A systematic review and meta-analysis on efficacy of low dose aspirin on the management of COVID-19

Manal Banaser1*, Mutaman Jarrar2,3, Ayed Alqahtani4, Abdulelah Banaser5, Waleed Albaker6

ABSTRACT
COVID-19 pandemic has increased thrombotic risk by 35%. This pandemic led to millions of deaths due to various comorbidities and organ failure. Repurposing aspirin usage to manage COVID-19 hospitalized patients is a logical approach for preventing cardiovascular disease and comorbidities that increase mortality risk. However, several earlier investigations found inconsistent outcomes. This study aims to assess primary and secondary effects in COVID-19 patients with or without aspirin. We performed a multi-database electronic search including Cochrane, Embase, Scopus, and PubMed from date of inception to November 2021 using search terms: (“Coronavirus Disease 2019” OR “COVID-19” OR “SARS-CoV-2” OR “2019-nCoV”) AND (“Acetylsalicylic acid” OR “acetylsalicylate” OR “aspirin” OR “antiplatelet”) AND (“mortality” OR “severe” OR “severity”). Eight retrospective studies met the study criteria comprising 7,171 aspirin users and 8,327 non-aspirin users in COVID-19. Aspirin administration significantly reduces mortality risk (RR: 0.51, 95% CI: 0.46-0.57, I² = 85.05, p-value <0.001, τ² = 0.028, Z-value: -11.44, p-value <0.001). Aspirin used in COVID-19 patients demonstrated reduced bleeding risk (RR: 0.80, 95 CI%: 0.34-1.9) and reduced risk for the necessity of mechanical ventilation (RR: 0.70; 95% CI: 0.54-0.90, I² = 0%, p-value: 0.41, τ² = 0%) when compared with COVID-19 patients without aspirin use. The present review found administration of a low dose of aspirin in COVID-19 patients significantly reduced mortality risk.

Keywords: Low dose aspirin, mortality, COVID-19, thrombosis, antiplatelet drug.

Introduction
Despite the international recommendations to prevent COVID_19 [1], chemical substance such as aspirin could help to reduce mortality risk in Covid-19 patients. The SARS-CoV-2, cause of the ongoing COVID-19 pandemic, has increased thrombotic risk in multiple vascular beds by 35% [2]. Di Minno et al. [3], in their meta-analysis, have demonstrated a high occurrence of thrombosis in COVID-19 patients. Thrombosis in association with COVID-19 usually causes most organ failure and death [4]. Specific laboratory findings like increased fibrin D-dimer, C-reactive protein, and fibrinogen level in COVID-19 patients have demonstrated poor outcomes [5]. Also, autopsy and clinical studies of COVID-19 patients show increased risk of venous thrombosis, ischemic stroke, and microthrombi [2]. Platelet activation may be a potential therapeutic choice in COVID-19 patients with thrombotic events. Repurposing of “non-steroidal anti-inflammatory drugs” (NSAIDs) and other medications have been employed in COVID-19 patients since the COVID-19 outbreak. However, most NSAIDS demonstrate controversial effects on COVID-19 [6]. Besides dexamethasone, aspirin reduced the occurrence of “acute respiratory distress syndrome” in severe patients without COVID-19 and improved the mortality rate [7,8]. Thrombo-inflammatory responses in COVID-19 patients cause significant complications and demonstrate a high mortality rate.
Acetylsalicylic acid (aspirin) demonstrated a varying effect, including reducing pain and fever, alleviating inflammatory response, inhibiting platelets activation and aggregation, and preventing RNA viral propagation of SARS-CoV-2 [9].

Ho et al. [10] conducted a retrospective study to repurpose anti-platelet drugs or even aspirin that failed to link the association of improvements of clinical outcomes in COVID-19 patients using antiplatelets. Only a few studies were conducted from various parts of the world to study the efficacy of aspirin uses in COVID-19 patients. Therefore, we performed a meta-analysis of eligible literature to determine the pooled outcomes of aspirin use in COVID-19 patients. This study evaluates the association of low-dose aspirin use on mortality rate and the mechanical ventilation required among COVID-19 positive patients.

Methodology

We followed “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines” [11].

Literature search

We explored Cochrane, Scopus, Embase, and PubMed databases sequentially from the date of inception to November 2021. We performed an electronic search to discover the potential articles using key search terms: (“Coronavirus Disease 2019” OR “COVID-19” OR “SARS-CoV-2” OR “2019-nCoV”) AND (“Acetylsalicylic acid” OR “acetylsalicylate” OR “Aspirin” OR “antiplatelet”) AND (“mortality” OR “severe” or “severity”). We have used Boolean terms and similar keywords to find their intersection. Also, Search keywords matching was done based on different databases. We manually reviewed references of relevant articles and abstracts of scientific papers.

Study criteria

We included only those articles that meet the following study criteria: 1) randomized and observational study; 2) patients tested positive for COVID-19; 3) On low dose aspirin therapy (i.e., 75-325 mg); 4) All gender; 5) patients admitted to hospital or ICU with “positive reverse transcriptase-polymerase chain reaction test”; and 6) cardiovascular diseases related on COVID-19 infections (hypotension, hypertension, arrhythmia, myocarditis/ carditis, sudden cardiac death, heart failure). Patients were only included in the aspirin arm if they had seven days of aspirin use before hospital admission or administration within 48 hours of hospitalization. Patients in the non-aspirin arm have never taken aspirin before or during their hospitalization. The articles were excluded if the article met the following criteria: 1) review articles, 2) no full text available, 3) editorial letter/ commentaries, 4) non-research letter, 5) animal studies, 6) case report, and 7) no reporting of a death in the interventional and control arm. Articles published in English were only searched.

Outcomes assessed

All types of mortality, including 14 days or 28/30 days, were measured as primary outcomes in the hospital setting. Secondary outcomes were assessed, including the incidence of bleeding, thrombosis, and mechanical ventilation required among the COVID patients receiving aspirin and non-aspirin.

Study selection, data extraction, and study quality assessment

Two authors evaluated each identified article individually to eliminate duplicates that did not meet the study criteria. An independent third-party reviewer resolved any discrepancies. We conducted a full-text review if the abstract of relevant articles could not demonstrate specific results. We selected eligible research studies and evaluated full-text articles based on the study criteria. We performed data extraction after full-text analysis. We designed data collection form using Microsoft word. Two authors independently extracted article details like country, study design, study period, total population, patients in aspirin and non-aspirin group, mean age, comorbidities, and adjusted mortality estimate rate. Similarly, the “Newcastle-Ottawa Scale (NOS)” assessed risk of bias of the study.

Data synthesis and statistical assessment

Comprehensive meta-analysis (CMA) software version 3 determined the pooled effect of primary and secondary outcomes obtained from eligible articles [12]. This study assesses the risk ratio derived from total events occurring from each group, hazard ratio, odds ratio, and relative risk. This analysis would determine the overall risk ratio, p-value at the level of significance, heterogeneity. If the two-tailed p-value < 0.05, the outcome is statistically significant. One study removed assessed any substantial heterogeneity level. Egger’s test and Funnel plot determined the publication bias.

Results

Literature search and characteristics of study

Our electronic literature searches using Boolean and search terms identified 1,874 unique records. Removal of duplicated articles was performed using endnote V2 [13]. Twenty-five relevant literatures were eligible for full-text inspection after the removal of duplicates. The literature screening process is summarized in the
Efficacy of low dose aspirin on the management of COVID-19

PRISMA flow [14] diagram in Figure 1. All eligible eight studies were retrospective cohort studies with 15,682 COVID-19 patients, including 7,171 aspirin users and 8,327 non-aspirin users. Out of eight studies, two in China, four in the United States, and one in Israel and Iran were conducted. Most of the studies have reported 81 mg of aspirin use. Study characteristics of all eligible research literature are summarized in Table 1.

Measure of primary outcome

Measure of association aspirin use on mortality rate of COVID-19 patients

CMA with fixed effect model determined the overall risk ratio of mortality with aspirin therapy in COVID-19 patients. The administration of aspirin reduced the risk of mortality (RR: 0.51, 95% CI: 0.46-0.57, \( F = 85.05, p\text{-value} < 0.001, r^2 = 0.028, Z\text{-value: -11.44, } p\text{-value} < 0.001 \)), as in Figure 2. The pooled RR signifies lesser mortality rates among the aspirin group than non-aspirin groups with COVID-positive. Osborne et al. [18] had a larger sample size when compared with other eligible studies that significantly affect the overall RR (as in Figures 2 and 3). The sensitivity analysis carried by one study exclusion of Osborne et al. [19] significantly reduced heterogeneity \( (I^2 = 58.13\%, p\text{-value} = 0.026) \). However, the administration of aspirin is associated with an insignificant decrease in mortality risk (RR: 0.86, 95% CI: 0.69-1.05).

Measure of secondary outcome

Association of aspirin use with thrombosis and bleeding risk

Only two studies, i.e., Chow et al. [15] and Sahai et al. [21], demonstrated the thrombosis event with diversifying results. Chow et al. [15] described insignificant thrombotic events (8.2% vs. 8.9%, \( p\text{-value} = 0.82 \)) among aspirin and non-aspirin users. The authors have reported thrombotic events as any incidence of pulmonary embolism, ST-elevation myocardial infarction, peripheral artery occlusion, ischemic stroke, and deep vein thrombosis. Remarkably, Sahai et al. [21] demonstrated an increased occurrence of thrombotic events, including thrombotic stroke (9.3% vs. 2.8%, \( p\text{-value} = 0.005 \)), myocardial infarction, and venous thrombosis in COVID-19 patients. Chow et al. [15] reported bleeding events occurring among both groups that demonstrated a comparable incidence of 6.1% in the aspirin arm and 7.6% in non-
<table>
<thead>
<tr>
<th>Reference study</th>
<th>Country</th>
<th>Study design</th>
<th>Study period</th>
<th>Total population</th>
<th>Aspirin dose (mg)</th>
<th>Mean age</th>
<th>Non-aspirin (NA)</th>
<th>Aspirin (A)</th>
<th>CAD</th>
<th>HTN</th>
<th>Diabetes NOS</th>
<th>Adjusted mortality estimate</th>
<th>Adjusted mortality estimate 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>[14] USA</td>
<td>R, O, M</td>
<td>Retrospective</td>
<td>March 2020 to July 2020</td>
<td>412</td>
<td>98</td>
<td>314</td>
<td>98</td>
<td>314</td>
<td>81</td>
<td>55</td>
<td>61 versus NA</td>
<td>HR: 0.53 (0.31-0.90)</td>
<td>35.19 8</td>
</tr>
<tr>
<td>[15] China</td>
<td>R, S</td>
<td>Observational</td>
<td>January 30, 2020 to March 30, 2020</td>
<td>232</td>
<td>28</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>100</td>
<td>60</td>
<td>54 versus 68</td>
<td>HR: 0.52 (0.34-0.81)</td>
<td>9 12.10</td>
</tr>
<tr>
<td>[16] USA</td>
<td>PSM, R, M</td>
<td>Multicentric</td>
<td>March 2020 to June 2020</td>
<td>638</td>
<td>319</td>
<td>319</td>
<td>81</td>
<td>81</td>
<td>319</td>
<td>81</td>
<td>81</td>
<td>HR: 0.52 (0.34-0.81)</td>
<td>7 26.74</td>
</tr>
<tr>
<td>[17] Israel</td>
<td>R, O, M</td>
<td>Retrospective</td>
<td>February 1 to June 30, 2020</td>
<td>662</td>
<td>73</td>
<td>589</td>
<td>81</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>80 versus 83</td>
<td>HR: 0.52 (0.34-0.81)</td>
<td>8</td>
</tr>
<tr>
<td>[18] USA</td>
<td>PSM, R, M</td>
<td>Retrospective</td>
<td>March 2020 to September 30, 2020</td>
<td>12,600</td>
<td>6,300</td>
<td>6,300</td>
<td>NR</td>
<td>58</td>
<td>60</td>
<td>60</td>
<td>58</td>
<td>OR: 0.38 (0.33-0.45)</td>
<td>8 26.74</td>
</tr>
<tr>
<td>[19] China</td>
<td>R, O, S</td>
<td>Observational</td>
<td>January 10 to March 30, 2020</td>
<td>183</td>
<td>52</td>
<td>131</td>
<td>75-150</td>
<td>NR</td>
<td>69.7</td>
<td>71.8</td>
<td>NR</td>
<td>OR: 0.94 (0.41-2.17)</td>
<td>8 21.90</td>
</tr>
<tr>
<td>[20] USA</td>
<td>PSM, R, M</td>
<td>Retrospective</td>
<td>March 13 to May 13, 2020</td>
<td>496</td>
<td>248</td>
<td>248</td>
<td>81</td>
<td>81</td>
<td>81</td>
<td>81</td>
<td>81</td>
<td>OR: 0.94 (0.51-1.61)</td>
<td>8 21.90</td>
</tr>
<tr>
<td>[21] Iran</td>
<td>R, S</td>
<td>Single centre</td>
<td>January 30 to April 5, 2020</td>
<td>459</td>
<td>53</td>
<td>406</td>
<td>low dose, unspecified</td>
<td>61.8</td>
<td>NR</td>
<td>40.30</td>
<td>64.60</td>
<td>OR: 0.38 (0.27,0.50)</td>
<td>7 25.19</td>
</tr>
</tbody>
</table>

R: Retrospective; O: Observational; M: Multicentric; S: Single centre; PSM: Propensity Score Matched; CAD: Coronary artery disease; HTN: Hypertension.
aspirin users. The aspirin used in COVID-19 patients has reduced bleeding risk (RR: 0.80, 95 CI%: 0.34-1.9).

**COVID-19 patients required mechanical ventilation with the use of aspirin**

Only two out of eight studies measured mechanical ventilation required among the COVID-19 patients receiving aspirin [15,20]. The aspirin use among COVID-19 patients demonstrated a reduced risk for the necessity of mechanical ventilation (RR: 0.70; 95% CI: 0.54-0.90, $I^2 = 0\%$, $p$-value: 0.41, $\tau^2 = 0\%$) (Figure 4).

**Assessment of publication bias and risk of bias**

All the eligible research literatures were high-quality studies, demonstrating NOS $\geq$ 7 (Table 1). CMA measured publication bias. The funnel plot was asymmetrical (Figure 5), indicating a significant level of publishing bias. The uneven distribution of samples across diverse research could be a source of bias. Osborne et al. [19] had a larger sample size across each arm, while Liu et al. [16] had a smaller sample...
Efficacy of low dose aspirin on the management of COVID-19

Also, Eggers’s test demonstrated publication bias with intercept 1.94, SE: 1.29, 95% CI: -1.22-5.10, one-tailed p-value: 0.091 and two-tailed p-value: 0.18 [23].

Discussion

This meta-analysis demonstrated that the low-dose aspirin administration in COVID-19 patients had reduced mortality risk with a low level of certainty. The mortality risk in COVID-19 patients using aspirin is almost half compared to patients not receiving aspirin. However, the outcome of our study was in contrast with the finding of the meta-analysis by Salah et al. [24], who demonstrated no association among aspirin administration in COVID-19 positive patients and mortality. The significant difference between our meta-analysis and the previous study is the number of included articles and the modified statistical approach. Using an adjusted risk ratio in a retrospective study is significant in changing multivariable as a confounder and altering the overall outcome. We used adjusted RR estimation based on each study. If RR could not be determined from the study, we selected event number and total population across each study.

Our primary objective is to minimize the death rate from the COVID-19 pandemic. Several investigations have revealed thrombosis as a primary cause of death in severe COVID-19 positive individuals [2,3]. Thus, the “Indian Council of Medical Research and the National Institute of Health” advised using of anticoagulants in severe COVID-19 cases [25,26].

Aspirin is an antithrombotic and antiplatelet drug. Aspirin prevents thrombosis and thrombo-inflammation by inhibiting platelets aggregation with Cyclooxygenase inhibitor (COX) and thromboxane A2. Aspirin is mostly used as prophylaxis for thrombosis in various cerebrovascular and cardiovascular diseases [27,28].

Aspirin act as an analgesic, antiviral, anti-inflammatory, antipyretic, and immunomodulator. Aspirin inhibits
COX-1 ad thromboxane A2 at 75-81 mg low dose. Mohamed-Hussein et al. [29] described that aspirin blocks prostaglandin E2 in macrophages and limits viral replication. Aspirin also inhibits the “K-light chain enhancer of the activated B-cell pathway”, uncoupling oxidative phosphorylation with inducible nitric oxide, and production of cytomegaly virus-induced reactive oxygen species and advancement of mitochondrial permeability. Aspirin cause hemoglobin degradation, contributing to pro-inflammatory mediators that result in lower RNA synthesis as observed in human CoV-229E and coronavirus [5,29].

Platelet neutrophil aggregation and platelet activation cause thrombus and lead to lung damage. Early aspirin therapy restores the pulmonary functioning at endothelial cells [15,30]. Poor prognosis usually occurs due to increased coagulation and inflammatory laboratory value with more severe COVID-19 infection. These elevations cause myocardial injuries related to morbidity [28,31]. Aspirin administration provides beneficial outcomes and improves severe complications, including thrombosis, sepsis, multi-organ dysfunction, and death [28].

Limitations

All the eligible studies were retrospective. Therefore, there is a great possibility of selection and outcome bias. Also, the exact cause of mortality among the COVID-19 patients in the eligible study was not classified. Also, All the eligible studies failed to provide details about benefits on comorbidities. Since most eligible studies only focus on mortality, the prediction for bleeding risk and sub-group analysis could not be assessed due to limited data availability. Moreover, most of the studies also failed to report aspirin dose, duration and timing of administration. Also, COVID-19 patients receiving aspirin have significantly more comorbidities. Patients with more comorbidities in the aspirin group demonstrated poorer clinical outcomes than non-aspirin. Thus, the PSM minimize bias to adjusted RR. Thus, the overall pooled effects of this meta-analysis demonstrated a significantly reduced mortality rate.

Therefore, significant double-blinded parallel or cross over placebo-controlled randomized controlled trials with valid protocols are required to assess and confirm the beneficial outcome among the COVID-19 patients.

Conclusion

Aspirin use demonstrated significantly reduced mortality risk in COVID-19 patients. Also, Aspirin use among COVID patients required less mechanical ventilation than non-aspirin.

List of Abbreviations

CMA Comprehensive meta-analysis
NSAID Non-steroidal anti-inflammatory drugs

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent to participate

Not applicable.

Ethical approval

Not applicable.

Author details


Efficacy of low dose aspirin on the management of COVID-19


