Original Article

The prognostic role of anticoagulants in COVID-19 patients: national COVID-19 cohort in South Korea

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Background: There currently exists a paucity of data on whether pre-admission anticoagulants use may have benefits among COVID-19 patients by preventing COVID-19 associated thromboembolism. The aim of this study was to assess the association between pre-admission anticoagulants use and COVID-19 adverse outcomes.

Methods: We conducted a population-based cohort studying using the Health Insurance Review and Assessment Service (HIRA) claims data released by the South Korean government. Our study population consisted of South Koreans who were aged 40 years or older and hospitalized with COVID-19 between 1 January 2020 through 15 May 2020. We defined anticoagulants users as individuals with inpatient and outpatient prescription records in 120 days before cohort entry. Our primary endpoint was a composite of all-cause death, intensive care unit (ICU) admission, and mechanical ventilation use. Individual components of the primary endpoint were secondary endpoints. We compared the risk of endpoints between the anticoagulants users and non-users by logistic regression models, with the standardized mortality ratio weighting (SMRW) adjustment.

Results: In our cohort of 4,349 patients, for the primary endpoint of mortality, mechanical ventilation and ICU admission, no difference was noted between anticoagulants users and non-users (SMRW OR 1.11, 95% CI: 0.60–2.05). No differences were noted, among individual components. No effect modification was observed by age, sex, history of atrial fibrillation and thromboembolism, and history of cardiovascular disease. When applying the inverse probability of treatment weighting (IPTW) and SMRW with doubly robust methods in sensitivity analysis, anticoagulants use was associated with increased odds of the primary endpoint.

Conclusions: Pre-admission anticoagulants were not determined to have a protective role against severe COVID-19 outcomes.

Keywords: Anticoagulant; COVID-19

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corresponding COVID-19 disease can result in respiratory, gastrointestinal, neurological and other atypical symptoms (1). In up to one-third of COVID-19 patients, coagulation abnormalities may occur, termed COVID-19-associated coagulopathy (CAC) (2). CAC is associated with increased venous (pulmonary embolism, deep vein thrombosis) and arterial (myocardial infarction and stroke) thromboembolic events (3).

Anticoagulants may have a role in preventing and treating CAC, according to a Cochrane systematic review reporting on hospitalized COVID-19 patients and outcomes associated with anticoagulants (4). Four studies compared heparin use to no treatment with respect to mortality (5-8), two (5,8) reported that anticoagulants decrease the odds of mortality, and two (6,7) reported there was no difference in odds of mortality between anticoagulants and lack of anticoagulants use. Trinh *et al.* compared therapeutic enoxaparin to prophylactic heparin, or prophylactic enoxaparin, and reported that 58% of patients receiving therapeutic anticoagulation had a significantly increased 35 days survival rate compared to just 14% in the prophylactic anticoagulation group (9).

Current clinical guidelines recommend for all acutely ill hospitalized COVID-19 patients to start a prophylactic-dose anticoagulation with low molecular weight heparin, unless contraindicated (10). Given the benefit of preventing deep vein thrombosis or pulmonary embolism in hospitalized patients for COVID-19, patients who were on anticoagulants before admission could have better outcome. Alternatively, patients who were on anticoagulants before hospitalization could have indication for anticoagulants use already, such as deep vein thrombosis, pulmonary embolisms or atrial fibrillation, which could lead to worse outcome. However, there exists limited published literature on the effects of pre-admission use of anticoagulants for hospitalized COVID-19 patients (11).

Given the paucity of data in the published literature there is a need for more rigorous investigations into the association between pre-admission anticoagulants use and COVID-19 outcomes. The aim of this study was to assess the association between pre-admission anticoagulants use and COVID-19 outcomes. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3466/rc).

Methods

Data source and study population

The #OpenData4COVID19 project, launched on March 27, 2020 by the Ministry of Health and Welfare (MOHW) of Korea, released a nationwide, individual-level, and de-identified dataset on COVID-19 patients. This dataset is based on the health insurance claims database maintained by the Health Insurance Review and Assessment Service (HIRA) of South Korea, the sole nationwide governmental agency that operates a fee-for-service reimbursement system. The dataset covers all individuals who were tested by a reverse transcription-polymerase chain reaction (RT-PCR) method for COVID-19 (as of May 15, 2020). The information in the dataset was extracted from their claim records from the previous 3 years and includes each subject's basic demographic information, healthcare utilization history, including diagnosis results, treatments, medications, and prescriptions from both inpatient and outpatient settings.

The HIRA COVID-19 dataset identified 234,427 consecutive individuals who received the RT-PCR test between January 1, 2020 and May 15, 2020. Seven thousand and five hundred ninety subjects were coded as positive for SARS-CoV-2 according to domestic codes (Appendix 1). We excluded individuals with age <40 years, since it is less likely that younger individuals experience severe COVID-19 adverse outcomes regardless of the anticoagulants use, and as anticoagulants use is less common in these younger patients, its use might be associated with higher risk features that are less generalizable to the general public. This left 4,610 individuals. Among them, our study cohort included 4,349 individuals for precise outcome measurement who were hospitalized for COVID-19 (*Figure 1*). We defined the cohort entry date as the date of admission for COVID-19 hospitalization. This cohort was followed up until May 15, 2020 or the date of discharge, whichever came first. In South Korea, most of the individuals who tested positive during this time interval were mandatorily hospitalized regardless of symptom for infection control purpose until full recovery, which is defined by two negative test results within 24 hours and the cessation of fever without medication use (12). Due to temporary unavailability of health facilities, a small number of test-positive individuals were not hospitalized.

This study was approved by the Human Investigation Review Board of Public Institutional Bioethics Committee designated by the MOHW. The requirement of informed

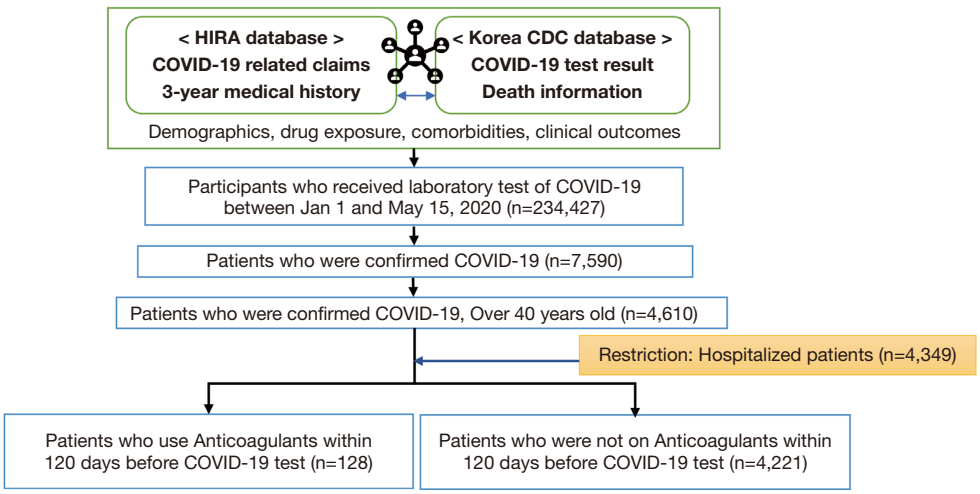

Figure 1 Population-based cohort study design using the HIRA and KDCA database of South Korea. HIRA, Health Insurance Review and Assessment Service; CDC, Centers for Disease Control and Prevention; KDCA, Korean Disease Control and Prevention Agency.

consent was waived due to the retrospective study design and anonymity of the HIRA database (IRB # P01-2020-1262-001). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Endpoints

Our primary endpoint was a composite endpoint of all-cause death, intensive care unit (ICU) admission, and mechanical ventilation use. We set secondary endpoints as the individual components of the composite endpoint. Each endpoint was defined from in-hospital ICD-10 codes and national procedures codes (Table S1).

Exposure

Individuals who had inpatient or outpatient prescription records of anticoagulants within 120 days of cohort entry (i.e., ascertainment window set to −120 to 0 d) were classified as anticoagulants users. We classified other individuals as non-users. We identified anticoagulants from anatomical therapeutic chemical (ATC) codes in claim records (Table S1).

Statistical analysis

The baseline characteristics for anticoagulants users and non-users were summarized by means with standard deviations (for continuous variables) and counts with percentage (for categorical variables). To investigate imbalances of covariate distributions between the two user groups, we calculated absolute standard difference (Asd) for each variable. Typically, a value with Asd ≤0.1 was preferred for indicating balance; Asd ≤0.2 was deemed acceptable for this analysis.

We conducted outcome analysis by employing the standardized mortality ratio weighting (SMRW) approach (13,14) as a main analysis, where the weight uses propensity scores (PSs). There was only a small number of anticoagulants users (128/4,349=3%) in our study population, and the SMRW approach is optimally suitable to attain covariate balance in such rare-exposure studies. The PS, a probability of a user to receive anticoagulants, was estimated by the multivariable logistic regression model that includes all potential confounders as predictors. The potential confounders we considered included age (in years), age square, health insurance type at cohort entry, 20 pre-exposure comorbidities, and 12 pre-exposure co-medications (Appendix 1). A balanced pseudo-population was created by weighting the anticoagulants users by 1 and the non-users by PS/(1-PS). Then, we fitted a univariate weighted logistic regression and estimated odds ratio (OR) with 95% confidence intervals (CI) to measure the effect size of anticoagulants use on each endpoint. In addition, to compare with methods with fewer adjustments, we estimated the ORs by unweighted univariate logistic regression models and unweighted multivariate logistic regression models that adjust for sex, age, insurance type,

history of hypertension, and history of diabetes. For descriptive purposes, we reported the counts of the primary and secondary endpoints for each group.

We considered a subgroup analysis for the risk of the primary endpoint, stratified by (I) age, classified into two groups (<65 and ≥65 years), (II) sex, (III) history of atrial fibrillation and thromboembolism, and (IV) history of coronary artery disease, transient ischemic attack (TIA), stroke, and peripheral vascular disease. For each stratification, we conducted an SMRW-weighted trivariate logistic regression model that included the exposure variable, stratification indicator, and their interaction as predictors. We obtained the P value of the interaction term (P for interaction) to evaluate the significance of effect modification.

We examined the sensitivity of results against the choice of working definitions in two settings. First, we relaxed the study population from the hospitalized COVID-19 patients with age ≥40 years to confirmed COVID-19 positive patients with age ≥40 years. Second, to exclude short-term prescription and discontinuation of anticoagulants use before hospitalization, we narrowed down ascertaining window of the anticoagulants exposure, from 120 to 90 days. We repeated the outcome analysis for each change of the settings.

We investigated the sensitivity of the results against the choice of statistical methods by considering the following alternative statistical approaches. First, to improve comparability between the two groups, we excluded individuals with extreme PS values (PS <0.01 or PS >0.99) (SMR weighting with trimming). Second, to further adjust the imbalance after SMRW adjustment and obtain doubly robust estimates, we fitted a weighted multivariable regression where the weight is given by the SMRW and the predictors include confounders with SMRW-adjusted Asd more than 0.1 [SMR weighting with doubly robust method (15)]. Third, we fitted our main analysis where the weight was replaced with the standard inverse probability weighting (IPT weighting), 1/PS for the user group and 1/(1-PS) for the non-user group. Fourth, in our unweighted multivariable logistic regression model in the main analysis, we additionally included the estimated PSs to other covariates (outcome adjustment model). Finally, we used propensity score matching (PS matching). All statistical analyses were conducted using R 3.5.2.

Results

Four thousand and three hundred forty-nine hospitalized adults for COVID-19 were identified and included in this analysis. After SMR weighting, there were acceptable balances in all covariates except antiplatelet medication use which still has slight imbalance between users and non-users (*Table 1*).

For the primary endpoint of mortality, mechanical ventilation and ICU admission, no significant difference was noted between anticoagulants users and non-users (SMRW OR 1.11, 95% CI: 0.60–2.05). No differences were noted, among individual components (*Table 2*).

In stratified analyses of the primary endpoint by age, sex, history of atrial fibrillation and thromboembolism, and history of coronary artery disease, TIA, stroke, and peripheral vascular disease, there existed no effect modification (*Table 3*).

The results from the sensitivity analyses showed significant associations of adverse outcomes with anticoagulants use in some analysis, which were not seen in the main analysis (Tables S2-S5). When applying IPT weighting, anticoagulants use was associated with increased odds of the primary endpoint (OR 2.56, 95% CI: 1.01–6.11) and ICU admission (OR 2.94, 95% CI: 1.05–8.22). With SMR weighting with doubly robust methods, anticoagulants use was associated with increased odds of the primary endpoint (OR 1.34, 95% CI: 1.10–1.53), all cause death (OR 1.55, 95% CI: 1.26–1.90), and mechanical ventilation (OR 1.84, 95% CI: 1.33–2.54). Anticoagulants use was also associated with increased odds of mechanical ventilation when including all confirmed COVID-19 patients (OR 2.16, 95% CI: 1.03–4.51), redefining exposure windows to 90 days before and including the date of cohort entry in all confirmed COVID-19 patients (OR 2.54, 95% CI: 1.16–5.56) and in hospitalized COVID-19 patients (OR 2.42, 95% CI: 1.09–5.35), applying SMR weighting with iscrepa (OR 2.19, 95% CI: 1.01–4.77), or PS matching (OR 3.31, 95% CI: 1.47–7.45).

Discussion

This study reports on one of the largest South Korean datasets of COVID-19 patients for analysis of association between anticoagulants and COVID-19 outcomes. Our dataset reports on a nationwide study that was completely enumerated, which include most of the COVID-19 confirmed patients across the entire spectrum of COVID-19 severity (from asymptomatic to critical COVID-19 infection). This paper therefore presents on a unique cohort, as other previously-published papers

Table 1 Baseline sociodemographic and clinical characteristics of hospitalized adult patients with COVID-19 in South Korea, as of May 15, 2020

Characteristic	Before SMRW			After SMRW[§]		
	User* (n=128)	Non-user (n=4,221)	aSD	User (n=128)	Non-user (n=124)	aSD
Age (years; mean ± SD)	72.4±12.1	59.9±12.3	1.03	72.4±12.1	73.2±13.3	0.07
40–49	7 (5.5)	901 (21.3)		7 (5.5)	4 (3.2)	
50–59	12 (9.4)	1,395 (33.0)		12 (9.4)	20 (16.0)	
60–69	29 (22.7)	1,034 (24.5)		29 (22.7)	28 (22.7)	
70–79	40 (31.3)	531 (12.6)		40 (31.3)	22 (17.4)	
80–89	33 (25.8)	300 (7.1)		33 (25.8)	35 (28.0)	
90+	7 (5.5)	60 (1.4)		7 (5.5)	16 (12.7)	
Sex						
Male	58 (45.3)	1,551 (36.7)	0.17	58 (45.3)	55 (44.2)	0.02
Female	70 (54.7)	2,670 (63.3)		70 (54.7)	69 (55.8)	
Health insurance type						
Medical insurance	102 (79.7)	3,729 (88.3)	0.24	102 (79.7)	91 (73.5)	0.15
Medical aid	26 (20.3)	492 (11.7)		26 (20.3)	33 (26.5)	
Comorbidities						
Arrhythmias	20 (15.6)	99 (2.3)	0.48	20 (15.6)	19 (14.9)	0.02
Asthma	27 (21.1)	420 (10.0)	0.31	27 (21.1)	24 (19.2)	0.05
Atrial fibrillation	45 (35.2)	30 (0.7)	1.00	45 (35.2)	40 (32.5)	0.06
Autoimmune disease	11 (8.6)	241 (5.7)	0.11	11 (8.6)	12 (9.7)	0.04
Chronic lung disease	69 (53.9)	1,357 (32.1)	0.45	69 (53.9)	73 (58.7)	0.10
Coronary artery disease	34 (26.6)	292 (6.9)	0.55	34 (26.6)	29 (23.5)	0.07
Dementia	29 (22.7)	285 (6.8)	0.46	29 (22.7)	28 (22.8)	0.00
Diabetes mellitus	45 (35.2)	792 (18.8)	0.38	45 (35.2)	50 (40.2)	0.10
Heart failure	35 (27.3)	153 (3.6)	0.69	35 (27.3)	32 (25.4)	0.04
Hyperlipidemia	53 (41.4)	1,373 (32.5)	0.18	53 (41.4)	49 (39.7)	0.03
Hypertension	75 (58.6)	1,074 (25.4)	0.71	75 (58.6)	70 (56.4)	0.04
Kidney disease	13 (10.2)	46 (1.1)	0.40	13 (10.2)	11 (9.2)	0.03
Liver disease	7 (5.5)	189 (4.5)	0.05	7 (5.5)	7 (5.6)	0.01
Malignancy	15 (11.7)	210 (5.0)	0.25	15 (11.7)	20 (16.4)	0.14
Other cerebrovascular diseases	15 (11.7)	233 (5.5)	0.22	15 (11.7)	14 (11.4)	0.01
Peripheral vascular disease	31 (24.2)	363 (8.6)	0.43	31 (24.2)	30 (23.9)	0.01
Pneumonia including tuberculosis	18 (14.1)	293 (6.9)	0.23	18 (14.1)	14 (11.3)	0.08
Psychiatric disorders	53 (41.4)	1,061 (25.1)	0.35	53 (41.4)	51 (40.9)	0.01
Stroke or TIA	28 (21.9)	275 (6.5)	0.45	28 (21.9)	28 (22.7)	0.02
Thromboembolism	24 (18.8)	208 (4.9)	0.44	24 (18.8)	25 (19.7)	0.02

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Before SMRW			After SMRW[§]		
	User* (n=128)	Non-user (n=4,221)	aSD	User (n=128)	Non-user (n=124)	aSD
Medications						
Acetaminophen	39 (30.5)	909 (21.5)	0.20	39 (30.5)	39 (31.6)	0.03
Antibacterials	64 (50.0)	1,558 (36.9)	0.27	64 (50.0)	68 (54.4)	0.09
Antidementia	27 (21.1)	321 (7.6)	0.39	27 (21.1)	27 (21.6)	0.01
Antidepressants	23 (18.0)	391 (9.3)	0.26	23 (18.0)	23 (18.7)	0.02
Antidiabetics	36 (28.1)	578 (13.7)	0.36	36 (28.1)	41 (33.0)	0.11
Antiplatelets	32 (25.0)	547 (13.0)	0.31	32 (25.0)	43 (34.6)	0.21
Antipsychotics	27 (21.1)	581 (13.8)	0.19	27 (21.1)	26 (20.8)	0.01
Antivirals	3 (2.3)	135 (3.2)	0.05	3 (2.3)	3 (2.3)	0.00
Anxiolytics	33 (25.8)	670 (15.9)	0.25	33 (25.8)	25 (20.5)	0.13
Immunosuppressant	51 (39.8)	1,094 (25.9)	0.30	51 (39.8)	53 (42.3)	0.05
Lipid lowering agents including statin	63 (49.2)	1,002 (23.7)	0.55	63 (49.2)	58 (46.8)	0.05
NSAIDs	79 (61.7)	2,059 (48.8)	0.26	79 (61.7)	78 (62.3)	0.01

Mean and standard deviation were reported for continuous variables. Frequency and percentage were reported for categorical variables. *, patients prescribed anticoagulants within 120 days prior to cohort entry were regarded as anticoagulants users, and otherwise patients were defined as non-users. [§], weighted cohort using the SMRW. SMRW, standardized mortality ratio weighting; aSD, absolute standardized difference; TIA, transient cerebral ischemic attack; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2 Risk of adverse clinical outcomes associated with anticoagulants users compared with non-users adult patients with COVID-19

Characteristic	Number of patients	Number of events	Cumulative incidence (%)	Odds ratio (95% confidence interval)		
				Unadjusted*	Adjusted[§]	SMR weighted[#]
Primary endpoint (all-cause death, mechanical ventilation use, ICU admission)						
Non-user	4,221	458	10.9	1.00 (reference)	1.00 (reference)	1.00 (reference)
User	128	38	29.7	3.47 (2.35–5.13)	1.79 (1.18–2.72)	1.11 (0.60–2.05)
All-cause death						
Non-user	4,221	190	4.5	1.00 (reference)	1.00 (reference)	1.00 (reference)
User	128	27	21.1	5.67 (3.62–8.89)	2.02 (1.22–3.35)	0.99 (0.48–2.08)
Mechanical ventilation use						
Non-user	4,221	112	2.7	1.00 (reference)	1.00 (reference)	1.00 (reference)
User	128	11	8.6	3.45 (1.81–6.58)	1.61 (0.82–3.14)	2.12 (0.99–4.54)
ICU admission						
Non-user	4,221	312	7.4	1.00 (reference)	1.00 (reference)	1.00 (reference)
User	128	18	14.1	2.05 (1.23–3.42)	1.51 (0.89–2.56)	1.32 (0.60–2.92)

*, unweighted univariable logistic regression model; [§], unweighted multivariable logistic regression model adjusted for age, sex, insurance type, history of diabetes and history of hypertension; [#], SMR-weighted univariable logistic model. SMR weight, standardized mortality ratio weight; ICU, intensive care unit.

Table 3 Risk of primary endpoint associated with anticoagulants when stratified for age, sex, history of atrial fibrillation and thromboembolism, and coronary artery disease, TIA, stroke, and peripheral vascular disease

Characteristic	Number of patients	Cumulative incidence (%)		SMRW adjusted odds ratio (95% confidence interval)	P for intersection
		User	Non-user		
Age group (years)					
<65	2,944	20.6	6.6	2.39 (0.88–6.50)	0.1143
≥65	1,405	33.3	20.4	0.86 (0.40–1.87)	
Sex					
Male	1,609	31.0	14.2	1.46 (0.72–2.96)	0.3784
Female	2,740	14.2	14.3	0.86 (0.34–2.20)	
History of atrial fibrillation, thromboembolism					
No	4,244	23.1	10.7	1.11 (0.63–1.95)	0.8527
Yes	105	40.0	25.5	0.97 (0.28–3.36)	
History of TIA, stroke, coronary artery disease and peripheral vascular disease					
No	3,525	29.5	9.3	1.40 (0.66–2.98)	0.4108
Yes	824	29.9	17.8	0.84 (0.32–2.19)	

TIA, transient cerebral ischemic attack; SMRW, standardized mortality ratio weighting.

typically report on hospitalized COVID-19 patients with moderate to critically ill COVID-19 infection. When considered along with the fact that PSs were used to control for confounding, this may be one of the most robust claims datasets published in the world.

Our main analysis finds that hospitalized COVID-19 patients who have been administered anticoagulants before admission experience a similar odds of suffering from the endpoints of all-cause mortality, mechanical ventilation and ICU admissions. These results are in line with those previously published by Klok *et al.* (16), Russo *et al.* (17) and Sivaloganathan *et al.* (18), which reported no association between baseline oral anticoagulants and adverse COVID-19 outcomes, including mortality (16-18) and ICU admission (18).

There was a discrepancy between this main primary endpoint analysis and corresponding analyses by alternative statistical approaches, especially the IPT weighting approaches and the SMR weighting with doubly robust method. However, Hajage *et al.* (13) and Ross *et al.* (14) noted that, in rare exposure regime such as our study, the IPT weighting as well as regression adjustment approaches could possibly be biased with inflated variance. In addition, since the SMR weighting with doubly robust method was first proposed in Moodie *et al.* (15), its empirical properties in the rare exposure regime is yet to be explored in the statistics literature and further statistical research is needed to understand its behavior, which is out of the scope of this study. Thus, to our knowledge, the main SMR weighting approach appears to have produced the most robust and reliable result.

Our study population noticeably differs from previously published trials. The study population were ICU patients for Klok *et al.* (16), emergency room patients for Russo *et al.* (17), and hospitalized patients for Sivaloganathan *et al.* (18), whereas our analysis reports on a nationwide cohort of all patients admitted for COVID-19 to South Korean hospitals. As much as 94.3% of all confirmed COVID-19 patients ≥40 years of age (n=4,610) were hospitalized (n=4,349) regardless of presence of symptom or disease severity in our study. This manifestation is a result of the South Korean government's mandate for admitting all COVID-19 patients during the time interval studied to limit spread of the COVID-19 infection, including asymptomatic infections. As a result, this study provides a more complete picture, as it reports on the entire spectrum of COVID-19 patients, from asymptomatic to critical COVID-19 patients. This may explain why some sensitivity analyses, using different statistical methods, exposure windows and including all confirmed COVID-19 patients, showed an association

between adverse COVID-19 outcomes and preadmissions anticoagulants use. It is possible that our main results may have been skewed towards the null due to the inclusion of patients with non-severe COVID-19 infection in our population, as the benefit of preventing thromboembolisms with pre-admission anticoagulants is more likely to have a beneficial effect in patients with more severe COVID-19 (and therefore more prone to have said thromboembolic complications). On the other hand, patients who were already on anticoagulants prior to hospitalization may be at higher risk for poorer outcomes, due to their elevated pre-existing risk for deep vein thrombosis, pulmonary embolisms and atrial fibrillations (and therefore the use of anticoagulants). As well, patients with atrial fibrillation commonly present underlying comorbidities such as obesity, diabetes melilites, hypertension, heart failure and condition. When all considered, these comorbidities could have lead to a net worse result in sensitivity analysis.

It is important to mention that our study was not a randomized controlled study, and hence residual confounding may still exist. Additionally, as this study employs an administrative claims database, there are intrinsic limitations such as lack of baseline demographics, smoking history, and body weight data. Additionally, while the study cohort is large relative to other reports, the size did not allow for meaningful assessments of the primary endpoint effects according to different types and doses of anticoagulation medications.

In summary, we report on a South Korean nationwide claims database and find that pre-admissions anticoagulants use may not have a protective role against severe COVID-19 outcomes.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3466/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3466/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3466/coif). CBS serves as an unpaid Editor-in-Chief of *Annals of Palliative Medicine*. YGC reports that his work was supported, in part, by 2020R1G1A1A01006229 awarded by the National Research Foundation of Korea. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Human Investigation Review Board of Public Institutional Bioethics Committee designated by the MOHW. The requirement of informed consent was waived due to the retrospective study design and anonymity of the HIRA database (IRB # P01-2020-1262-001). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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