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.

American Journal of Emergency Medicine 43 (2021) 27–30

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

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

Effect of antiplatelet treatments on patients with COVID-19 infection: A systematic review and meta-analysis

Yushu Wang [a,1], Guangyu Ao [b,1], Basma Nasr [c], Xin Qi [d,*]

[a] Department of Cardiology, Chengdu First People's Hospital, Chengdu, Sichuan, China
[b] Department of Nephrology, Chengdu First People's Hospital, Chengdu, Sichuan, China
[c] Department of Cardiology, West China Hospital of Sichuan University, Chengdu, Sichuan, China
[d] Department of Neurology, Chengdu Third People's Hospital, Chengdu, Sichuan, China

ARTICLE INFO

Article history:
Received 12 November 2020
Received in revised form 7 January 2021
Accepted 9 January 2021

Keywords:
COVID-19
Antiplatelet
Severe
Mortality
Meta-analysis

ABSTRACT

Despite the rationale that early anti-platelet would lower the risk of major organ dysfunction, the effectiveness of this approach remains controversial. Therefore, we perform a systematic review and meta-analysis to investigate the effect of antiplatelet treatments on patients with COVID-19 infection. An electronic search was carried out in Pubmed, Embase, Cochrane library, Web of Science, MEDLINE, Wanfang and China National Knowledge Infrastructure (CNKI). Meta-analysis and statistical analyses were completed with using the RevMan 5.3 and Stata 12.0. A total of 9 articles representing data from 5970 participants were included in this study. The meta-analysis showed antiplatelet agents were not associated with higher risk of severe COVID-19 disease (OR = 0.98, 95%CI: 0.64 to 1.50, $P = 0.94$; $I2 = 65\%$), while an adjusted analysis indicated that antiplatelet agents was not associated with an increased risk of mortality (OR = 0.65, 95%CI: 0.40 to 1.06, $P = 0.498$; $I2 = 0\%$). The results of this study reveal that while there is no significant benefit on mortality demonstrated with the use of antiplatelet agents, the upper bound of the confidence interval suggests that there is unlikely to be a compelling risk of harm associated with this practice. The benefit and risk of the use of antiplatelet agents should be fully considered especially in the presence of thrombocytopenia status in patients with COVID-19.

Dear Editor,

Coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has led to an unprecedented global health crisis with over 8.5 million confirmed cases worldwide and over 107,600 deaths as of 12 October 2020. Patients with s Severe SARS-COV-2 Infection associated with sepsis, respiratory failure, heart failure, and acute kidney and cardiac injury are prone to develop multiple organ injury resulting in unsuppressed platelet activation that induces a destructive inflammation [1]. Furthermore, the interaction of activated platelets with neutrophils contributes to the degradation of extracellular matrix proteins and thrombin generation, which could relate to disseminated intravascular coagulation (DIC) and a hypercoagulable state [2]. Thus, an early anti-platelet, which inhibits uncontrolled platelet adhesion, aggregation, and activation, would lower the risk of major organ dysfunction. However, despite the rationale for antiplatelet therapy, the effectiveness of this approach remains controversial. Therefore, we aimed to perform a systematic review and meta-analysis in order to investigate the effect of antiplatelet treatments on patients with COVID-19 infection.

An electronic search of the PubMed, Embase, Cochrane library, Web of Science, MEDLINE, and China National Knowledge Infrastructure (CNKI) databases was conducted from inception to September 2020 with no language restrictions. The following key words and/or medical subject heading terms searched were applied: ("novel coronavirus" or "2019-nCoV" or "coronavirus disease 2019" or "SARS-CoV-2" or "COVID-19") and (antiplatelet or aspirin or ticagrelor or prasugrel or clopidogrel). A manual search of additional articles was conducted using references from related articles and published reviews to seek potentially relevant citations.

Two independent investigators (YW and GA) performed the initial screening of titles and abstracts. Full-length articles of identified studies were retrieved. Studies were included if they (1) enrolled patients diagnosed with COVID-19 infection; (2) provided information on antiplatelet agents for preventing thrombosis events in patients with severe or non-severe cases or between death and survivors; (3) the availability of an odds ratio (OR) with 95% confidence intervals (CI) for overall survival, or relevant clinical events from which it could be calculated. Studies were excluded if they were abstracts, conferences, editorials, or

* Corresponding author at: No.82 North Qinglong Street, Qingyang District, Chengdu 610016, Sichuan, China.
E-mail address: qixinchengdu@163.com (X. Qi).
[1] Yushu Wang and Guangyu Ao contributed equally to this work.

https://doi.org/10.1016/j.ajem.2021.01.016
0735-6757/

Figure 1A

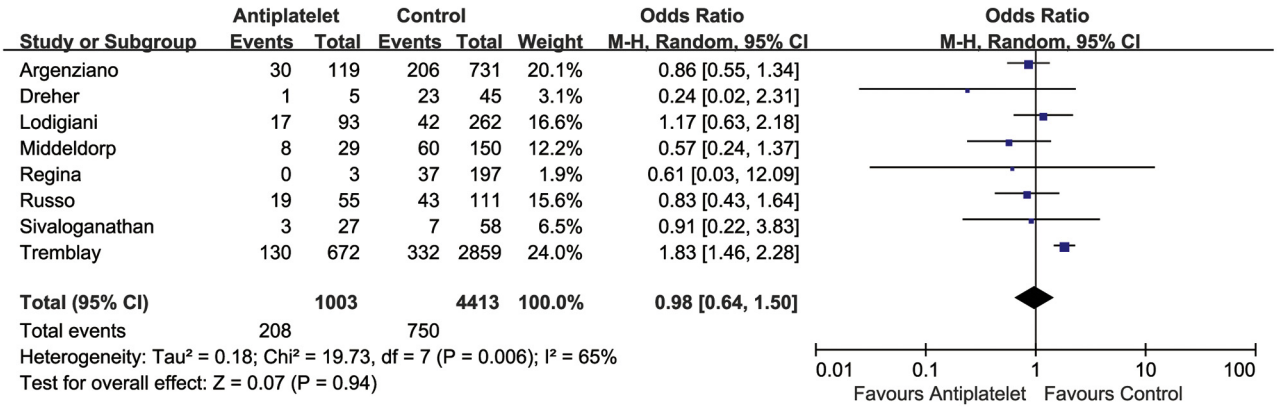

Figure 1B

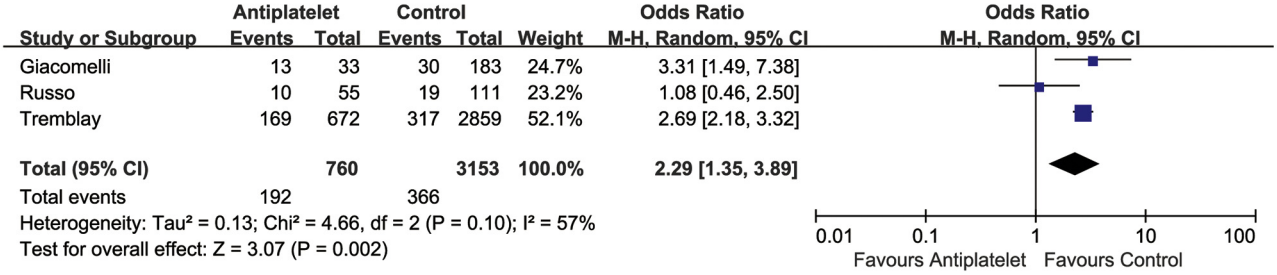

Figure 1C

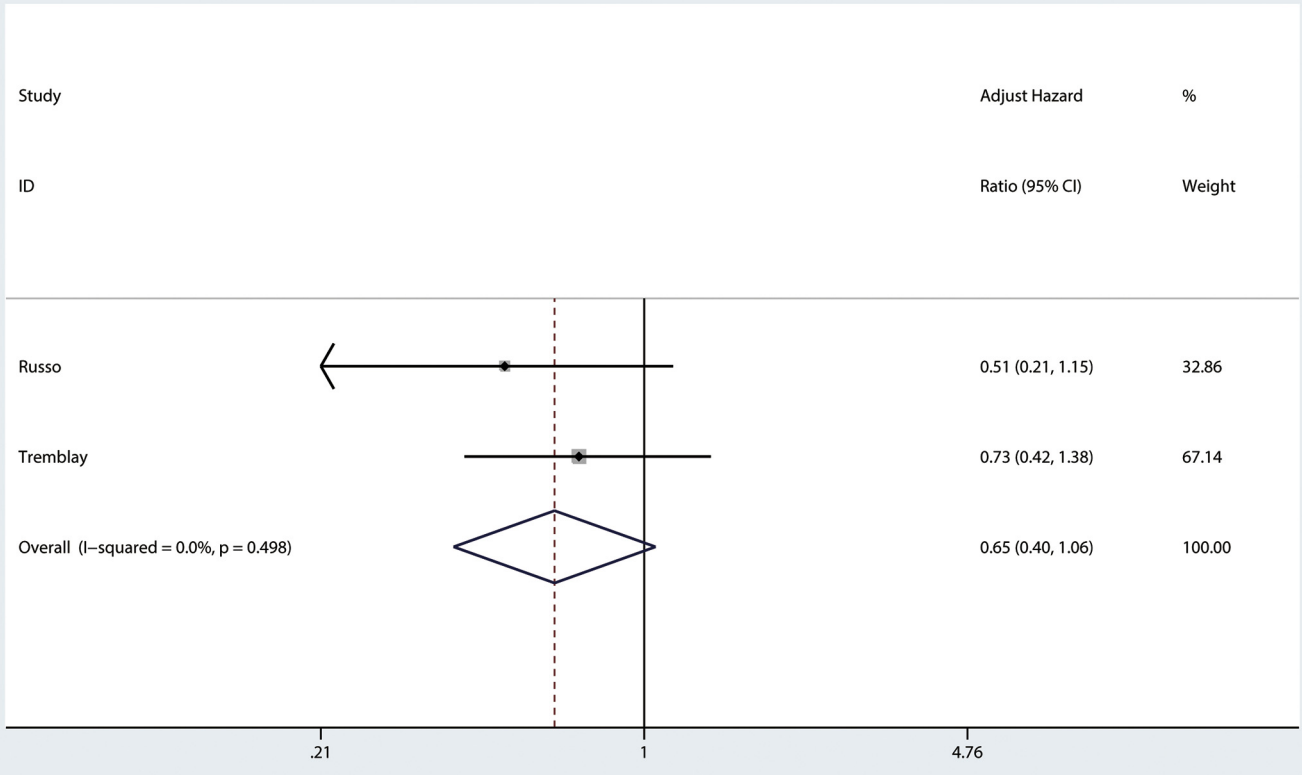

Fig. 1. A Association between antiplatelet agents and severe COVID-19. B Association between antiplatelet agents and mortality in pooled analysis of unadjusted results. C Association between antiplatelet agents and mortality in pooled analysis of adjusted results.

reviews. Decisions regarding eligibility were exclusively made according to pre-specified selection criteria. Any differing decision was resolved by consensus or discussion with the third investigator (XQ).

Two main investigators (YW and GA) independently extracted the data and reached a consensus on all items. The following items were extracted from each study if available: name of the first author, the year of publication, study design, region, number of participants, age of patients, number of male and female participants, type of antiplatelet/anticoagulant agents, and outcomes of interest. The endpoint was the effect of antiplatelet agents on mortality and disease severity of COVID-19. For non-random controlled studies, risk of bias/quality of studies was evaluated using a nine-item Newcastle-Ottawa Scale (NOS) by two investigators independently (YW and GA). If necessary, a third investigator was consulted for any discrepancies. Studies with a NOS score of ≥7 were considered high-quality studies, whereas ones with <7 were considered low-quality studies.

Meta-analysis and statistical analyses were performed using the RevMan 5.3 (Cochrane Collaboration) and Stata 12.0 (StataCorp). Unadjusted odds ratios (ORs) and adjusted hazard ratio (HR) with 95% CIs were used as the summary statistics for dichotomous outcomes. Cochrane chi-square test (Q test) and the I^2 statistics were calculated to detect heterogeneity, with an I^2 less than 25%, 25% to 50%, and greater than 50% corresponding to low, moderate, and high heterogeneity, respectively. In case of low level of heterogeneity ($I^2 < 50\%$), a fixed-effect model was used, otherwise a random-effect model was used. Sensitivity analysis was conducted to evaluate a single trial's influence on overall effect estimated by sequentially excluding one study. If substantial heterogeneity was presented in the meta-analysis, subgroup analysis was conducted based on the countries. $P < 0.05$ was considered statistically significant. This study is registered with PROSPERO, number CRD42020214382.

We meticulously retrieved 483 potentially eligible literatures by searching electronic databases. Among them, 92 literatures were excluded due to duplicated searches. Subsequently, 349 studies were regarded as absolute irrelevant studies by examining titles and abstracts. A full-text of 42 studies was entirely reviewed; however, 33 records were excluded because they were abstract, conferences, reviews, had no comparison between antithrombic therapy and control groups, or outcomes were not reported. Therefore, a total of 9 full-text studies with 5970 patients were included in the final analysis (Fig. 1) [3-11]. The sample size of patients ranged from 50 to 3772. Seven studies were mainly from European countries and two studies from America. Among these studies, only two studies were prospective in design, and the rest were retrospective. All studies were published in English. Pooled analysis of adjusted results included studies from Russo et al. [4] and Trembay et al. [6] which used propensity-score matching methods by adjusting factors including age, gender, race, and commodities. The characteristics of the study are shown in Table 1. The overall quality of included studies was high with NOS scores ≥7. The quality of the included articles is assessed and displayed in Table S1. The meta-analysis showed that antiplatelet agents were not associated with higher risk of severe COVID-19 disease (OR = 0.98, 95%CI: 0.64 to 1.50, $P = 0.94$; $I^2 = 65\%$) (Fig. 1A). Moreover, a significant association between antiplatelet agents and higher risk of mortality were found in patients with COVID-19 (OR = 2.29, 95%CI: 1.35 to 3.89, $P = 0.002$; $I^2 = 57\%$) (Fig. 1B). The results were derived from three studies that provided the unadjusted estimates. However, the adjusted results of two studies were pooled which indicated that antiplatelet agents were not associated with an increased risk of mortality in COVID-19 patients (OR = 0.65, 95%CI: 0.40 to 1.06, $P = 0.498$; $I^2 = 0\%$) (Fig. 1C). According to the subgroup analysis based on countries, analysis of studies from European countries indicated that antiplatelet agents were associated with lower risk of severe COVID-19 disease (OR = 0.85, 95%CI: 0.58 to 1.25, $P = 0.41$; $I^2 = 0\%$). In addition, sensitivity analyses by omitting each study at a time did not significantly alter the overall results.

The current systematic review and meta-analysis suggested that while there is no significant benefit on mortality demonstrated with the use of antiplatelet agents, the upper bound of the confidence interval suggests that there is unlikely to be a compelling risk of harm associated with this practice. However, the benefit and risk of the use of antiplatelet agents should be fully considered especially in the presence of thrombocytopenia status in patients with COVID-19. Combined adjusted analysis of two studies using a propensity matching analysis where patients were matched to co-morbidities showed no advantage or disadvantage of using antiplatelet agents. A number of risk factors for severe or dead COVID-19 have been reported, including old age, male, hypertension, diabetes, chronic kidney disease and cardiovascular disease [12,13]. In our pooled analysis of adjusted results of two studies, Russo et al. [4] and Tremblay et al. [6] have adjusted comorbidities such as age, smoke, chronic obstructive pulmonary disease, hypertension, diabetes, coronary artery disease, heart failure, obesity, stroke, and chronic kidney disease. While the results of our unadjusted analysis, in which it revealed an association of increased mortality in COVID-19 patients on antiplatelet agents, could be accounted for co-morbidities

Table 1
Characteristics of included studies.

Study	Country	Study design	Age[a]	Sample size	Sex		Antiplatelet therapy used	Definition of severity used	Definition of Covid-19 infection used
					Male	Female			
Lodigiani [3]	Italy	Retrospective	66 (55–75)	388	264	124	Aspirin	ICU	SARS-CoV-2 RT-PCR (+)
Russo [4]	Italy	Retrospective	67.7 ± 15.2	192	115	77	44 were taking acetylsalicylic acid, 5 P2Y12 inhibitor and 6 double antiplatelet therapy	ARDS	SARS-CoV-2 RT-PCR (+)
Giacomelli [5]	Italy	Prospective	NR	233	161	72	Anti-platelet agents	NR	SARS-CoV-2 RT-PCR (+)
Tremblay [6]	America	Retrospective	56.6 ± 18.2	3772	2067	1705	Anti-platelets	Intubation mechanical ventilation	SARS-CoV-2 RT-PCR (+)
Argenziano [7]	America	Retrospective	NR	850	511	339	NSAIDs	ICU	SARS-CoV-2 RT-PCR (+)
Middeldorp [8]	Netherlands	Retrospective	61 ± 14	198	130	68	Antiplatelet therapy	ICU	SARS-CoV-2 RT-PCR (+)
Sivaloganathan [9]	United Kingdom	Prospective	79.3	87	NR	NR	18 were on aspirin, 8 on clopidogrel, and 3 on both	ICU	SARS-CoV-2 RT-PCR (+)
Dreher [10]	German	Retrospective	65 (58,76)	50	33	17	NSAIDs	ARDS	SARS-CoV-2 RT-PCR (+)
Regina [11]	Switzerland	Retrospective	70 (55,81)	200	120	80	NSAIDs	Mechanical ventilation	SARS-CoV-2 RT-PCR (+)

[a] Age data presented as median (IQR) or mean (SD); SARS-CoV-2: 2019 severe acute respiratory syndrome coronavirus 2; RT-PCR: Real-time reverse transcription polymerase chain reaction; ICU: intensive care units; ARDS: acute respiratory distress syndrome; NSAIDs: nonsteroidal anti-inflammatory drugs; NR, not reported.

as patients on antiplatelet agents may already have existing comorbidities such as cardiovascular disease, diabetes, or other factors that can lead to increased risk of higher mortality rate not directly associated with the efficacy of antiplatelet agents. Our results should be interpreted with caution. Most of the studies included were retrospective in design and results were based on unadjusted analysis, which could be subject to selection bias and potential confounders. Data on type and dose of antiplatelet agents were lacking in most included studies, hence, cannot be further analyzed. In conclusion, the results of this study indicate that antiplatelet agents might protect against the development of severe COVID-19 disease. Randomized controlled trials are highly needed and of paramount importance to investigate whether the use of antiplatelet agents might be beneficial in COVID-19 infection.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2021.01.016.

Credit Author Statement

Yushu Wang and Xin Qi design this study together. Yushu Wang was working for literature review and data collection. Xin Qi was working for organizing and analyzing data. Guangyu Ao and Yushu Wang were working for article writing and revise.

Funding/Acknowledgments

none.

Declaration of Competing Interest

None of the authors have conflicts of interest to declare.

References

[1] Henn V, Slupsky JR, Gräfe M, Anagnostopoulos I, Förster R, Müller-Berghaus G, et al. CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. Nature. 1998;391:591–4. https://doi.org/10.1038/35393.

[2] Manfredi AA, Ramirez GA, Rovere-Querini P, Maugeri N. The neutrophil's choice: phagocytose vs make neutrophil extracellular traps. Front Immunol. 2018;9:288. https://doi.org/10.3389/fimmu.2018.00288.

[3] Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan. Italy Thromb Res. 2020;191:9–14. https://doi.org/10.1016/j.thromres.2020.04.024.

[4] Russo V, Di Maio M, Attena E, Silverio A, Scudiero F, Celentani D, et al. Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: a multicenter observational study. Pharmacol Res. 2020;159:104965. https://doi.org/10.1016/j.phrs.2020.104965.

[5] Giacomelli A, Ridolfo AL, Milazzo L, Oreni L, Bernacchia D, Siano M, et al. 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: a prospective cohort study. Pharmacol Res. 2020;158:104931. https://doi.org/10.1016/j.phrs.2020.104931.

[6] Tremblay D, van Gerwen M, Alsen M, Thibaud S, Kessler A, Venugopal S, et al. Impact of anticoagulation prior to COVID-19 infection: a propensity score-matched cohort study. Blood. 2020;136(1):144–7. https://doi.org/10.1182/blood.2020006941.

[7] Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barr RG, Chang BP, Chau KH, Choi JJ, Gavin N, et al. Characterization and clinical course of 1000 patients with COVID-19 in New York: retrospective case series. Preprint medRxiv doi: https://doi.org/10.1101/2020.04.20.20072116.

[8] Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18(8):1995–2002. https://doi.org/10.1111/jth.14888.

[9] Sivaloganathan H, Ladikou EE, Chevassut T. COVID-19 mortality in patients on anticoagulants and antiplatelet agents [published online ahead of print, 2020 Jun 25]. Br J Haematol. 2020. https://doi.org/10.1111/bjh.16968.

[10] Dreher M, Kersten A, Bickenbach J, Balfanz P, Hartmann B, Cornelissen C, et al. The characteristics of 50 hospitalized COVID-19 patients with and without ARDS. Dtsch Arztebl Int. 2020;117(16):271–8. https://doi.org/10.3238/arztebl.2020.0271.

[11] Regina J, Papadimitriou-Olivgeris M, Burger R, Filippidis P, Tschopp J, Desgranges F, Viala B, Kampouri E, Rochat L, Haefliger D, et al. Epidemiology, risk factors and clinical course of SARS-CoV-2 infected patients in a Swiss university hospital: an observational retrospective study. medRxiv. doi:https://doi.org/10.1101/2020.05.11.20097741

[12] Xu Huayan, Hou Keke, Xu Rong, Li Zhenlin, Fu Hang, Wen Lingyi, et al. Clinical Characteristics and Risk Factors of Cardiac Involvement in COVID-19. J Am Heart Assoc. 2020;9(18) e016807.

[13] Zhou Fei, Yu Ting, Ronghui Du, Fan Guohui, Liu Ying, Liu Zhibo, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.