysis, anticoagulant users were nearly three times more likely than those in the no treatment group to have severe disease on admission (odds ratio [OR]: 2.93, 95% confidence interval [CI]: 1.99–4.33, p < 0.1). However, in the PS-matched cohort analysis, the prevalence of severe disease was similar in both the groups: 53.3% (112/
210) in the no treatment group and 50.5% (53/105) in the anticoagulant group, and there was no significant difference in the prevalence of severe illness between the two groups (adjusted OR: 0.89, 95% CI: 0.56–1.43, p = 0.63).

The associations between anticoagulant use and elevated D-dimer on admission, and elevated D-dimer and/or severe illness on admission were also evaluated. In the crude analysis, anticoagulant users were more likely to have elevated D-dimer on admission than those in the no treatment group. However, in the PS-matched cohort analysis, there was no significant difference in the prevalence of elevated D-dimer between the two groups.

#### 3.4. Effect of antiplatelet agents on disease severity on admission and elevated D-dimer

The effect of antiplatelet agents on disease severity on admission and elevated D-dimer are summarized in Table 3. In the crude analysis, antiplatelet agent users were nearly three times more likely to have severe disease on admission than those in the no treatment group (OR: 2.82, 95% CI: 2.15–3.72, p < 0.001). However, in the PS-matched analysis, there was no significant difference in the prevalence of severe illness between the no treatment (53.5%, 232/434) and antiplatelet agent user groups (50.0%, 108/217) (adjusted OR: 0.86, 95% CI: 0.62–1.20, p = 0.375). A similar trend was observed in the analyses of elevated D-dimer on admission and elevated D-dimer and/or severe disease on admission. The mean standardized differences for most measured covariates were reduced to <0.2 for each PS-matched cohort, suggesting a significant bias reduction (Fig. 1).

### 4. Discussion

Using a large Japanese inpatient COVID-19 cohort, we examined whether oral anticoagulant and antiplatelet medication prior to admission prevented severe illness on admission. Some papers reported that neither anticoagulants nor antiplatelet agents use before admission significantly affected mortality in COVID-19 patients [7–10]. There are three important differences between our study and ours: First, our sample size was considerably larger. Second, they used mortality as an outcome and we used the severity of illness at the time of hospitalization as an outcome. Third, our study was performed in a Japanese population.

The cumulative COVID-19 mortality was 924.94, 747.57, 643.77, and 623.33 persons per million in the USA, France, UK, and Italy, respectively, compared to 39.23 persons per million in Japan as of April 2021 [12]. Japanese patients may differ from European patients in terms of characteristics such as the number of underlying diseases, social behaviors, social culture, and coronavirus resistance gene mutations, and the virulence of the predominant circulating strains [13]. The frequency of cardiovascular complications, diabetes mellitus, and obesity among patients hospitalized with COVID-19 in Japan is lower than that found among patients hospitalized with COVID-19 in Western countries [6]. Nevertheless, before statistical adjustment, the patients that had taken anticoagulants or antiplatelet agents were almost three times more likely to have severe disease on admission than those on neither drug, suggesting that the patient background health status (such as pre-existing cardiovascular diseases) and taking these drugs were strongly associated with disease severity. In the PS-matched analysis, there was no significant reduction in the prevalence of severe disease on admission among those taking anticoagulants and antiplatelet agents; however, the use of these drugs was associated with a slight decrease in disease severity on admission. Similarly, in the PS matched cohort, anticoagulation/antiplatelet therapy prior to admission tended to be associated with less common elevation of D-dimer; however, the difference was not statistically significant.

Since there were some patients with severe disease on admission who did not have elevated D-dimer, factors other than thrombus formation were considered to be related to the severity of the disease. Therefore, anticoagulation or antiplatelet therapy prior to admission alone may not have been sufficient to prevent severe disease on admission. In the crude analysis, there were significantly more patients with D-dimer elevation and/or severe disease on admission in the anticoagulation/antiplatelet therapy group. Thus, there may have been a residual confounding effect due to the presence of missing background data, even after thorough adjustment using PS matching. These results suggest that the continuation of medication might be desirable for patients with underlying diseases, even during the COVID pandemic.

This study had some limitations. First, the number of patients taking both anticoagulants and antiplatelet medications was small; therefore, we could not to assess the association between disease severity on admission and concurrent use of both types of medication. Second, in this study, the disease severity was assessed only at admission, which may underrepresent the possible clinical outcomes of COVID-19 after admission, such as mortality, disease severity at 21 days after onset, and thromboembolic events. There is a need to examine the effect of using anticoagulant and antiplatelet therapy after hospitalization in different populations, including the Japanese population.

In summary, in hospitalized Japanese COVID-19 patients, pre-hospitalization anticoagulant and antiplatelet medication use were associated with mildly reduced disease severity on admission, but the difference was not statistically significant. Suppression of the mechanism of hypercoagulability is an important factor for preventing severe disease in COVID-19 patients. Further studies are necessary to determine the precise value of managing hypercoagulability in these patients.

### Funding

This research was funded by the Health and Labor Sciences Research Grant, “Research for risk assessment and implementation of crisis management functions for emerging and re-emerging infectious diseases.”

### Author contribution statement

TT, YU, and KH contributed equally to this manuscript and were responsible for the organization and coordination of the trial. TT and KH wrote the manuscript. NO was the chief investigator and responsible for the data analysis. TT, YU, KH, NM, HO, HH, and MI discussed the data. All authors contributed to the writing of the final manuscript. All authors have approved the final version of the manuscript for publication.

### Declaration of competing interest

The authors declare no conflict of interest.

### Acknowledgments

We thank all the participating facilities for their care of COVID-19 patients and cooperation on Data entry to the registry.

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