Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection and Chemotherapy 27 (2021) 1498–1503

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

Original Article

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

Tomiteru Togano [a,*], Yukari Uemura [b], Yusuke Asai [c], Kayoko Hayakawa [c,d], Nobuaki Matsunaga [c], Mari Terada [b,d], Hiroshi Ohtsu [b], Setsuko Suzuki [d], Ako Toyoda [b], Hisao Hara [e], Rubuna Sato [d], Masahiro Ishikane [c,d], Noriko Kinoshita-Iwamoto [c,d], Akira Hangaishi [a], Norio Ohmagari [c,d]

[a] Department of Hematology, National Center for Global Health and Medicine, Tokyo, Japan
[b] Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan
[c] AMR Clinical Reference Center, National Center for Global Health and Medicine, Tokyo, Japan
[d] Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan
[e] Department of Cardiology, National Center for Global Health and Medicine, Tokyo, Japan

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 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

* Corresponding author. Department of Hematology, National Center for Global Health and Medicine, 1-12-1 Toyama Shinjuku-ku, Tokyo, 162-8655, Japan.
E-mail address: ttogano@hosp.ncgm.go.jp (T. Togano).

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

Table 1
Comparison of the characteristics of patients with and without anticoagulant/antiplatelet drugs.

Baseline parapemeters[a]	No treatment group (n = 3921), n(%)	Anticoagulant group (n = 105), n (%)	Antiplatelet group (n = 218), n (%)	Comparison of the characteristics of patients with and without anticoagulant agents				Comparison of the characteristics of patients with and without antiplatelet agents			
				OR (95% CI)	p value[b]	Adjusted OR (95% CI)	p value[b]	OR (95% CI)	p value[b]	Adjusted OR (95% CI)	p value[b]
Age, median (IQR)	49 (33, 65)	81 (71, 85)	76 (68, 82)	1.08 (1.06–1.09)	<.0001	1.06 (1.05–1.08)	<.0001	1.07 (1.06–1.08)	<.0001	1.04 (1.03–1.06)	<.0001
Male sex	2332 (59.5%)	62 (59%)	148 (67.9%)	0.96 (0.65–1.43)	0.857	1.36 (0.83–2.24)	0.2225	1.44 (1.08–1.93)	0.0139	1.95 (1.29–2.94)	0.0014
BMI (>25)	995 (25.4%)	16 (15.2%)	45 (20.6%)	0.54 (0.31–0.92)	0.0227	0.88 (0.47–1.62)	0.6742	0.78 (0.55–1.09)	0.0011	0.79 (0.5–1.23)	0.29
Current or past smoking history	1469 (37.5%)	41 (39%)	106 (48.6%)	1.02 (0.84–1.25)	0.8357	1.15 (0.69–1.9)	0.5932	1.58 (1.2–2.07)	0.0156	1.4 (0.96–2.04)	0.08
Daily or occasional alcohol intake	2794 (71.3%)	64 (61%)	138 (63.3%)	0.64 (0.43–0.96)	0.0293	0.91 (0.58–1.43)	0.6828	0.7 (0.53–0.94)	0.0156	1.07 (0.74–1.55)	0.71
Myocardial infaction/Congestive heart failure	62 (1.6%)	35 (33.3%)	49 (22.5%)	18.14 (11.6–28.38)	<.0001	6.05 (3.64–10.07)	<.0001	11.74 (8.06–17.11)	<.0001	3.05 (1.9–4.89)	<.0001
Peripheral vascular disease	24 (0.6%)	5 (4.8%)	19 (8.7%)	4.76 (1.85–12.28)	0.0012	1.41 (0.49–3.99)	0.52	13.16 (7.25–23.88)	<.0001	4.5 (2.11–9.64)	0.0001
Cerebrovascular disease	112 (2.9%)	22 (21%)	80 (36.7%)	5.45 (3.33–8.91)	<.0001	1.43 (0.79–2.6)	0.24	16.84 (12.17–23.3)	<.0001	6.81 (4.48–10.37)	<.0001
Paralysis	28 (0.7%)	6 (5.7%)	11 (5%)	6.37 (2.64–15.4)	<.0001	1.74 (0.61–4.94)	0.30	6.24 (3.12–12.49)	<.0001	0.65 (0.27–1.57)	0.33
Dementia	159 (4.1%)	22 (21%)	46 (21.1%)	5.09 (3.11–8.31)	<.0001	0.85 (0.47–1.55)	0.60	5.68 (3.97–8.13)	<.0001	1.26 (0.77–2.06)	0.36
COPD/Chronic lung disease/ Bronchial asthma	295 (7.5%)	14 (13.3%)	34 (15.6%)	1.78 (1–3.16)	0.0485	0.93 (0.49–1.78)	0.8372	2.22 (1.51–3.26)	<.0001	1.31 (0.82–2.11)	0.26
Liver dysfunction	78 (2%)	4 (3.8%)	7 (3.2%)	1.89 (0.68–5.25)	0.028	1.15 (0.38–3.5)	0.803	1.6 (0.73–3.5)	0.243	0.92 (0.37–2.29)	0.85
Peptic ulcer disease	21 (0.5%)	0 (0.0%)	4 (1.8%)	NA		1.09 (0.67–1.78)	0.73	3.56 (1.21–10.48)	0.0208	2.37 (0.67–8.34)	0.18
Hypertension	633 (16.1%)	42 (40%)	131 (60.1%)	2.95 (1.98–4.39)	<.0001	1.09 (0.67–1.78)	0.73	7.48 (5.63–9.92)	<.0001	2.14 (1.46–3.14)	<.0001
Hyperlipidemia	341 (8.7%)	12 (11.4%)	81 (37.2%)	1.14 (0.62–2.09)	0.6807	0.55 (0.28–1.09)	0.09	6.15 (4.58–8.27)	<.0001	2.65 (1.8–3.91)	<.0001
Diabetes	478 (12.2%)	28 (26.7%)	95 (43.6%)	2.26 (1.46–3.52)	0.0003	1.1 (0.68–1.78)	0.7008	5.37 (4.05–7.13)	<.0001	2.34 (1.66–3.31)	<.0001
Obesity	180 (4.6%)	3 (2.9%)	13 (6%)	0.6 (0.19–1.91)	0.39	0.81 (0.23–2.91)	0.75	1.33 (0.75–2.38)	0.33	0.93 (0.43–1.99)	0.84
Moderate to severe renal dysfunction/ Haemodialysis before admission	27 (0.7%)	1 (1%)	13 (6%)	0.99 (0.13–7.24)	0.9885	0.19 (0.02–1.53)	0.12	9.06 (4.62–17.74)	<.0001	3.1 (1.3–7.38)	0.0106
Solid tumor/Metastatic solid tumor	141 (3.6%)	8 (7.6%)	9 (4.1%)	2.19 (1.05–4.59)	0.04	0.88 (0.39–1.96)	0.749	1.12 (0.56–2.23)	0.75	0.43 (0.19–0.95)	0.04
Leukemia/Lymphoma	38 (1%)	2 (1.9%)	8 (3.7%)	1.73 (0.41–7.21)	0.4533	0.67 (0.13–3.49)	0.63	3.8 (1.75–8.21)	0.0007	2.76 (0.83–9.15)	0.098
Collagen disease	36 (0.9%)	2 (1.9%)	8 (3.7%)	1.81 (0.43–7.56)	0.4174	1.03 (0.22–4.77)	0.97	4 (1.84–8.68)	0.0005	4 (1.44–11.07)	0.008
Immunosuppression	92 (2.3%)	5 (4.8%)	10 (4.6%)	1.98 (0.79–4.96)	0.1454	1.7 (0.59–4.91)	0.92	1.95 (1–3.79)	0.0497	1.13 (0.44–2.92)	0.8004
ACEI	38 (1%)	5 (4.8%)	21 (9.6%)	3.46 (1.36–8.8)	0.0092	0.95 (0.33–2.68)	0.92	9.87 (5.75–16.96)	<.0001	4 (2.07–7.75)	<.0001
ARB	343 (8.7%)	28 (26.7%)	73 (33.5%)	3.25 (2.09–5.07)	<.0001	1.61 (0.95–2.73)	0.07	4.96 (3.67–6.7)	<.0001	1.53 (1.03–2.25)	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.

[a] Definitions are as described previously.

[b] chi-suqared test between treatment and no treatment.

Table 2
Effect of anticoagulant agents on disease severity on admission and elevated D-dimer.

Disease severity on admission			
Anticoagulant group	No treatment group	Odds ratio[a] (95% CI)	P value
Crude cohort			
50.5% (53/105)	25.8% (1011/3921)	2.93 (1.99–4.33)	<0.001
PS-matched cohort			
50.5% (53/105)	53.3% (112/210)	0.89 (0.56–1.43)	0.63
D-dimer ≥ 1 mg/ml on admission			
Anticoagulant group	No treatment group	Odds ratio[a] (95% CI)	P value
Crude cohort			
27.9% (19/68)	12.5% (304/2434)	2.93 (1.99–4.33)	<.0001
PS-matched cohort			
27.9% (19/68)	34.1% (43/126)	0.75 (0.39–1.43)	0.379
D-dimer ≥ 1 mg/ml on admission and/or disease severity of admission			
Anticoagulant group	No treatment group	Odds ratio[a] (95% CI)	P value
Crude cohort			
58.1% (61/105)	28.8% (1128/3921)	2.83 (2.15–3.72)	<0.001
PS-matched cohort			
58.1% (61/105)	62.4% (131/210)	0.84 (0.52–1.35)	0.463

[a] Adjusted odds ratio for PS matched cohort.

Table 3
Effect of antiplatelet agents on disease severity on admission and elevated D-dimer.

Disease severity on admission			
Antiplatelet group	No treatment group	Odds ratio[a] (95% CI)	P value
Crude cohort			
49.5% (108/218)	25.8% (1011/3921)	2.82 (2.15–3.72)	<0.001
PS-matched cohort			
49.5% (108/217)	53.5% (232/434)	0.86 (0.62–1.20)	0.375
D-dimer ≥ 1 mg/ml on admission			
Antiplatelet group	No treatment group	Odds ratio[a] (95% CI)	P value
Crude cohort			
26.0% (32/123)	12.5% (304/2434)	2.46 (1.62–3.75)	<.0001
PS-matched cohort			
26.0% (32/123)	29.9% (76/254)	0.83 (0.51–1.33)	0.432
D-dimer ≥ 1 mg/ml on admission and/or disease severity of admission			
Antiplatelet group	No treatment group	Odds ratio[a] (95% CI)	P value
Crude cohort			
53.2% (116/218)	28.8% (1128/3921)	2.93 (1.99–4.33)	<0.001
PS-matched cohort			
53.5% (116/217)	57.8% (251/434)	0.84 (0.60–1.16)	0.289

[a] Adjusted odds ratio for PS matched cohort.

details of which have been reported previously [6]. In this current study, the inclusion criteria for enrollment were Japanese, excluding non-Japanese, having a positive severe acute respiratory syndrome coronavirus 2 test result, and inpatient treatment at a health care facility.

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, SpO_2 ≤94% on room air, or tachypnea (respiratory rate ≥24 breaths per minute) [11]. "Anticoagulant agents" included warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban. "Antiplatelet agents" included aspirin, clopidogrel, ticlopidine, 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 on admission was ≥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/

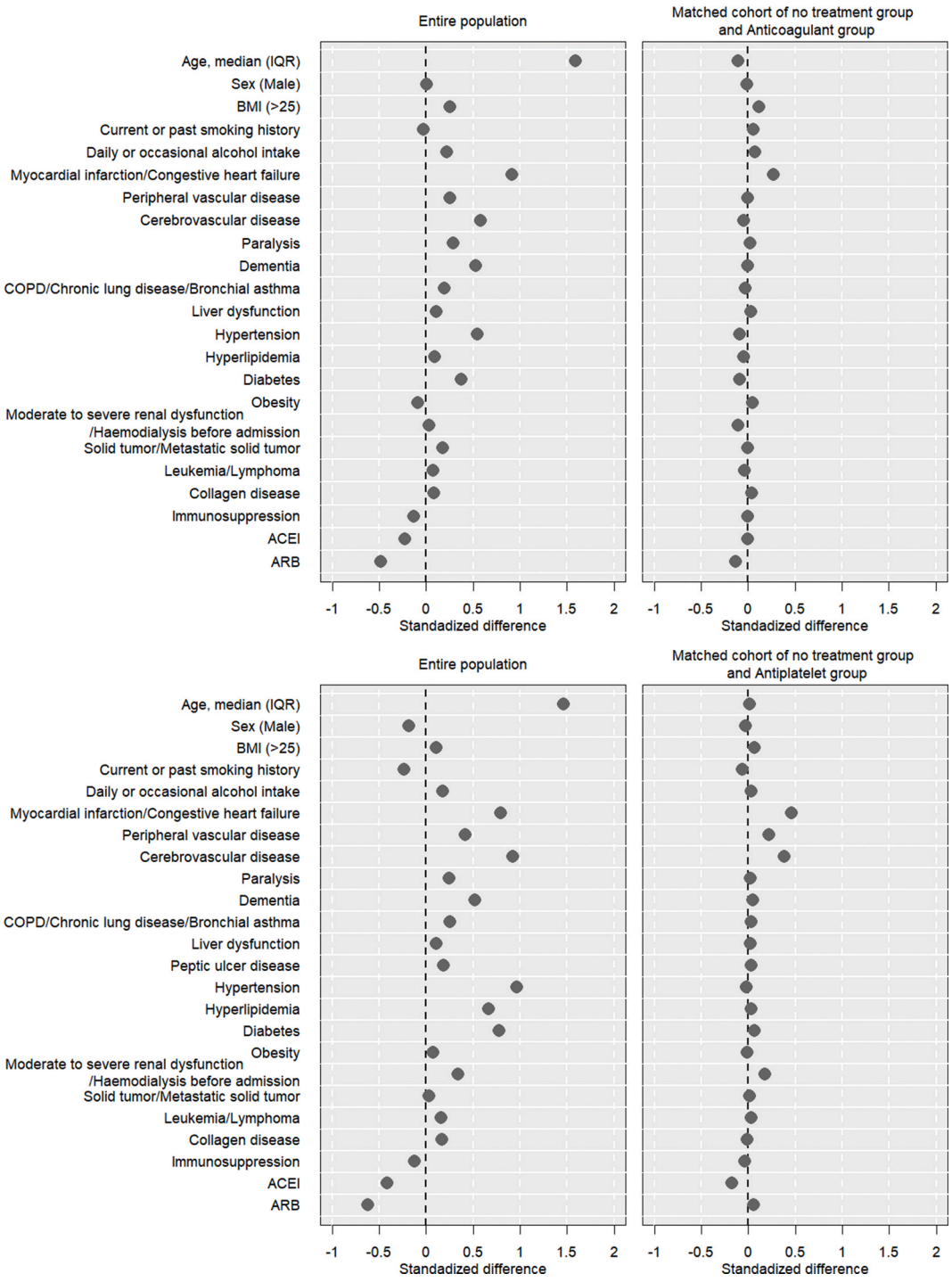

Fig. 1. (a
) The Entire population and matched cohort of no treatment group and anticoagulant agents,
(b) The Entire population and matched cohort of no treatment group and antiplatelet agentsThe mean standardized differences for most measured covariates were reduced to <0.2 for each PS-matched cohort, suggesting a significant bias reduction.

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) 4 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 their 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 drugs, 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.

References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. China novel coronavirus investigating and research team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33.
[2] Pena ALB, Oliveira RA, Severo RG, Simões E Silva AC. COVID-19 related coagulopathy: what is known up to now. Curr Med Chem 2020;28(21):4207–25.
[3] Kermani-Alghoraishi M, Ghahramani R. A review of venous thromboembolism phenomena in COVID-19 patients. Curr Probl Cardiol 2021;46:100692.
[4] Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76:122–4.
[5] Viecca M, Radovanovic D, Forleo GB, Santus P. Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study. Pharmacol Res 2020; 158:104950.

[6] Matsunaga N, Hayakawa K, Terada M, Ohtsu H, Asai Y, Tsuzuki S, et al. Clinical epidemiology of hospitalized patients with COVID-19 in Japan: report of the COVID-19 REGISTRY Japan. Clin Infect Dis 2020 Sep 28:ciaa1470.
[7] Russo V, Di Maio M, Attena E, Silverio A, Scudiero F, Celentani D, et al. Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: a multicenter observational study. Pharmacol Res 2020;159:104965.
[8] Sivaloganathan H, Ladikou EE, Chevassut T. COVID-19 mortality in patients on anticoagulants and antiplatelet agents. Br J Haematol 2020;190:e192–5.
[9] Tremblay D, van Gerwen M, Alsen M, Thibaud S, Kessler A, Venugopal S, et al. Impact of anticoagulation prior to COVID-19 infection: a propensity score-matched cohort study. Blood 2020;136:144–7.
[10] Wang Y, Ao G, Nasr B, Qi X. Effect of antiplatelet treatments on patients with COVID-19 infection: a systematic review and meta-analysis. Am J Emerg Med 2021;43:27–30.
[11] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. ACTT-1 study group members. Remdesivir for the treatment of covid-19 - final report. N Engl J Med 2020;383:1813–26.
[12] WHO coronavirus (COVID-19) dashboard. 2021.
[13] Yamamoto N, Bauer G. Apparent difference in fatalities between Central Europe and East Asia due to SARS-COV-2 and COVID-19: four hypotheses for possible explanation. Med Hypotheses 2020;144:110160.