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Pre-hospital antiplatelet medication use on COVID-19 disease severity

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ABSTRACT

Objective: To evaluate the association between pre-hospitalization antiplatelet medication use and COVID-19 disease severity.
Design: Retrospective cohort study.
Setting: Inpatient units at The Mount Sinai Hospital.
Patients: Adults age ≥18 admitted between March 1, 2020 and April 9, 2020 with confirmed COVID-19 infection with at least 28 days follow-up.
Measurements: We captured baseline demographic, pre-hospitalization antiplatelet medication use, and clinical encounter data for all patients who met inclusion criteria. The primary endpoint was peak score on a 6-point modified ordinal scale (MOS), which is based on World Health Organization blueprint R&S groups, used to grade severity of illness through clinical outcomes of interest. Scores indicate the following: 1 – COVID-19 infection not requiring hospitalization, 2 – requiring hospitalization but not supplemental oxygen, 3 – hospitalization requiring supplemental oxygen, 4 – hospitalization requiring high-flow nasal cannula (HFNC) or non-invasive positive pressure ventilation (NIPPV), 5 – hospitalization requiring intubation or extracorporeal membrane oxygenation (ECMO), 6 – death. Multivariable adjusted partial proportional odds model (PPOM) was performed to examine the association between pre-hospitalization antiplatelet medication use and likelihood of each MOS score.
Main Results: Of 762 people admitted with COVID-19, 239 (31.4%) used antiplatelet medications pre-hospitalization while 523 (68.6%) did not. Antiplatelet users were older and had more co-morbidities at baseline. Before adjusting for covariates, patients who used antiplatelet medications pre-hospitalization were more likely than non-users to have peak MOS score 6 (death, OR 1.75, 95% CI 1.21–2.52), peak MOS score ≥5 (intubation/ECMO or death, OR 1.4, 95% CI 1.00–1.98) and peak MOS score ≥4 (HFNC, NIPPV, intubation/ECMO or death, OR 1.40, 95% CI 1.01–1.94). On multivariable adjusted PPOM analysis controlling for 13 covariates, there were no longer any significant differences in peak MOS scores between users and non-users.
Conclusions: After adjusting for covariates, pre-hospital antiplatelet use was not associated with COVID-19 severity in hospitalized patients.

Introduction

Progressive respiratory failure in the form of the acute respiratory distress syndrome (ARDS) is a major driver of morbidity and mortality in COVID-19 patients.[1] Some patients with COVID-19 respiratory failure demonstrate severe hypoxemia despite having near normal compliance, a combination atypical for ARDS.[2] This disconnect between gas exchange and lung mechanics may be explained by pulmonary thrombi as endothelial injury and thromboembolic events

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are increasingly recognized as an essential component of COVID-19 pathophysiology.[3,4] Autopsy studies have confirmed that in the lungs, formation of fibrin thrombi in alveolar capillaries is a predominant feature, particularly in severe COVID-19.[5] Fibrin, together with activated platelets, induces the formation of microthrombi and contributes to acute lung injury.[6] Overall, ninety percent of patients hospitalized with COVID-19 pneumonia have increased D-dimer concentrations, with concentrations greater than 1 μg/mL associated with greater mortality.[1] COVID-19 coagulopathy has become a widely recognized phenomenon, with even risk of stroke and acute coronary syndrome being elevated in COVID-19 patients.[7,8]

Recently, the use of treatment dose anticoagulation in hospitalized COVID-19 patients has been associated with improved outcomes.[9] However, to date, few studies have evaluated the potential effect of antiplatelet agents on COVID-19. Platelets participate both in hemostasis and the immune system. Specifically, in patients with COVID-19 infection, platelets have been shown to be hyperresponsive, as they are more prone to release inflammatory cytokines IL-1β and soluble CD40L and sensitize platelet activation signaling pathways involving protein kinase C.[10] This increase in activation and aggregation of platelets contributes to the thrombosis seen in COVID-19 infections. Zaid et al isolated SARS-CoV-2 RNA in platelets with COVID-19 infection but not in healthy patients, suggesting that platelets are involved in the dissemination of the virus as well. There is also evidence that the hyperactivated platelets interact with the cardiovascular system to cause microvascular thrombi with subsequent myocardial injury, as well as promotion of rupture of pre-existing atherosclerotic plaques due to systemic cytokine and immune cell activation.[11]

We hypothesized that antiplatelet therapy early in disease course could reduce severity of COVID-19-related acute lung injury by limiting platelet activation, formation of platelet-neutrophil aggregates, and formation of microthrombi known to be a part of COVID-19 pathogenesis.[6] Our objective was to identify and characterize any association between antiplatelet use and COVID-19 disease. We retrospectively assessed the association between antiplatelet use and COVID-19 illness severity in COVID-19 patients hospitalized at a tertiary care center while controlling for anticipated confounders associated with antiplatelet use.

Methods

We conducted a retrospective study of all people admitted to The Mount Sinai Hospital between March 1, 2020 and April 9, 2020 with confirmed COVID-19 infections. This study of human subjects was approved by the Mount Sinai Institutional Review Board (IRB-20-03525). Inclusion criteria were age $\geq$18, confirmed COVID-19 infection by reverse transcriptase polymerase chain reaction (RT-PCR) with follow-up until discharge, death, or at least 28 days inpatient (i.e. still hospitalized at time of data cut-off). If patients had multiple admissions within the study window, only the first admission with confirmed COVID-19 infection was included. We excluded patients transferred from outside hospitals or those admitted for planned surgical procedures.

Our exposure of interest was pre-hospitalization antiplatelet medication use, defined as documented home antiplatelet medication use in the medical record at the time of admission with or without continuation after admission. Baseline demographic and clinical encounter data were captured using standardized criteria via individual patient chart review by trained abstractors, with data being collected from appropriate sections of the electronic medical record. The senior investigators then reviewed selected charts from each abstractor to ensure quality and accuracy of data collection. The control population consisted of patients not exposed to antiplatelet agents at home or during hospitalization.

To capture multiple clinical outcomes of interest, the primary endpoint was peak score on a 6-point modified ordinal scale (MOS) which combines two outpatient categories of the 7-point scale recommended by the World Health Organization blueprint R&S group.[12] Scores indicate the following: 1 – COVID-19 infection not requiring hospitalization, 2 – requiring hospitalization but not supplemental oxygen, 3 – hospitalization requiring supplemental oxygen, 4 – hospitalization requiring high-flow nasal cannula (HFNC) or non-invasive positive pressure ventilation (NIPPV), 5 – hospitalization requiring intubation or extracorporeal membrane oxygenation (ECMO), 6 – death. Currently, ordinal scales are the most commonly used endpoint among COVID-19 clinical trials, facilitating more consistent comparisons of outcomes across clinical studies.[13]

The observational nature of the study risked unequal distribution of clinically significant covariates between antiplatelet users and non-users. Using multivariable partial proportional odds model (PPOM) suitable for ordinal outcomes, we adjusted for 13 baseline characteristics (patient age, sex, body mass index (BMI), and smoking history, and history of stroke/transient ischemic attack (TIA), diabetes mellitus, hypertension, coronary artery disease (CAD), congestive heart failure, peripheral vascular disease, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and HIV) in addition to the exposure variable. A sensitivity analysis was planned to assess the subset of home antiplatelet users whose medications were also administered during admission, defined as at least one dose administered following admission. All analyses were performed using SAS Enterprise Guide® (version 7.1, SAS Institute Inc, Cary, NC) and R (version 3.6.2).

Results

Of 1,269 people hospitalized with COVID-19 infection from 3/1/2020 to 4/16/2020, 762 fit the inclusion criteria and had complete data, of which 239 (31.4%) used antiplatelet drugs at home and 523 (68.6%) did not. Of the 239 users, 199 (83.3%) patients were taking aspirin alone, 9 (3.8%) patients used clopidogrel alone, and 1 (0.4%) patient used ticagrelor alone. Thirty (12.6%) patients of the 239 users were on dual antiplatelet therapy (DAPT), of which 24 (80.0%) patients used aspirin and clopidogrel, 5 (16.7%) used aspirin and ticagrelor, and 1 (3.3%) used aspirin and prasugrel. Patients with pre-hospitalization antiplatelet use were older (mean age 69.6 vs 58.5 years, p <0.001) and had a higher frequency of comorbidities, including stroke/TIA, diabetes mellitus, CAD, CKD, hypertension, and peripheral vascular disease (Table 1).

Fig. 1 shows the distribution of MOS scores between the two groups. Unadjusted analysis revealed that patients who used

Table 1
Clinical and Demographic Characteristics of the Sample

	Pre-Hospitalization Antiplatelet Use		p-value
	Non-Users (n = 524)	Users (n = 239)	
Age, years	58.5 ± 16.2	69.6 ± 12.5	<0.0001
Sex, female	239 (45.70)	95 (39.75)	0.125
BMI[a], kg/m2	30.0 ± 7.4	29.0 ± 6.5	0.137
Smoker	161 (30.78)	117 (48.95)	<0.0001
HIV	16 (3.06)	6 (2.51)	0.675
Stroke or TIA[b]	24 (4.59)	39 (16.32)	<0.0001
Diabetes mellitus	152 (29.06)	139 (58.16)	<0.0001
Hypertension	258 (49.33)	214 (89.54)	<0.0001
Coronary artery disease	32 (6.12)	100 (41.84)	<0.0001
Heart failure	32 (6.12)	45 (18.83)	<0.0001
COPD[c]	36 (6.88)	15 (6.28)	0.756
Chronic kidney disease	65 (12.43)	70 (29.29)	<0.0001
Peripheral vascular disease	12 (2.29)	25 (10.46)	<0.0001

[a] BMI = body mass index
[b] TIA = transient ischemic attack
[c] COPD = chronic obstructive pulmonary disease.

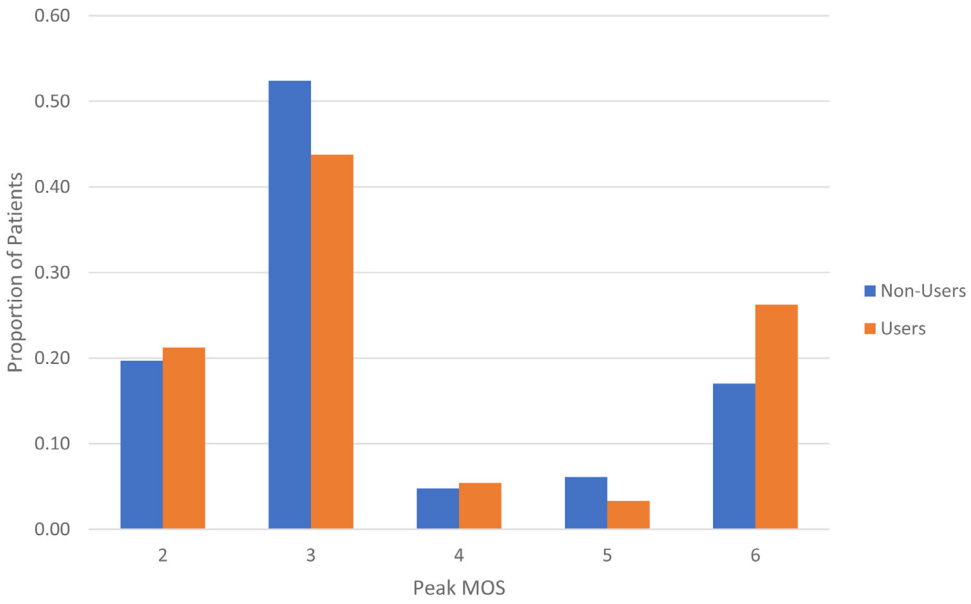

Fig. 1. Distribution of Peak MOS Among Pre-Hospitalization Antiplatelet Users and Non-Users

Table 2
Unadjusted and Adjusted Odds Ratio for Pre-Hospitalization Antiplatelet Users Compared to Non-Users

	Unadjusted		Adjusted	
Peak MOS[a]	OR[b]	95% CI[c]	OR	95% CI
6 vs. 5 to 2	1.75	1.21 - 2.52	1.13	0.70 - 1.82
6 to 5 vs. 4 to 2	1.40	1.00 - 1.98	1.02	0.66 - 1.57
6 to 4 vs. 3 to 2	1.40	1.01 - 1.94	0.98	0.65 - 1.46
6 to 3 vs. 2	0.90	0.62 - 1.32	0.88	0.55 - 1.41

[a] MOS = modified ordinal scale
[b] OR = odds ratio
[c] CI = confidence interval.

antiplatelets pre-hospitalization were more likely than patients not using antiplatelet agents to have a peak MOS score of 6 (death, OR 1.75, 95% CI 1.21 – 2.52), ≥5 (intubation/ECMO or death, OR 1.40, 95% CI 1.00 – 1.98) and ≥4 (HFNC, NIPPV, intubation/ECMO or death, OR 1.40, 95% CI 1.01 – 1.94). Importantly, from our multivariable PPOM analysis controlling for 13 covariates, there were no statistically significant differences in peak MOS scores between those with pre-hospitalization antiplatelet use and those without pre-hospitalization antiplatelet use (Table 2). No significant differences were found in the prevalence of patients with peak MOS 6 (OR 1.13), ≥5 (OR 1.02), ≥4 (OR 0.98), or ≥3 (requiring any supplemental oxygen, OR 0.88). Of the home antiplatelet users, 182 (76.2%) were continued on antiplatelets in the hospital and the sensitivity analysis again showed no difference in peak MOS scores on multivariable adjusted analysis. We did not have sufficient patients on DAPT to conduct meaningful comparisons to patients on single agents or non-users.

Discussion

In our single center study, before adjustment, patients who used antiplatelets had worse outcomes, likely owing to patients being older with more comorbidities. However, after controlling for clinically relevant covariates, pre-hospital use of antiplatelet agents was not associated with COVID-19 disease severity in hospitalized patients.

This study has a number of limitations. First, antiplatelet users' potential predisposition towards severe disease may not have been fully captured by our analysis, and thus unmeasured confounders may have eliminated potential benefits of antiplatelet use. Furthermore, the retrospective nature of this study prevented uniform antiplatelet doses and durations among patients, the standardization of which may yield different results. A randomized controlled trial setting would address both of these limitations, and at least one such study is currently underway.[14]

Our study builds upon a body of recently published retrospective studies and small prospective studies which have reported conflicting results. While some have demonstrated decreased disease severity and/or mortality associated with antiplatelet use, others have found no benefit, with methodology differing significantly between studies.[15–18] As an addition to field, our findings are most in line with a systemic review and meta-analysis by Wang et al which concluded that antiplatelet use was neither associated with significant mortality benefit nor harm in COVID-19.[19] Furthermore, our study although not designed to assess the efficacy of in-hospital antiplatelet use, included a sensitivity analysis for antiplatelet users who continued therapy in the hospital and found no effect on disease severity.

In addition to the aforementioned methodological limitations, there are several pathophysiologic factors that may explain the lack of benefit seen with home antiplatelet use. It is possible that microthrombi in COVID-19 are composed more heavily of fibrin rather than platelets, which could also explain recent promise seen with anticoagulants. Since the majority of our patients were on aspirin monotherapy, potential benefit derived from dual antiplatelet therapy could not be adequately assessed. Similarly, benefits from other classes of antiplatelet agents, in particular $P2Y_{12}$ inhibitors, which have been associated with reductions in inflammatory markers and improved mortality in sepsis, could not be discerned.[20] Furthermore, although we were able to assess for not only differences in mortality but also in disease severity, our study captured only hospitalized COVID-19 patients and thus we could not assess whether antiplatelet agents might prevent mild COVID-19 cases from requiring hospitalization in the first place. Additionally, the thrombotic sequelae of COVID-19 may be associated with but not causative in severe COVID-19. Indeed the marked inflammatory response that COVID-19 often precipitates, which incidentally promotes formation of microthrombi, may be a more central driver of morbidity and mortality.

Conclusions

After controlling for clinically relevant covariates, no association between pre-hospital antiplatelet agent and COVID-19 disease

severity was observed in hospitalized patients. Based on these findings, we have not found sufficient evidence to recommend routine antiplatelet use as a part of COVID-19 treatment. However, randomized controlled trials are needed to fully assess potential utility of antiplatelets in this setting. Future studies may also consider investigating the protective effects of dual antiplatelet therapy or specific classes of antiplatelets, particularly $P2Y_{12}$ inhibitors, which have been associated with reductions in inflammatory markers and improved mortality in sepsis. Additionally, use of antiplatelet agents in combination with now established standard-of-care antivirals and anti-inflammatory agents should be investigated to identify any potentiating relationships. Finally, an increasing body of evidence indicates clinically significant increases in non-pulmonary thrombotic events in COVID-19 patients, including higher stroke risk and acute coronary syndrome risk.[7,8] Considering the established role of antiplatelet agents in the acute management of both conditions, future studies might assess whether antiplatelet agents limit the thromboembolic sequelae in neurologic or coronary settings.

Author Contributions

Darren Pan and Ada Ip performed chart review and wrote the manuscript. Serena Zhan performed statistical analysis and contributed to writing and editing. Isaac Wasserman, Daniel J. Snyder, Alexandra Z. Agathis, Nikhil Shamapant, Jeong Yun Yang, and Akila Pai performed chart review and contributed to editing. Madhu Mazumdar contributed to editing and provided critical feedback which helped to shape the manuscript. Hooman Poor edited, provided guidance regarding overall direction, and contributed to writing the manuscript.

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