Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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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

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ABSTRACT

Background: This study aimed to investigate whether the active prescription of low-dose aspirin during or prior to hospitalization affects mortality in patients with coronavirus disease 2019 (COVID-19). Aspirin is often prescribed for secondary prevention in patients with cardiovascular disease and other comorbidities that might increase mortality, and may therefore falsely demonstrate increased mortality. To reduce bias, only studies that performed an adjusted analysis were included in this review.
Methods: A systematic literature search of PubMed, Scopus, Embase and Clinicaltrials.gov was performed, from inception until 16 April 2021. The exposure was active prescription of low-dose aspirin during or prior to hospitalization. The primary outcome was mortality. The pooled adjusted effect estimate was reported as relative risk (RR).
Results: Six eligible studies were included in this meta-analysis, comprising 13,993 patients. The studies had low-to-moderate risk of bias based on the Newcastle–Ottawa Scale. The meta-analysis indicated that the use of low-dose aspirin was independently associated with reduced mortality {RR 0.46 [95% confidence interval (CI) 0.35–0.61], $P < 0.001$; $I^2 = 36.2\%$}. Subgroup analysis on in-hospital low-dose aspirin administration also showed a significant reduction in mortality [RR 0.39 (95% CI 0.16–0.96), $P < 0.001$; $I^2 = 47.0\%$].
Conclusion: Use of low-dose aspirin is independently associated with reduced mortality in patients with COVID-19, with low certainty of evidence.

Introduction

Repurposing of available drugs for patients with coronavirus disease 2019 (COVID-19) has gained interest due to the scarcity of drugs proven to be useful in these patients. Dexamethasone, statins, metformin, dipeptidyl peptidase-4 inhibitors and renin–angiotensin system inhibitors have shown clinical benefits for severe and critically ill patients, especially those who are mechanically ventilated (Castiglione et al., 2020; Lim and Pranata, 2020a; Lukito et al., 2020; Pranata et al., 2020c; Rakhmat et al., 2021). However, apart from dexamethasone, the evidence is limited and often disproved by other similar studies.

Coagulopathy plays a central role in the pathomechanism of COVID-19, which leads to end-organ complications and death (Huang et al., 2020; Lim et al., 2020; Pranata et al., 2021e,f). COVID-19 has been linked with increased thromboembolic complications such as venous thromboembolism (VTE), stroke and myocardial infarction (Barnes et al., 2020; Nishiga et al., 2020; Porfidia and Pola, 2020; Wichmann et al., 2020). Aspirin, also known as acetylsalicylic acid, is potentially beneficial in patients with COVID-19 due to its antithrombotic nature. Aspirin primarily acts by inhibiting platelet function through irreversible inhibition of cyclo-oxygenase (COX) activity. Low-dose aspirin inhibits COX-1, resulting in reduced thromboxane A2 synthesis (Bianconi et al.,

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2020; Mohamed-Hussein et al., 2020). This study aimed to investigate whether the active prescription of low-dose aspirin during or prior to hospitalization affects mortality in patients with COVID-19. Aspirin is often prescribed for secondary prevention in patients with cardiovascular disease and other comorbidities that might be associated with increased mortality in patients with COVID-19 (Pranata et al., 2020a; Yonas et al., 2020), and therefore may falsely demonstrate increased mortality. To reduce such bias, only studies that performed an adjusted analysis with or without the use of propensity score matching were included in this review. In addition, only patients that had an active prescription for aspirin were included, by excluding studies with unclear information on whether aspirin use was historical or current, to ensure that aspirin was active in the system during COVID-19.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines, and has been registered in PROSPERO (CRD42021249440).

Search strategy and study selection

A systematic literature search of PubMed, Scopus, Embase and Clinicaltrials.gov was performed from inception until 16 April 2021 using the keywords: (Coronavirus Disease 2019 OR COVID-19 OR SARS-CoV-2 OR 2019-nCoV) AND (aspirin OR acetylsalicylic acid OR acetylsalicylate). The titles and abstracts of the articles were screened and assessed for eligibility based on the inclusion and exclusion criteria. Discrepancies were resolved by discussion.

Inclusion and exclusion criteria

Exposure was use of low-dose aspirin, defined as active prescription of low-dose aspirin (75–325 mg daily) during or prior to hospitalization (maximum 7 days). Studies with unclear information on whether the use of aspirin was historical or current were excluded. The control group consisted of patients with no active prescription of low-dose aspirin during or prior to hospitalization. The primary outcome was mortality.

Studies that met the following criteria were included: (1) observational studies or randomized controlled trials evaluating patients hospitalized for COVID-19; (2) studies that compared patients using low-dose aspirin with a control group; and (3) adjusted effect estimate for mortality.

Abstract-only publications, non-research letters, reviews, commentaries and editorials were excluded. No language restrictions were imposed.

Data extraction

Two authors independently performed data extraction from the included studies. The data of interest were: first author, study design, sample size, percentage of severe COVID-19, inclusion criteria, age, male sex, hypertension, diabetes, coronary artery disease, adjusted effect estimates for mortality, and adjustment factors. Discrepancies were resolved by discussion.

Risk-of-bias assessment

Two independent authors used the Newcastle–Ottawa Scale (NOS) for cohort studies (Wells et al., 2000) to assess the risk of bias. NOS comprises three domains: (1) selection; (2)

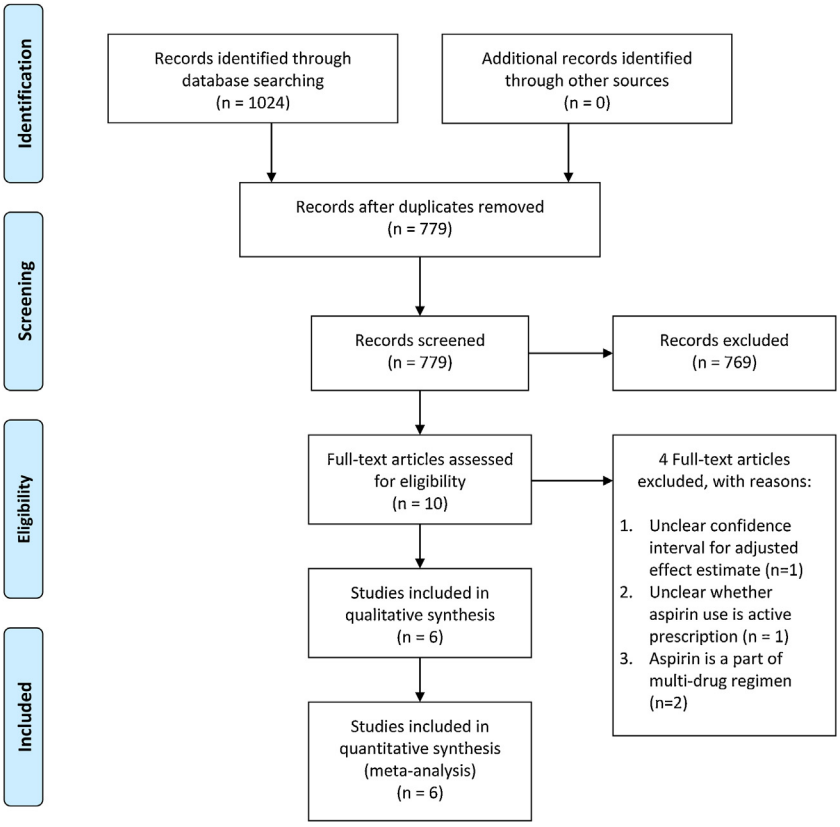

Figure 1. PRISMA flowchart.

comparability; and (3) outcome of the included studies. Discrepancies were resolved by discussion. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to determine the certainty of evidence.

Outcome and pooled effect estimate

The primary outcome was mortality, defined as clinically validated death. The adjusted effect estimates of the included studies were pooled, and reported as relative risk (RR), defined as adjusted odds ratio, adjusted risk ratio or adjusted hazard ratio.

Statistical analysis

STATA 16.0 (Stata Corp., College Station, TX, USA) was used to perform the meta-analysis. The adjusted RRs for use of low-dose aspirin and mortality were pooled using empirical Bayes random-effects model, irrespective of heterogeneity. $P \leq 0.05$ for the pooled effect estimates was taken to indicate statistical significance. Cochran's Q test and I^2 statistic were used to evaluate heterogeneity; $I^2 > 50\%$ and/or $P < 0.10$ indicated substantial heterogeneity. Funnel plot analysis and Egger's test were used to assess publication bias and small-study effects. Non-parametric trim-and-fill analysis was performed due to the asymmetric funnel plot. Subgroup analysis was performed for studies that clearly indicated in-hospital use of low-dose aspirin.

Results

Baseline characteristics

The database search identified 10 potentially eligible studies. One study was excluded due to an unclear confidence interval (CI) for the adjusted effect estimate; the study showed a significant reduction in mortality with aspirin on univariate analysis (Karruli et al., 2021). Another study did not clearly report whether the use of aspirin was an active prescription or a history of exposure; the study reported that there was no significant difference in terms of mortality (Alamdari et al., 2020). Two studies were excluded because aspirin was part of a multi-drug regimen. Kevorkian et al. (2021) found that use of corticoid, aspirin, anticoagulant, colchicine and furosemide reduced mortality in hospitalized non-critically ill patients with COVID-19. Lima-Morales et al. (2021) showed that use of ivermectin, azithromycin, montelukast and aspirin reduced the risk of mortality in ambulatory patients with COVID-19. Therefore, six eligible studies were included in this meta-analysis, comprising 13,993 patients (Figure 1) (Chow et al., 2021; Liu et al., 2021; Meizlish et al., 2021; Merzon et al., 2021; Osborne et al., 2021; Yuan et al., 2021). Baseline characteristics of the included studies can be seen in Table 1. Three studies were propensity-score-matched cohort studies (1:1). The inclusion and exclusion criteria of the studies are displayed in Table S1 (see online Supplementary material).

Low-dose aspirin and mortality

Meta-analysis indicated that the use of low-dose aspirin was independently associated with reduced mortality [RR 0.46 (95% CI 0.35–0.61), $P < 0.001$; $I^2 = 36.2\%$, $P = 0.155$] (Figure 2). Subgroup analysis on in-hospital administration of low-dose aspirin also showed a significant reduction in mortality [RR 0.39 (95% CI 0.16–0.96), $P < 0.001$; $I^2 = 47.0\%$, $P = 0.170$].

Publication bias

Funnel plot analysis showed slight asymmetry (Figure 3A), and after non-parametric trim-and-fill analysis (Linear 0 estimator,

Table 1
Baseline characteristics of the included studies.

Authors	Design	Sample	Received aspirin	Use of aspirin	Dose of aspirin	Age (years)	Male (%)	Hypertension (%)	Diabetes (%)	CAD (%)	Adjustment factors	NOS
Chow et al. (2021)	Multi-centre RO	412	23.7	Within 24 h of hospital admission or in the 7 days before hospital admission	81 mg	53	55	59	35	13	Demographics and comorbidities	8
Liu et al. (2021)	PSM 1:1 single-centre RO	48 (PSM)	50	In hospital to prevent embolic events	100 mg	56	50	26	12	8	Clinical characteristics, comorbidities, laboratories and medication	9
Meizlish et al. (2021)	PSM 1:1 multi-centre RO	638	50	In hospital	81 mg	>60: 46	63	Unclear	Unclear	Unclear	Age, anticoagulation other than prophylactic dose, male sex, obesity, cardiovascular disease, African-American race, D-dimer and admission Rothman Index	9
Merzon et al. (2021)	Multi-centre RO	112	14	For primary prevention of CVD	Low dose (mg unspecified)	63	55	41	43	0	Sex, age, smoking status, use of medication and comorbidities	7
Osborne et al. (2021)	PSM 1:1 multi-centre RO	12,600	50	Active aspirin prescription by the centre's pharmacy at the time of a positive COVID-19 laboratory test	Dose unspecified	67	96	81	51	Unclear	Age, gender and CAN score	8
Yuan et al. (2021)	Single-centre RO	183	28.4	Patients with COVID-19 with CAD	Low dose (75–150 mg)	71	54	56	22	100	Age, sex and chronic kidney disease	8

CAD, coronary artery disease; CAN, Care Assessment Needs; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; PSM, propensity score matched; RO, retrospective observational; NOS, Newcastle–Ottawa Scale.

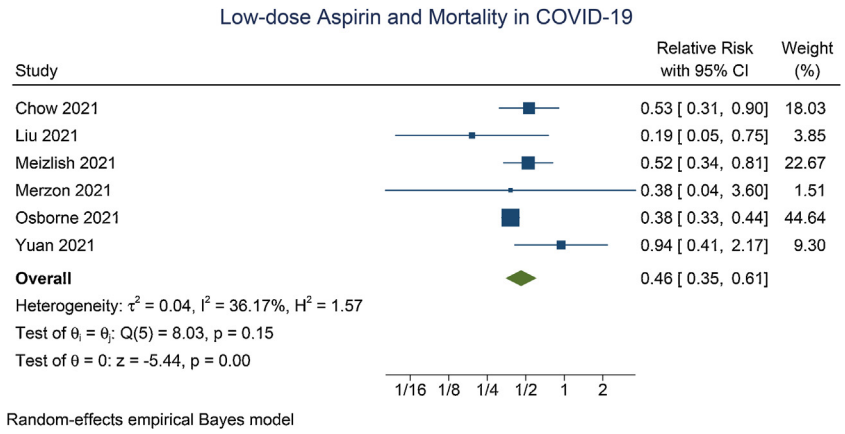

Figure 2. Low-dose aspirin and mortality in patients with coronavirus disease 2019. CI, confidence interval.

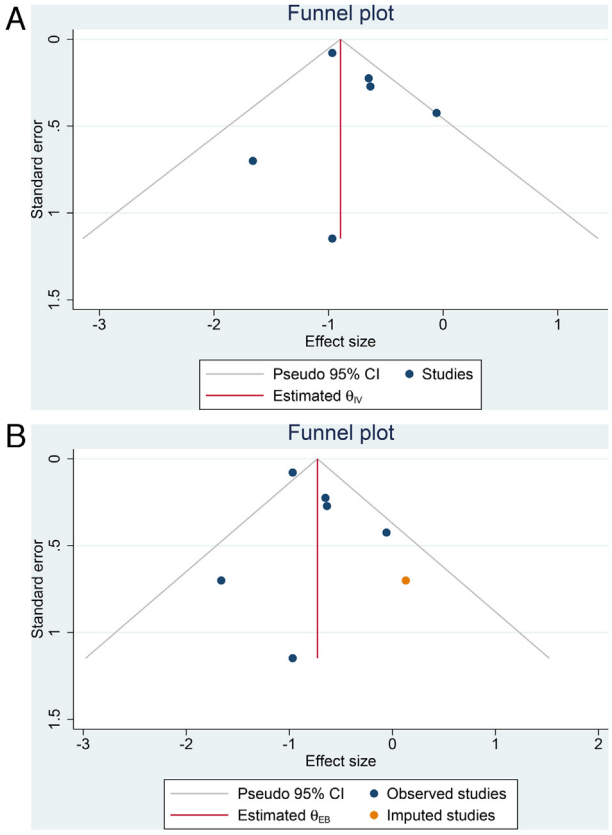

Figure 3. Publication bias. (A) Funnel plot. (B) Non-parametric trim-and-fill analysis. CI, confidence interval.

right side), the pooled effect estimate remained significant [RR 0.48 (95% CI 0.36–0.65)] (Figure 3B). Egger's test was not significant for small-study effects (P = 0.777).

Risk-of-bias assessment

The studies had low-to-moderate risk of bias based on NOS. GRADE assessment showed low certainty of evidence for the mortality-reducing effect of low-dose aspirin, mainly due to the retrospective nature of the studies and possibility of selection and publication bias (Table 2).

Discussion

This meta-analysis found that the use of low-dose aspirin is independently associated with reduced mortality in patients with COVID-19, with low certainty of evidence.

Aspirin is an antithrombotic agent traditionally prescribed in patients with cardiovascular and cerebrovascular diseases, as well as various non-communicable diseases (Lim and Pranata, 2020b; Pranata et al., 2020a; Yang et al., 2020). These comorbidities are also associated with higher severity and mortality related to COVID-19, and patients with these chronic, systemic or frail conditions often take aspirin routinely prior to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection (Tuty Kuswardhani et al., 2020; Pranata et al., 2021a,b,c). Thus, patients who use aspirin routinely may have more comorbidities than patients who do not use aspirin routinely. This may lead to poorer clinical outcomes in patients receiving aspirin. To minimize bias, only studies that performed an adjusted analysis with or without the use of propensity score matching were included in this review. There was an apparent benefit of the use of aspirin after pooling these studies.

Aspirin exerts not only antithrombotic, but also analgesic, antipyretic, antiviral, anti-inflammatory and immunomodulatory actions. Aspirin primarily acts by inhibiting platelet function through irreversible inhibition of COX activity. At low doses (75–81 mg/day), aspirin inhibits COX-1 and thus thromboxane A2 synthesis by platelets is reduced (antithrombotic). At intermediate-to-high doses (650–4000 mg/day), aspirin inactivates COX-1 and COX-2; blocks generation of prostaglandins; and has analgesic, antipyretic and anti-inflammatory effects (Bianconi et al., 2020; Mohamed-Hussein et al., 2020). Its antiviral activity is not clearly understood, but it seems to limit viral replication by blocking prostaglandin E2 in macrophages and upregulating generation of type I interferon (Mohamed-Hussein et al., 2020). Aspirin also downregulates the nuclear factor kappa-light-chain enhancer of activated B cells pathway, formation of cytomegalovirus-induced reactive oxygen species, inducible nitric oxide synthase and oxidative phosphorylation uncoupling, and enhances mitochondrial permeability. Aspirin-induced overactivation of haem-oxygenase-1 may lead to haem degradation, which contributes as a pro-inflammatory mediator, while D,L-lysine acetylsalicylate reduction may result in lower RNA synthesis and replication, as seen in the human CoV-229E and Middle East respiratory syndrome coronavirus (Bianconi et al., 2020).

Early antiplatelet therapy may be helpful in the setting of viral pneumonia, given its inhibitory activity on platelet activation and

Table 2
GRADE assessment.

Certainty assessment							Effect estimate (95% CI)	Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Mortality								
6	Observational studies	Serious[a]	Not serious	Not serious	Not serious	1) Publication bias strongly suspected[b]. 2) Strong association. 3) All plausible residual confounding would reduce the demonstrated effect	RR 0.46 (0.35–0.61)	⨁⨁◯◯ Low

CI, confidence interval; RR, relative risk.
[a] Retrospective studies and possible selection bias.
[b] Asymmetric funnel plot.

platelet–neutrophil aggregation, which is pivotal in thrombus generation with subsequent lung damage, and increased lipoxin synthesis, which restores the function of pulmonary endothelial cells (Middleton et al., 2016; Chow et al., 2021; Xin et al., 2020). In critically ill individuals without COVID-19, the use of aspirin was associated with a lower risk of acute respiratory distress syndrome (ARDS) and death (Wang et al., 2016; Du et al., 2018). Thus, the effect may extend beyond COVID-19-specific pathologies. In patients with COVID-19, there are high rates of VTE and disseminated intravascular coagulation due to the hypercoagulable and hyperaggregability state (Bianconi et al., 2020; Pavoni et al., 2020; Chow et al., 2021). Elevation of inflammatory and coagulation parameters and derangement of various laboratory values are noted in patients with more severe SARS-CoV-2 infection, indicating a poor prognosis (Huang et al., 2020; Akbar et al., 2021). These alterations may lead to cardiac injuries that have been strongly associated with mortality (Pranata et al., 2020b; Martha et al., 2021; Wibowo et al., 2021a,b) As a cytokine storm is the underlying mechanism behind the multi-system inflammatory process in severe COVID-19, the use of aspirin could theoretically represent a promising option in improving patient outcomes and hindering the development of fatal complications, including ARDS, coagulopathy, sepsis, multi-organ dysfunction and death (Lim et al., 2020; Pranata et al., 2021e).

Aspirin has been found to reduce the generation of C-reactive protein, interleukin-6 and macrophage colony-stimulating factor, and therefore helps in mitigating the cytokine storm as well as exerting cardiorespiratory protective actions (Mehta et al., 2020). Moreover, aspirin led to markedly lower initial plasma fibrinogen levels through fibrinogen acetylation and fibrinolysis acceleration, therefore decreasing the risk of thrombotic and bleeding events (Chow et al., 2021) However, aspirin belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs), the use of which is controversial in COVID-19 because they can exacerbate the progression of lung disease. Use of NSAIDs can alter neutrophil function and delay bacterial clearance and resolution of inflammation (Little, 2020; Micallef et al., 2020; Giollo et al., 2021). Nevertheless, the evidence is vague, and this meta-analysis indicates that the use of aspirin is beneficial.

Clinical implications

Given its widespread availability, low cost, possible efficacy and good safety profile, low-dose aspirin should be considered in the treatment of severe and critically ill COVID-19 patients. However, contraindications and the adverse effects of aspirin must always be kept in mind, especially relating to allergy, bleeding risk and Reye's syndrome in children. Given the low certainty of evidence, the risks and benefits should be weighted before administering aspirin in patients with COVID-19.

Limitations

This study has several limitations. The included studies were mainly retrospective and thus prone to bias. Cause of mortality in the included studies was not differentiated into thromboembolism, cardiovascular or all-cause mortality; as such, the authors were unable to provide details with regards to benefit. The prediction of bleeding risk is lacking due to limited data availability. There is a possibility of selection bias because of its observational nature; patients who require aspirin may be at higher risk due to underlying comorbidities or at higher risk of thrombosis, although this is partly mitigated by the multi-variable analysis and propensity score matching in several studies. However, in this case, the confounders would reduce the demonstrated effect and may actually increase the benefit. Concomitant use of angiotensin receptor blockers, anticoagulants and statins, known to decrease mortality, may potentially confound the analysis (Kow and Hasan, 2020; Lemos et al., 2020; Pranata et al., 2020c; Wijaya et al., 2020; Permana et al., 2021). Additionally, although these analyses were adjusted for confounders, this does not necessarily mean that adjustments were made for all confounders. There may be confounders that were not reported and analysed by the authors of the included studies. Further large double-blind, placebo-controlled randomized controlled trials are needed for a definite conclusion.

Conclusion

Use of low-dose aspirin is independently associated with reduced mortality in patients with COVID-19, with low certainty of evidence.

Authors' contributions

Januar Wibawa Martha: conceptualization, investigation, writing – review and editing, supervision.

Raymond Pranata: conceptualization, methodology, software, data curation, formal analysis (meta-analysis), investigation, validation, writing – original draft, writing – review and editing.

Michael Anthonius Lim: data curation, investigation, writing – original draft.

Arief Wibowo: investigation, writing – original draft.

Mohammad Rizki Akbar: investigation, writing – review and editing.

Conflict of interest

None declared.

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Ethical approval

Not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.05.016.

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