Efficacy and safety of antiplatelet agents in patients with COVID-19 a systematic review and meta-analysis of observational studies

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Systematic Review

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Abstract

Coagulopathy and thrombotic events have been reported in patients with coronavirus disease 2019 (COVID-19) frequently. However, the use of antiplatelet agents in COVID-19 is yet to be investigated. This article systematically reviewed the relationship between use of antiplatelet agents and major outcomes of COVID-19 patients. In total, 12 studies met our eligibility criteria. Due to high heterogeneity, we excluded three studies with high risk of bias. The result showed that antiplatelet therapy did not related to a higher mortality of COVID-19 patients (OR=1.01, 95% CI=0.77-1.33, I²=0%, P=0.88). However, the use of antiplatelet agents was associated with a lower risk of ICU admission (OR=0.63, 95% CI= 0.40-0.98, I²=0%, P=0.68) and mechanical ventilation (OR=0.57, 95% CI= 0.38-0.85, I²=0%, P=0.75) compared with those without antiplatelets. In conclusion, current results did not support that antiplatelets will cause greater mortality in patients with COVID-19 infection. Antiplatelet agents should be continued in COVID-19 patients, unless clinically indicated.

Introduction

An outbreak of coronavirus disease 2019 (COVID-19) is responded to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) occurred[1]. It has been declared as a global pandemic on 11 March 2020. Until 30 March 2020, more than 12 million have been infected, and over 2.8 million deaths in COVID-19[2]. A prominent signature of COVID-19 is high risk of thrombosis, which complicates SARS-CoV-2 infection[3].

SARS-CoV-2 leads to diffuse endothelial inflammation and dysfunction via angiotensin converting enzyme (ACE-2) receptors, which will disturb the hemostatic balance[4]. Simultaneously, platelet adhesion and aggregation initiated, thromboinflammatory process developed gradually. Activation of platelet has been considered to be crucial for promoting the pathogenesis by maintaining the severe inflammatory in respiratory system, which exacerbated acute lung injury and death at the late postinfarction time points[5, 6].

Since there is no validate treatment, many existing drugs have been tried for the treatment of COVID-19. Aspirin is a typical antiplatelet agent with strong anti-inflammatory and anti-thrombotic effects, which is related to the reduced mortality and lower risk of acute respiratory distress syndrome in severe patients without COVID-19[7, 8]. However, current use of aspirin for patients with COVID-19 is still controversial.

Our understanding of the efficacy and safety of antiplatelet agents in COVID-19 still in early stages. Until now, few randomized clinical trial data regarding to antiplatelet agents for patients with COVID-19 could be obtained. Hence, summarizing the efficacy and safety of antiplatelet agents in COVID-19 patients timely may help more physicians to administer antiplatelet agents properly. In this review, we summarized the association between antiplatelet drugs and adverse outcomes of patients with COVID-19, and analyzed the benefits and risks.

Method

2.1 Literature search

This review was conducted in accordance with the guidelines of preferred reporting items stated in the system review and meta-analysis (PRISMA) to ensure high quality of evidence. PubMed, MEDLINE, Google Scholar, Scopus, the Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL), and Chinese databases (CNKI, WANFANG and Sino Med) were searched from beginning to 31 March 2021 to update our preliminary results. The search was restricted for English and Chinese articles, which were published after 31st of December, 2019. The full search strategy is included in (Figure 1).

2.2 Inclusion and Exclusion Criteria

The searched articles were imported into EndNote reference management software. Two independent investigators screened the title/abstracts firstly to identify potentially eligible studies, then any duplicate is removed. Observational studies about antiplatelet agents on adults (≥ 18 years) patients with COVID-19, except for narrative reviews or opinion-based publications, were included, and other relevant information. When the information was incomplete in the articles, we attempted to contact the corresponding authors to get it.

2.3 Data extraction

Data was extracted and coded in the electronic spreadsheet by two reviewers. Baseline characteristics: title, study year, first author, study country, sample size, etc. Patient characteristics: age, gender, intervention measures and the name of antiplatelet agents, etc. Outcome: number of deaths, number of patients with mechanical ventilation, intensive care unit (ICU) admission.

2.4 Statistical analysis

In this study, the statistical analyses were performed with Cochrane RevMan 5.3. The Newcastle-Ottawa Scale (NOS) was applied for assessing the quality of cohort and case control was used to evaluate the included studies[9]. The scores were recorded in the electronic spreadsheet by two reviewers. They were blinded to each other's decisions. If there was any disagreement, it was resolved by discussion or consultation with the third review.

For dichotomous variables, Mantel-Haenszel formula was applied for the calculation of odds ratios (OR) and 95% confidence intervals (95% CI). The level of heterogeneity among the studies was assessed by I^2 statistic. If $I^2 \leq 50\%$, suggesting that the results were homogeneous, and the fixed effect model was used. If $I^2 > 50\%$, accompanied by $P < 0.05$, indicating that the results were heterogeneous, so the random effects model was performed in the present analysis. If significant heterogeneity was found, the analysis of subgroups will be conducted. Funnel plots were used to assess publication bias.

Results

3.1 Patient characteristics

The characteristics of patients included in this study are shown in **Table 1**.

All of the selected studies were published in 2020 and 2021 with different sample patient sizes that ranged from 31 to 26346 patients. The average age of the subjects was ranged from 52 to 79. Eleven included studies compared mortality outcomes of COVID-19 patients using antiplatelet agents with non-users. Two studies compared mechanical ventilation outcomes, while 2 compared ICU admission outcomes, respectively. Nine studies included 30582 patients with COVID-19 totally, 7184/30582(23.5%) of who were treated with aspirin alone. Three studies were conducted in China, 3 in the USA, 2 in the UK, and 1 each from Italy, Iran, and Israel. The results of the quality assessment of the selected studies are presented in Supplementary Table S1 and S2.

3.2 Meta-analysis

3.2.1 Use of antiplatelet agents and mortality of COVID-19 patients

The mortality analysis included eleven studies. In the studies included, 7260 COVID-19 patients treated with antiplatelet agents and 23673 without antiplatelet agents. The risk associated with antiplatelet therapy and death was verified. Overall, the risk of mortality in patients with antiplatelet agents was similar to those without antiplatelet agents (OR = 0.67, 95 % CI: 0.41-1.09, $I^2=89\%$, $P < 0.001$) (**Figure 2A**). However, there was high heterogeneity among the included studies. In the following sensitivity analysis, we excluded three studies with high risk of bias. Without obvious heterogeneity, the pooled adjusted result indicated no significant association between antiplatelet agents and mortality (OR=1.01, 95% CI=0.77-1.33, $I^2=0\%$, $P=0.88$) (**Figure 2B**).

3.2.2 Use of antiplatelet agents and risk of mechanical ventilation, ICU admission in COVID-19 patients

Two studies provided the data in terms of antiplatelet agents and the risk of ICU admission in COVID-19 patients. Fixed-effect model was used for further assessment, for low heterogeneity in these studies. The result suggested that patients with antiplatelet agents at a lower risk of ICU admission (OR=0.63, 95% CI= 0.40-0.98, $I^2=0\%$, $P=0.68$) (**Figure 3A**). Two studies were evaluated for antiplatelet agents and the risk of mechanical ventilation. We observed that patients who have received antiplatelet agents got a lower risk of mechanical ventilation (OR=0.57, 95% CI= 0.38-0.85, $I^2=0\%$, $P=0.75$) (**Figure 3B**).

3.2.3 Subgroup analysis

To further explore the correlation between antiplatelet agents and mortality, subgroup analysis was conducted. The detailed results are presented in **Figure 4**. In the subgroup analysis, we observed that the age of patients was associated with the risk of mortality (OR=1.46, 95% CI: 1.08-1.97, $I^2=37\%$, $P=0.12$). In addition, other subgroup analysis results showed no statistical significance (all $p>0.05$).

3.2.4 Publication bias

The test for publication bias was conducted by funnel plot (**Figure 5**). Good symmetry was shown and studies were distributed on both sides of the pooled outcome clearly. It indicated that there was no significant publication bias in current studies.

Discussion

This review included 12 articles, more than 30,000 COVID-19 cases encompassed. Our findings suggest that antiplatelet therapy did not increase the risk of death in COVID-19 patients. However, patients who received antiplatelet agents were associated with a lower risk of ICU admission and mechanical ventilation. This review has provided a rationale for the rational use of antiplatelet agents during the COVID-19 pandemic.

Up to date, no consensus guidelines are available for antiplatelet therapy in COVID-19, while conflicting results of mortality were reported by the various clinical studies. Liu, et al. (2020), Liu, et al. (2021), Meizlish, et al. (2021), Merzon, et al. (2021), Osborne, et al. (2021) reported that antiplatelet therapy was associated with lower risk of mortality compared with non-antiplatelet agents users[10-14]. It has been reported that SARS-CoV-2 participant in the activation of platelets directly and promote thrombosis, which might be an important cause for the high incidence of thrombotic events in COVID-19 patients[6] [4, 15]. According to this theory, COVID-19 patients may profit from antiplatelet therapy. However, Sahai, et al. (2020), Alamdari, et al. (2020), Chow, et al. (2021), Russo, et al. (2020), Yuan, et al. (2020) have shown that there was no difference on mortality between patients with and without antiplatelet agents[16-20]. Giacomelli, et al. (2020) found that non-survivors were more frequently being treated with anti-platelet agents[21]. Conclusions presented above show that antiplatelet agents have no significant benefit on mortality. For most COVID-19 patients present of comorbidities and risk factor of the death, a full consideration should be taken for advantages and disadvantages of antiplatelet therapy.

Patients with COVID-19 has a high incidence of thromboembolic events[22]. Among non-COVID-19 patients, antiplatelet agents are strongly related to a lower incidence of thrombotic events[23]. But our results showed that treatment with antiplatelet agents was not associated with mortality in COVID-19 patients. The results reported by Husam, et al. suggested no protective effect of aspirin in patients with COVID-19[24]. Patients receiving antiplatelet agents tend to have risk factors of death from COVID-19, including diabetes, coronary heart disease, etc. Therefore, it is possible that we have underestimated the protective effects of antiplatelet agents on COVID-19 mortality.

This review also has several limitations. First, it included a broad range of COVID-19 patients, lack of uniform diagnostic criteria of SARS-CoV-2 infection. Second, deficiency of clinical data precluded us in evaluating some variables such as duration of antiplatelet agents use, dosage, etc. Third, the studies from different countries lead to heterogeneity in definition of antiplatelet therapy and experiment design. Fourth, except for aspirin, outcomes of other kinds of antiplatelets in the COVID-19 patients are also of interest. Finally, more studies are needed to confirm long-term outcomes in COVID-19 patients who received antiplatelet agents.

In conclusion, our results suggested that the use of antiplatelet agents did not lead to an increasing mortality in COVID-19 patients. Additionally, the available evidence indicates that antiplatelet therapy results in lower risk of ICU admission and mechanical ventilation. Antiplatelet agents should be continued in COVID-19 patients, unless clinically indicated.

Declarations

Authors' contributions

B.H.S. conceived the study and revised the manuscript critically for important intellectual content. Y.H. made substantial contributions to its design, acquisition, analysis and interpretation of data. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interest.

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Tables

Table 1. Characteristics of the Included Studies.

Author	Year	Country	Study design	Study period	Treat with antiplatelet agents	No antiplatelet agents	Average age	Sex		Antiplatelet agents used	Outcomes
								Male	Female		
Alamdari, et al.	2020	Iran	Single center study	January 2020 to April 2020	53	406	62	320	139	Aspirin	Mortality
Chow, et al.	2021	USA	Multicenter study	March 2020 to July 2020	98	314	55	244	168	Aspirin	Mechanical ventilation, ICU admission, mortality
Giacomelli, et al.	2020	Italy	Single center study	February 2020 to March 2020	33	200	61	161	72	-	Mortality
Liu, et al.	2020	China	Multicenter study	February 2020 to March 2020	14	17	56	21	10	Dipyridamole	Mortality
Liu, et al.	2021	China	Single center study	January 2020 to March 2020	28	204	52	32	16	Aspirin	Mortality
Meizlish, et al.	2021	UK	Multicenter study	March 2020 to June 2020	319	1821	-	1396	1389	Aspirin	Mortality
Merzon, et al.	2021	Israel	Multicenter study	February 2020 to June 2020	7	105	59	61	51	Aspirin	Mortality
Osborne, et al.	2021	USA	Multicenter study	March 2020 to August 2020	6324	20022	58	23487	2859	Aspirin	Mortality
Russo, et al.	2020	Italy	Multicenter study	February 2020 to April 2020	55	147	68	115	77	Aspirin	Mortality
Sahai,et al.	2020	USA	Multicenter study	March 2020 to May 2020	248	248	-	-	-	Aspirin	Mortality
Sivaloganathan, et al.	2020	UK	Single center study	March 2020 to April 2020	29	58	79			Aspirin, clopidogrel	Mortality, ICU
Yuan, et al.	2020	China	Single center study	January 2020 to March 2020	52	131	71	99	84	Aspirin	Mortality

Figures

Figure 1

Flow diagram of study selection and identification.

Figure 2

Forest plot examining the association between the use of antiplatelet agents and mortality outcomes in COVID-19 patients.

A

B

Figure 3

Forest plot examining the association between the use of antiplatelet agents and the risk of ICU admission (A) and mechanical ventilation (B) in COVID-19 patients.

Figure 4

Forest plot examining the association between the use of antiplatelet agents and mortality outcomes in COVID-19 patients. (A) Subgroup analysis by factor of age. (B) Subgroup analysis by factor of region. (C) Subgroup analysis of by factor of type of study.

Figure 5

Funnel plots for assessment of publication bias.

Supplementary Files

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