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Original Article

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Effect of Aspirin Use on the Adverse Outcomes in Patients Hospitalized for COVID-19

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Abstract

Background: Coronavirus disease 2019 (COVID-19) triggers multiple components of the immune system and causes inflammation of endothelial walls across vascular beds, resulting in respiratory failure, arterial and venous thrombosis, myocardial injury, and multi-organ failure leading to death. Early in the COVID-19 pandemic, aspirin was suggested for the treatment of symptomatic individuals, given its analgesic, antipyretic, anti-inflammatory, anti-thrombotic, and antiviral effects. This study aimed to evaluate the association of aspirin use with various clinical outcomes in patients hospitalized for COVID-19.

Methods: This was a retrospective study involving patients aged ≥ 18 years and hospitalized for COVID-19 from March 2020 to October 2020. Primary outcomes were acute cardiovascular events (ST elevation myocardial infarction (STEMI), type 1 non-ST elevation myocardial infarction (NSTEMI), acute congestive heart failure (CHF), and acute stroke) and death. Secondary outcomes were respiratory failure, need for mechanical ventilation, and acute deep vein thrombosis (DVT)/pulmonary embolism (PE).

Results: Of 376 patients hospitalized for COVID-19, 128 were taking aspirin. Significant proportions of native Americans were hospitalized for COVID-19 in both aspirin (22.7%) and non-aspirin (24.6%) groups. Between aspirin and non-aspirin groups, no significant differences were found with regard to mechanical ventilator support (21.1% vs. 15.3%, P = 0.16), acute cardiovascular events (7.8% vs. 5.2%, P = 0.32), acute DVT/PE (3.9% vs. 5.2%, P = 0.9), readmission rate (13.3% vs. 12.9%, P = 0.91) and mortality (23.4% vs. 20.2%, P = 0.5); however, the median duration of mechanical ventilation was significantly shorter (7 vs. 9 days, P = 0.04) and median length of hospitalization was significantly longer (5.5 vs. 4 days, P = 0.01) in aspirin group compared to non-aspirin group.

Conclusion: No significant differences were found in acute cardiovascular events, acute DVT/PE, mechanical ventilator support, and mortality rate between hospitalized COVID-19 patients who were taking aspirin compared to those not taking aspirin. However, larger studies are required to confirm our findings.

Keywords: Aspirin; Coronavirus disease 2019; Mortality; Hypoxia; Mechanical ventilation; ST-elevation myocardial infarction; Non-ST elevation myocardial infarction; Acute cerebrovascular accidents

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) affected over 767 million people resulting in over 6.9 million deaths globally [1]. Infection by SARS-CoV-2 triggers multiple components of the immune system, including the innate and adaptive portions as well as antibody response [2]. Based on the current scientific data, SARS-CoV-2 infection is characterized by reduced interferon (IFN)-1 and IFN-3 responses and does trigger multiple pro-inflammatory cytokines, including interleukin (IL)-1B, IL-6, tumor necrosis factor (TNF), and interleukin-1 receptor antagonist (IL-1RA) [2, 3]. These inflammatory molecules are likely to play a significant role in myocardial injury, even though the exact pathophysiology is unknown [4]. Additionally, viral inclusion bodies have been observed under electron microscopy in association with inflammation of endothelial walls across vascular beds of different organs, suggesting the significant role that anti-inflammatory drugs could play in COVID-19 patients [5]. Furthermore, several studies have demonstrated an association of COVID-19 with arterial and venous thrombosis [6-8], even on autopsy [9].

Aspirin is known for its anti-inflammatory function and is used to treat various inflammatory conditions such as Kawasaki disease, pericarditis, and rheumatic fever. The properties of aspirin: anti-inflammatory by inhibition of cyclooxygenase

(COX), anti-viral via inhibition of viral replication by inhibiting prostaglandin E2 (PGE2) in macrophages and upregulation of type 1 IFN synthesis, and its anticoagulant effects via inhibition of platelet aggregation, may collectively play an important role in inflammatory cytokine storm and coagulation dysfunction in severe and fatal cases of COVID-19 [10, 11]. Early in the COVID-19 pandemic, aspirin was suggested for the treatment of symptomatic individuals given its analgesic, antipyretic, anti-inflammatory, anti-thrombotic, and antiviral effects, thus combating essentially all aspects of this pathogen simultaneously [12]. In addition to what is known already about the cardioprotective effects of aspirin, Geiger et al described aspirin, as well as its metabolite, salicylic acid, directly reducing SARS-CoV-2 replication possibly via inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NFKB) [13]. Aspirin's immunomodulatory effects have also been demonstrated to work via inhibition of delayed rectifier potassium channels on the surface of T-lymphocytes [14]. This study aimed to evaluate the association of aspirin use with various clinical outcomes, including myocardial injury, acute deep vein thrombosis (DVT)/pulmonary embolism (PE), acute stroke, length of hospitalization, and mortality rate in patients hospitalized for COVID-19.

Materials and Methods

This was an observational retrospective study conducted from March 2020 to October 2020 after obtaining approval from the Institutional Review Board (IRB) at the University of North Carolina (UNC) Health Southeastern Hospital. This study was conducted in compliance with the institution's ethical standards on human subjects, and informed consent was not required. All patients who were aged ≥ 18 years and hospitalized for COVID-19 were included in the study. Data were collected and de-identified by chart review. The variables of interest included patient demographics, comorbid conditions (diabetes mellitus, hypertension, coronary artery disease (CAD), hyperlipidemia, atrial fibrillation, history of DVT or PE, congestive heart failure (CHF), chronic lung disease (CLD), chronic kidney disease (CKD)), home medications, inflammatory markers (D-dimer, lactate dehydrogenase (LDH), ferritin, procalcitonin), chest X-ray findings, inpatient medications, hypoxia (SpO_2 < 94%), use of mechanical ventilation, acute medical problems (ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) type 1, acute CHF, acute cerebrovascular accidents (CVA), acute DVT/PE, acute kidney injury (AKI)), length of hospitalization, readmission, and death.

Primary outcomes were acute cardiovascular events (STEMI, NSTEMI type 1, acute CHF, acute stroke) and death in patients who were taking aspirin compared to those who were not taking them. Secondary outcomes were hypoxia, defined as SpO_2 < 94%, need for and length of mechanical ventilation, acute DVT/PE, and readmission rate.

Frequencies/percentages were generated for categorical variables to estimate the rate/proportions of the variables of interest. For continuous variables, measures of central tendency such as mean (or median, as necessary) and dispersion, namely standard deviation (or the range, as appropriate), were computed. Group differences between those taking aspirin vs. those not taking aspirin were explored using Chi-square tests or independent samples *t*-tests depending on the nature of the outcome of interest - categorical or continuous, respectively. Where appropriate, a Kaplan-Meier (K-M) analysis was conducted. Further, multivariable logistic regression analysis was conducted to account for any confounding factors in the association between aspirin use and the outcomes of interest. All statistical tests were considered significant wherever $P \leq 0.05$.

Results

Of 376 patients hospitalized for COVID-19 from March 2020 to October 2020, 128 patients were taking aspirin, most of which were females in both aspirin (52.3%) and non-aspirin 59.3% groups (Table 1). The mean age of patients was 66.8 and 59.8 years in the aspirin and non-aspirin groups, respectively. Significant proportions of native Americans were hospitalized for COVID-19 in both aspirin (22.7%) and non-aspirin (24.6%) groups (Table 1). The mean body mass index was 32.71 and 32.4 in the aspirin and non-aspirin groups, respectively (Table 1). A significantly higher proportion of patients had hypoxia in the aspirin group compared to the non-aspirin group (71.1% vs. 54.4%, P = 0.002); however, there was no significant difference in the percentage of people requiring oxygen support via nasal cannula (64.1% vs. 57.3%, P = 0.204), high flow oxygen support (35.2% vs. 28.2%, P = 0.163) and mechanical ventilator support (21.1% vs. 15.3%, P = 0.16) (Table 2). Nonetheless, the median duration of mechanical ventilation was significantly shorter in the aspirin group compared to the non-aspirin group (7 vs. 9 days, P = 0.036) (Table 2). Further, there were no significant differences between aspirin and non-aspirin groups with regard to the levels of inflammatory markers on presentation and at peak (D-dimer, P = 0.91, P = 0.24; LDH, P = 0.93, P = 0.9; ferritin, P = 0.45, P = 0.56; procalcitonin, P = 0.98, P = 0.76) (Table 2). Significantly higher proportions of patients in the aspirin group compared to the non-aspirin group had noticeable chest X-ray changes (82.8% vs. 74.2%, P = 0.06), and were treated with antibiotics (88.3% vs. 79%, P = 0.03), remdesivir (52.3% vs. 33.9%, P = 0.001) and dexamethasone (71.9% vs. 52.4%, P = 0.00) (Table 2). There were no statistically significant differences between the aspirin and the non-aspirin groups with regard to acute cardiovascular events (7.8% vs. 5.2%, P = 0.32) and acute DVT/PE (3.9% vs. 5.2%, P = 0.9); however, a significantly higher percentage of patients in the aspirin group had AKI (44.5% vs. 30.2%, P = 0.006). The median length of hospitalization was significantly longer in the aspirin group compared to the non-aspirin group (5.5 vs. 4 days, P = 0.01); this could reflect the fact that the patients on aspirin were likely sicker compared to the patients not on aspirin (Fig. 1). There was no significant difference in readmission rate (13.3% vs. 12.9%, P = 0.91) and mortality (23.4% vs. 20.2%, P = 0.5) (Table 2).

Table 1. Demographics and Other Baseline Characteristics of COVID-19 Patients Included in the Study

	On aspirin (n = 128)	Not on aspirin (n = 248)
Gender, % (n)		
Male	47.7 (61)	40.7 (101)
Female	52.3 (67)	59.3 (147)
Age (mean ± SD)	66.79 ± 12.27	59.79 ± 18.80
Race/ethnicity, % (n)		
Non-Hispanic Whites	35.2 (45)	28.2 (70)
Non-Hispanic Blacks	40.6 (52)	35.1 (87)
Native American	22.7 (29)	24.6 (61)
Others/Hispanic-Latino/Asian	1.6 (2)	12.1 (30)
BMI (mean ± SD)	32.71 ± 8.84	32.40 ± 9.78
Obesity		
Overweight (BMI 25.0 - 29.9), % (n)	26.6 (34)	27.8 (69)
Class I obesity (BMI 30 - 34.9), % (n)	28.9 (37)	19.8 (49)
Class II obesity (BMI 35 - 39.9), % (n)	13.3 (17)	10.9 (27)
Class III obesity (BMI ≥ 40), % (n)	16.4 (21)	17.3 (43)
Pre-existing/chronic medical problems, % (n)		
Diabetes mellites	63.3 (81)	41.9 (104)
Hypertension	89.8 (115)	73.8 (183)
Hyperlipidemia	70.3 (90)	48.4 (120)
Atrial fibrillation	10.9 (14)	5.6 (14)
History of DVT/PE	3.9 (5)	5.2 (13)
CAD	41.4 (53)	15.7 (39)
CHF	18.8 (24)	10.1 (25)
Chronic lung disease	28.1 (36)	15.7 (39)
CKD	21.1 (27)	21.4 (53)
On chronic dialysis	3.1 (4)	6.9 (17)
Medication prior to admission		
On antiplatelet therapy, % (n)		
Clopidogrel	0	13.3 (33)
Ticagrelor	0	1.6 (4)
Dual antiplatelet therapy	10.9 (14)	0
On anticoagulation, % (n)		
Coumadin	2.3 (3)	1.2 (3)
Apixaban	4.7 (6)	6.0 (15)
Rivaroxaban	3.1 (4)	1.2 (3)
Enoxaparin	0.8 (1)	0.8 (2)

BMI: body mass index; CAD: coronary artery disease; CHF: congestive heart failure; CKD: chronic kidney disease; COVID-19: coronavirus disease 2019; DVT: deep vein thrombosis; PE: pulmonary embolism; SD: standard deviation.

The effects of age, race, gender, aspirin use, diabetes mellitus, hypertension, CAD, and CKD on the odds of developing hypoxia, requiring mechanical ventilation, acute DVT/PE, readmission rate, and mortality were evaluated using multivariable logistic regression analysis (Tables 3-7). Non-Hispanic Whites and patients younger than 65 years old had significantly higher odds of developing hypoxia (P = 0.049, odds ratio (OR) 2.43, 95% confidence interval (CI) 1.004 - 5.86; P = 0.006, OR 1.95, 95% CI 1.21 - 3.14) respectively (Table 3). Furthermore, the odds of developing acute DVT/PE were significantly higher in male patients (P = 0.011, OR 7.76, 95% CI 1.61 - 37.51) and lower in patients with CKD

Table 2. Comparative Analysis of Variables of Interest Between COVID-19 Patients on Aspirin and Those Not on Aspirin

	On aspirin (n = 128)	Not on aspirin (n = 248)	P
Hypoxia (SpO_2 < 94%), % (n)	71.1 (91)	54.4 (135)	0.002
O_2 support, % (n)			
On nasal cannula O_2 support	64.1 (82)	57.3 (142)	0.204
On high flow oxygen (≥ 6 L/min)	35.2 (45)	28.2 (70)	0.163
On mechanical ventilation, % (n)	21.1 (27)	15.3 (38)	0.159
Duration of mechanical ventilation (days) (median (IQR))	7 (7)	9 (11)	0.036
Inflammatory markers			
D-dimer			
On presentation (median (IQR))	0.990 (1.71)	1.12 (1.415)	0.905
Peak (median (IQR))	1.63 (3.458)	1.32 (1.752)	0.241
LDH			
On presentation (mean ± SD)	300.57 (168.05)	315.89 (244.78)	0.930
Peak (mean ± SD)	331.33 (150.22)	382.15 (379.18)	0.886
Ferritin			
On presentation (median (IQR))	490.6 (666.95)	581.6 (1,265.1)	0.450
Peak (median (IQR))	649.1 (900.73)	818.4 (1,715.0)	0.561
Procalcitonin			
On presentation (median (IQR))	0.505 (0.355)	0.74 (0.768)	0.976
Peak (median (IQR))	0.83 (0.99)	0.90 (2.515)	0.764
Positive chest X-ray findings, % (n)	82.8 (106)	74.2 (184)	0.060
Inpatient medications			
Received therapeutic enoxaparin	35.9 (46)	29.8 (74)	0.230
Received antibiotics	88.3 (113)	79.0 (196)	0.026
Received remdesivir	52.3 (67)	33.9 (84)	0.001
Received dexamethasone	71.9 (92)	52.4 (130)	0.000
Received convalescent plasma	5.5 (7)	8.5 (21)	0.295
Acute medical problems, % (n)			
Cardiovascular events (STEMI, type 1 NSTEMI, CHF, CVA)	7.8 (10)	5.2 (13)	0.318
DVT/PE	3.9 (5)	5.2 (13)	0.575
AKI	44.5 (57)	30.2 (75)	0.006
Needed dialysis for AKI	3.9 (5)	6.9 (17)	0.242
Length of hospitalization (days) (median (IQR))	5.50 (7.75)	4.00 (6.00)	0.011
Readmissions, % (n)	13.3 (17)	12.9 (32)	0.913
Death, % (n)	23.4 (30)	20.2 (50)	0.473

AKI: acute kidney injury; CHF: congestive heart failure; COVID-19: coronavirus disease 2019; CVA: cerebrovascular accident; DVT: deep vein thrombosis; IQR: interquartile range; LDH: lactate dehydrogenase; NSTEMI: non-ST elevation myocardial infarction; PE: pulmonary embolism; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction.

(P = 0.001, OR 0.15, 95% CI 0.05 - 0.47). Moreover, patients with CKD had lower odds of readmission (P = 0.01, OR 0.4, 95% CI 0.20 - 0.8), and patients aged < 65 years had higher odds of death from COVID-19 (P ≤ 0.00, OR 2.88, 95% CI 1.61 - 5.15). Nonetheless, multivariable logistic regression did not show any association of aspirin use with hypoxia, requirement of mechanical ventilation, acute DVT/PE, readmission, and mortality rates.

Discussion

Our study did not show statistically significant associations between aspirin use and any primary or secondary outcomes, in-

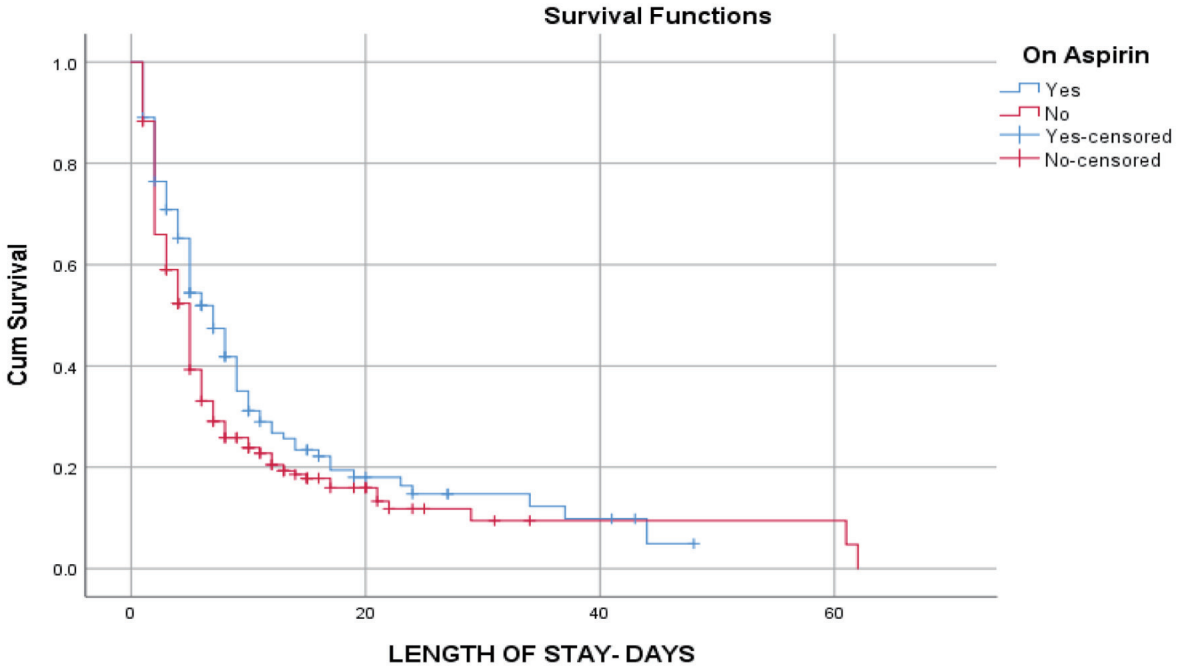

Figure 1. Kaplan-Meier curve showing cumulative survival and length of stay of patients on aspirin compared to patients not on aspirin. Patients on aspirin stayed longer in the hospital compared to those not on aspirin from approximately 5 up to 40 days.

cluding acute cardiovascular events, overall mortality, acute DVT/PE, need for mechanical ventilation, or readmission rate. Nonetheless, multiple significant observations were made outside of the primary and secondary outcomes, including a larger number of patients taking aspirin experienced respiratory failure (defined as SpO_2 < 94%) and AKI. Prehospital aspirin use has been implicated in decreasing the risk of intensive care unit (ICU) admission and mechanical ventilation without significant effect on mortality [15], and some even suggested the use of troponin and D-dimer levels to guide aspirin therapy [16]. Additionally, the duration of mechanical ventilation was significantly shorter in patients taking aspirin, which could potentially attenuate the endothelial inflammation observed in COVID-19 infection. Furthermore, our study also showed a higher proportion of both men and patients with CKD taking aspirin experienced acute DVT or PE. The exact significance of this remains unclear, although it is well-known that patients with CKD do experience higher levels of platelet dysfunction and hypercoagulability than others [17].

To this point, several studies have evaluated the association between not only aspirin but also non-steroidal anti-

Table 3. Multivariable Logistic Regression Analysis for Hypoxia in Hospitalized COVID-19 Patients

	B	SE	Wald	df	Sig. (P)	Exp(B) (OR)	95% CI for EXP(B)	
							Lower	Upper
On aspirin	-0.504	0.258	3.824	1	0.051	0.604	0.365	1.001
Gender (male)	-0.200	0.229	0.763	1	0.382	0.818	0.522	1.283
Recategorized race			3.965	3	0.265			
Non-Hispanic Whites	0.886	0.450	3.878	1	0.049	2.426	1.004	5.859
Non-Hispanic Blacks	0.663	0.449	2.183	1	0.140	1.940	0.805	4.675
Native Americans	0.752	0.470	2.562	1	0.109	2.121	0.845	5.329
Diabetes mellitus	-0.367	0.238	2.381	1	0.123	0.693	0.434	1.104
Hypertension	-0.569	0.304	3.514	1	0.061	0.566	0.312	1.026
Coronary artery disease	-0.103	0.297	0.120	1	0.729	0.903	0.505	1.614
Chronic kidney disease	-0.198	0.296	0.450	1	0.502	0.820	0.459	1.464
Age dichotomized (< 65 years)	0.668	0.243	7.547	1	0.006	1.950	1.211	3.141
Constant	-0.520	0.469	1.226	1	0.268	0.595		

CI: confidence interval; COVID-19: coronavirus disease 2019; OR: odds ratio; SE: standard error.

Table 4. Multivariable Logistic Regression Analysis for Mechanical Ventilation in COVID-19 Patients

	B	SE	Wald	df	Sig. (P)	Exp(B) (OR)	95% CI for EXP(B)	
							Lower	Upper
On aspirin	-0.361	0.308	1.378	1	0.240	0.697	0.381	1.274
Gender (male)	-0.545	0.287	3.610	1	0.057	0.580	0.331	1.017
Recategorized race			0.456	3	0.928			
Non-Hispanic Whites	0.300	0.589	0.260	1	0.610	1.350	0.425	4.286
Non-Hispanic Blacks	0.105	0.575	0.033	1	0.855	1.111	0.360	3.426
Native Americans	0.227	0.602	0.142	1	0.707	1.254	0.385	4.084
Diabetes mellitus	-0.161	0.295	0.298	1	0.585	0.851	0.477	1.518
Hypertension	-0.343	0.432	0.631	1	0.427	0.710	0.305	1.654
Coronary artery disease	0.575	0.360	2.554	1	0.110	1.777	0.878	3.596
Chronic kidney disease	-0.437	0.338	1.669	1	0.196	0.646	0.333	1.253
Age dichotomized (< 65 years)	0.514	0.305	2.843	1	0.092	1.671	0.920	3.037
Constant	1.863	0.626	8.846	1	0.003	6.440		

CI: confidence interval; COVID-19: coronavirus disease 2019; OR: odds ratio; SE: standard error.

inflammatory drugs (NSAIDs) in general, as well as various doses of anticoagulation, and morbidity and mortality associated with COVID-19 infections. One of the most notable of these studies, the RECOVERY trial, a randomized controlled trial (RCT) that assigned COVID-19 patients to receive either aspirin or usual care, demonstrated no reduction in either 28-day mortality or risk of progressing to invasive mechanical ventilation or death but did find a small increase in discharged rate within 28 days [18]. Zhao et al demonstrated with a meta-analysis involving multiple NSAIDs (including aspirin) that NSAIDs use prior to admission or diagnosis of COVID-19 was not associated with an increased rate of hospitalizations, mechanical ventilation, or length of hospital stay; however, their use was, in fact, associated with not only a decreased risk of severe infection and death but also an increase in the risk of stroke [19]. Interestingly, another meta-analysis conducted by Zong et al included 23 observational studies and four RCTs [20]. Analysis of the observational studies did demonstrate lower mortality risk in patients taking antiplatelet medication; however, this was lost after the inclusion of the four RCTs, indicating a lack of benefit in adding these medications to the repertoire of the others used to treat primary COVID-19 infection [20]. Further demonstration of the lack of mortality benefit has also been made elsewhere [21, 22]. One study even showed an increased risk of hospitalization in patients taking aspirin at the time of diagnosis [23].

Numerous studies have demonstrated a pure mortality reduction in COVID-19 patients without other deleterious effects.

Table 5. Multivariable Logistic Regression Analysis for DVT/PE in Hospitalized COVID-19 Patients

	B	SE	Wald	df	Sig. (P)	Exp(B) (OR)	95% CI for EXP(B)	
							Lower	Upper
On aspirin	-0.195	0.622	0.099	1	0.753	0.823	0.243	2.781
Gender (male)	2.049	0.804	6.501	1	0.011	7.759	1.606	37.483
Recategorized race			2.613	3	0.455			
Non-Hispanic Whites	-18.030	6374.539	0.000	1	0.998	0.000	0.000	
Non-Hispanic Blacks	-18.406	6374.539	0.000	1	0.998	0.000	0.000	
Native Americans	-17.258	6374.539	0.000	1	0.998	0.000	0.000	
Diabetes mellitus	0.731	0.562	1.693	1	0.193	2.077	0.691	6.244
Hypertension	-0.666	0.849	0.614	1	0.433	0.514	0.097	2.716
Coronary artery disease	0.452	0.689	0.431	1	0.512	1.572	0.407	6.067
Chronic kidney disease	-1.934	0.601	10.363	1	0.001	0.145	0.045	0.469
Age dichotomized (< 65 years)	-0.957	0.591	2.618	1	0.106	0.384	0.121	1.224
Constant	21.833	6374.539	0.000	1	0.997			

CI: confidence interval; COVID-19: coronavirus disease 2019; OR: odds ratio; SE: standard error.

Table 6. Multivariable Logistic Regression Analysis for Readmission in COVID-19 Patients

	B	SE	Wald	df	Sig. (P)	Exp(B) (OR)	95% CI for EXP(B)	
							Lower	Upper
On aspirin	0.057	0.357	0.025	1	0.874	1.058	0.525	2.132
Gender (male)	-0.068	0.328	0.043	1	0.836	0.934	0.491	1.777
Recategorized race			1.089	3	0.780			
Non-Hispanic Whites	0.622	0.657	0.898	1	0.343	1.863	0.514	6.745
Non-Hispanic Blacks	0.468	0.634	0.544	1	0.461	1.596	0.461	5.527
Native Americans	0.320	0.655	0.239	1	0.625	1.377	0.381	4.976
Diabetes mellitus	0.221	0.334	0.436	1	0.509	1.247	0.647	2.401
Hypertension	-0.650	0.545	1.420	1	0.233	0.522	0.179	1.520
Coronary artery disease	-0.259	0.373	0.480	1	0.488	0.772	0.371	1.605
Chronic kidney disease	-0.918	0.352	6.807	1	0.009	0.400	0.201	0.796
Age dichotomized (< 65 years)	0.337	0.353	0.908	1	0.341	1.401	0.700	2.800
Constant	2.101	0.724	8.434	1	0.004	8.175		

CI: confidence interval; COVID-19: coronavirus disease 2019; OR: odds ratio; SE: standard error.

A meta-analysis performed by Su et al, which included not only retrospective and prospective cohort studies but also four RCTs, noted that specifically, the cohort studies demonstrated mortality reduction, not the RCTs, although significance was not lost after the inclusion of the RCTs within the final analysis [24]. Another study performed by Chow et al also found that aspirin use, defined either as use within 24 h of or in the 7 days prior to hospital admission, was associated with reduced risk for mechanical ventilation, ICU admission, and in-hospital mortality [25]. Furthermore, a multicenter, retrospective study performed by Sisinni et al examined patients already using low-dose aspirin daily for 7 days prior to hospital admission for COVID-19 and found that at 30 days, less number of patients utilizing aspirin prior to admission experienced a composite of in-hospital mortality and/or need for respiratory support upgrade [26]. Similarly, multiple other studies, including meta-analyses and prospective and retrospective observational cohort studies, have demonstrated mortality reduction in COVID-19 patients taking aspirin either prior to admission or after admission [11, 27-30]. In contrast, our study did not demonstrate mortality benefit with the use of aspirin. In line with our results, multiple studies have also demonstrated no link between mortality in patients with COVID-19 and aspirin use [21, 31].

Some studies have investigated the use of not only antiplatelet agents but anticoagulants and immunomodulatory therapies as well. An interesting study by Lima-Morales et al examined the efficacy of the multidrug regimen azithromycin, montelukast, ivermectin, and aspirin in ambulatory COVID-19

Table 7. Multivariable Logistic Regression Analysis for Mortality in COVID-19 Patients

	B	SE	Wald	df	Sig. (P)	Exp(B) (OR)	95% CI for EXP(B)	
							Lower	Upper
On aspirin	-0.155	0.294	0.278	1	0.598	0.856	0.481	1.524
Gender (male)	-0.319	0.272	1.369	1	0.242	0.727	0.427	1.240
Recategorized race			2.967	3	0.397			
Non-Hispanic Whites	0.026	0.625	0.002	1	0.966	1.027	0.302	3.495
Non-Hispanic Blacks	-0.474	0.609	0.606	1	0.436	0.622	0.188	2.054
Native Americans	-0.487	0.627	0.603	1	0.437	0.615	0.180	2.099
Diabetes mellitus	0.065	0.278	0.054	1	0.816	1.067	0.618	1.841
Hypertension	0.026	0.393	0.004	1	0.947	1.026	0.475	2.216
Coronary artery disease	0.377	0.330	1.303	1	0.254	1.458	0.763	2.785
Chronic kidney disease	-0.559	0.312	3.195	1	0.074	0.572	0.310	1.055
Age dichotomized (< 65 years)	1.058	0.296	12.761	1	< 0.001	2.881	1.612	5.148
Constant	1.361	0.642	4.500	1	0.034	3.899		

CI: confidence interval; COVID-19: coronavirus disease 2019; OR: odds ratio; SE: standard error.

patients and found higher rates of recovery and lower rates of hospitalization and death at 14 days after diagnosis [32]. Undoubtedly, however, it is difficult to associate these results with any one drug. Eikelboom et al examined the use of colchicine, representative of one treatment arm, as well as the combination of aspirin and rivaroxaban, the other arm, in symptomatic COVID-19 patients and found no effect on mortality or disease progression in either group [33]. However, a significant number of patients in the aspirin/rivaroxaban group experienced bleeding events [33], further highlighting the need for new trials evaluating not only mortality reduction but also rates of adverse effects, some of which can be, without a doubt, life-threatening.

Given the amount of conflicting information regarding aspirin and other antiplatelet or anticoagulant use in COVID-19 patients existing within the literature, more trials are needed to determine if there is a true association between aspirin use and mortality associated with COVID-19 infection. Additionally, it is evident that these benefits, if and when they are determined, must be carefully weighed against the risks of these medications, such as bleeding, increased need for organ support, or even lapses in efficacy due to, for example, higher levels of thromboxanes in elderly or obese patients, driving resistance to aspirin [34]. Nonetheless, at this time, prescribing aspirin-containing medications to patients diagnosed with COVID-19, whether inside or outside of the hospital, should be a highly individualized process and should involve consideration of previous use, comorbidities, and bleeding propensity.

Strengths and limitations

It is important to note that this study's limitations include a small sample size and a lack of longer follow-up. This study was done in a community hospital setting with a rural population involving a significant number of native American, Hispanic, and African American participants, which is the greatest strength of this study.

Conclusion

Our study found no significant association between aspirin use and primary or secondary endpoints, including acute cardiovascular events, overall mortality, acute DVT/PE, need for mechanical ventilation, or readmission rate. However, existing literature about aspirin use in COVID-19 patients is highly conflicting, and future large-scale studies are needed to delineate its advantages and disadvantages clearly.

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Conflict of Interest

Authors have no conflict of interest to declare.

Informed Consent

Informed consent was not required.

Author Contributions

Poornima Vinod: writing-original draft, writing and editing, visualization, supervision, resources, project administration, methodology, investigation, data curation, and conceptualization. Vinod Krishnappa: writing-original draft, writing-review and editing, resources, investigation, data curation, and conceptualization. William Rathell: writing-original draft, writing-review and editing, resources, investigation, data curation, and conceptualization. Saira Amir: writing-review and editing, resources, investigation, data curation, and conceptualization. Subrina Sundil: writing-review and editing, resources, investigation, data curation, and conceptualization. Godwin Dogbey: statistical analysis, methodology, investigation, data curation, and conceptualization. Hiten Patel: writing-review and editing, conceptualization, and supervision. William Herzog: writing-review and editing, conceptualization, and supervision.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References

1. WHO COVID-19 dashboard. 2023. Available from: https://covid19.who.int.
2. Garcia LF. Immune response, inflammation, and the clinical spectrum of COVID-19. Front Immunol. 2020;11:1441. doi pubmed pmc
3. Declercq J, De Leeuw E, Lambrecht BN. Inflammasomes and IL-1 family cytokines in SARS-CoV-2 infection: from prognostic marker to therapeutic agent. Cytokine. 2022;157:155934. doi pubmed pmc
4. Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: possible mechanisms. Life Sci. 2020;253:117723. doi pubmed pmc
5. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417-1418. doi pubmed pmc
6. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, 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. doi pubmed pmc
7. 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. doi pubmed pmc
8. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Muller MCA, Bouman CCS, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18(8):1995-2002. doi pubmed pmc
9. Rapkiewicz AV, Mai X, Carsons SE, Pittaluga S, Kleiner DE, Berger JS, Thomas S, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: a case series. EClinicalMedicine. 2020;24:100434. doi pubmed pmc
10. Coulombe F, Jaworska J, Verway M, Tzelepis F, Massoud A, Gillard J, Wong G, et al. Targeted prostaglandin E2 inhibition enhances antiviral immunity through induction of type I interferon and apoptosis in macrophages. Immunity. 2014;40(4):554-568. doi pubmed
11. Wijaya I, Andhika R, Huang I, Purwiga A, Budiman KY. The effects of aspirin on the outcome of COVID-19: a systematic review and meta-analysis. Clin Epidemiol Glob Health. 2021;12:100883. doi pubmed pmc
12. Bianconi V, Violi F, Fallarino F, Pignatelli P, Sahebkar A, Pirro M. Is acetylsalicylic acid a safe and potentially useful choice for adult patients with COVID-19? Drugs. 2020;80(14):1383-1396. doi pubmed pmc
13. Geiger N, Konig EM, Oberwinkler H, Roll V, Diesendorf V, Fahr S, Obernolte H, et al. Acetylsalicylic acid and salicylic acid inhibit SARS-CoV-2 replication in precision-cut lung slices. Vaccines (Basel). 2022;10(10):1619. doi pubmed pmc
14. Kazama I, Senzaki M. Does immunosuppressive property of non-steroidal anti-inflammatory drugs (NSAIDs) reduce COVID-19 vaccine-induced systemic side effects? Drug Discov Ther. 2021;15(5):278-280. doi pubmed
15. Sayed Ahmed HA, Merrell E, Ismail M, Joudeh AI, Riley JB, Shawkat A, Habeb H, et al. Rationales and uncertainties for aspirin use in COVID-19: a narrative review. Fam Med Community Health. 2021;9(2):e000741. doi pubmed pmc
16. Mohamed-Hussein AAR, Aly KME, Ibrahim MAA. Should aspirin be used for prophylaxis of COVID-19-induced coagulopathy? Med Hypotheses. 2020;144:109975. doi pubmed pmc
17. Nunns GR, Moore EE, Chapman MP, Moore HB, Stettler GR, Peltz E, Burlew CC, et al. The hypercoagulability paradox of chronic kidney disease: the role of fibrinogen. Am J Surg. 2017;214(6):1215-1218. doi pubmed pmc
18. Group RC. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2022;399(10320):143-151. doi pubmed pmc
19. Zhao H, Huang S, Huang S, Liu F, Shao W, Mei K, Ma J, et al. Prevalence of NSAID use among people with COVID-19 and the association with COVID-19-related outcomes: systematic review and meta-analysis. Br J Clin Pharmacol. 2022;88(12):5113-5127. doi pubmed pmc
20. Zong X, Wang X, Liu Y, Li Z, Wang W, Wei D, Chen Z. Antiplatelet therapy for patients with COVID-19: systematic review and meta-analysis of observational studies and randomized controlled trials. Front Med (Lausanne). 2022;9:965790. doi pubmed pmc
21. Yuan S, Chen P, Li H, Chen C, Wang F, Wang DW. Mortality and pre-hospitalization use of low-dose aspirin in COVID-19 patients with coronary artery disease. J Cell Mol Med. 2021;25(2):1263-1273. doi pubmed pmc
22. Connors JM, Brooks MM, Sciurba FC, Krishnan JA, Bledsoe JR, Kindzelski A, Baucom AL, et al. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. JAMA. 2021;326(17):1703-1712. doi pubmed pmc
23. Morrison FJ, Su M, Turchin A. COVID-19 outcomes in patients taking cardioprotective medications. PLoS One. 2022;17(10):e0275787. doi pubmed pmc
24. Su W, Miao H, Guo Z, Chen Q, Huang T, Ding R. Associations between the use of aspirin or other antiplatelet drugs and all-cause mortality among patients with COVID-19: a meta-analysis. Front Pharmacol. 2022;13:989903. doi pubmed pmc
25. Chow JH, Khanna AK, Kethireddy S, Yamane D, Levine A, Jackson AM, McCurdy MT, et al. Aspirin use is associated with decreased mechanical ventilation, intensive care unit admission, and in-hospital mortality in hospitalized patients with coronavirus disease 2019. Anesth Analg. 2021;132(4):930-941. doi pubmed
26. Sisinni A, Rossi L, Battista A, Poletti E, Battista F, Battista RA, Malagoli A, et al. Pre-admission acetylsalicylic acid therapy and impact on in-hospital outcome in COVID-19 patients: the ASA-CARE study. Int J Cardiol. 2021;344:240-245. doi pubmed pmc
27. Srinivasan A, Brown J, Krishnamani PP, Cornett B, Kesavan RB, Sarva ST, Raza SA, et al. Aspirin use is associated with decreased inpatient mortality in patients with COVID-19: a meta-analysis. Am Heart J Plus. 2022;20:100191. doi pubmed pmc
28. Martha JW, Pranata R, Lim MA, Wibowo A, Akbar MR. Active prescription of low-dose aspirin during or prior to hospitalization and mortality in COVID-19: a systematic review and meta-analysis of adjusted effect estimates. Int J Infect Dis. 2021;108:6-12. doi pubmed pmc
29. Lal A, Garces JPD, Bansal V, Tekin A, Zec S, Khanna AK, Warner MA, et al. Pre-hospital aspirin use and patient outcomes in COVID-19: results from the International Viral Infection and Respiratory Illness Universal Study (VIRUS). Arch Bronconeumol. 2022;58(11):746-753. doi pubmed pmc
30. Meizlish ML, Goshua G, Liu Y, Fine R, Amin K, Chang E, DeFilippo N, et al. Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: a propensity score-matched analysis. Am J Hematol. 2021;96(4):471-479. doi pubmed pmc
31. Lund LC, Kristensen KB, Reilev M, Christensen S, Thomsen RW, Christiansen CF, Stovring H, et al. Adverse outcomes and mortality in users of non-steroidal

anti-inflammatory drugs who tested positive for SARS-CoV-2: a Danish nationwide cohort study. PLoS Med. 2020;17(9):e1003308. doi pubmed pmc
32. Lima-Morales R, Mendez-Hernandez P, Flores YN, Osorno-Romero P, Sancho-Hernandez CR, Cuecuecha-Rugerio E, Nava-Zamora A, et al. Effectiveness of a multidrug therapy consisting of ivermectin, azithromycin, montelukast, and acetylsalicylic acid to prevent hospitalization and death among ambulatory COVID-19 cases in Tlaxcala, Mexico. Int J Infect Dis. 2021;105:598-605. doi pubmed pmc
33. Eikelboom JW, Jolly SS, Belley-Cote EP, Whitlock RP, Rangarajan S, Xu L, Heenan L, et al. Colchicine and the combination of rivaroxaban and aspirin in patients hospitalised with COVID-19 (ACT): an open-label, factorial, randomised, controlled trial. Lancet Respir Med. 2022;10(12):1169-1177. doi pubmed pmc
34. Chiang KC, Gupta A. Aspirin resistance in obese and elderly patients with COVID-19? Am J Med. 2021;134(4):e297. doi pubmed pmc