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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Clinical Epidemiology and Global Health 12 (2021) 100883

Contents lists available at ScienceDirect

Clinical Epidemiology and Global Health

journal homepage: www.elsevier.com/locate/cegh

The effects of aspirin on the outcome of COVID-19: A systematic review and meta-analysis

Indra Wijaya [a,*], Rizky Andhika [b], Ian Huang [c], Aga Purwiga [c], Kevin Yonatan Budiman [c]

[a] Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital, Bandung, Indonesia
[b] Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital, Bandung, Indonesia
[c] Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital, Bandung, Indonesia

ARTICLE INFO

Keywords:
Aspirin
Acetylsalicylic acid
SARS-CoV-2
COVID-19
Mortality

ABSTRACT

Background: Repurposing the use of aspirin to treat hospitalized patients with COVID-19 is a sensible approach. However, several previous studies showed conflicting results. This meta-analysis was aimed to assess the effect of aspirin on the outcome in patients with COVID-19.

Methods: Systematic search using relevant keywords was carried out via several electronic databases until February 21, 2021. Research studies on adults COVID-19 patients with documentation on the use of aspirin and reported our outcomes of interest were included in the analysis. Our main outcome of interest was all types of mortality, while the incidence of thrombosis and bleeding were considered as secondary outcomes. Estimated risk estimates of the included studies were then pooled using DerSimonian-Laird random-effect models regardless heterogeneity.

Results: Seven studies with a total of 34,415 patients were included in this systematic review and meta-analysis. The use of aspirin was associated with a reduced risk of mortality (RR 0.56, 95% CI 0.38–0.81, P = 0.002; I^2: 68%, P = 0.005). Sensitivity analysis by differentiating in-hospital (active aspirin prescription) and pre-hospital use of aspirin could significantly reduce the heterogeneity (I^2: 1%, P = 0.4). Only one study reported the incidence of major bleeding between aspirin and non-aspirin users (6.1% vs. 7.6%, P = 0.61). The association between the use of aspirin and the incidence of thrombosis were contradictory in two studies.

Conclusion: The use of aspirin was significantly associated with a reduced risk of mortality among patients with COVID-19. Due to limited studies, the effect of aspirin on the incidence of thrombosis and bleeding in patients with COVID-19 could not be drawn definitively.

1. Introduction

The arrival of promising SARS-CoV-2 vaccination seems could end this pandemic by developing specific antibodies to prevent severe COVID-19 infection, however, treatment for hospitalized patients with COVID-19 should not be disregarded, especially in patients with multi-comorbidities.[1–3] In order to expedite the discovery of treatment option for COVID-19, drug repurposing approach is considered as an attractive strategy due to its superiority over conventional strategy in terms of time, cost, and safety.[4]

Among those option, repurposing the use of acetylsalicylic acid (ASA, aspirin) is a reasonable choice. Aspirin is well-known for its anti-inflammatory, analgesic, and antithrombotic properties.[5] It has been suggested as an antiviral agent due to its effect against DNA and RNA viruses.[6] Aspirin was previously reported as capable in reducing RNA synthesis and replication of human coronavirus-299E (CoV-229E) and Middle East Respiratory Syndrome (MERS)-CoV in one *in vitro* study.[7] Remarkably, the use of aspirin in COVID-19 is still controversial due to conflicting results. Chow et al. showed the use of aspirin was associated with improved outcome among hospitalized patients with COVID-19,[8] while Yuan et al. and Sahai et al. reported otherwise.[9,10]

Therefore, this systematic review was aimed to assess the effect of aspirin on the outcome of hospitalized patients with COVID-19.

* Corresponding author.
E-mail addresses: indrawijayaipd@gmail.com, indra.wijaya@unpad.ac.id (I. Wijaya), rizkyandhikaipd@gmail.com (R. Andhika), ianhuang2108@gmail.com (I. Huang), aga.purwiga@gmail.com (A. Purwiga), kevinyb@icloud.com (K.Y. Budiman).

https://doi.org/10.1016/j.cegh.2021.100883
Received 8 June 2021; Received in revised form 4 October 2021; Accepted 26 October 2021
Available online 30 October 2021
2213-3984/© 2021 Published by Elsevier B.V. on behalf of INDIACLEN. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

2. Methods

This systematic review and meta-analysis followed The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11]

2.1. Eligibility criteria

The inclusion criteria were: (1) Research studies (either non-randomized or randomized studies) with no language restriction, (2) in hospitalized adults patients (>18 years old) with confirmed COVID-19 based on reverse transcriptase - polymerase chain reaction (RT-PCR) test, (3) receiving aspirin, and (4) reported our clinical outcomes of interest. Our main outcome of interest was all types of mortality, including in-hospital mortality and 14- or 28-days (30-days) mortality. Additional secondary outcome were the reported incidence of thrombosis and bleeding.

The exclusion criteria were: (1) abstract-only publication, (2) review articles, (3) commentaries/editorial/viewpoints, and 4) non-research letters.

2.2. Search strategy

PubMed, EuropePMC, and SCOPUS, were the electronic databases used for the systematic search in this study. (("COVID-19" AND "aspirin") OR ("SARS-CoV-2" AND "aspirin") OR ("COVID-19" AND "acetylsalicylic acid") OR ("SARS-CoV-2" AND "acetylsalicylic acid")) AND ("mortality" OR "severe" or "severity"), were the relevant keywords used to perform a literature search from the date of inception up to February 21, 2021. After obtaining the initial results, any duplicate records were removed. Potential articles were sorted after titles and abstracts screening. Afterwards, the full texts of the remaining articles were assessed for relevance based on eligibility criteria.

2.3. Data collection and study quality assessment

Systematic searching of studies, study inclusion assessment, data extraction, and risk of bias assessment were conducted independently by three authors. Variables included for data extraction were first author, year, study design, location, total samples, age, gender, use of aspirin, use of concurrent anticoagulants, mortality, adjusted effect estimate, covariates adjustment, incidence of thrombosis and bleeding. All the data were then contained within a pre-built form. The Newcastle–Ottawa Scale (NOS), a risk of bias tool assessment tool for non-randomized studies,[12] was used by the three authors for quality assessment and risk of bias in the studies. A study which scored ≥7 was considered as a high-quality study. Any disagreements of data extraction and quality assessment were resolved through discussion.

2.4. Data synthesis and statistical analysis

Meta-analysis of the included studies was conducted using STATA 16 (StataCorp LLC, Texas, US). Reported measures of odds ratio (OR), hazard ratio (HR), and risk ratio of the outcomes of interests were considered as equivalent measures of risk estimates and would be defined as relative risk (RR) in this study. DerSimonian-Laird random-effect models were used to pool RRs of all included studies regardless of its heterogeneity. Two-tailed p-value was used and a value ≤ 0.05 was considered statistically significant. Inter-study heterogeneity was assessed using I^2 statistics with a value > 50% or P-value <0.10 suggesting significant heterogeneity. Any significant heterogeneity was further assessed with leave-one-out sensitivity analysis. Funnel-plot analysis and Egger's test were used for assessing the risk of publication bias.

3. Results

3.1. Study selection and characteristics

There were 2204 records from our initial searches, which was reduced to 1895 after duplicates removal [Fig. 1]. We excluded 1882 records after title and abstract screening. After assessing 13 full-texts of the remaining articles for eligibility, 6 articles were excluded from the final analysis. The exclusion were due to the absence of outcome of interest (n = 2), meta-analysis (n = 2), case series (n = 1), and aspirin was concurrently used in combination with other drugs (n = 1).

Thereby, seven studies with a total of 34,415 patients included in this systematic review and meta-analysis.[8,10,13–17] The characteristics of the included studies are shown in Table 1.

3.2. Aspirin and mortality

The use of aspirin was associated with a reduced risk of mortality (RR 0.54, 95% CI 0.37–0.79, P = 0.002; I^2: 68%, P = 0.003) [Fig. 2]. Leave-one out sensitivity analysis by excluding Alamdari et al. could significantly reduce the heterogeneity (I^2: 36%, P = 0.17). Moreover, further sensitivity analysis by differentiating in-hospital (active aspirin prescription) and pre-hospital use of aspirin could reduce the heterogeneity to negligible (RR 0.41, 95% CI 0.35–0.48, P < 0.00001; I^2: 1%, P = 0.4). Yuan et al. and Alamdari et al. were the only studies which defined aspirin group as pre-hospital use of aspirin without any documentation of its use while being hospitalized.[9,16]

3.3. Aspirin, bleeding events, and incidence of thrombosis

The incidence of bleeding among patients taking aspirin was reported by Chow et al. with comparable incidence on both groups (6.1% vs. 7.6%, p = 0.61),[8] whereas the rest of the included studies did not report any account of bleeding events. Chow et al. defined the incidence of major bleeding as either bleeding that led to a hemoglobin <7 g/dL and required red blood cells (RBC) transfusion, bleeding that needed transfusion ≥2 packs of RBC in 24 h, intracranial bleeding, gastrointestinal bleeding required RBC transfusion, ocular bleeding, nasopharyngeal bleeding that required intervention, or any bleeding that required surgical intervention.[8]

Two studies reported the incidence of thrombosis with contradictory results.[10,18] Chow et al. reported insignificant difference of overt thrombotic events, which they defined as any incidences of deep vein thrombosis, pulmonary embolism, ischemic stroke, peripheral arterial occlusion, or ST-elevation myocardial infarction, between aspirin users and non-aspirin users (8.2% vs 8.9%, P = 0.82). Remarkably, Sahai et al. showed increased incidence of thrombotic stroke (3.6% vs 0.4%, P = 0.036) and composite thrombotic events, which included myocardial infarction, thrombotic stroke, venous thromboembolism (9.3% vs. 2.8%, P = 0.005) among patients taking aspirin10.

3.4. Study quality assessment and risk of bias

All the included studies were considered as high-quality studies, as depicted by NOS ≥7 (Table 1). The funnel plot for the association between the use of aspirins and mortality was asymmetrical [Fig. 3]. Small study effects assessment using Egger's test was significant (P = 0.042).

4. Discussion

This current meta-analysis showed that the use of aspirin was significantly associated with a reduced risk of mortality among patients with COVID-19. The risk of mortality is almost halved if compared to COVID-19 patients not taking aspirin. Remarkably, the result of our study was contradicting with previous meta-analysis by Salah et al.[19] which reported no associations between the use of aspirin and risk of

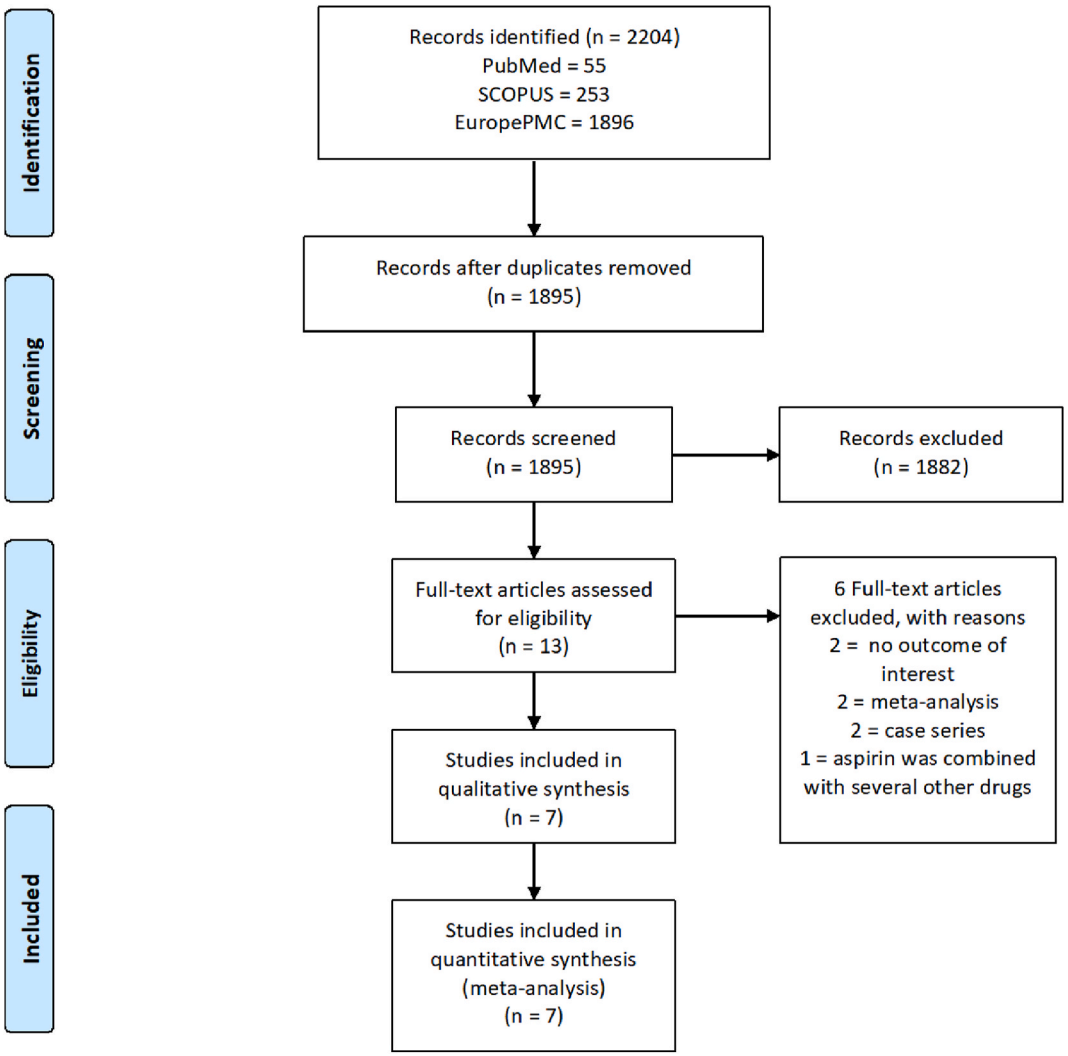

Fig. 1. PRISMA flow diagram.

mortality in patients with COVID-19. The notable differences between the previous study and our meta-analysis were the quantity of the included studies and a different statistical approach. Salah et al. calculated unadjusted risk ratio based on number of events per total between aspirin and non-aspirin users,[19] while we used adjusted risk estimates based on each individual studies calculation. Using adjusted risk estimates is important in retrospective studies in which multi-variables could become confounders and affect the outcomes of interest. For example, Chow et al. showed risk ratio of 1.14 (95% CI 0.78–1.68) based on Salah et al. analytical calculation.[19] While this was not incorrect, it was an unadjusted risk estimate with unequal baseline characteristics between the two groups as reported by Chow et al.[8] It was only after adjustment that they found a significant association between the use of aspirin and in-hospital mortality (HR 0.53, 95% CI 0.31–0.90, P = 0.02).[8] Furthermore, our finding was in line with Martha et al. which also used adjusted risk estimates and found significant association between aspirin and reduced risk of mortality in smaller number of studies.[20]

While we found the benefits of aspirin in reducing mortality among patients with COVID-19, we also noted the high heterogeneity between studies. In our sensitivity analysis, we found that the differentiation between in-hospital use (active use) and pre-hospital use was the major issue. The distinction between those two groups was able to reduce heterogeneity significantly. This differentiation has previously been demonstrated to be important in COVID-19 patients taking chronic drugs (e.g. statins) which ultimately affected study outcome.[21]

Aspirin, a commonly known antiplatelet agent, carries anti-inflammatory, analgesic, antipyretic, and anti-thrombotic effects by inhibiting prostaglandin (PG) and thromboxane (TX) production through irreversible inactivation of both cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2).[22] Moreover, antiviral properties of aspirin have previously been documented in both DNA and RNA viruses, including cytomegalovirus, varicella-zoster virus, rhinovirus, coxsackie virus, hepatitis c virus, H1N1 influenza virus, MERS-CoV, and CoV-229E.[6,7,23–25] Aspirin exhibits its antiviral properties mainly through the modulation of nuclear factor kappa beta (NF-κB) pathway,[7,26] although NF-κB-independent antiviral effects have also been documented.[27] NF-κB is a protein transcription factor that acts as a regulator of innate immunity against wide range of invading pathogens.[28] Viruses interfere the NF-κB signalling pathway by encoding several NF-κB inhibitors and ultimately escape the host immunity.[29]

It is widely recognized that there are distinct phases in SARS-CoV-2 infection, including the early phase of viral invasion response and the latter phase of host systemic inflammatory response,[30] which ultimately may lead to lethal multi organ failure through the unopposed state of hyperinflammation and hypercoagulation.[31,32] Theoretically, aspirin might have roles in both phases (Table 2). In the early phase of the disease, antiviral and anti-inflammation features of aspirin might reduce viral replications and limiting the release of pro-inflammatory mediators, respectively. Hence, administration of aspirin in this phase might

Table 1
Baseline Characteristics of the included studies.

Authors (year)	Design (Location)	Sample (Aspirin vs Non-Aspirin)	Male (%)	Age	CAD (%)	Aspirin Administration	Aspirin Inititation (Days)	Anticoagulation	Mortality (Aspirin vs Non-Aspirin)	Adjusted Estimate (95% CI)	Adjusted covariates (or PSM)	Thrombosis (%)	Bleeding (%)	NOS
Chow (2020)	RC, Multi-center (USA)	412 (98 vs 314)	62.2 vs 58.3	61 (55–72) vs 52 (37–65)	34.7 vs 5.7	81 mg OD, 6 days (3–12 days), in-hospital	0 (0–1 days)	Therapeutic-dose of Heparin: 27 (27.6) vs 77 (24.5)	In-hospital: 26 (26.5) vs 73 (23.2)	aHR: 0.53 (0.31–0.90)	Age, gender, BMI, ethnicity, HTN, DM, CAD, home beta-blocker, renal disease	8 (8.2) vs 28 (8.9), p = 0.82	6 (6.1) vs 24 (7.6), p = 0.61	8
Liu (2021)	RC, Single-Center (China)	232 (28 vs 204) After PSM Cohort 1:1 (24 vs 24)	64.3 vs 53.4	69.5 (61–77) vs 54 (42–65)	53.6 vs 1.5	100 mg OD, minimum 5 days, in-hospital	NA	NA	30-day: 1 (3.6) vs 9 (4.4) PSM 30-day: 1 (4.17) vs 7 (29.2)	PSMHR: 0.19 (0.05–0.78)	Age, gender, comorbidities, symptoms on admission, main laboratory findings on admission, and systemic corticosteroids medication	NA	NA	9
Osborne (2020)	RC, Multi-Center (USA)	28350 (6842 vs 21508) After PSM 1:1 (6814 vs 6814)	95.3 vs 87.2	67.5 vs 55.5	NA	NA, In-hospital	NA	NA	PSM 30-day: 4.3 vs 10.5	OR:0.68 (0.59–0.77) aOR: (0.33–0.45)	age, gender, and CAN score	NA	NA	8
Sahai (2020)	RC, Multi-center (USA)	1994 (285 vs 1709) After PSM 1:1 (248 vs 248)	60.4 vs 48.7	70.0 vs 50.6	36.4 vs 8.3	81 mg OD, in-hospital	NA	Therapeutic-dose: 56 (19.6) vs 94 (5.5) Prophylactic-dose: 215 (75.4) vs 355 (20.8)	PSM in-hospital: 33 (13.3) vs 38 (15.3)	aOR: 0.5 (0.51–1.41)	Demographics, and all clinical covariates	Thrombotic stroke: 9 (3.6) vs 1 (0.40) MI: 5 (2.0) vs 2 (0.81) VTE: 10 (4.0) vs 4 (1.6) Composite: 23 (9.3) vs 7 (2.8)	NA	8
Meizlish (2021)	RC, Multi-Center (USA)	2785 (964 vs 1821) After PSM 1:1 (319 vs 319)	50 vs 50	>60 years: 54.2 vs 54.2	54.5 vs 55.5	81 mg OD, in-hospital	NA	Therapeutic/ Intermediate-dose: 194 (60.8) vs 156 (48.9) Prophylactic-dose: 125 (39.2) vs 163 (51.1)	In-hospital: 153 (15.9) vs 230 (12.6)	aHR: 0.522 (0.336–0.812)	Anticoagulation, Age, Sex, Obesity, cardiovascular disease, Africal-American race, D-dimer, Rothman Index	NA	NA	8
Yuan (2020)	RC, Single-Center (China)	183 (52 vs 131)	59.6 vs 51.9	69.7 vs 71.8	100 vs 100	75–150 mg OD, Pre-hospital	NA	NA	In-hospital: 11 (21.2) vs 29 (22.1)	aOR 0.944 (0.411–2.172)	Age, sex, CKD	NA	NA	8
Alamdari (2020)	RC, Single Center (Iran)	459 (53 vs 406)	69.7	61.8	40.3	NA, Pre-hospital	NA	NA	In-hospital: 9 (16.9) vs 54 (13.3)	OR: 1.28 (0.67–2.43)	Not adjusted	NA	NA	7

BMI: Body-mass Index; CAD: Coronary artery disease; CAN: Care Assessment Need; CI: Confidence Interval; CKD: Chronic Kidney Disease; DM: Diabetes Mellitus; HTN: Hypertension; NA: Not Available; NOS: Newcastle-Ottawa Scale; PSM: Propensity-Score Matching; RC: Retrospective Cohort; aOR: Adjusted Odds Ratio; aHR: Adjusted Hazard Ratio.
Data is mainly presented as Aspirin users (%) vs Non-Aspirin users (%), if not available, total percentage in both groups will be presented.

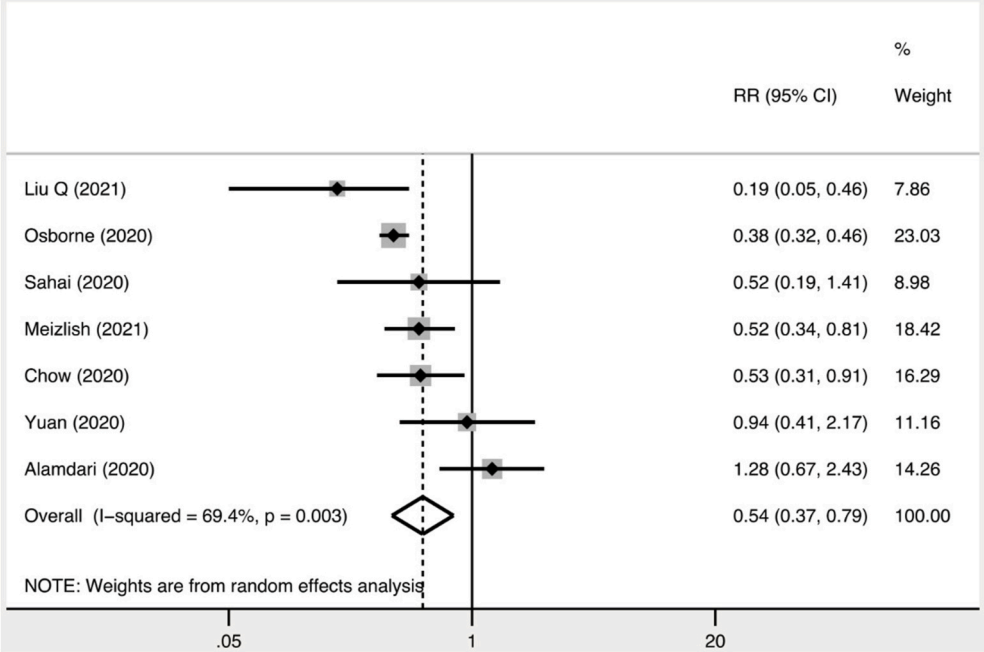

Fig. 2. Forest plot showing overall effect estimates of Aspirin and risk of mortality. RR: Relative Risk; CI: Confidence Interval.

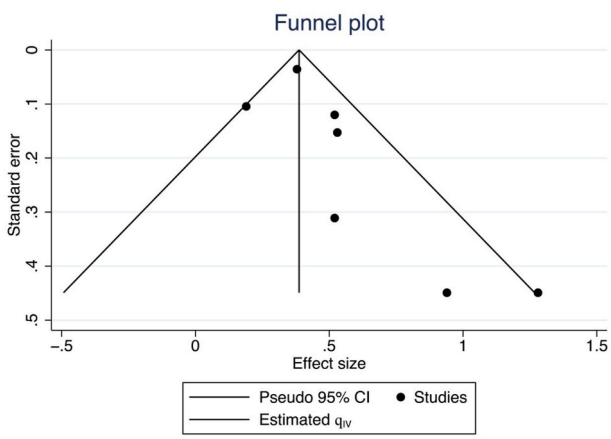

Fig. 3. Funnel plot of aspirin and mortality.

supposedly reduce the risk of developing severe COVID-19. On the other hand, in the late phase of illness where hyperinflammation and hypercoagulable state ensue, introducing aspirin might probably reduce the severity of cytokine storm syndrome through modulation of inflammation, and may prevent fatal thrombosis via several pathways, including acetylation of prothrombin and platelets membranes, and impairing the neutrophil extracellular traps.[33]

Although this meta-analysis showed evidence of potential benefits of using aspirin among patients with COVID-19, there were several concerns before its implementation in clinical practice. All the included studies were retrospective in nature, therefore, the strength of the association could not be measured accurately. The dose, number of days, and timing of aspirin administration were mostly not reported in all studies, therefore, further randomized controlled trials with appropriate blinding and valid study protocols are necessary to evaluate and confirm its benefit among patients with COVID-19. Lastly, asymmetrical funnel plot and positive Egger's test should be taken into account for the possibility of publication bias.

Table 2
Possible role of Aspirin in COVID-19.

Possible role of Aspirin in SARS-CoV-2	Molecular mechanism of action	References
Anti-inflammatory effect	Non-selective inhibitor of cyclo-oxygenase (COX-1 and COX-2) enzymes	34
	Inducing overactivation Heme oxygenase-1	35
Modulation of immune system and inhibition of viral replication and/or entry	Reducing reactive oxygen species (ROS) production and nuclear factor kappa beta (NF-κB) activation	7,26
	Stimulating over-expression of ubiquitin-protein ligase E6A, adenylosuccinate lyase, and nibrin	25
	Enhancing proteosomal degradation of claudin-1	36
	Reducing virus affinity to CCAAT/enhancer-binding protein-beta (C/EBP-β)	37
	Enhancing the expression and activity of Cu/Zn superoxide dismutase (SOD1)	38
	Inhibiting of prostaglandin-E2 (PGE2) activity in macrophages and upregulating of interferon type I (IFN–I) production	39
	Dose dependent anti-viral activity with unknown molecular mechanism	6
	D-L lysine acetylsalicylate interferes NF- κB activation	7
Anti-thrombotic effect	Inhibiting the production of Thromboxane-A2	22,34,
	Acetylation of proteins (e.g., fibrinogen) involved in the coagulation cascade	33

5. Conclusion

The use of aspirin was significantly associated with a reduced risk of mortality among patients with COVID-19. Due to limited studies, the effect of aspirin on the incidence of thrombosis and bleeding in patients

with COVID-19 could not be drawn definitively.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Data availability

The data used to support the findings of this study are included in the article.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgement

None.

References

1 Pranata R, Supriyadi R, Huang I, et al. The association between chronic kidney disease and new onset renal replacement therapy on the outcome of COVID-19 patients: a meta-analysis. *Clin Med Insights Circulatory, Respir Pulm Med*. 2020;14. https://doi.org/10.1177/1179548420959165, 117954842095916.
2 Andhika R, Huang I, Wijaya I. Severity of COVID-19 in end-stage kidney disease patients on chronic dialysis. *Ther Apher Dial*. 2020;50. https://doi.org/10.1111/1744-9987.13597.
3 Pranata R, Henrina J, Lim MA, et al. Clinical frailty scale and mortality in COVID-19: a systematic review and dose-response meta-analysis. *Arch Gerontol Geriatr*. 2021;93: 104324. https://doi.org/10.1016/j.archger.2020.104324.
4 Singh TU, Parida S, Lingaraju MC, Kesavan M, Kumar D, Singh RK. Drug repurposing approach to fight COVID-19. *Pharmacol Rep*. 2020;72:1479–1508. https://doi.org/10.1007/s43440-020-00155-6.
5 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;80:1383–1396. https://doi.org/10.1007/s40265-020-01365-1.
6 Glatthaar-Saalmüller B, Mair KH, Saalmüller A. Antiviral activity of aspirin against RNA viruses of the respiratory tract-an in vitro study. *Influenza Other Respi Viruses*. 2017;11:85–92. https://doi.org/10.1111/irv.12421.
7 Müller C, Karl N, Ziebuhr J, Pleschka S. L-lysine acetylsalicylate+ glycine impairs coronavirus replication. *J Antivir Antiretrovir*. 2016;8:142–150.
8 Chow JH, Khanna AK, Kethireddy S, 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: 930–941. https://doi.org/10.1213/ANE.0000000000005292.
9 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;25:1263–1273. https://doi.org/10.1111/jcmm.16198.
10 Sahai A, Bhandari R, Koupenova M, et al. SARS-CoV-2 receptors are expressed on human platelets and the effect of aspirin on clinical outcomes in COVID-19 patients. *Res Sq*. 2020. https://doi.org/10.21203/rs.3.rs-119031/v1.
11 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:332–336. https://doi.org/10.1136/bmj.b2535.
12 Wells G, Shea B, O'Connell D, et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*; 2013. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed August 17, 2020.
13 Liu Q, Huang N, Li A, et al. Effect of low-dose aspirin on mortality and viral duration of the hospitalized adults with COVID-19. *Medicine (Baltim)*. 2021;100, e24544. https://doi.org/10.1097/MD.0000000000024544.
14 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;25:1263–1273. https://doi.org/10.1111/jcmm.16198.
15 Osborne TF, Veigulis ZP, Arreola DM, Mahajan SM, Röösli E, Curtin CM. Association of mortality and aspirin prescription for COVID-19 patients at the Veterans Health Administration. *PLoS One*. 2021;16, e0246825. https://doi.org/10.1371/journal.pone.0246825.
16 Alamdari NM, Afaghi S, Rahimi FS, et al. Mortality risk factors among hospitalized COVID-19 patients in a major referral center in Iran. *Tohoku J Exp Med*. 2020;252: 73–84. https://doi.org/10.1620/tjem.252.73.
17 Meizlish ML, Goshua G, Liu Y, et al. Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: a propensity score-matched analysis. *Am J Hematol*. 2021. https://doi.org/10.1002/ajh.26102.
18 Chow LC, Chew LP, Leong TS, Mohamad Tazuddin EE, Chua HH. Thrombosis and bleeding as presentation of COVID-19 infection with polycythemia vera. A case report. *SN Compr Clin Med*. 2020:1–5. https://doi.org/10.1007/s42399-020-00537-0.
19 Salah HM, Mehta JL. Meta-analysis of the effect of aspirin on mortality in COVID-19. *Am J Cardiol*. 2021;142:158–159. https://doi.org/10.1016/j.amjcard.2020.12.073.
20 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. https://doi.org/10.1016/j.ijid.2021.05.016.
21 Permana H, Huang I, Purwiga A, et al. In-hospital use of statins is associated with a reduced risk of mortality in coronavirus-2019 (COVID-19): systematic review and meta-analysis. *Pharmacol Rep*. 2021. https://doi.org/10.1007/s43440-021-00233-3.
22 Diaz T, Trachtenberg BH, Abraham SJK, KosagiSharaf R, Durant-Archibold AA. Aspirin bioactivity for prevention of cardiovascular injury in COVID-19. *Front Cardiovasc Med*. 2020;7:562708. https://doi.org/10.3389/fcvm.2020.562708.
23 Speir E, Yu ZX, Ferrans VJ, Huang ES, Epstein SE. Aspirin attenuates cytomegalovirus infectivity and gene expression mediated by cyclooxygenase-2 in coronary artery smooth muscle cells. *Circ Res*. 1998;83:210–216. https://doi.org/10.1161/01.RES.83.2.210.
24 Primache V, Binda S, De Benedittis G, Barbi M. In vitro activity of acetylsalicylic acid on replication of varicella-zoster virus. *New Microbiol*. 1998;21:397–401.
25 Sánchez-García A, Ríos-Ibarra CP, Rincón-Sánchez AR, et al. Use of proteomic analysis tools to identify HCV-proteins down-regulated by acetylsalicylic acid. *Ann Hepatol*. 2013;12:725–732. https://doi.org/10.1016/s1665-2681(19)31313-4.
26 Mazur I, Wurzer WJ, Ehrhardt C, et al. Acetylsalicylic acid (ASA) blocks influenza virus propagation via its NF-κB-inhibiting activity. *Cell Microbiol*. 2007;9:1683–1694.
27 Liao CL, Lin YL, Wu BC, et al. Salicylates inhibit flavivirus replication independently of blocking nuclear factor kappa B activation. *J Virol*. 2001;75:7828–7839. https://doi.org/10.1128/jvi.75.17.7828-7839.2001.
28 Albensi BC. What is nuclear factor kappa B (NF-κB) doing in and to the mitochondrion? *Front Cell Dev Biol*. 2019;7:154. https://doi.org/10.3389/fcell.2019.00154.
29 Deng L, Zeng Q, Wang M, et al. Suppression of NF-κB activity: a viral immune evasion mechanism. *Viruses*. 2018;10. https://doi.org/10.3390/v10080409.
30 Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant*. 2020;39:405–407. https://doi.org/10.1016/j.healun.2020.03.012.
31 Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. *Ther Adv Respir Dis*. 2020;14. https://doi.org/10.1177/1753466620937175, 175346662093717.
32 Wijaya I, Andhika R, Huang I. The use of therapeutic-dose anticoagulation and its effect on mortality in patients with COVID-19: a systematic review. *Clin Appl Thromb Hemost*. 2020;26. https://doi.org/10.1177/1076029620960797, 107602962096079.
33 Undas A, Brummel-Ziedins KE, Mann KG. Antithrombotic properties of aspirin and resistance to aspirin: beyond strictly antiplatelet actions. *Blood*. 2007;109: 2285–2292.
34 Crescente M, Menke L, Chan MV, Armstrong PC, Warner TD. Eicosanoids in platelets and the effect of their modulation by aspirin in the cardiovascular system (and beyond). *Br J Pharmacol*. 2019;176:988–999. https://doi.org/10.1111/bph.14196.
35 Wu B, Wu Y, Tang W. Heme catabolic pathway in inflammation and immune disorders. *Front Pharmacol*. 2019;10:825. https://doi.org/10.3389/fphar.2019.00825.
36 Yin P, Zhang L. Aspirin inhibits hepatitis C virus entry by downregulating claudin-1. *J Viral Hepat*. 2016;23:62–64. https://doi.org/10.1111/jvh.12446.
37 Ríos-Ibarra CP, Lozano-Sepulveda S, Muñoz-Espinosa L, Rincón-Sánchez AR, Cordova-Fletes C, Rivas-Estilla AMG. Downregulation of inducible nitric oxide synthase (iNOS) expression is implicated in the antiviral activity of acetylsalicylic acid in HCV-expressing cells. *Arch Virol*. 2014;159:3321–3328. https://doi.org/10.1007/s00705-014-2201-5.
38 Rivas-Estilla AM, Bryan-Marrugo OL, Trujillo-Murillo K, et al. Cu/Zn superoxide dismutase (SOD1) induction is implicated in the antioxidative and antiviral activity of acetylsalicylic acid in HCV-expressing cells. *Am J Physiol Gastrointest Liver Physiol*. 2012;302. https://doi.org/10.1152/ajpgi.00237.2011.
39 Coulombe F, Jaworska J, Verway M, et al. Targeted prostaglandin E2 inhibition enhances antiviral immunity through induction of type I interferon and apoptosis in macrophages. *Immunity*. 2014;40:554–568.