European Journal of Clinical Pharmacology (2022) 78:1403–1420
https://doi.org/10.1007/s00228-022-03356-5

CLINICAL TRIAL

Does aspirin have an effect on risk of death in patients with COVID-19? A meta-analysis

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Received: 14 March 2022 / Accepted: 14 June 2022 / Published online: 22 June 2022

Abstract

Purpose The coronavirus disease 2019 (COVID-19) pandemic has shown unprecedented impact world-wide since the eruption in late 2019. Importantly, emerging reports suggest an increased risk of thromboembolism development in patients with COVID-19. Meanwhile, it is found that aspirin reduced mortality in critically ill patients with non-COVID-19 acute respiratory distress syndrome. Therefore, a meta-analysis was performed to investigate the effects of aspirin on COVID-19 mortality.

Methods A systematic literature search was conducted in 10 electronic databases and 4 registries. Random effects models were used to calculate pooled relative risks (RRs) with 95% confidence intervals (Cis) to estimate the effect of aspirin on COVID-19 mortality. Relevant subgroup analyses and sensitivity analyses were also performed.

Results The results showed that aspirin use was associated with a reduction in COVID-19 mortality (adjusted RR 0.69; 95% CI 0.50–0.95; $P<0.001$). Subgroup analysis found that the low-dose group was associated with a reduced COVID-19 mortality (adjusted RR 0.64; 95% CI 0.48–0.85; $P<0.01$). Aspirin use was associated with reduced COVID-19 mortality in Europe and America (crude RR 0.71; 95% CI 0.52–0.98; $P=0.04$), and results from cohort studies suggested that aspirin use was a protective factor for COVID-19 mortality (adjusted RR 0.73; 95% CI 0.52–0.99; $P=0.04$). Meanwhile, aspirin use was not associated with bleeding risk (crude RR 1.22; 95% CI 0.80–1.87; $P=0.96$).

Conclusions This meta-analysis found that aspirin use was associated with a reduction in mortality in patients with COVID-19 and not with an increased risk of bleeding.

Keywords Aspirin · COVID-19 · Mortality · Bleed · Meta-analysis

Introduction

Globally, more than 430 million cases of COVID-19 have been reported and 5.9 million deaths have been recorded as of February 25, 2022 [1]. To reduce the risk of death associated with COVID-19, several drugs have been repurposed for COVID-19 treatment. Meanwhile, it is well-known that coagulation dysfunction plays a central role in the pathology of COVID-19, which leads to end-organ complications and death [2]. It has been observed that thrombocytopenia and thrombotic complications are common in patients with COVID-19 and lead to higher mortality [3, 4]. Specifically, COVID-19 has been associated with growing incidence of thromboembolic complications such as venous thromboembolism (VTE), stroke, and myocardial infarction [5, 6]. The meta-analysis of clinical studies also showed a higher incidence of venous thromboembolism in patients with COVID-19 [7]. Furthermore, emerging evidences have suggested that

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COVID-19 patients in the terminal stages are at a greater risk of thromboembolism-related morbidity [8–10]. Some studies have indicated that the use of anticoagulants or antiplatelet agents in high-risk COVID-19 patients is beneficial. McBane et al. [11] have pointed out the role of anticoagulation in patients with COVID-19. Sivaloganathan et al. [12] identified that antiplatelet agents were also beneficial for patients with COVID-19.

Aspirin is a well-known anti-inflammatory agent that exhibits antiplatelet property by irreversibly inhibiting cyclooxygenase (COX), an enzyme that activates thromboxane [13]. Surprisingly, thromboinflammation turns out to be a major cause of morbidity and mortality in patients with COVID-19 [14]. It has also been documented that aspirin is associated with a reduction in death from acute respiratory distress syndrome in critically ill patients with non-coronavirus diseases [15, 16]. Although it seemed reasonable to include aspirin in the routine treatment of COVID-19 based on this assumption, Yuan et al. [17] failed to demonstrate an association between aspirin use and increased mortality in patients with COVID-19 in their retrospective investigation. Other studies, however, have since indicated that aspirin reduces mortality in COVID-19 patients [18]. Therefore, we conducted a meta-analysis of existing studies to investigate the effect of aspirin on mortality in patients with COVID-19.

Materials and methods

Study design

This study has been registered (registration number: CRD42021241027) with the PROSPERO database before April 7, 2021 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021241027). We used the Cochrane Handbook for Systematic Reviews of Interventions for the preparation and conduct of this meta-analysis [19]. We reported this meta-analysis with reference to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [20].

Search strategy

The literature searching was completed before May 25, 2022 for relevant available articles from the following databases: (1) PubMed; (2) Ovid MEDLINE; (3) Scopus; (4) Embase; (5) Cochrane library; (6) Web of Science; (7) Sinomed (CBM); (8) China National Knowledge Infrastructure (CNKI); (9) Wanfang Data Knowledge Service Platform; and (10) China Science and Technology Journal VIP Database. The registration search was completed by 22 February 2022 and the relevant data retrieved were from the following registration pools: (1) ClinicalTrials.gov; (2) International Clinical Trials Registry Platform (ICTRP); (3) The EU Clinical Trials Register; and (4) Chinese Clinical Trial Registry. The relevant retrieval strategy was as follows: ("aspirin" or "acetylsalicylic acid" or "non-steroidal anti-inflammatory drug" or "non-steroidal anti-inflammatory drugs") and ("COVID 19" or "COVID-19 Virus Disease" or "2019-nCoV Infection" or "Coronavirus Disease 2019 Virus" or "SARS-CoV-2 Infection") (see Supplementary Information: Table S1). Relevant Chinese technical terms for the Chinese databases were used to search for published articles. Furthermore, references of all relevant articles and reviews were retrieved to search for additional eligible studies.

Inclusion and exclusion criteria

Inclusion criteria

Studies were included in this meta-analysis if they met the following criteria: (1) The exposure factor was aspirin; (2) the outcome event was mortality related to COVID-19; (3) investigated the preadmission/pre-diagnosis or ongoing use of aspirin on the mortality risk of COVID-19; (4) relative risks (RRs) or odds ratios (ORs) or hazard ratios (HRs) and 95% confidence intervals (CIs) or data to calculate them were provided; (5) if there were multiple publications from the same population, the study with larger sample sizes or more available information was selected.

Exclusion criteria

Exclusion criteria include the following: (1) non-steroidal anti-inflammatory drugs (NSAIDs) which did not include aspirin; (2) the patients were not COVID-19 patients; (3) literature with irrelevant topics, duplicate publications, and no relevant data; (4) comments or letters to the editor, case reports, and only abstract; and (5) preprint servers, such as medRxiv/bioRxiv.

Data extraction

After deleting duplicates, all abstracts and titles were filtered independently by two reviewers (S. Ma and W. Su) to remove the irrelevant articles. We downloaded and read the full text of the potential research, and incorporate the studies that met the selection criteria into these systematic reviews. Two independent investigators (S. Ma and W. Su) extracted data from included articles. Data extraction included the following: first author name, year of publication, study location, study methods, sample size, aspirin use, primary and secondary outcomes, adverse effects, the raw data which included the patient number of trial group (aspirin) and

control group, and adjusted RRs/ORs/HRs with corresponding 95% CIs.

Quality assessment

For case–control and cohort studies, two investigators (S. Ma and W. Su) assessed the methodological quality of included studies independently, by using the nine-star Newcastle Ottawa scale (NOS) [21]. Each study was evaluated based on eight items that were divided into four categories, including the selection of cohort studies, comparability, and results, or exposure to case–control studies. Each included study will be characterized as being at low-quality, moderate-quality, or high-quality according to the scores assessed on NOS (0–3, 4–6, 7–9, respectively). For the randomized controlled trial (RCT) study, two reviewers (S. Ma and W. Su) independently assessed the risk of bias in each study using the Cochrane Risk of Bias tool [22]. We evaluated sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. For the cross-sectional study, two researchers independently assessed the methodological quality of the included studies using a 7-point Crombie scale [23]. The discrepancy for assessment was resolved by discussion or consultation with a third investigator (C. Sun). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to determine the certainty of evidence [24].

Statistical analysis

Statistical analyses of all data were performed with the Stata (version 15.0; Stata Corp, College Station, TX) and RevMan (version 5.3; Cochrane library) software. The extracted raw data were used to calculate the pooled RR with 95% CI to evaluate the strength of association between aspirin use and the risk of COVID-19-related death. When multiple data were provided in the study, the effect value that controls the most confounders was selected. If studies did not report a summary risk estimate for aspirin use, a summary risk estimate was calculated using risk estimates for each of the aspirin use categories. Subgroup analyses were also conducted to investigate the relationship between aspirin use and risk of COVID-19 mortality based on aspirin dose, study region, study design, and other adverse effects. HRs were directly considered RRs [25, 26], and ORs were transformed into RRs, if necessary, with this formula: $RR = OR/[(1 - P_0) + (P_0 \times OR)]$, in which P_0 is the incidence of the outcome of interest in the non-exposed group [27]. The standard error of the resulting converted RR was then determined with the following formula: $SElog(RR) = SElog(OR) \times log(RR)/log(OR)$, which could also be used to calculate the upper and lower limits of the CI by applying this formula to the upper and lower confidence limits of the adjusted odds ratio [28]. In order to promote the results of our study beyond the included studies, random effects model is the most appropriate meta-analysis model [29]. And a random effects model was selected a priori over the fixed effect model to capture between-study variability introduced by differences in underlying populations and study design; this was deemed particularly important due to our consideration of observational evidence. Sensitivity analysis was performed to explore whether one study exerts substantial impact on the result [30]. Assessment of publication bias was assessed by funnel plots qualitatively, and Begg test and Egger's test quantitatively [31]. Meanwhile, we report separately for adjusted and unadjusted estimates. In all the analyses, *P* values less than 0.05 were considered statistically significant.

Results

Study selection and characteristics

A database and register search resulted in the identification of 5139 records, and 219 potentially relevant studies were selected after removing duplicates and screening titles and abstracts. Of the 219 potentially relevant studies, a total of 18 studies met the inclusion criteria, including 11 cohort studies [17, 18, 32–40], 3 case–control studies [41–43], 3 cross-sectional studies [44–46], and 1 RCT [47]. Google Scholar and Baidu Scholar were also searched. Finally, 481 records were identified as potentially relevant to this study. However, these records were excluded as they were merely duplicates to the studies in the databases and the registries. The detailed process of literature screening is shown in Fig. S1.

Thereby, seventeen studies with a total of 49,041 subjects were eventually included in this meta-analysis. The characteristics of the included studies are shown in Table 1.

Overall meta-analysis of aspirin use on COVID-19 mortality

The results showed that aspirin use was associated with a reduction in COVID-19 mortality (crude RR 0.80; 95% CI 0.63–0.93; $P < 0.01$; $I^2 = 87\%$) by using the random effects model, where the adjusted estimate was 0.69 (95% CI 0.50–0.95; $P < 0.001$; $I^2 = 88\%$) and the unadjusted estimate was 1.00 (95% CI 0.99–1.02; $P = 0.93$; $I^2 = 0\%$; Fig. 1).

Table 1 General characteristics and quality score for included in the meta-analysis

First author	Year	Study region	Methods	Population	Interventions (number of patients, *n*)	Outcomes	Adjusted RR (95% CI)	Covariate adjustment	Study quality score	Adverse effect
Chow et al. [18]	2020	USA	Cohort study	Age—range, 37–72 years, % male: 59.2; laboratory-confirmed SARS-CoV-2 infection by qualitative real-time polymerase chain reaction (PCR)	Aspirin 81 mg/day ($n=98$); no aspirin ($n=314$)	**Primary outcome:** need for mechanical ventilation **Secondary outcomes**: ICU admission and in-hospital mortality	0.53 (0.13–0.90)	Age, gender, BMI, race, hypertension, diabetes mellitus, coronary artery disease, renal disease, liver disease, and home beta blocker use	8[a]	Adjusted RR not reported [reported incidence of major bleeding: aspirin: 6/98; non-aspirin: 24/314] 0.80 (0.34–1.90)
Liu et al. [41]	2021	China	Case–control study	Age—range, 44–67 years, % male: 50.4; pharyngeal swabs were collected after admission; laboratory-confirmed SARS-CoV-2 infection by qualitative real-time reverse transcriptase–polymerase chain reactions (RT-PCR)	Aspirin 100 mg/day ($n=24$); non-aspirin ($n=24$)	Viral duration (days); 30-d mortality; 60-d mortality	0.19 (0.05–0.78)	Age, gender, chronic obstructive pulmonary disease, chronic kidney disease, diabetes, hypertension, cerebrovascular disease, coronary disease	8[a]	NA

Table 1 (continued)

First author	Year	Study region	Methods	Population	Interventions (number of patients, *n*)	Outcomes	Adjusted RR (95% CI)	Covariate adjustment	Study quality score	Adverse effect
Meizlish et al. [36]	2021	USA	Cohort study	Age – median, 70 years, % male: 63.3; diagnosis of COVID-19 established via a nasopharyngeal polymerase chain reaction test	Aspirin 81 mg/day ($n=319$); non-aspirin ($n=319$)	**Primary outcomes**: in-hospital death, measured as cumulative incidence of in-hospital death, with cumulative incidence of hospital discharge as a competing risk	0.522 (0.336–0.812)	Age, aspirin and antiplatelet therapy use, male sex, obesity, cardiovascular disease, African-American race, DDmax (maximum D-dimer value during first 30 days of hospitalization), and admission RI (Rothman Index)	8[a]	NA
Merzon et al. [44]	2021	Israel	Retrospective cross-sectional study	Age – mean, 62.9 years, % male: 55.4; % currently smoking: 5.71; tested positive in an RT-PCR assay designed to detect infection with COVID-19	Low-dose aspirin ($n=73$); non-aspirin ($n=589$)	**Primary outcome:** COVID-19 infection rate **Secondary outcomes:** COVID-19 disease duration and COVID-19 mortality	0.362 (0.020–6.471)	Sex, age, smoking status, medication use, and comorbidities	6[b]	NA
Osborne et al. [37]	2020	USA	Cohort study	Veterans, age – mean, 67.3 years, % male: 95.5; identify the first positive COVID-19 polymerase chain reaction (PCR) results	Aspirin ($n=6300$); non-aspirin ($n=6300$)	14-day and 30-day all-cause mortality within or outside of hospital care	0.395 (0.334–0.476)	Age, gender, race, hypertension, chronic pulmonary disease, congestive heart failure, diabetes	8[a]	NA

Table 1 (continued)

First author	Year	Study region	Methods	Population	Interventions (number of patients, *n*)	Outcomes	Adjusted RR (95% CI)	Covariate adjustment	Study quality score	Adverse effect
Sahai et al. [38]	2021	USA	Cohort study	Age – mean, 53.4 years, % male: 48.9; tested positive for the SARS-CoV-2 amplicon by RT-PCR testing	Aspirin 81 mg/day ($n=248$); no aspirin ($n=248$)	**Primary outcome:** COVID-19 mortality **Secondary outcomes:** SARS-CoV-2 infection rate, myocardial infarction (MI), thrombotic stroke, and venous thromboembolism (VTE)	0.85 (0.51–1.41)	Age, sex, race, ethnicity, platelet count, smoking status, respiratory support, use of vasopressor, hemodynamic instability, comorbidities, comedications	7[a]	NA
Yuan et al. [17]	2020	China	Cohort study	Coronary artery disease, age – mean, 71.2 years, % male: 54.1; tested positive for the SARS-CoV-2 amplicon by RT-PCR testing	Aspirin 150 mg/day ($n=52$); non-aspirin ($n=131$)	**Primary outcome:** COVID-19 infection rate **Secondary outcomes:** COVID-19 mortality and critically ill	0.956 (0.472–1.727)	Age, sex, comorbidities	7[a]	NA
Vahedian-Azimi et al. [39]	2021	Iran	Cohort study	Age – mean, 54.85 years; % male: 67.3; % diagnosis of COVID-19 was confirmed by a positive reverse transcription–polymerase chain reaction (RT-PCR) assay of a specimen obtained by nasopharyngeal swab	Aspirin ($n=337$); non-aspirin ($n=250$)	**Primary outcome:** in-hospital mortality **Secondary outcomes:** intensive care unit (ICU) admission	0.76 (0.3–1.92)	Age, sex, lockdown, and other drugs simultaneously	7[a]	NA

Table 1 (continued)

First author	Year	Study region	Methods	Population	Interventions (number of patients, *n*)	Outcomes	Adjusted RR (95% CI)	Covariate adjustment	Study quality score	Adverse effect
Kim et al. [34]	2021	South Korea	Cohort study	Age—range, 20–80 years, % male: 44.1; tested positive for the SARS-CoV-2 amplicon by RT-PCR testing	Aspirin ($n=139$); non-aspirin ($n=155$)	**Primary outcome:** the positivity of laboratory test results for COVID-19 **Secondary outcomes:** conventional oxygen therapy, intensive care unit, mechanical ventilation, or death	Adjusted RR not reported [reported incidence of mortality: aspirin: 119/139; non-aspirin: 131/155] 1.002 (0.987–1.016)	NA	7[a]	NA
Husain et al. [46]	2022	Bangladesh	Retrospective cross-sectional study	Age—range, 15–51 years, % male: 64.3; adult COVID-19 patients either diagnosed with RT-PCR, or categorized as probable cases (as per the World Health Organization case definition protocol) by medical doctors were enrolled as participants	Aspirin ($n=11$); non-aspirin ($n=31$)	**Primary outcome:** complications among COVID-19 patients **Secondary outcomes:** death	Adjusted RR not reported [reported incidence of mortality: aspirin: 0/11; non-aspirin: 3/31] 0.404 (0.022–4.366)	NA	6[b]	NA

Table 1 (continued)

First author	Year	Study region	Methods	Population	Interventions (number of patients, *n*)	Outcomes	Adjusted RR (95% CI)	Covariate adjustment	Study quality score	Adverse effect
Haji Aghajani et al. [33]	2021	Iran	Cohort study	Age – mean, 61.64 years; % male: 54.89; patients with confirmed severe to critical COVID 19, based on reverse transcriptase polymerase chain reaction (rt PCR)	Aspirin 80 mg/day ($n=366$); non-aspirin ($n=655$)	**Primary outcome:** mortality rate of the patients **Secondary outcomes:** mechanical ventilation and duration of hospitalization	0.753 (0.573–0.991)	Age, sex, BMI, smoking, hypertension, diabetes mellitus, coronary artery disease, cancer, respiratory disorder, immunosuppressive disorder, chronic kidney disease, and others	8[a]	NA
Formiga et al. [32]	2021	Spain	Cohort study	Age – mean, 68.5 years, % male: 57.5; % smoking behavior: 69.6; patients were diagnosed by polymerase chain reaction (PCR) test or rapid antigenic test for SARS-CoV-2 taken from a nasopharyngeal sample, sputum, or bronchoalveolar lavage	Aspirin ($n=3291$); non-aspirin ($n=2885$)	**Primary outcome:** in-hospital mortality **Secondary outcomes:** the development of symptomatic deep venous thrombosis (DVT) or pulmonary embolism (PE), the requirement of high-flow nasal cannula (HFNC), noninvasive mechanical ventilation (NIMV), invasive mechanical ventilation (IMV), ICU admission	1.05 (0.92–1.19)	Age, gender, BMI, smoking behavior, degree of dependency, arterial hypertension, chronic heart failure, Charlson index, respiratory rate, PaO2/FiO2, lymphocyte count, C-reactive protein, lactate dehydrogenase, low-molecular-weight heparin and others	7[a]	NA

Table 1 (continued)

First author	Year	Study region	Methods	Population	Interventions (number of patients, *n*)	Outcomes	Adjusted RR (95% CI)	Covariate adjustment	Study quality score	Adverse effect
Son et al. [42]	2021	South Korea	Case–control study	Age—range, 20–80 years, % male: 36.7; % currently smoking: 12.3; the laboratory diagnosis of SARS-CoV-2 infection in Korea was based on the KCDC and WHO guidelines, which recommended polymerase chain reaction amplification of the viral E gene as a screening test and amplification of the RdRp region of the orf1b gene as a confirmatory test	Aspirin ($n=68$); non-aspirin ($n=188$)	**Primary outcome:** SARS-CoV-2 infection status **Secondary outcomes:** intensive care unit admission; use of vasopressors, high-flow oxygen therapy, renal replacement therapy, extracorporeal membrane oxygenation, and mortality	0.76 (0.34–1.71)	Sex, age, residential area, and income level, comorbidities, Charlson comorbidity index, and health screening findings	7[a]	NA

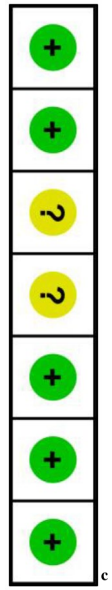
Table 1 (continued)

First author	Year	Study region	Methods	Population	Interventions (number of patients, *n*)	Outcomes	Adjusted RR (95% CI)	Covariate adjustment	Study quality score	Adverse effect
Alamdari et al. [45]	2020	Iran	Retrospective cross-sectional study	Age – mean, 61.79 years, % male: 69.7; % currently smoking: 28.5; then, nasopharyngeal sampling for reverse transcriptase polymerase chain reaction (RT-PCR) was performed as the verifying test for diagnosis of all suspected patients	Aspirin ($n=53$); non-aspirin ($n=406$)	**Primary outcome:** prognostic factors related to fatality **Secondary outcomes:** complications during the admission, drug history, clinical presentation, and vital signs	Adjusted RR not reported [reported incidence of mortality: aspirin: 9/53; non-aspirin: 54/406] 1.234 (0.701–2.042)	NA	6[b]	NA
Lodigiani et al. [35]	2020	Italy	Cohort study	Age – mean, 66 years, % male: 68; % currently smoking: 11.6; consecutive adult symptomatic patients with laboratory-proven COVID-19	Aspirin ($n=6$); non-aspirin ($n=22$)	**Primary outcome:** any thromboembolic complication, including venous thromboembolism (VTE), ischemic stroke, and acute coronary syndrome (ACS)/ myocardial infarction (MI) **Secondary outcomes:** overt disseminated intravascular coagulation (DIC)	Adjusted RR not reported [reported incidence of mortality: aspirin: 2/6; non-aspirin: 5/22] 1.328 (0.432–2.764)	NA	7[a]	NA

Table 1 (continued)

First author	Year	Study region	Methods	Population	Interventions (number of patients, *n*)	Outcomes	Adjusted RR (95% CI)	Covariate adjustment	Study quality score	Adverse effect
Viecca et al. [43]	2020	Italy	Case–control study	Age – mean, 61.8 years, % male: 80; partial arterial pressure of oxygen to fraction of inspired oxygen ratio (PaO2/FiO2) ratio 250 mmHg requiring helmet continuous positive airway pressure (CPAP), bilateral pulmonary infiltrates, a laboratory-confirmed positive nasal swab for SARS-CoV-2 and a D-dimer value 3 times the laboratory upper level of normal	Aspirin 75 mg/day ($n=5$); non-aspirin ($n=5$)	**Primary outcome:** change in partial pressure of oxygen **Secondary outcomes:** degree of intensity of the respiratory support 72 and 168 h after study treatment initiation; days on CPAP after treatment initiation; major and minor cardiac and non-cardiac adverse events from study drug initiation until end of hospital stay	Adjusted RR not reported [reported incidence of mortality: aspirin: 1/5; non-aspirin: 3/5] 0.552 (0.116–1.280)	NA	6[a]	NA
An et al. [40]	2020	South Korea	Cohort study	Age – mean, 44.97 years, % male: 39.9; % hypertension: 18.2, % diabetes mellitus: 10.0; the study included 10,237 Korean patients who had tested positive for COVID-19	Aspirin ($n=498$); non-aspirin ($n=9739$)	**Primary outcome:** mortality from COVID-19 **Secondary outcomes:** factors associated with mortality and performance of machine learning	1.19 (0.79–1.79)	Age, sex, income level, residence, household type, disability, symptom, and infection route	7[a]	NA

Table 1 (continued)

First author	Year	Study region	Methods	Population	Interventions (number of patients, *n*)	Outcomes	Adjusted RR (95% CI)	Covariate adjustment	Study quality score	Adverse effect
RECOVERY Collaborative Group [47]	2022	UK	Randomized controlled trial	Age – mean, 59.2 years, % male: 61.8; patients admitted to hospital were eligible for the trial if they had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial	Aspirin 150 mg/day ($n=7351$); usual care ($n=7541$)	**Primary outcome:** all-cause mortality **Secondary outcomes:** time to discharge from hospital, and, among patients not on invasive mechanical ventilation at randomization, progression to invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death	0.96 (0.89–1.04)	NA	 [c]	Any major bleeding: 1.55 (1.16–2.07)

RR relative risk, *NA* not Available

[a]the Newcastle Ottawa Scale (NOS)

[b]Combie

[c]Cochrane risk of bias instrument: random sequence generation, +; allocation concealment, +; blinding of participants and personnel, ?; blinding of outcome assessment, ?; incomplete outcome data, +; selective reporting, +; other bias, +

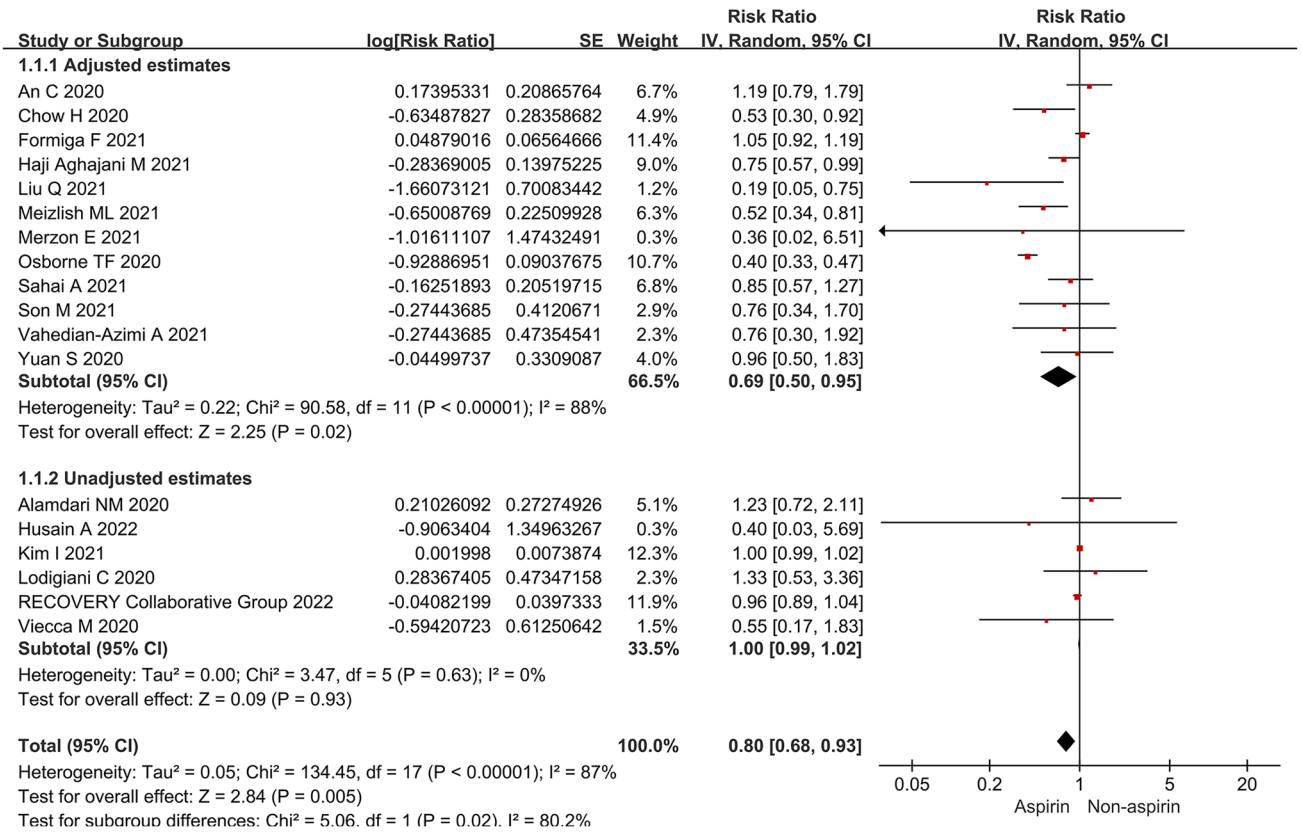


Fig. 1 Results of a meta-analysis of aspirin use on COVID-19 mortality

Subgroup analysis

For the dosing of aspirin, we extracted data from 18 studies. The results found that the low-dose group (80–100 mg/day) reduced mortality in COVID-19 (crude RR 0.64; 95% CI 0.50–0.83; $P<0.01$, $I^2=31\%$; adjusted RR 0.64; 95% CI 0.48–0.85; $P<0.01$, $I^2=44\%$). In contrast, both the medium dose group (150 mg/day, crude RR 0.96; 95% CI 0.89–1.04; $P=0.3$, $I^2=0\%$) and the unknown dose group (crude RR 0.87; 95% CI 0.65–1.16; $P=0.34$, $I^2=92\%$) were not associated with mortality from COVID-19.

Subgroup analysis by study region showed that aspirin administration was associated with reduced COVID-19 mortality in Europe and America (crude RR 0.71; 95% CI 0.52–0.98; $P=0.04$, $I^2=93\%$), but adjusted estimates found no association between aspirin administration and reduced COVID-19 mortality (adjusted RR 0.96; 95% CI 0.89–1.04; $P=0.30$, $I^2=61\%$). In contrast, aspirin was not associated with mortality from COVID-19 in Asia (crude RR 0.89; 95% CI 0.73–1.08; $P=0.24$, $I^2=34\%$; adjusted RR 0.79; 95% CI 0.56–1.12; $P=0.19$, $I^2=29\%$).

The results of the subgroup analysis based on the study design showed that aspirin use was a protective factor for mortality in COVID-19 (crude RR 0.78; 95% CI 0.61–0.97; $P=0.03$, $I^2=92\%$; adjusted RR 0.73; 95% CI 0.52–0.99; $P=0.04$, $I^2=90\%$) in the subgroup of cohort study. In contrast, results from other study designs showed that aspirin was not associated with mortality from COVID-19.

The results of all subgroup analyses are shown in Table 2.

Secondary analysis of adverse events

In terms of the risk of adverse events, there were two studies included [18, 47], and aspirin use was not associated with the occurrence of bleeding (crude RR 1.22; 95% CI 0.80–1.87; $P=0.96$, $I^2=80\%$). However, due to the limited number of included studies, sensitivity analysis and publication bias test were not conducted.

Study quality assessment and risk of bias

All the included observational studies were considered high-quality studies, as depicted by NOS > 7 and Combie > 6. The included RCT study was also considered to be a high-quality study (Table 1). There was a low to moderate risk of bias in the NOS-based assessment, and the GRADE assessment showed low certainty in the evidence for aspirin to reduce COVID-19 mortality and the

Table 2 Subgroup analysis according to different doses, regions, and study designs

Subgroup	Covariate	Number of studies	Number of participants, *N*	I^2 (%)	RR	95% CI	*P*
Overall	Adjusted	12	33,316	88	*0.69*	*0.50–0.95*	< 0.001
	Unadjusted	6	15,725	0	1.00	0.99–1.02	0.93
	Crude	18	49,041	87.4	*0.80*	*0.68–0.93*	< 0.001
Aspirin dose							
80–100 mg/day	Adjusted	5	2615	44.3	*0.64*	*0.48–0.85*	0.002
	Unadjusted	1	10	NA	0.55	0.12–1.28	0.33
	Crude	6	2625	31.4	*0.64*	*0.50–0.83*	< 0.001
150 mg/day	Adjusted	1	183	NA	0.96	0.50–1.83	0.89
	Unadjusted	1	14,892	NA	0.96	0.89–1.04	0.30
	Crude	2	15,075	0	0.96	0.89–1.04	0.30
Unknown	Adjusted	6	30,518	93.9	0.76	0.43–1.34	0.34
	Unadjusted	4	823	0	1.00	0.99–1.02	0.77
	Crude	10	31,341	91.8	0.87	0.65–1.16	0.34
Region							
Asia	Adjusted	7	12,994	29.1	0.79	0.56–1.12	0.19
	Unadjusted	3	795	0	1.00	0.99–1.02	0.77
	Crude	10	13,789	29.7	0.93	0.78–1.10	0.40
Europe and America	Adjusted	5	20,322	94.7	0.73	0.50–1.07	0.08
	Unadjusted	3	14,930	61.0	0.96	0.89–1.04	0.30
	Crude	8	35,252	93.0	*0.71*	*0.52–0.98*	0.04
Study design							
Cohort study	Adjusted	9	32,350	90.7	*0.73*	*0.52–0.99*	0.04
	Unadjusted	2	322	0	1.00	0.99–1.02	0.78
	Crude	11	32,672	92.0	*0.78*	*0.61–0.97*	0.03
Case–control study	Adjusted	2	304	65.6	0.43	0.11–1.63	0.21
	Unadjusted	1	10	NA	0.55	0.17–1.83	0.33
	Crude	3	314	31.3	0.50	0.23–1.07	0.07
Cross-sectional study	Adjusted	1	662	NA	0.38	0.02–6.51	0.30
	Unadjusted	2	501	0	1.18	0.70–1.99	0.53
	Crude	3	1163	0	1.14	0.68–1.90	0.62
RCT	Unadjusted	1	14,892	NA	0.96	0.89–1.04	0.30

RR relative risks, *95% CI* 95% confidence interval, *RCT* randomized controlled trial, *NA* not available
The italicized values indicates statistical significance

occurrence of adverse events, mainly due to the retrospective nature of the studies and the potential for selection and publication bias (Fig. S2). Although the funnel plot of the correlation between aspirin use and mortality was asymmetric (Fig. S3), neither the Begg's test ($P = 0.495 > 0.05$) nor the Egger's test ($P = 0.059 > 0.05$) found publication bias.

Sensitivity analysis

Removing the Osborne et al. [37] study resulted in a significant decrease in heterogeneity. However, it did not change the overall effect value. This may be due to the larger sample size and weights of the Osborne study.

Discussion

In this analysis, aspirin use has been shown to be independently associated with a reduced risk of death in patients with COVID-19, but the heterogeneity of the overall estimate is high ($I^2 = 88\%$) and the certainty of the evidence is low. Notably, our findings contradict the previous meta-analysis by Salah and Mehta [48] who reported there was no association between aspirin use and risk of death in patients with COVID-19. The significant differences between the previous study and our meta-analysis were the number of studies included. Also we found no association between cardiovascular drug (including aspirin) use and risk of death in patients with COVID-19 as reported by Asiimwe et al. [49, 50]. The reason may be that the

exclusion criteria for inclusion in these two studies were different from our study.

On the one hand, COVID-19 causes various inflammatory responses in the body [51], and aspirin is a common antiplatelet agent with anti-inflammatory, analgesic, antipyretic, and antithrombotic effects through irreversible inactivation of cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2), inhibiting the production of prostaglandins (PG) and thromboxane (TX) [52]. On the other hand, patients with COVID-19 are in a hypercoagulable and hyper-aggregated state, with a high incidence of venous thromboembolism and disseminated intravascular coagulation [18, 53]. Aspirin can lead to the inhibition of arachidonic acid synthesis in the body, which further prevents the synthesis of thromboxane A2 (TXA2) and promotes platelet agglutination, thus reducing the occurrence of unfavorable outcomes, such as deaths, in COVID-19 [52]. In addition, aspirin is found to exhibit antiviral properties against DNA and RNA viruses such as cytomegalovirus, varicella-zoster virus, rhinovirus, coxsackievirus, hepatitis C virus, H1N1 influenza virus, MERS-CoV, and CoV-229E [54–57]. The antiviral action of aspirin is primarily mediated through modulation of the nuclear factor-kB (NF-kB) pathway [58]. Virus-infected cells produce reactive oxygen species (ROS), which in turn stimulates NF-kB, resulting in the expression of viral and cellular genes implicated in immune and inflammatory responses. Aspirin, on the other hand, inhibits virus-induced NF-kB activation by lowering ROS, thus achieving antiviral effect [55].

In addition, there are differences in COX-2 expression levels between people of different demographic characteristics, which leads to disparities in aspirin sensitivity [59, 60]. Furthermore, while taking aspirin, distinct net clinical benefits were identified between people of different demographic characteristics which might be due to variations in pharmacokinetic and pharmacodynamic profiles [61]. These factors might explain why aspirin's effect on COVID-19 mortality differed among demographics in the current research. However, adjusted estimates found no demographic difference in the effect of aspirin on COVID-19 mortality. This could be because the majority of the studies we included were observational studies without sufficient evidence to explain this difference and warrant further studies in RCTs to confirm.

Nonetheless, different dosage of aspirin seems to have different effects on the risk of death in COVID-19. It is indicated that low doses of aspirin have mainly antiplatelet effects, while high doses exhibit anti-inflammatory effects. This peculiar phenomenon is observed in several studies that investigated the distinct effect of aspirin on platelet aggregation induced by certain bacteria strains [62, 63]. Moreover, a meta-analysis research by Martha et al., which included six studies comprising 13,933 patients, also agreed individuals taking aspirin were significantly and independently associated with reduced overall mortality [64]. Therefore, the potential dosage effect of aspirin contributing to antithrombotic effect should not be neglected. However, as most of the included studies were observational, our study does not provide sufficient evidence to conclude that it is the dosing.

Although this meta-analysis shows a potential benefit of aspirin use in patients with COVID-19, there are several limitations to this study. First, most of the included studies were retrospective and prone to bias, and the observational studies were not ideal for our study objectives and did not provide sufficient evidence to argue our point. The causes of death in the included studies were not distinguished as thromboembolic, cardiovascular, or all-cause mortality; therefore, the authors were unable to provide details of the benefits. Second, the prediction of bleeding risk was not sufficiently accurate due to limited data. There were only two included studies reported the bleeding risk as adverse events; therefore, the conclusion regarding the bleeding risk should be interpreted with caution and more studies are needed to further explore the adverse events of aspirin use in COVID-19 patients. Finally, although some analyses were adjusted for confounders, this does not necessarily mean that all confounders were adjusted for. There may be confounding factors that were not reported and analyzed by the authors included in the study. Therefore, further randomized controlled trials with appropriate blinding and validated study protocols are needed to assess and confirm their benefits for patients with COVID-19.

Conclusions

This meta-analysis found that aspirin use was independently associated with a reduced risk of death in patients with COVID-19, and not with an increased risk of bleeding. However, the heterogeneity of the overall estimates was high and the certainty of the GRADE assessment evidence was low. At the same time, this study provides supportive evidence for the potential benefits of aspirin and warrants further studies in RCTs to confirm.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00228-022-03356-5.

Acknowledgements We appreciate all authors for their contributions, and support from AMITA Health Saint Joseph Hospital Chicago and Anhui Medical University.

Author contribution Shaodi Ma and Yehuan Sun designed research; Shaodi Ma, Wanying Su, and Haixia Liu conducted literature search; Shaodi Ma, Wanying Su, and Chenyu Sun analyzed and interpreted data; and Shaodi Ma and Wanying Su wrote the paper. Chenyu Sun, Guangbo Qu, Weihang Xia, Peng Xie, Birong Wu, Juan Gao, and Linya Feng provided critical opinion. Chenyu Sun, Scott Lowe, and Zhen

Zhou revised the paper. Shaodi Ma, Wanying Su, and Chenyu Sun had primary responsibility for final content. All authors read and approved the final manuscript.

Availability of data and materials All data generated or analyzed in this study are from the original published study and are included in this published article.

Declarations

Ethics approval and consent to participate This article does not contain any studies with human participants or animals performed by any of the authors. We did not use individual data but published data. These data have been widely utilized in research and are generally available. Therefore, we confirm that any aspect of the work covered in this manuscript has been conducted with ethical approval. And this study has been registered (registration number: CRD42021241027) with the PROSPERO (International Prospective Register of Systematic Reviews) and was conducted according to the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) statement.

Consent for publication All individuals gave written informed consent for publication. The authors are responsible for the reported research, and have participated in the concept and design, analysis and interpretation of data, drafting or revising of the manuscript, and have approved the manuscript as submitted.

Conflict of interest The authors declare no competing interests.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors. We did not use individual data but published data. These data have been widely utilized in research and are generally available.

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