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Aspirin Use is Associated with Decreased Mechanical Ventilation, ICU Admission, and In-Hospital Mortality in Hospitalized Patients with COVID-19

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This report describes a cohort observational clinical study. The authors state that the report includes every item in the STROBE checklist for cohort studies.

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Abstract

Background: Coronavirus disease-2019 (COVID-19) is associated with hypercoagulability and increased thrombotic risk in critically ill patients. To our knowledge, no studies have evaluated whether aspirin use is associated with reduced risk of mechanical ventilation, intensive care unit (ICU) admission, and in-hospital mortality.

Methods: A retrospective, observational cohort study of adult patients admitted with COVID-19 to multiple hospitals in the United States between March 2020 and July 2020 was performed. The primary outcome was the need for mechanical ventilation. Secondary outcomes were ICU admission and in-hospital mortality. Adjusted hazard ratios for study outcomes were calculated using Cox proportional hazards models after adjustment for the effects of demographics and co-morbid conditions.

Results: Four hundred twelve patients were included in the study. Three hundred fourteen patients (76.3%) did not receive aspirin, while 98 patients (23.7%) received aspirin within 24 hours of admission or 7 days prior to admission. Aspirin use had a crude association with less mechanical ventilation (35.7% aspirin vs. 48.4% non-aspirin, p=0.03) and ICU admission (38.8% aspirin vs. 51.0% non-aspirin, p=0.04), but no crude association with in-hospital mortality (26.5% aspirin vs. 23.2% non-aspirin, p=0.51). After adjusting for 8 confounding variables, aspirin use was independently associated with decreased risk of mechanical ventilation (adjusted HR 0.56, 95% CI 0.37-0.85, p=0.007), ICU admission (adjusted HR 0.57, 95% CI 0.38-0.85, p=0.005), and in-hospital mortality (adjusted HR 0.53, 95% CI 0.31-0.90, p=0.02). There were no differences in major bleeding (p=0.69) or overt thrombosis (p=0.82) between aspirin users and non-aspirin users.

Conclusions: Aspirin use may be associated with improved outcomes in hospitalized COVID-19 patients. However, a sufficiently powered randomized controlled trial is needed to assess whether a causal relationship exists between aspirin use and reduced lung injury and mortality in COVID-19 patients.

Glossary of Terms

ALI = acute lung injury

APACHE II = Acute Physiology and Chronic Health Evaluation II

ARDS = acute respiratory distress syndrome

BiPAP = bilevel positive airway pressure

BMI = body mass index

BP = blood pressure

bpm = beats per minute

CAD = coronary artery disease

CI = confidence interval

COVID-19 = Coronavirus disease 2019

COX-1 = cyclooxygenase-1

COX-2 = cyclooxygenase-2

CPAP = continuous positive airway pressure

CRP = C-Reactive Protein

CRUSH COVID = Collaborative Research to Understand the Sequelae of Harm in COVID

DM = diabetes mellitus

DVT = Deep vein thrombosis

FiO2 = fraction of inspired oxygen

GI = gastrointestinal

HR = hazard ratio

HR = heart rate

HTN = hypertension

ICU = intensive care unit

IL-6: interleukin-6

INR = international normalized ratio

IQR = interquartile range

IRB = Institutional Review Board

LIPS-A = Lung Injury Prevention Study with Aspirin

LPM = liters per minute

PaO2 = partial pressure of oxygen

PCR = polymerase chain reaction

PEEP = positive end expiratory pressure

PT = prothrombin time

PTT = partial thromboplastin time

qSOFA = quick sequential organ failure assessment

RBC = red blood cell

REDCap = Research Electronic Data Capture

SARS-CoV-2 = Severe acute respiratory syndrome coronavirus-2

SOFA = sequential organ failure assessment

SpO2 = peripheral capillary oxygen saturation

WBC = white blood cell

Key Points

Question: Is aspirin use associated with less mechanical ventilation in COVID-19 patients?

Findings: In an observational cohort study of 412 adult patients with COVID-19, aspirin use was associated with a significantly lower rate of mechanical ventilation, ICU admission, and in-hospital mortality after controlling for confounding variables.

Meaning: Aspirin may have lung protective effects and reduce the need for mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized COVID-19 patients.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected over 18.5 million people and caused 700,000 deaths worldwide.[1] The majority of coronavirus disease 2019 (COVID-19) cases are mild, but critical illness has been reported in 6-19% of patients.[2,3] Although pneumonia and acute respiratory distress syndrome (ARDS) are hallmarks of the disease, thrombotic complications have been reported in 25-42% of patients and are associated with increased mortality.[4-6] Evidence of hypercoagulability has been observed on viscoelastic coagulation testing and COVID-19 patients frequently have elevated D-dimer and fibrinogen concentration.[7] Deep vein thrombosis (DVT) and arterial thrombosis are relatively common, and on autopsy, megakaryocytes and platelet-rich thrombi have been observed in the heart, lung, and kidneys of COVID-19 patients.[7-10] Furthermore, alveolar capillary microthrombosis has been observed at a rate nine times higher than in influenza patients and is thought to contribute to the severe lung injury and hypoxemia that occurs in COVID-19 patients.[11]

A prior study suggested that systemic anticoagulation reduces mortality in mechanically ventilated COVID-19 patients.[12] Low dose aspirin has been utilized for prevention of stroke and myocardial infarction in high risk patients, and the US Preventive Services Task Force recommends its use in adults with elevated cardiovascular risk.[13] Aspirin's reduces cardiovascular events, although a recent randomized control trial and meta-analysis found that it also increases the risk for major bleeding.[14,15] In ARDS, aspirin has been studied with mixed results, where some studies have demonstrated benefit and others have not.[16-21]

Given its widespread availability, low-cost, and numerous studies supporting its efficacy and safety in patients with cardiovascular disease, we evaluated aspirin's impact on clinical outcomes in hospitalized patients with COVID-19.[14,15,22,23] Our primary study objective was to evaluate

whether aspirin use was associated with the need for mechanical ventilation, and we hypothesized that aspirin use would be associated with a reduced risk of mechanical ventilation. Secondarily, we evaluated whether aspirin use was associated with a reduced risk for intensive care unit (ICU) admission and in-hospital mortality.

Methods

Patients

COVID-19 patients admitted to the hospital between March 2020 and July 2020 were abstracted from the multicenter Collaborative Research to Understand the Sequelae of Harm in COVID (CRUSH COVID) registry. This registry contains data on COVID-19 patients from multiple institutions, and 4 hospitals had entered the majority of data as of July 2020: the University of Maryland Medical Center, Wake Forest Baptist Medical Center, Northeast Georgia Health System, and George Washington University Hospital. Data entry for all patients was managed using Research Electronic Data Capture (REDCap).[24]

The study was reviewed and approved by the Institutional Review Board (IRB) at the University of Maryland, Baltimore, which served as the central IRB for all sites. The requirement for written informed consent was waived by the IRB and the study was conducted in accordance with the ethical principles described in the Declaration of Helsinki. Patients were included if they were ≥18 years old and had laboratory-confirmed SARS-CoV-2 infection by qualitative real-time polymerase chain reaction (PCR). Patients were excluded if they had a do-not-intubate or do-not-resuscitate order at admission or if they remained an inpatient at the time of analysis.

Study data

Patient demographics, comorbidities, medications, laboratory data, and outcome data were recorded. Major bleeding was defined as bleeding that led to a hemoglobin < 7 g/dL and required red blood cell (RBC) transfusion, bleeding that led to transfusion of ≥ 2 RBC units in 24 hours, intracranial bleeding, gastrointestinal bleeding requiring RBC transfusion, bleeding that required surgical intervention, nasopharyngeal bleeding that required intervention, or ocular bleeding. Overt thrombosis was defined as DVT, pulmonary embolism, peripheral arterial occlusion, ischemic stroke, or ST-elevation myocardial infarction.

Respiratory parameters prior to intubation were collected, which included peripheral capillary oxygen saturation (SpO_2), fraction of inspired oxygen (FiO_2), oxygen flow, type of oxygen support, and partial pressure of oxygen (PaO_2). Mechanical ventilation parameters after intubation were collected which included ventilator mode, tidal volume, tidal volume per predicted body weight, set pressure, positive end expiratory pressure (PEEP), FiO2, peak pressure, plateau pressure, PaO_2, and PaO_2/FiO_2 ratio.

A*spirin use definition*

Aspirin use was defined as administration within 24 hours of hospital admission or in the 7 days prior to hospital admission. This definition was selected based on aspirin's prolonged duration of action as an irreversible platelet inhibitor and because of aspirin's rapid onset within 0-4 hours when chewed or swallowed.[25] If aspirin was administered after an outcome occurred (i.e. after mechanical ventilation), then that patient was categorized in the non-aspirin group for analysis of that outcome

Study outcomes

The study's primary outcome was the need for invasive mechanical ventilation, inclusive of ventilation with an endotracheal or tracheostomy tube, and exclusive of non-invasive ventilation both continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP). Secondary outcomes were ICU admission and in-hospital mortality. The biologic plausibility for our hypothesis was based on aspirin's ability to irreversibly inhibit platelet aggregation in the lungs, which could reduce pulmonary microthrombi and subsequent lung injury.

tatistical analysis

Patients were stratified by whether or not they received aspirin. Nonparametric continuous variables such as body mass index (BMI), admission vital signs, clinical prediction scores, initial laboratory values, adverse events, and mechanical ventilation parameters were summarized as the median and interquartile range and were compared between groups using the Mann-Whitney U Test. Categorical variables such as demographic information, comorbidities, receipt of other investigational therapeutics, type of oxygen support, mechanical ventilation mode, and outcomes were reported as the number and percentage of patients and were compared between groups using the Chi-squared test. P-values <0.05 were considered statistically significant.

Chi-square tests were performed to measure the crude association between aspirin use and the need for mechanical ventilation, ICU admission, and in-hospital mortality. Cox-proportional hazards models were fit to determine the adjusted associations between aspirin use and outcomes after controlling for confounders. Selection of confounders was based on recommendations in the published epidemiology literature.[26,27] We adjusted for variables that were pre-existing and were associated with aspirin use and the outcome or solely the outcome including: age, gender, BMI, race, hypertension, diabetes mellitus, coronary artery disease, renal disease, liver disease,

and home beta blocker use. Variables that were believed to be in the causal pathway or occurred after aspirin use began were not adjusted for. Because aspirin, as a cyclooxygenase-1 (COX-1) inhibitor, modifies inflammatory and coagulation responses, these variables were considered to be in the causal pathway and were not adjusted for.

The proportional hazards assumption was tested graphically by plotting scaled Schoenfeld residuals and numerically using the Kolmogorov-type Supremum Test, and no serious violations of the proportional hazards assumption were observed. To maximize inclusion of confounders in our final model, a liberal p-value of 0.2 was used for likelihood ratio testing to enter and remove variables from the model using forward stepwise regression. Because age, BMI, race, coronary artery disease, hypertension, and diabetes mellitus are established risk factors for poor outcome in COVID-19 patients, these variables were forced into the final model and were not subject to entry and removal criteria.[28] Patients with a negative time to event (i.e. mechanical ventilation occurred prior to hospital admission) were removed from the analysis for that particular outcome. A 95% confidence interval (CI) was calculated for each adjusted hazard ratio.

A subgroup analysis with a Cox-proportional hazard model was performed in the cohort of patients who were not mechanically ventilated at admission. This group included all patients who were admitted on room air, standard nasal cannula oxygen, high-flow nasal cannula oxygen, non-rebreather oxygen mask, CPAP, and BiPap. In addition, another sensitivity analysis with an E-Value was performed to estimate the magnitude of an unadjusted confounding variable that would be needed to mitigate the association between aspirin use and the need for mechanical ventilation.[29]

Given the retrospective nature of our study, *a priori* sample size calculation was not performed, however, *post hoc* calculations indicated that with the observed mechanical ventilation rate of 48.4% in the non-aspirin group, our sample size allowed for detection of a 11.7% reduction in the rate of mechanical ventilation, given an alpha of 5% and 80% power. In addition, with 9 independent variables in the Cox-proportional hazards model, a minimum of 90 mechanically ventilated patients would be necessary to create a parsimonious model and sufficiently adjust for confounding variables. Statistical analysis was performed using SPSS Statistics 25 (IBM Corporation, Somers, NY) and R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). The final analysis was confirmed using SAS 9.3 (SAS Corporation, Cary, NC, USA).

Results

Four hundred twelve patients were included in the study. Median age was 55 years (interquartile range [IQR] 41-66 years) and 59.2% of patients were male (**Table 1**). Ninety-eight patients (23.7%) received aspirin, while 314 patients (76.3%) did not. Of those who received aspirin, 75.5% were taking it prior to admission and 86.7% received it within 24 hours of hospital admission. Median time to aspirin administration in the hospital was 0 days (IQR 0-1 days), median dose was 81mg (IQR 81-81 mg), and median treatment duration was 6 days (IQR 3-12 days). Patients who received aspirin had significantly higher rates of hypertension, diabetes mellitus, coronary artery disease, and renal disease ($p<0.001$). Furthermore, significantly more patients taking aspirin were on home beta blockers ($p<0.001$) and had liver disease ($p=0.04$). The proportion of patients in each group receiving other therapeutics including azithromycin, convalescent plasma, dexamethasone, therapeutic heparin, hydroxychloroquine, remdesivir, and tocilizumab did not differ.

Admission vital signs and laboratory values did not differ between groups, except for fibrinogen concentration (aspirin median 524 mg/dL vs. non-aspirin 635 mg/dL, p=0.009), which was significantly lower in patients taking aspirin. Initial fibrinogen concentration was measured at a median of 1 day after hospital admission (IQR 0-3 days) and there was no difference in timing between groups. Patients receiving aspirin were on significantly less oxygen support at admission compared to patients not receiving aspirin (p=0.005). Specifically, a higher proportion of patients receiving aspirin were admitted to the hospital on room air or standard nasal cannula oxygen, while patients not on aspirin were admitted more frequently with high flow nasal cannula oxygen, a non-rebreather oxygen mask, CPAP, BiPAP, or an endotracheal tube and mechanical ventilation (**Table 1**).

The quick sequential organ failure assessment (qSOFA) score at hospital admission, as well as the qSOFA and sequential organ failure assessment (SOFA) scores at ICU admission did not differ between groups. However, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score at ICU admission was significantly higher in the aspirin group (**Table 1**).

Patients were in severe hypoxemic respiratory failure just prior to intubation, with a median PaO_2 of 70 mmHg (IQR 55-84), median SpO_2 of 92% (IQR 86-96%), and a median FiO_2 of 100% (IQR 80-100%) on 15 liters per minute (IQR 8-40). Immediately prior to intubation, high flow nasal cannula oxygen was utilized 35.6% of the time, followed by non-rebreather oxygen mask (21.2%), standard nasal cannula oxygen (18.5%), BiPAP (5.5%), and CPAP (1.4%). Pre-intubation oxygen support was unknown in 15.8% of cases due the inability to access records from referring institutions.

Once on mechanical ventilation, patients were most frequently ventilated with volume control ventilation (41.2%), followed by pressure regulated volume control (28.9%), pressure control ventilation (16.6%), airway pressure release ventilation (APRV) (8.6%), pressure support ventilation (2.1%), synchronous intermittent mandatory ventilation (SIMV) (1.6%), and other modes (1.1%). Median tidal volume was 440 mL (IQR 400-460 mL), with a set pressure of 22 cmH_2O (IQR 14-26 cmH_2O), PEEP of 10 cmH_2O (IQR 9-14 cmH_2O), and FiO_2 of 80% (IQR 55-100%). The median tidal volume per predicted body weight was 6.6 mL/kg (median 6.1-7.3 mL/kg), initial peak pressure was 29 cmH_2O (IQR 24-33 cmH_2O) and median plateau pressure was 21 cmH_2O (IQR 16-27 cmH_2O). The initial PaO2 was a median of 100 mmHg (IQR 75-145 mmHg) for a calculated median PaO_2/FiO_2 ratio of 146 (IQR 92-237). There were no statistically significant differences in respiratory parameters between groups.

On unadjusted analysis, patients receiving aspirin had significantly lower rates of mechanical ventilation (35.7% [35/98] aspirin vs. 48.4% [152/314] non-aspirin, p=0.03) and ICU admission (38.8% [38/98] aspirin vs. 51.0% [160/314] non-aspirin, p=0.04). There was no crude difference in in-hospital mortality (26.5% [26/98] aspirin vs. 23.2% [73/314] non-aspirin, p=0.51) between groups. In addition, there was no difference in the rate of major bleeding (6.1% aspirin [6/98] vs. 7.6% non-aspirin [24/314], p=0.61), or overt thrombosis (8.2% [8/98] aspirin vs. 8.9% [28/314] non-aspirin, p=0.82) between groups.

After adjusting for confounding variables in the Cox-proportional hazards model, aspirin use was independently associated with a reduced risk for mechanical ventilation, which was the primary study outcome (adjusted hazard ratio [HR] 0.56, 95% CI 0.37-0.85, p=0.007). As secondary outcomes, aspirin use was also associated with a reduction in the risk of ICU admission (adjusted

HR 0.57, 95% CI 0.38-0.85, p=0.005) and in-hospital mortality (adjusted HR 0.53, 95% CI 0.31-0.90, p=0.02) (**Table 2)**.

In our subgroup analysis of patients who did not require mechanical ventilation at admission, these favorable associations between aspirin and mechanical ventilation (adjusted HR 0.63, 95% CI 0.40-1.00, p=0.05), ICU admission (adjusted HR 0.64, 95% CI 0.41-0.99, p=0.046), and in-hospital mortality (adjusted HR 0.45, 95% CI 0.24-0.85, p=0.01) persisted. A Forest plot was constructed showing each of the primary and secondary outcomes to graphically depict adjusted differences in hazards between groups (**Figure 1**). The survival function for in-hospital mortality was constructed from our Cox-proportional hazards model, and aspirin use was plotted as a separate line to visualize the cumulative differences in survival between groups (**Figure 2**).

In our sensitivity analysis, we found that an unexplained confounder would need to be associated with both aspirin use and mechanical ventilation at a risk ratio of 2.35 to mitigate the relationship between these variables and make the hazard ratio equal to 1, while controlling for other covariates in our model (E-Value 2.35, upper confidence limit 1.48). The upper confidence limit for the risk ratio can be interpreted as the lowest risk ratio that an unobserved confounder would have to have with both aspirin use and mechanical ventilation, after controlling for other covariates in the model, in order to make the hazard ratio equal to 1.

We performed an additional sensitivity analysis of the primary outcome and stratified patients by timing of aspirin use. This sensitivity analysis was underpowered, but may be helpful for planning future studies. The rates of ICU admission in those receiving aspirin only in the 7 days prior to hospitalization, only in the first 24 hours of hospitalization, or in both timeframes were 46.2%, 20.8%, and 39.3%, respectively. This resulted in an adjusted HR of 0.78 (95% CI 0.32-

1.95), 0.36 (95% CI 0.15-0.89), and 0.71(95% CI 0.44-1.16) for these three timeframes, respectively.

Discussion

In a multi-center cohort study of 412 COVID-19 patients, aspirin use was independently associated with a lower risk of mechanical ventilation, ICU admission, and in-hospital mortality. With an emphasis on avoiding mechanical ventilation in COVID-19 patients, these results are clinically significant. Mechanistically, COVID-19 is associated with hypercoagulability and pulmonary microthrombosis, and aspirin may mitigate these effects.[11,30] Aspirin is inexpensive, widely available, and has a well described risk profile. These attributes, in conjunction with our pilot data, support aspirin's role as a potential adjunctive therapeutic in COVID-19.

The prothrombotic and hypercoagulable state that is induced by COVID-19 is well described, and a prior study has shown that systemic anticoagulation with heparin can reduce mortality in mechanically ventilated COVID-19 patients.[12] Aspirin may have a similar impact due to its antiplatelet and anti-inflammatory properties, as an inhibitor of COX-1, which decreases thromboxane A_2 synthesis, platelet aggregation, and thrombus formation.[31] Aspirin's potential benefits in lung injury are thought to be related to reduced platelet-neutrophil aggregates in the lungs, reduced inflammation, and increased lipoxin formation, which restores pulmonary endothelial cell function.[21] These protective effects may be augmented in a disease such as COVID-19, where the procoagulant tendency is unusually high and endothelial cell dysfunction is common.

Aspirin's anti-inflammatory properties may also contribute to its lung protective effects in COVID-19. Aspirin has been shown to decrease the production of interleukin-6 (IL-6), C-reactive protein (CRP), and macrophage colony stimulating factor in patients with cardiovascular disease, and in COVID-19, these actions could reduce the incidence of cytokine storm.[32,33] In our study, patients on aspirin had significantly lower initial plasma fibrinogen concentration, which might be explained by aspirin's effect on the acetylation of fibrinogen and acceleration of fibrinolysis.[34] Aspirin also has an inhibitory effect on cyclooxygenase-2 (COX-2), which decreases IL-6 and CRP production.[32]

Several studies have examined aspirin's possible beneficial effect in ARDS. Erlich and colleagues evaluated 161 patients at risk of acute lung injury (ALI), of which 79 received antiplatelet therapy at admission.[18] Of the patients in the antiplatelet group, 75 (94.9%) were on aspirin. The study found that antiplatelet agents were associated with a reduction in the incidence of ALI and ARDS (adjusted risk ratio 0.34, 95% CI 0.13-0.88, P=0.03).[18] Chen and colleagues examined 1,149 patients at high risk of ARDS and found that pre-hospital aspirin administration was associated with a reduction in ARDS after adjustment for confounding variables (adjusted OR 0.66, 95% CI 0.46-0.94, p=0.02).[17] The reduced incidence of ARDS persisted when examining only patients with sepsis (adjusted OR 0.61, 95% CI 0.41-0.90, p=0.01).[17] Another study of high-risk patients found that although aspirin was associated with a reduction in ALI on univariable analysis (OR 0.65, 95% CI 0.46-0.90, p=0.01), the association was not statistically significant on multivariable analysis (pooled OR 0.70, 95% CI 0.48-1.03, p=0.072).[20] Taken together, a meta-analysis of these three studies found that aspirin was associated with an overall reduced incidence of ARDS (pooled OR 0.59, 95% CI 0.36-0.98).[21]

When examining mortality as an outcome, pre-hospital or in-hospital aspirin use in ARDS patients is associated with a reduction in ICU mortality (adjusted OR 0.38, 95% CI 0.15-0.6, p=0.04), but not in-hospital mortality (adjusted OR 0.91, 95% CI 0.46-1.78, p=0.78).[16] The Lung Injury Prevention Study with Aspirin (LIPS-A) clinical trial examined 390 patients at high risk for ARDS who were randomized to aspirin or placebo, and found that aspirin did not prevent ARDS at 7 days (p=0.53) or improve 28-day survival (p=0.92).[19] However, there are important differences between our study and those previously published. Our study limited enrollment to patients with a single diagnosis of COVID-19, as opposed to other studies, which enrolled all patients at high risk for ARDS. In those that reported baseline risk factors for ARDS, the spectrum of diagnoses was broad: sepsis, non-cardiogenic shock, aspiration, pancreatitis, pneumonia, positive shock index, and trauma.[18,19] This heterogeneity may have diluted and confounded aspirin's effects.

In addition, not all causes of ARDS are associated with hypercoagulability, as in the case of COVID-19. In a single center study, SARS-CoV-2 infection was shown to be associated with pulmonary embolism at a rate of 20.6%, which was three times higher than in all patients admitted to the ICU during the same time interval (20.6% SARS-CoV-2 vs. 6.1% control, absolute risk increase 14.4%, 95% CI 6.1-22.8). This rate was more than double the rate observed in influenza patients admitted to the ICU (20.6% SARS-CoV-2 vs. 7.5% influenza, absolute risk increase 13.1%, 95% CI 1.9-24.3).[35] Furthermore on autopsy, alveolar microthrombi have been reported to be present at a rate 9 times higher than in influenza patients.[11] Because hypercoagulability is common in COVID-19, aspirin's effect size may be larger in this population and this may explain why our analysis was able to detect statistically

significant associations with reduced mechanical ventilation, ICU admission, and in-hospital mortality, whereas some previous studies did not find these benefits.

There is now substantial evidence that COVID-19 is a systemic disease affecting the vasculature, and that SARS-CoV-2 causes vascular endothelialitis involving the pulmonary capillary endothelium.[10,36] Electron microscopy and histological analyses have demonstrated that SARS-CoV-2 infects endothelial cells in multiple organs causing endothelialitis, impaired microcirculation, and apoptosis, all of which leads to inflammation and microthrombosis.[36] Microthrombosis has been well described in autopsies of COVID-19 patients, and excess megakaryocytes have been observed in the heart, lungs, and kidneys of deceased patients.[10,11] Aspirin, as an irreversible anti-platelet agent, may prevent platelets produced from these megakaryocytes from aggregating and creating microthrombi.[10]

In our study, we did not observe a lower rate of overt thrombosis in aspirin users, but this may be due to the low number of reported events in each group or due to reporting bias from avoidance of diagnostic imaging. Importantly, the presence of microthrombi does not correlate with overt thrombosis. Microthrombosis is better diagnosed with videomicroscopes, dark field imaging, and spectral imaging.[37,38] These non-invasive methods measure the flow and velocity of cells in the microcirculation and allow for the visualization and quantification of flow on a capillary-level. However, these tools are neither widely available nor standard of care. Although a reduction in microthrombosis is a plausible mechanism to explain our findings, the hypothesis that aspirin inhibits microthrombosis in COVID-19 needs to be further explored in mechanistic studies.

Aspirin has been shown to increase bleeding risk in a randomized control trial (HR 1.38, 95% CI 1.18-1.62, $p<0.001$) and systematic review (HR 1.43, 95% CI 1.30-1.56).[14,15] Patients in these two large studies were treated with aspirin for the primary prevention of cardiovascular disease,

and these patients did not have acute illness, which is an important distinction from our cohort. In our analysis, we did not find a significant increase in major bleeding in patients who received aspirin. This difference may be explained by the fact that patients with COVID-19 are frequently hypercoagulable, thrombocytopenia is uncommon in COVID-19 patients, and the risk of bleeding appears to be low (2-3%), even with systemic heparinization.[12] Nevertheless, aspirin could increase bleeding risk to some degree (particularly gastrointestinal bleeding), and larger studies should be performed to better assess bleeding risk in patients with COVID-19 who are treated with aspirin.

The limitations of our study include its observational design and modest sample size, which limits generalizability and the ability to completely adjust for confounding. At a minimum, 10-20 subjects should be included per independent variable in a multivariable regression model.[39] Our Cox-proportional hazard model consisted of 187 mechanically ventilated patients and 9 independent variables. This meets the minimum sample size requirement of 10-20 subjects per included variable, but is far from the ideal size of 40 subjects per variable, which is necessary to achieve parsimony.[39] However, the confounders that we did include are very specific for their association with exposure and outcome.[28] Additionally, patients in the aspirin group may have received different medical care due to their increased comorbidities, leading to treatment biases. Also, we did not record the presence of other medications that are associated with hypercoagulability such as oral contraceptives and hormone replacement therapy, and differences in the use of these drugs may have confounded our results. Imaging for the detection of thrombotic events was at the discretion of the treating clinician, which may have introduced additional bias and skewed the reporting of thrombotic events. Lastly, inflammatory markers were not measured universally in all patients, which may have skewed our results.

In summary, our analysis suggests that aspirin use may have beneficial effects in patients with COVID-19. Mechanistically, these findings are plausible given aspirin's irreversible anti-platelet effect and the frequent hypercoagulability observed in COVID-19 patients. The results of our study are intriguing, especially because aspirin has been thoroughly studied in chronic cardiovascular disease, has a well-described safety profile, and is readily available throughout the world. The preliminary, hypothesis-generating nature of our study provides the basis for a larger study, which will be needed to confirm our findings and assess the extent to which the relationships observed in our study are causal. Until a randomized controlled trial of aspirin is performed, it is imperative to exercise cautious optimism and deliberately balance aspirin's known risks against its potential benefits in patients afflicted by COVID-19.

References

1. World Health Organization. Coronavirus disease (COVID-19) outbreak. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Published 2020. Accessed 06-Aug, 2020.
2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA.* 2020.
3. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-1720.
4. Klok FA, Kruip M, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res.* 2020;191:148-150.
5. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(6):1421-1424.
6. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost.* 2020.
7. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. *Thromb Haemost.* 2020.
8. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis Shutdown Correlates to Thromboembolic Events in Severe COVID-19 Infection. *J Am Coll Surg.* 2020.
9. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost.* 2020.

10. Rapkiewicz AV, Mai X, Carsons SE, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: A case series. *EClinicalMedicine.* 2020 (EPub ahead of print).

11. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med.* 2020.

12. Paranjpe I, Fuster V, Lala A, et al. Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19. *J Am Coll Cardiol.* 2020.

13. Guirguis-Blake JM, Evans CV, Senger CA, O'Connor EA, Whitlock EP. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2016;164(12):804-813.

14. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis. *JAMA.* 2019;321(3):277-287.

15. McNeil JJ, Wolfe R, Woods RL, et al. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *N Engl J Med.* 2018;379(16):1509-1518.

16. Boyle AJ, Di Gangi S, Hamid UI, et al. Aspirin therapy in patients with acute respiratory distress syndrome (ARDS) is associated with reduced intensive care unit mortality: a prospective analysis. *Crit Care.* 2015;19:109.

17. Chen W, Janz DR, Bastarache JA, et al. Prehospital aspirin use is associated with reduced risk of acute respiratory distress syndrome in critically ill patients: a propensity-adjusted analysis. *Crit Care Med.* 2015;43(4):801-807.

18. Erlich JM, Talmor DS, Cartin-Ceba R, Gajic O, Kor DJ. Prehospitalization antiplatelet therapy is associated with a reduced incidence of acute lung injury: a population-based cohort study. *Chest.* 2011;139(2):289-295.

19. Kor DJ, Carter RE, Park PK, et al. Effect of Aspirin on Development of ARDS in At-Risk Patients Presenting to the Emergency Department: The LIPS-A Randomized Clinical Trial. *JAMA.* 2016;315(22):2406-2414.

20. Kor DJ, Erlich J, Gong MN, et al. Association of prehospitalization aspirin therapy and acute lung injury: results of a multicenter international observational study of at-risk patients. *Crit Care Med.* 2011;39(11):2393-2400.

21. Panka BA, de Grooth HJ, Spoelstra-de Man AM, Looney MR, Tuinman PR. Prevention or Treatment of Ards With Aspirin: A Review of Preclinical Models and Meta-Analysis of Clinical Studies. *Shock.* 2017;47(1):13-21.

22. Bowman L, Mafham M, Stevens W, et al. ASCEND: A Study of Cardiovascular Events iN Diabetes: Characteristics of a randomized trial of aspirin and of omega-3 fatty acid supplementation in 15,480 people with diabetes. *Am Heart J.* 2018;198:135-144.

23. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2018;392(10152):1036-1046.

24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.

25. Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e89S-e119S.

26. VanderWeele TJ, Shpitser I. On the definition of a confounder. *Ann Stat.* 2013;41(1):196-220.

27. VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol.* 2019;34(3):211-219.

28. Zhou F., Yu T., Du R., et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet.* 2020.

29. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med.* 2017;167(4):268-274.

30. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020.

31. Warner TD, Nylander S, Whatling C. Anti-platelet therapy: cyclo-oxygenase inhibition and the use of aspirin with particular regard to dual anti-platelet therapy. *Br J Clin Pharmacol.* 2011;72(4):619-633.

32. Ikonomidis I, Andreotti F, Economou E, Stefanadis C, Toutouzas P, Nihoyannopoulos P. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation.* 1999;100(8):793-798.

33. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020;395(10229):1033-1034.

34. Bjornsson TD, Schneider DE, Berger H, Jr. Aspirin acetylates fibrinogen and enhances fibrinolysis. Fibrinolytic effect is independent of changes in plasminogen activator levels. *J Pharmacol Exp Ther.* 1989;250(1):154-161.

35. Poissy J, Goutay J, Caplan M, et al. Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. *Circulation.* 2020;142(2):184-186.

36. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* 2020;395(10234):1417-1418.

37. Trzeciak S, Dellinger RP, Parrillo JE, et al. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. *Ann Emerg Med.* 2007;49(1):88-98, 98 e81-82.

38. Arnold RC, Parrillo JE, Phillip Dellinger R, et al. Point-of-care assessment of microvascular blood flow in critically ill patients. *Intensive Care Med.* 2009;35(10):1761-1766.

39. Vetter TR, Schober P. Regression: The Apple Does Not Fall Far From the Tree. *Anesth Analg.* 2018;127(1):277-283.

Figure Legend

Figure 1. Forest plot of adjusted hazard ratios with aspirin use. 95% confidence intervals for adjusted hazard ratios are plotted.

Abbreviations: ICU = intensive care unit, HR = hazard ratio, CI = confidence interval

Figure 2. Survival function for in-hospital mortality. Patients are stratified by aspirin use. Patients discharged within the study period are right censored. Aspirin use was associated with a decreased hazard for in-hospital mortality (adjusted HR = 0.53, 95% CI 0.31-0.90, p=0.02).

Abbreviations: HR = hazard ratio CI = confidence interval

Table 1: Demographic Characteristics at Admission by Aspirin Use

Variable	No Aspirin (N=314)	Aspirin (N=98)	p*
Demographics			
Age, years	52 (37-65)	61 (55-72)	<0.001
Male	183 (58.3)	61 (62.2)	0.49
BMI (kg/m^2)	30.6 (26.5-35.9)	28.4 (25.5-33.6)	0.16
Race			0.05
African American	172 (54.8)	54 (55.1)	
Asian	10 (3.2)	7 (7.1)	
Caucasian	66 (21)	26 (26.5)	
Hispanic/Latino	66 (21)	11 (11.2)	
Other	0 (0.0)	0 (0.0)	
Comorbidities and Medications			
Hypertension	165 (52.5)	77 (78.6)	<0.001
Diabetes mellitus	91 (29)	54 (55.1)	<0.001
Coronary artery disease	18 (5.7)	34 (34.7)	<0.001
Renal disease	39 (12.4)	31 (31.6)	<0.001
Liver disease	21 (6.7)	13 (13.3)	0.04
Home beta-blocker	53 (16.9)	34 (34.7)	<0.001
Aspirin within 7 days of admission	0 (0)	74 (75.5)	
Dose, mg	0 (0-0)	81 (81-81)	
In-hospital aspirin	0 (0)	85 (86.7)	
Dose, mg	0 (0-0)	81 (81-81)	
Days from admission to initiation	0 (0-0)	0 (0-1)	
Duration of therapy, days	0 (0-0)	6 (3-12)	
Admission Vital Signs			
Systolic BP, mmHg	126 (113-142)	130 (115-150)	0.14
Diastolic BP, mmHg	73 (62-85)	74 (62-84)	0.70
HR, bpm	92 (81-106)	87 (77-102)	0.04
RR	20 (18-24)	20 (18-25)	0.89
SpO_2, %	96 (94-98)	97 (94-99)	0.10
Temperature, °C	37.2 (36.8-37.9)	37.1 (36.7-37.7)	0.53
Clinical Prediction Scores			
Hospital admission qSOFA	1 (0-1)	1 (0-1)	0.28
ICU admission qSOFA	2 (1-2)	2 (1-2)	0.98
ICU admission SOFA score	7 (3-9)	6 (3-9)	0.56
ICU admission APACHE II score	15 (10-21)	18 (14-25)	0.03
Admission Oxygen Support			
Oxygen Device			0.005
Room air	142 (45.2)	52 (53.1)	
Standard nasal cannula	72 (22.9)	32 (32.7)	
High flow nasal cannula	24 (7.6)	4 (4.1)	
Non-rebreather mask	19 (6.1)	3 (3.1)	
CPAP	0 (0.0)	0 (0.0)	
BiPap	0 (0.0)	1 (1.0)	
Endotracheal Tube	57 (18.2)	6 (6.1)	

Initial Laboratory Values			
WBC, K/μL	7.1 (5.3-10.8)	7.5 (5.3-10)	0.21
Lymphocytes, K/μL	1.1 (0.8-1.7)	1.1 (0.7-1.7)	0.44
Hemoglobin, g/dL	12.7 (11.3-14.1)	12.3 (10.1-13.5)	0.01
Platelets, K/μL	209 (159-286)	191 (137-267)	0.17
INR	1.1 (1-1.2)	1.1 (1-1.3)	0.90
PT, s	14 (13-16)	14 (13-15)	0.73
PTT, s	31 (28-36)	31 (28-36)	0.07
Ferritin, ng/mL	457 (178-1047)	398 (150-1078)	0.76
Interleukin-6, pg/mL	30.3 (7.1-159)	23.1 (5-84)	0.48
C-reactive protein, mg/L	15 (5-35)	6 (3-19)	0.62
D-dimer, ng/mL	1370 (700-3480)	1340 (890-3180)	0.94
Troponin, ng/mL	0.02 (0.01-0.04)	0.02 (0.02-0.13)	0.72
Fibrinogen, ng/mL	635 (448-763)	524 (461-630)	0.009
Lactate, mmol/L	1.7 (1.3-2.5)	1.7 (1.1-2.9)	0.05
Receipt of Other Therapeutics			
Azithromycin	143 (45.5)	40 (40.8)	0.41
Convalescent Plasma	22 (7)	8 (8.2)	0.70
Dexamethasone	18 (6.7)	3 (3.7)	0.32
Therapeutic Heparin	77 (24.5)	27 (27.6)	0.55
Hydroxychloroquine	101 (32.2)	28 (28.6)	0.50
Remdesivir	37 (11.8)	12 (12.2)	0.90
Tocilizumab	35 (11.1)	10 (10.2)	0.79
Outcomes			
Major bleeding	24 (7.6)	6 (6.1)	0.61
Overt thrombosis	28 (8.9)	8 (8.2)	0.82
Hospital LOS, days	8 (3-19)	9 (5-17)	0.91
Mechanical ventilation	152 (48.4)	35 (35.7)	0.03
ICU admission	160 (51.0)	38 (38.8)	0.04
ICU LOS, days	13 (6-23)	17 (7-29)	0.25
In-hospital mortality	73 (23.2)	26 (26.5)	0.51

* Categorical variables are reported as number (percent). Continuous variables are represented as median (interquartile range). Chi-squared test for categorical variables, Mann-Whitney U test for continuous variables, pairwise comparison between aspirin and non-aspirin group. Not all inflammatory marker data available for all patients (Ferritin, 357/412 patients; IL-6, 148/412; C-reactive protein, 353/412; D-dimer, 355/412; Fibrinogen, 214/412).

Abbreviations: BMI = body mass index, BP = blood pressure, HR = heart rate, bpm = beats per minute, SpO2 = peripheral capillary oxygen saturation, WBC = white blood cell, INR = international normalized ratio, PT = prothrombin time, PTT = partial thromboplastin time, qSOFA = quick sequential organ failure assessment, SOFA = sequential organ failure assessment, APACHE = Acute Physiology And Chronic Health Evaluation, ICU = intensive care unit, LPM = liters per minute, RBC = red blood cell, GI = gastrointestinal.

Table 2: Cox proportional hazards model

Variable	B	Adjusted HR	P
Mechanical Ventilation			
Age (per year)	0.01	1.01 (1.00-1.03)	0.02
BMI (per kg/m^2)	0.02	1.02 (1.01-1.04)	0.001
Ethnicity			<0.001
African American	-0.34	0.71 (0.48-1.06)	0.10
Asian	0.34	1.41 (0.65-3.06)	0.38
Hispanic/Latino	0.57	1.77 (1.11-2.85)	0.02
HTN	0.21	1.23 (0.82-1.83)	0.31
DM	0.14	1.14 (0.80-1.65)	0.47
CAD	0.19	1.21 (0.72-2.02)	0.47
Home Beta Blocker	-0.33	0.72 (0.45-1.14)	0.16
Renal Disease	-0.30	0.74 (0.45-1.21)	0.23
Aspirin Use	-0.58	0.56 (0.37-0.85)	0.007
ICU Admission			
Age (per year)	0.01	1.01 (1.00-1.02)	0.07
Gender	-0.35	0.70 (0.52-0.95)	0.02
BMI (per kg/m^2)	0.02	1.02 (1.01-1.03)	0.002
Ethnicity			
African American	-0.35	0.71 (0.48-1.03)	0.07
Asian	0.03	1.03 (0.48-2.22)	0.94
Hispanic/Latino	0.48	1.62 (1.06-2.49)	0.03
HTN	0.16	1.17 (0.82-1.68)	0.39
DM	0.30	1.34 (0.97-1.87)	0.08
CAD	0.02	1.02 (0.62-1.66)	0.95
Renal Disease	-0.45	0.64 (0.40-1.01)	0.06
Liver Disease	-0.50	0.6 (0.32-1.13)	0.11
Aspirin Use	-0.57	0.57 (0.38-0.85)	0.005
In-Hospital Mortality			
Age (per year)	0.04	1.04 (1.02-1.06)	0.000
Gender	-0.41	0.66 (0.42-1.05)	0.08
BMI (per kg/m^2)	0.02	1.02 (1.01-1.04)	0.004
Ethnicity			0.02
African American	0.73	2.07 (1.13-3.81)	0.02
Asian	1.44	4.24 (1.62-11.08)	0.003
Hispanic/Latino	0.79	2.2 (1.07-4.54)	0.03
HTN	-0.18	0.84 (0.46-1.53)	0.57
DM	0.23	1.26 (0.80-20)	0.32
CAD	0.65	1.91 (1.06-3.42)	0.03
Home Beta Blocker	0.73	2.07 (1.22-3.52)	0.007
Renal Disease	0.44	1.55 (0.90-2.66)	0.12
Aspirin Use	-0.64	0.53 (0.31-0.90)	0.02

Cox Regression analyses performed to examine the effect of aspirin use on mechanical ventilation, ICU admission, and in-hospital mortality after controlling for demographics and co-morbidities. For ethnicity, the group are compared to the reference category of Caucasian. For gender, the group is compared to the reference category of male. Adjusted HRs are reported with 95% confidence intervals. Patients with a negative time to event (i.e. mechanical ventilation occurred prior to hospital admission) were removed from the analysis for that particular outcome. After cases with negative time were removed, there were 385, 409, and 410 cases in the Cox proportional hazards models for mechanical ventilation, ICU admission, and in-hospital mortality, respectively.

Abbreviations: HR = hazard ratio, BMI = body mass index, HTN = hypertension, DM = diabetes mellitus, CAD = coronary artery disease.

Figure 1

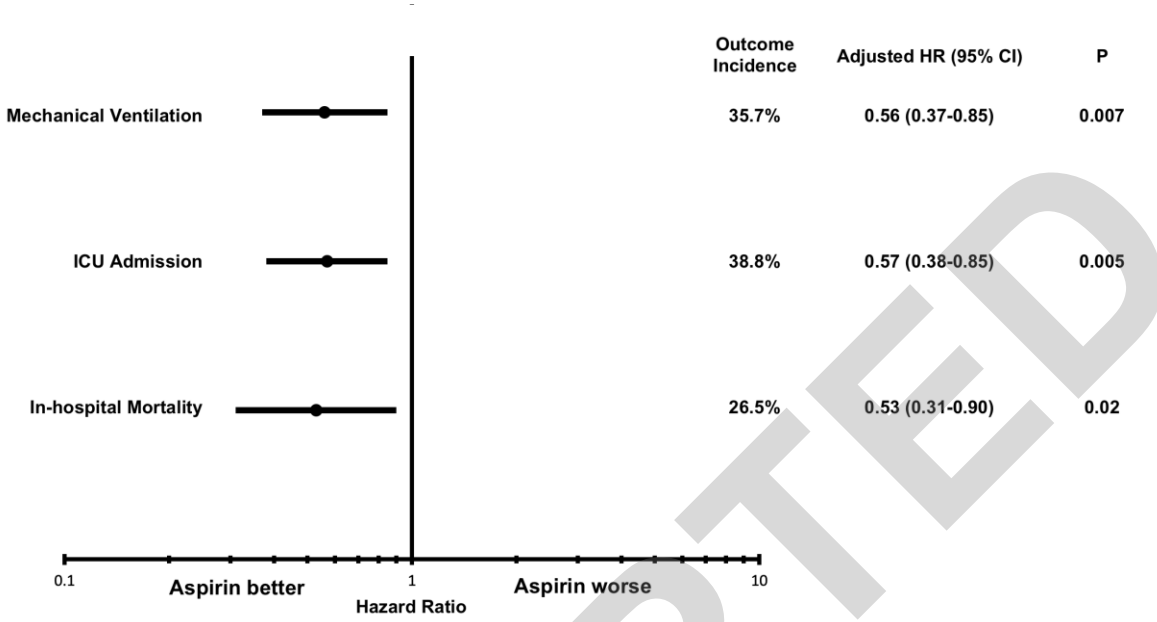

Figure 2