Anticoagulant or antiplatelet use and severe COVID-19 disease: A propensity score-matched territory-wide study

To the Editor:

We read the recent publication in *Pharmacological Research* on the impact of pre-admission antithrombotic therapy in coronavirus disease 2019 (COVID-19) patients with great interest [1]. A recent retrospective cohort study demonstrated that the use of heparin improved the 28-day mortality of severe COVID-19 patients at risk of sepsis-induced coagulopathy. [2] Another study found that patients who received treatment-dose anticoagulants were more likely to require invasive mechanical ventilation [3]. However, few population-based studies have examined the effects of prophylactic antithrombotic therapy on the risk of severe COVID-19. Thus, the present study aims to evaluate whether anticoagulant and anti-platelet use is associated with a lower risk of severe COVID-19 infection through a territory-wide, propensity score-matched cohort study.

Ethics approval for this study was obtained from the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. The inclusion criteria were patients who tested positive for the severe acute respiratory syndrome coronavirus-2 under reverse-transcriptase polymerase chain reaction (RT-PCR) between January 1st to August 22nd, 2020 in Hong Kong. The patient data were extracted from the Clinical Data Analysis and Reporting System (CDARS), a Hong Kong-wide electronic health record database that compiles data from all public hospitals to establish a comprehensive and accessible medical record for each patient, and has been used by our team and other groups to conduct population-based studies in the past [4]. The following information was extracted from CDARS: (1) demographics; (2) prior comorbidities; (3) hospitalization characteristics before the COVID-19 related admission; (4) medications prescribed; (5) laboratory tests (complete blood count, biochemical tests, cardiac function tests, C-reactive protein, and arterial blood gas); (6) the need for intensive care unit (ICU) admission and intubation. The codes from the International Classification of Disease-Ninth Edition (ICD-9) documenting the comorbidities and intubation procedure are shown in Supplementary Tables 1 and 2, respectively. Patient mortality was extracted from the Hong Kong Death Registry, a governmental registry compiling the registered death records of Hong Kong citizens. The primary outcome is the need for admission to the intensive care unit (ICU), intubation, or death followed-up until September 8th, 2020. Detailed information on the statistical analyses is shown in the Supplementary Appendix.

The procedures of data processing are detailed in Fig. 1. The present study consists of 4445 consecutive patients who have been tested positive for the severe acute respiratory syndrome coronavirus-2 (median age 44.8 years old, 95% CI: [28.9, 60.8]; 50% male). Of these, 212 met the primary outcome (Supplementary Table 3). The baseline clinical characteristics of the cohort stratified by anticoagulant or antiplatelet use before and after propensity score matching for baseline demographics, past medical comorbidities (including the Charlson Comorbidity Index score), medication history, platelet and prothrombin time/international normalized ratio (INR) are shown in Supplementary Table 4. The percentage of COVID-19 patients meeting the primary outcome was significantly higher in anticoagulants users compared to non-users, both before (n = 145/292, 41.7% vs. n = 67/4097, 1.6%; P < 0.0001) and after propensity score matching (n = 145/292, 41.7% vs. n = 46/696, 6.6%; P < 0.0001). Similarly, antiplatelet users also showed a higher percentage compared to non-users before (n = 70/292, 24.0% vs. n = 142/4153, 3.4%; P < 0.0001) and after matching (n = 70/292, 24.0% vs. n = 91/584, 15.6%; P < 0.0001). Kaplan-Meier curves stratified by anticoagulants or antiplatelets use for the unmatched and matched cohorts are shown in Fig. 2 and Fig. 3, respectively. Based on the propensity score-matched cohort, univariable Cox regression showed that the use of anticoagulants (hazard ratio [HR]: 4.65, 95% confidence interval [CI]: [3.36, 6.43], P < 0.0001) or antiplatelets (HR: 1.54, 95% CI: [1.13, 2.10], P = 0.0061) was associated with a higher risk of the primary outcome (Supplementary Table 5). For anticoagulant/antiplatelet users vs. non-users, the HR was 5.19 (95% CI: [3.89–6.90] P < 0.0001). Regarding individual drug classes, the use of dabigatran, enoxaparin, clopidogrel or aspirin was a significant predictor. Multivariate Cox analyses showed that anticoagulant/antiplatelet use remained a significant predictor after adjusting for age, past comorbidities and/or medication classes (Supplementary Table 6).

As the inclusion of PCR-positive asymptomatic cases may introduce bias. Subgroup analysis including only COVID-19 patients receiving anti-viral or steroid therapy (lopinavir/ritonavir, ribavirin, interferon beta-1b, hydroxychloroquine, steroids) was performed. This subgroup cohort consists of 1064 patients, in whom 82 (7.7%) met the primary outcome (Supplementary Table 7). Their unmatched and matched baseline characteristics are shown in Supplementary Table 8. After propensity score matching, univariate Cox regression showed that the use of antiplatelets/anticoagulants was a significant predictor of severe disease (HR: 8.88, 95% CI: [5.11, 15.43]; P < 0.0001; Supplementary Table 9). Regarding individual drug classes, only the use of edoxaban or enoxaparin was a significant predictor. The relationship between anticoagulant/antiplatelet use remained significant in multivariate Cox analyses adjusting for age, past comorbidities and/or medication classes (Supplementary Table 10).

Finally, 1:1 propensity score matching was performed between anticoagulant and antiplatelet users receiving antiviral/steroid therapy (n = 63 for each group, 28 patients prescribing both anticoagulants and antiplatelets were excluded; Supplementary Table 11). Univariate Cox regression showed that the use of antiplatelets was associated with a lower risk of severe disease compared to anticoagulant users (HR: 0.17,

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│           4445 hospitalized Covid-19 patients from             │
│            January 1st, 2020 to August 22nd, 2020              │
│   212 patients (4.77%) with intensive care admission/intubation/death │
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AC/AP cohort (N=4445)
531 users
    Death rate: 12.61%;
    ICU rate: 15.81%;
    Intubation rate: 17.7%.
3914 non-users
    Death rate: 0.74%;
    ICU rate: 0.3%;
    Intubation rate: 0.1%.

Antiviral therapy treated AC/AP cohort (N=1064)
162 users
    Death rate: 37.03%;
    ICU rate: 24.07%;
    Intubation rate: 22.83%.
902 non-users
    Death rate: 2.43%;
    ICU rate: 1.10%;
    Intubation rate: 1.33%.

Propensity score matching with 1:2 ratio
on demoographics, prior comorbidities (including Charlson score),
non-AC/AP medications, platelet and prothrombin time/INR

Control of AC/AP cohort (N=1593)
531 users
    Death rate: 12.61%;
    ICU rate: 15.81%;
    Intubation rate: 17.7%.
1062 non-users
    Death rate: 4.7%;
    ICU rate: 1.12%;
    Intubation rate: 0.75%.

Control of antiviral therapy treated AC/AP cohort (N=486)
162 users
    Death rate: 12.96%;
    ICU rate: 24.07%;
    Intubation rate: 22.83%.
324 non-users
    Death rate: 1.85%;
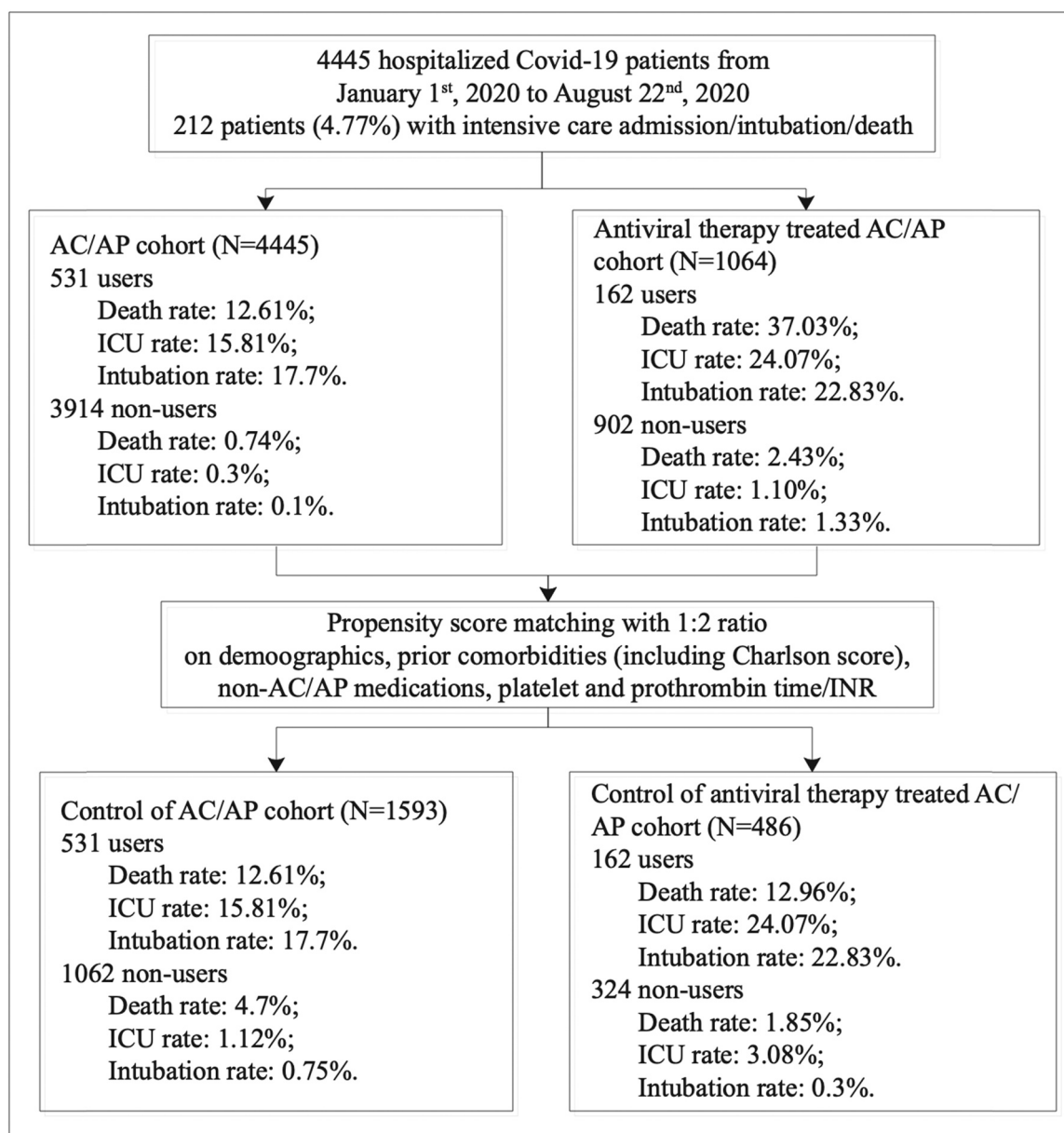   ICU rate: 3.08%;
    Intubation rate: 0.3%.

Fig. 1. Procedures of data processing.

95% CI: [0.07, 0.44]; $P < 0.0001$; Supplementary Table 12). The lower risk observed for antiplatelet users remained significant in multivariate Cox analyses adjusting for age, past comorbidities and/or medication classes (Supplementary Table 13).

COVID-19 has placed a significant burden on healthcare systems worldwide. It particularly affects patients with existing comorbidities more severely [5–7], complicated by important effects of individual drug classes [8–10] or drug-drug interactions [11]. Our data indicate that the use of anticoagulants or antiplatelets is associated with a higher risk of severe COVID-19 disease after propensity score matching in a Chinese cohort. However, antiplatelet use was associated with lower risk of severe disease compared to anticoagulant use. Our findings should be validated in future studies.

Funding

Conflicts of Interest

The authors declare no potential or actual conflicts of interest.

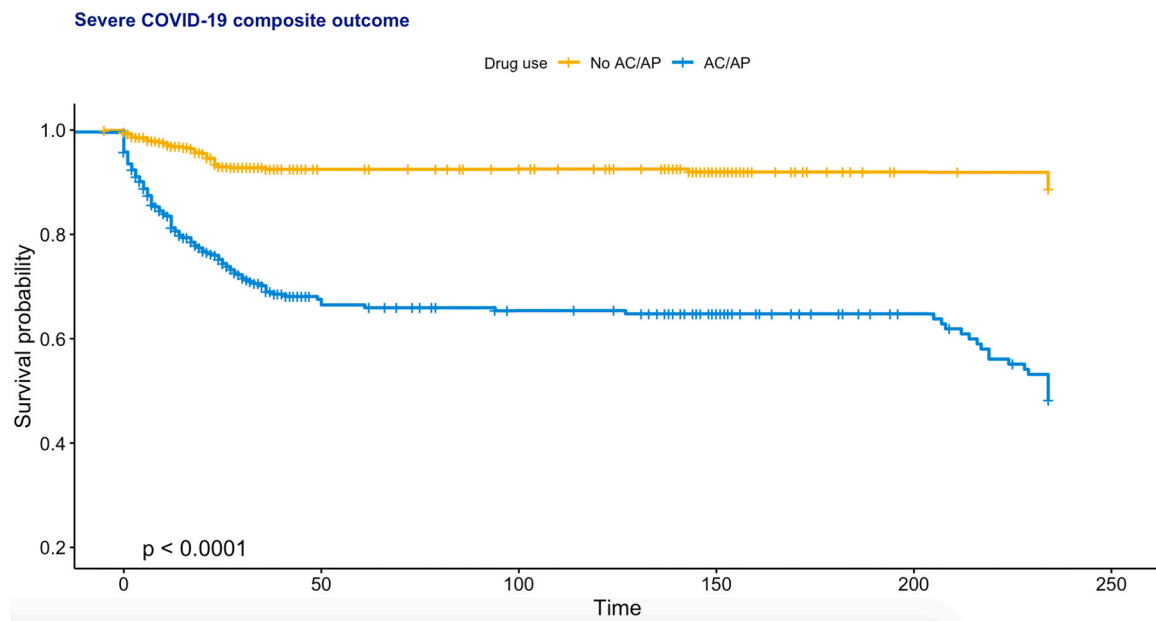**Severe COVID-19 composite outcome**

Fig. 2. Kaplan-Meier curve for the severe disease outcome in PCR-positive COVID-19 patients stratified by anticoagulant (AC)/ antiplatelet (AP) use after 1:2 propensity score matching.
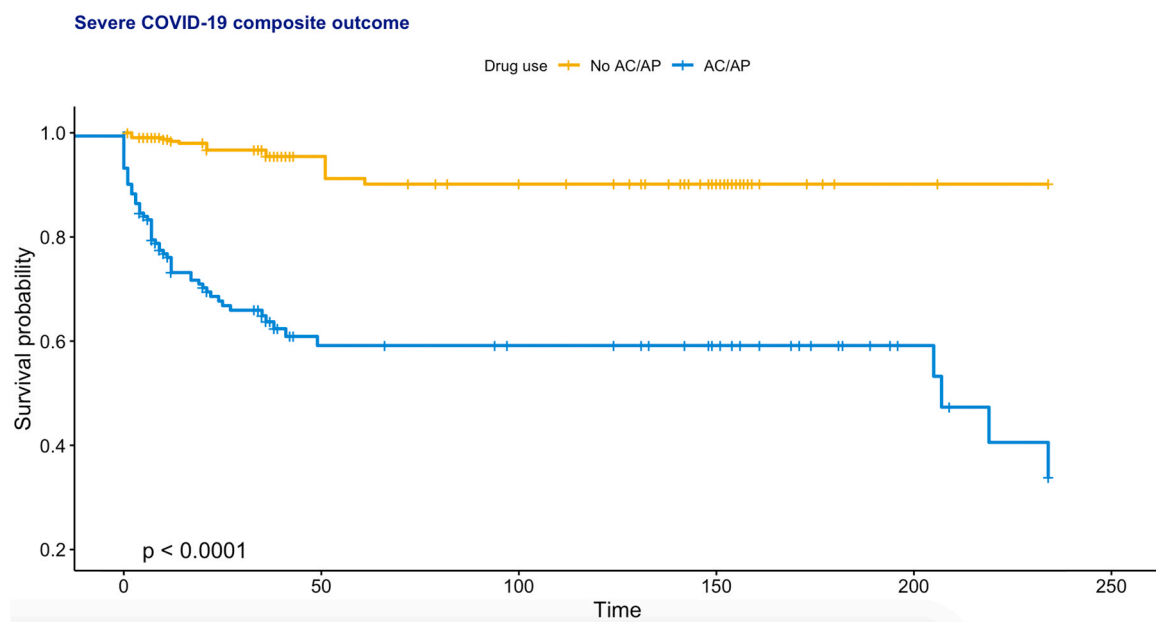
Severe COVID-19 composite outcome

Fig. 3. Kaplan-Meier curve for the severe disease outcome in PCR-positive COVID-19 patients receiving antiviral or steroid therapy, stratified by anticoagulant (AC)/ antiplatelet (AP) use after 1:2 propensity score matching.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2021.105473.

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Jiandong Zhou[a,1], Sharen Lee[b,1], Cosmos Liutao Guo[b], Carlin Chang[c], Tong Liu[d], Keith Sai Kit Leung[e,f], Abraham Ka Chung Wai[f], Bernard Man Yung Cheung[g], Gary Tse[d,*], Qingpeng Zhang[a,*]

[a] *School of Data Science, City University of Hong Kong, Hong Kong, China*
[b] *Cardiovascular Analytics Group, Laboratory of Cardiovascular Physiology, Hong Kong, China*
[c] *Division of Neurology, Department of Medicine, Queen Mary Hospital, Pokfulam, Hong Kong, China*
[d] *Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300211, China*
[e] *Aston Medical School, Aston University, Birmingham, United Kingdom*
[f] *Emergency Medicine Unit, LKS Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China*
[g] *Division of Clinical Pharmacology and Therapeutics, Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China*

[*] Corresponding authors.
E-mail addresses: Gary.tse@doctors.org.uk (G. Tse), qingpeng.zhang@cityu.edu.hk (Q. Zhang).

[1] Joint first authors.