Received: 14 February 2021 | Revised: 17 April 2021 | Accepted: 26 April 2021

DOI: 10.1002/jmv.27053

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Decreased in-hospital mortality associated with aspirin administration in hospitalized patients due to severe COVID-19

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Abstract

Hypercoagulability and thrombosis caused by coronavirus disease 2019 (COVID-19) are related to the higher mortality rate. Because of limited data on the antiplatelet effect, we aimed to evaluate the impact of aspirin add-on therapy on the outcome of the patients hospitalized due to severe COVID-19. In this cohort study, patients with a confirmed diagnosis of severe COVID-19 admitted to Imam Hossein Medical Center, Tehran, Iran from March 2019 to July 2020 were included. Demographics and related clinical data during their hospitalization were recorded. The mortality rate of the patients was considered as the primary outcome and its association with aspirin use was assessed. Nine hundred and ninety-one patients were included, of that 336 patients (34%) received aspirin during their hospitalization and 655 ones (66%) did not. Comorbidities were more prevalent in the patients who were receiving aspirin. Results from the multivariate COX proportional model demonstrated a significant independent association between aspirin use and reduction in the risk of in-hospital mortality (0.746 [0.560–0.994], $p = 0.046$). Aspirin use in hospitalized patients with COVID-19 is associated with a significant decrease in mortality rate. Further prospective randomized controlled trials are needed to assess the efficacy and adverse effects of aspirin administration in this population.

KEYWORDS

aspirin, cohort study, COVID-19, mortality, SARS coronaviruses, thromboembolism

1 | INTRODUCTION

From the beginning of the coronavirus disease 2019 (COVID-19) pandemic, different aspects of the disease pathology have been reported. Studies showed the significant effect of COVID-19 on increasing the risk of hypercoagulability and thrombosis that are associated with increased mortality.[1–4] Although the incidence rate of thrombotic complications of COVID-19 was initially reported 25%–42%, recent studies showed a higher prevalence of up to 85% despite using pharmacological thromboprophylaxis.[1,2,5] The benefit of using the anticoagulant to decrease the risk of these complications and improve the survival of the patients with COVID-19 was confirmed by many studies[3,6,7] but data about the effect of antiplatelet agents on these complications are limited.[2,7] Aspirin has been commonly recommended for the primary prevention of atherosclerotic cardiovascular diseases in high-risk patients.[2,8] As the thromboinflammatory syndrome is one of the suggested pathophysiological hypotheses in COVID-19,[5,7] the anti-inflammatory effect of aspirin

by the inhibition of cyclooxygenase-1 should also be considered as the potential benefit in the prevention of thrombotic complications of COVID-19 in addition to its antiplatelet effect.[2,5] In this study, we aimed to evaluate the impact of aspirin add-on therapy on the outcome of the patients hospitalized due to severe COVID-19.

2 | MATERIALS AND METHODS

2.1 | Setting and study population

This retrospective cohort study was conducted at Imam Hossein Medical Center, a tertiary teaching hospital, affiliated with Shahid Beheshti University of Medical Sciences in Tehran, Iran. Patients with confirmed severe to critical COVID-19, based on reverse transcriptase-polymerase chain reaction (rt-PCR), who admitted to the hospital from March 2019 to July 2020 were evaluated.[9] The study was performed following the declaration of Helsinki and the board of ethics committee approval. Age younger than 18 years old and diagnosis of COVID-19 based on clinical criteria without positive rt-PCR results were considered as exclusion criteria. Included patients in the study were divided into two groups, patients who received aspirin at the dose of 80 mg per day from the first day of admission during their hospitalization period, and subjects who did not.

2.2 | Study data

Baseline characteristics of enrolled patients including age, sex, body mass index (BMI), past medical and habitual history, and other related clinical data were recorded. Laboratory data regarding complete blood cell count, inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ferritin were extracted from the records. Besides agents used for the treatment of COVID-19, administration of beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) during hospitalization were also recorded.

All patients in both groups received the standard of care in the intensive care unit including oxygen supplementation and ventilation support, rehydration and electrolyte correction, vasoactive agents and antibiotic administration, and renal replacement support as needed. All support was provided by the attending intensive care unit specialists for all patients. Also, they received nutrition support provided by the center nutritionist to optimize their feed and nutrition plan based on their clinical status.

2.3 | Outcome

The mortality rate of patients was assessed as the primary outcome. The need for mechanical ventilation and duration of hospitalization were also considered as secondary outcomes.

2.4 | Statistical analysis

All patients were stratified based on their recorded data on aspirin use during their hospitalization. Quantitative data were analyzed for nonparametric distribution by the Kolmogorov–Smirnov test. Variables with parametric distribution were reported by means ± standard deviation and nonparametric distributed variables by median (interquartile range [IQR]). Data description for qualitative variables conducted using frequency (percentage). Independent *t-test* or Mann–Whitney test considered for bivariable analysis of parametric and nonparametric continuous variables, respectively. χ^2 test considered for analysis of categorical variables. The *p*-value of less than 0.05 was considered significant.

COX proportional hazard regression model was performed for the assessment of survival. The crude analysis of the association of variables and survival for the selection of predictors performed by univariable analysis. The selection of the best predictors was based on a *p*-value of less than 0.2 in univariable analysis. A multivariable stepwise COX regression model consisting of the selected variables was performed to assess the effect of aspirin add-on therapy on in-hospital mortality. Confounder factors selected based on previously published data on epidemiologic and clinical factors associated with death from COVID-19.[10] Adjustment of the model for two medication classes including ACEIs/ARB and beta-blockers and medications used to treat COVID-19, that is, antiviral agents and corticosteroids were considered.[11,12] Scaled Schoenfeld residual test with the significance of *p*-value of less than 0.05 is considered to assess the proportional hazard assumption in COX analysis. The proportional hazard with the 95% confidence interval was reported. A *p*-value of less than 0.05 was considered significant.

3 | RESULTS

In a duration of 5 months, 991 patients were included in the study, of that 544 patients (54.89%) were males and 447 ones (45.10%) were females. The mean age of patients was 61.640 ± 17.003 years. Baseline demographics and clinical characteristics of the patients are demonstrated in Table 1. Three hundred and thirty-six patients (34%) received aspirin during their hospitalization whereas 655 (66%) did not. Of those who received aspirin, 202 patients (60%) were taking the medication before hospital admission, and aspirin was initiated for the rest of them on the first day of hospital admission. Patients received aspirin during their hospitalization period for the median duration of 7 days. Regarding demographics, patients who received aspirin were older ($p < 0.001$) but no significant differences were observed in gender distribution and obesity between the two groups. We also did not detect any significant differences in initial vital signs between the two groups except for systolic blood pressure which was significantly higher in the group receiving aspirin ($p = 0.011$). Hypertension, diabetes, chronic kidney disease, and coronary artery disease were more prevalent in patients who received aspirin ($p < 0.001$), but there was no significant difference

TABLE 1 Patient demographics and related clinical and laboratory findings

Characteristics	Total (n = 991)	Received aspirin (n = 336)	Not-received aspirin (n = 655)	p value
Age (years)	61.64 ± 17.003	65.75 ± 14.33	58.50 ± 17.41	<0.001
Sex				
Male (%)	544 (54.89)	189 (56)	355 (54)	0.539
Female (%)	447 (45.11)	147 (44)	300 (46)	
Body mass index (kg/m^2)	27.051 ± 4.854	27.13 ± 5.13	27.01 ± 4.71	0.717
Vital signs				
Systolic blood pressure (mmHg)	117.59 ± 20.71	120.04 ± 19.04	116.3 ± 21.43	0.011
Diastolic blood pressure (mmHg)	74.69 ± 27.19	73.28 ± 10.46	77.38 ± 43.96	0.112
Pulse rate (beats/min)	89.55 ± 15.71	89.25 ± 17.01	89.7 ± 14.98	0.685
Respiratory rate (breath/min)	20.64 ± 7.92	20.3 ± 6/17	20.82 ± 8.7	0.355
O_2 saturation (%)	88.29 ± 7.82	88.48 ± 6.84	88.19 ± 8.3	0.598
Comorbidities				
Hypertension (%)	407 (41.07)	210 (62.5)	197 (30)	<0.001
Diabetes (%)	303 (30.58)	160 (47.61)	143 (21.83)	<0.001
Coronary artery disease (%)	194 (19.58)	137 (40.77)	57 (8.7)	<0.001
Chronic kidney disease (%)	102 (10.29)	40 (11.9)	23 (3.51)	<0.001
Malignancy (%)	42 (4.24)	9 (2.67)	33 (5.03)	0.081
COPD/Asthma (%)	87 (8.78)	34 (10.11)	39 (5.95)	0.114
Baseline laboratory data				
WBC (cell/μl)	6.90 (4.63)	8(3.62)	7.95(6.30)	0.572
Lymphocyte (cell/μl)	821.75 (1588.10)	886.90 (1578.55)	780.00(1587.20)	0.054
Hemoglobin (g/dl)	12.41 ± 2.08	12.23 ± 2.21	12.49 ± 2.00	0.068
Platelet (×10^3 cells/μl)	199.35 ± 92.22	194.44 ± 88.66	201.91 ± 93.99	0.231
INR	1.20 ± 0.48	1.24 ± 0.55	1.17 ± 0.43	0.091
PT	13.09 ± 5.09	13.47 ± 5.62	12.85 ± 4.72	0.116
PTT	28.25 ± 12.79	28.67 ± 14.8	27.99 ± 11.45	0.475
Lactate dehydrogenase	645.00 (403.00)	653.00 (421.25)	647.00 (446.00)	0.253
Ferritin	621.30 (964.00)	609.65 (1169.33)	637.05(737.13)	0.937
C-reactive protein	54.00 (53.10)	50.50 (57.30)	59.60 (44.53)	0.065
Erythrocyte sedimentation rate	52.74 ± 28.41	48.88 ± 27.25	62.98 ± 25.59	0.043
Creatine phosphokinase	130.00 (211.00)	124.00 (148.75)	110.50 (269.75)	0.533
Serum creatinine	1.40 (1.20)	1.70 (1.00)	1.20 (1.05)	<0.001
Serum urea	50.00 (45.00)	66.30 (58.28)	41.50 (35.30)	<0.001
Procalcitonin	0.73 (1.85)	0.87 (2.46)	0.77 (1.55)	0.616

Characteristics	Total (n = 991)	Received aspirin (n = 336)	Not-received aspirin (n = 655)	p value
D-dimer	799.20 (2434.00)	1171.00 (2200.25)	715.800 (2529.00)	0.648
Aspartate aminotransferase	26.00 (27.00)	36.20 (22.50)	33.00 (34.75)	0.107
Alanine aminotransferase	37.00 (29.50)	21.60 (29.25)	26.00 (24.35)	0.203
Medication used to treat COVID-19				
Hydroxychloroquine	553 (55.80)	174 (51.78)	379 (57.86)	0.068
Sofosbuvir	24 (2.42)	19 (5.65)	5 (0.76)	0.171
Lopinavir/ritonavir	557 (56.21)	180 (53.57)	377 (57.55)	0.231
Corticosteroid	287 (28.96)	101 (30.05)	186 (28.39)	0.585
Interferon Beta 1a	372 (37.54)	133 (39.58)	239 (36.48)	0.341
Remdesivir	46 (4.64)	18 (5.35)	28 (4.27)	0.443
Favipiravir	40 (4.04)	18 (5.35)	22 (3.35)	0.130

Abbreviations: COPD, chronic obtructive pulmonary disease; COVID-19, coronavirus disease 2019; INR, international normalized ratio; PT, prothrombin time; PTT, Partial thromboplastin time; WBC, white blood cells.

between the two arms of the study concerning malignancy (p = 0.081) and chronic pulmonary diseases (p = 0.114). The three most frequently reported signs and symptoms were dyspnea (63.1%), cough (53.0%), and fever (49.8%). Fever was reported in 156 (46.4%) of the patients who received aspirin and in 338 (51.6%) of them who did not (p = 0.123). Furthermore, fever was not significantly less prevalent in the patients who were receiving aspirin before hospital admission (p = 0.369). Fever was reported in 95 (47.1%) of patients who were receiving aspirin before hospitalization compared with 107 (53.0%) of patients who did not receive aspirin. Baseline laboratory data did not show any significant difference between the two groups except in ESR, serum urea, and creatinine levels (Table 1). Patients received hydroxychloroquine, lopinavir/ritonavir, corticosteroids, interferon beta 1a, remdesivir, and favipiravir for treatment of COVID-19. No significant differences were observed in the distribution of used medication between the two groups of the study.

In the comparison of the outcomes between patients who received aspirin and those who did not, the need for mechanical ventilation was in 54 (16.07%) and 90 (13.74%) patients, respectively (p = 0.324). The length of hospital stay was significantly longer in patients who received aspirin (p < 0.001) and the mortality occurred in 109 (32.4%) and 147 (22.44%) patients, respectively (p = 0.001).

Based on univariant Cox proportional regression for analysis of related variable to in-hospital mortality, aspirin use (1.021 [0.791–1.316]), age (1.033 [1.025–1.042]), gender (1.197 [0.930–1.540]), hypertension (1.534 [1.198–1.964]), coronary artery disease (1.330 [1.003–1.764]), chronic kidney disease (0.859 [0.702–1.052]), chronic respiratory diseases (1.194 [0.962–1.482]), beta-blockers (1.373 [1.052–1.793]), corticosteroid (1.204 [0.929–1.560]), lopinavir/ritonavir (1.219 [0.944–1.574]), and hydroxychloroquine (0.814 [0.634–1.044]) were collected to be assessed by the multivariate Cox regression model. Results from the stepwise multivariate Cox proportional model demonstrated that aspirin (0.753 [0.573–0.991], p = 0.043) was associated with decreased risk of in-hospital mortality. In contrast to aspirin, older age (1.035 [1.026–1.044], p < 0.001) was associated with the increased risk of in-hospital mortality. The association of different factors with mortality in the total population is represented in Table 2. In the assessment of the need for mechanical ventilation in the Cox regression model as the dependent variable, the Schoenfeld residual test for the proportionality evaluation of the model showed that the model does not fit the data (p = 0.002).

4 | DISCUSSION

In this cohort study, based on results from the bivariable analysis, the mortality and hospital length of stay were higher in the group of patients who received aspirin. By considering the higher prevalence of underlying conditions and older age in the aspirin group, it could be expected that these patients may experience a more severe course of the disease and a higher rate of mortality. By adjustment of the effect of underlying conditions and demographics, which could be related to the higher rate of mortality and severity of the disease course, the analysis revealed that aspirin has a protective effect on mortality.

Vascular and thrombotic events are relatively common in severe COVID-19. Some studies reported the association between severe COVID-19 and increased risk of endothelial damage, coagulation disorders, thromboembolic events, and severe pulmonary parenchymal

TABLE 2 Association of factors with patients outcome in Cox proportional hazard regression model

Variable	Crude HR*, 95% CI	*p* value	Adjusted HR, 95% CI	*p* value
In hospital mortality				
Age	1.033 [1.025-1.042]	<0.001	1.035 [1.026–1.044]	<0.001
Sex	1.197 [0.930-1.540]	0.162		
BMI > 30	0.999 [0.742-1.344]	0.996		
Smoking	0.931 [0.666-1.302]	0.679		
HTN	1.534 [1.198-1.964]	0.001		
DM	0.981 [0.754-1.277]	0.890		
CKD	0.859 [0.702-1.052]	0.143		
Cancer	1.370 [0.783-2.395]	0.269		
Respiratory disorder	1.194 [0.962-1.482]	0.107		
Immunosuppressive disorder	1.204 [0.674-2.152]	0.530		
CAD	1.330 [1.003-1.764]	0.047		
ACEi or ARB	1.006 [0.808-1.407]	0.647		
Beta blocker	1.373 [1.051-1.793]	0.020	1.273 [0.953–1.701]	0.102
Remdesivir	0.814 [0.455-1.455]	0.489		
Favipiravir	0.739 [0.429-1.272]	0.276		
Lopinavir/ritonavir	1.219 [0.944-1.574]	0.128	1.313 [1.015–1.698]	0.038
Hydroxychloroquine	0.814 [0.634-1.044]	0.106	0.805 [0.625–1.032]	0.087
Corticosteroid	1.204 [0.929-1.560]	0.159		
Interferon	1.149 [0.895-1.475]	0.273		
Heparin/Enoxaparin	0.832 [0.607-1.139]	0.251		
Aspirin	1.021 [0.791-1.316]	0.873	0.753 [0.573–0.991]	0.043

Note: The model was fitted based on the Schoenfeld residual test for the evaluation of proportional hazard assumption with $p = 0.267$.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension.
*Hazard ratio.

damage due to the conformation of micro thrombosis,[13,14] and the autopsy showed megakaryocytes platelet-rich thrombi in the heart, lung, and kidneys of these patients.[15,16] Also, these patients are prone to dehydration and accurate examination should be performed to diagnose the possible dehydration as a possible cause of hypercoagulopathy. Therefore, inhibition of platelet aggregation by aspirin could be helpful.[14] Different mechanisms for the protective role of aspirin in COVID-19 could be proposed[2,5,8] but further studies are needed to explore this effect.

The clinical benefits of aspirin use in the COVID-19 patients have been reported in few previous studies. In a retrospective cohort study of adult patients with COVID-19, the outcome of 98 patients who received aspirin was compared with those who did not. Aspirin use was defined as administration within 24 h of hospital admission or in the 7 days before it. The median treatment duration was 6 days. Aspirin use was associated with a significant decrease in the mortality rate (HR = 0.53). Also, these patients received less mechanical ventilation (35.7% vs. 48.4%) and had a lower ICU admission rate (38.8% vs. 51%).[2] These results corroborate the findings of ours about mortality (HR = 0.746), but we could not evaluate the effect of aspirin on mechanical ventilation and the rate of ICU admission. In another retrospective cohort study on 183 patients with coronary artery disease who were hospitalized due to COVID-19 disease, 52 patients used low-dose aspirin. There was no significant difference in mortality between those who take aspirin and those who did not (21.2% vs. 22.1%, respectively, $p = 0.885$). Aspirin use also could not significantly decrease the mortality rate in critically ill patients (44% vs. 45.9%, respectively, $p = 0.872$). Although it should be noted that the nonsignificant ($p = 0.893$) association of low-dose aspirin usage and mortality reported by the authors was according to a multivariate logistic regression model that was not adjusted for all confounders.[17]

To the best of our knowledge, our study is the largest study for the evaluation of aspirin effect in outcomes of the patients with severe to critical COVID-19, based on a multivariable model. We revealed that aspirin use was associated with a decrease in mortality.

The main limitations of our study were the retrospective pattern of the study and lack of data about the probable adverse effect of aspirin, such as bleeding components.

In conclusion, based on the result of our study, in patients who received aspirin, a relevant underlying condition such as hypertension, diabetes, and coronary artery disease was more prevalent. These patients had a more severe course of the disease and a longer duration of hospitalization. By adjustment of the effect of underlying conditions and confounding factors, aspirin use in severe hospitalized COVID-19 patients is independently associated with a 25% decrease in mortality rate. So, by considering all the probable described mechanisms and the results of other studies in this regard, we recommend using aspirin during the hospital stay for all patients with the diagnosis of severe COVID-19.

ACKNOWLEDGMENT

This study was supported via the Deputy of research and technology, Shahid Beheshti University of Medical Sciences, Iran. No specific grants from funding agencies, commercial, and non-profit sectors were received.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, study supervision: Mohammad Haji Aghajani. *Statistical analysis, drafting of the manuscript, technical support, acquisition of data*: Omid Moradi. *Drafting of the manuscript, statistical analysis, critical revision of the manuscript for important intellectual content:* Hossein Amini. *Drafting of the manuscript, Technical support:* Hamed Azhdari Tehrani. *Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, technical support*: Elham Pourheidar. *Drafting of the manuscript, technical support:* Mohammad M. Rabiei. *Study concept and design, acquisition of data, drafting of the manuscript, statistical analysis, administrative, and material support, critical revision of the manuscript for important intellectual content, study supervision:* Mohammad Sistanizad.

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How to cite this article: Haji Aghajani M, Moradi O, Amini H, et al. Decreased in-hospital mortality associated with aspirin administration in hospitalized patients due to severe COVID-19. *J Med Virol*. 2021;93:5390-5395. https://doi.org/10.1002/jmv.27053