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LETTER TO THE EDITOR

Use of antiplatelet drugs and the risk of mortality in patients with COVID-19: a meta-analysis

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Globally, there have been close to 130 million reported cases of coronavirus disease 2019 (COVID-19) as of 2nd April 2021, with 2.8 million deaths documented [1]. In order to reduce the risk of mortality associated with COVID-19, several drugs have been repurposed for its treatment. However, a drug with widespread availability around the globe is particularly desirable to be repurposed for the treatment of COVID-19, since it could be immediately trialed in large-scale studies, and immediate access could be guaranteed shall the drug is proven effective to reduce the risk of COVID-19 associated deaths. One of the first drugs to be introduced for routine usage in the medical field - aspirin (also known as acetylsalicylic acid), is still one of the most widely used medications, with an estimated 50–120 billion pills consumed each year [2]. In addition, it is one of the most researched drugs in the world, with an estimated 700–1000 clinical trials conducted annually [3].

A recent appraisal of evidence on the potential effects of aspirin in the context of COVID-19 suggests that aspirin deserves to be tested in patient population with COVID-19, based on the improved survival observed with the use of aspirin among patients with different types of infections, characterized by overactivation of the inflammation cascade and enhanced platelet reactivity [4]. Interestingly, thrombo-inflammation, which is a term coined to illustrate the coordinated activation of the inflammatory and thrombotic responses, is a major cause of morbidity and mortality in patients with COVID-19 [5]. Indeed, aspirin had been previously reported to reduce the risk of acute respiratory distress syndrome [6] and its associated mortality [7] in the critically ill non-COVID-19 population, which also happens to be the major complication that arises from thrombo-inflammatory responses in severe cases of COVID-19 with accompanied high mortality rate [8].

While it seems reasonable for aspirin or even antiplatelet agents as a whole to be repurposed for the treatment of COVID-19, the retrospective cohort study by Ho and colleagues [9] failed to demonstrate an association between the use of antiplatelets and improvement in clinical outcomes in patients with COVID-19. The aforementioned study [9] enrolled only patients with COVID-19 from the United States, whereas several studies from different parts of the world have since explored the association between the use of antiplatelets and clinical outcomes in patients with COVID-19. Thus, we performed a meta-analysis of the available studies to explore the overall effect of the use of antiplatelets in patients with COVID-19.

We performed a systematic literature search in electronic databases including PubMed, Google Scholar, Scopus, and preprint servers (medRxiv, Research Square, SSRN) with no language restriction for eligible studies published up to February 15, 2021. The search strategy was built based on the following keywords and their MeSH terms: "COVID-19", "SARS-CoV-2", "antiplatelet", "aspirin", and "acetylsalicylic acid". Two investigators (CSK and SSH) independently performed literature screening to identify eligible studies. The reference lists of relevant articles were also hand-searched for additional studies. Studies eligible for inclusion were studies with any design that investigated the preadmission/pre-diagnosis or ongoing use of antiplatelet on the risk of a fatal course of COVID-19 and reported adjusted measures of association. We excluded editorials or narrative reviews without original data. In addition, studies that provided no adjusted estimation were also excluded. The quality of observational studies was evaluated using the Newcastle-Ottawa Scale [10], with a score of >7 indicating high quality.

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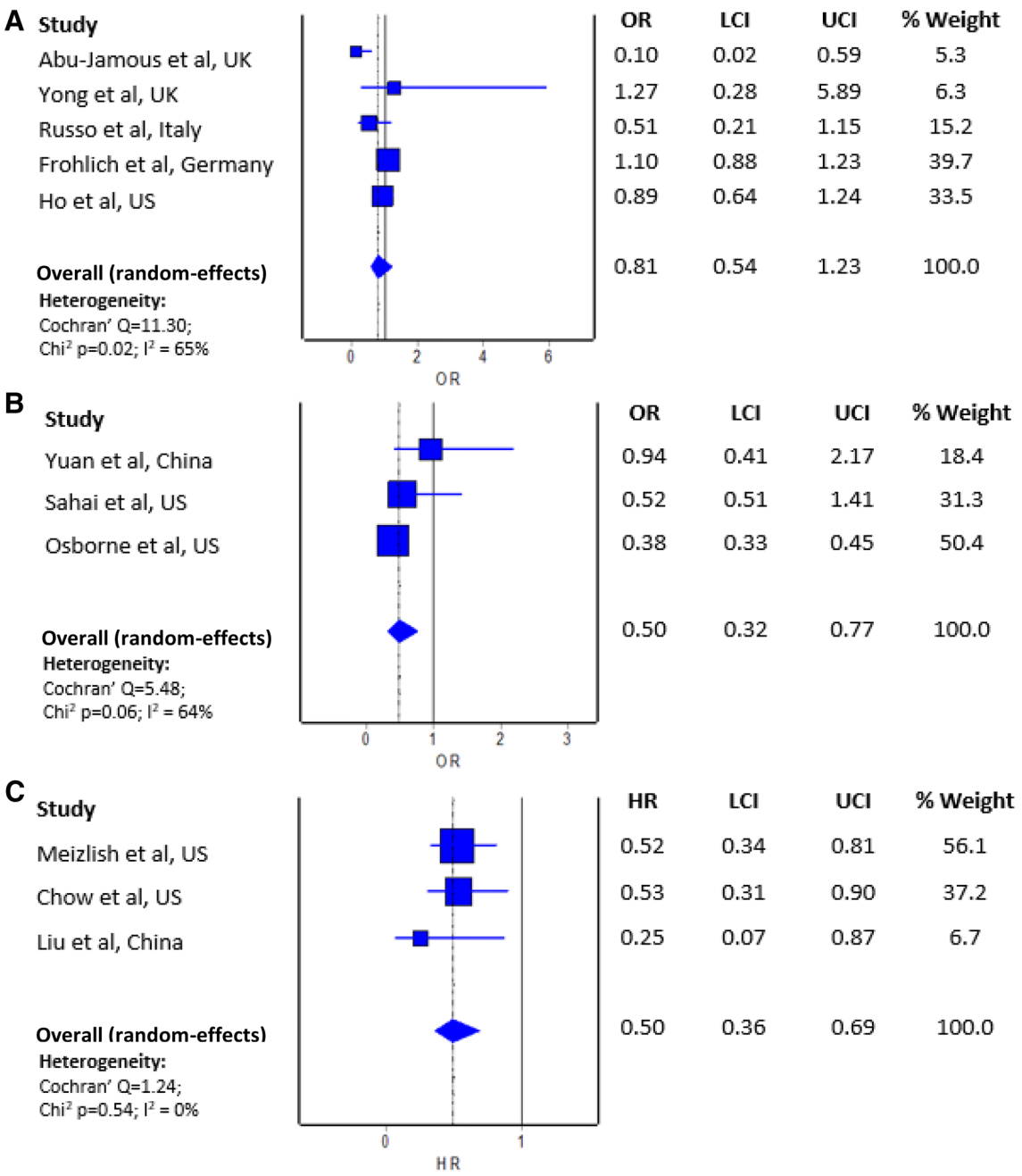

Fig. 1 Forest plot showing the pooled odds ratio (OR) or hazard ratio (HR) of mortality of patients with COVID-19 treated with antiplatelets versus no antiplatelets (**a**) and with aspirin versus no aspirin (**b**, **c**)

The outcome of interest was the development of a fatal course of COVID-19. Each included trial was independently evaluated by two investigators (CSK and SSH) who extracted the study characteristics. Data collected included authors, study design, country, patients' age, the total number of included patients, mortality outcomes, adjusted mortality estimates, and covariates. The disagreement between the two investigators related to the inclusion of studies, extraction of data, and quality appraisal of included studies was resolved through mutual discussions. Adjusted odds ratios or relative risks and the corresponding 95 % confidence intervals (CIs) from included studies were pooled using a random-effects model to produce pooled odds ratio and 95 % confidence interval. We examined the heterogeneity between studies using the I^2 statistics with 50 %, and using the $\chi 2$ test with $P < 0.10$, as the thresholds for statistically significant heterogeneity. All analyses were performed using Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

Table 1 Characteristics of included studies

Study	Country	Design	Total number of patients	Age (median/mean unless otherwise specified)	Mortality			Covariates adjustment	NOS
					Aspirin users (n/N; %)	Non-aspirin users (n/N; %)	Adjusted estimate (95% CI)		
Yuan et al. [11]	China	Retrospective, single center	183	Aspirin users = 69.7 Non-aspirin users = 71.8	11/52; 21.1	29/131; 22.1	OR = 0.94 (0.41–2.17)	Age, sex, comorbidities	6
Sahai et al. [12]	United States	Retrospective, multicenter	496	Aspirin users = 70.0 Non-aspirin users = 50.6	33/248; 13.3	38/248; 15.3	OR = 0.52 (0.51–1.41)	Age, sex, race, ethnicity, platelet count, smoking status, respiratory support, use of vasopressor, haemodynamic instability, comorbidities, comedications	7
Osborne et al. [13]	United States	Retrospective database review	12600	Aspirin users = 67.4 Non-aspirin users = 67.2	N/A	N/A	OR = 0.38 (0.33–0.45)	Age, sex, Care Assessment Need score	8
Meizlish et al. [14]	United States	Retrospective database review	638	N/A	N/A	N/A	HR = 0.52 (0.34–0.81)	Age, sex, race, body mass index, maximum D-dimer level during hospitalization, admission Rothman Index	8
Chow et al. [15]	United States	Retrospective, multicenter	412	Aspirin users = 61 Non-aspirin users = 52	26/98; 26.5	73/314; 23.2	HR = 0.53 (0.31–0.90)	Age, sex, ethnicity, body mass index, comorbidities, beta-blocker use	8

Table 1 (continued)

Study	Country	Design	Total number of patients	Age (median/mean unless otherwise specified)	Mortality			Covariates adjustment	NOS
					Aspirin users (n/N; %)	Non-aspirin users (n/N; %)	Adjusted estimate (95% CI)		
Liu et al. [16]	China	Retrospective, single center	48	Aspirin users = 74 (65.0-79.5) Non-aspirin users = 69 (61-0.0–76.0)	2/24 (8.3)	8/24 (33.3)	HR = 0.25 (0.07–0.87)	Age, sex, comorbidities, symptoms on admission, serum creatine kinase level, serum lactate dehydrogenase level, serum alanine aminotransferase level, serum C-reactive protein level, serum creatinine level, presence of leukocytopenia, presence of lymphocytopenia, serum hemoglobin level, presence of hypoproteinemia, presence of thrombocytopenia, use of systemic corticosteroids	8
					Antiplatelet users (n/N; %)	Non-antiplatelet users (n/N; %)	Adjusted estimate (95% CI)		
Abu-Jamous et al. [17]	United Kingdom	Retrospective database review	315	N/A	158/297; 53.2	2/18; 11.1	OR = 0.10 (0.02–0.59)	Age, sex, number of admissions	7
Yong et al. [18]	United Kingdom	Prospective, multicenter	3858	68.1 (8.1)	N/A	N/A	OR = 1.27 (0.28–5.89)	Age, sex, ethnicity, comorbidities, blood urea, serum creatinine, number of medications taken, body mass index, Townsend Deprivation index, smoking status	7
Russo et al. [19]	Italy	Retrospective, multicenter	192	67.7 (15.2)	10/55; 18.2	25/137; 18.2	RR = 0.51 (0.21–1.15)	Age, smoking status, comorbidities	7

Table 1 (continued)

					Antiplatelet users (n/N; %)	Non-antiplatelet users (n/N; %)	Adjusted estimate (95 % CI)		
Fröhlich et al. [20]	Germany	Retrospective database review	6637	70 (55–81)	314/912; 34.4	1058/5725; 18.5	OR = 1.10 (0.88–1.23)	Age, sex, body mass index, comorbidities, immunosuppressive agents	8
Ho et al. [9]	United States	Retrospective database review	28076	Antiplatelet users = 66 (55–77) Non-antiplatelet users = 41 (30–53)	N/A	N/A	OR = 0.89 (0.64–1.24)	Age, sex, race/ethnicity, body mass index, Charlson comorbidity index, comorbidities, smoking history, the week of COVID-19 diagnosis	8
Tremblay et al. [21]	United States	Retrospective database review	3772	Antiplatelet users = 68.8 (12.4) Non-antiplatelet users = 52.4 (17.6)	169/672; 25.1	398/3100	HR = 1.03 (0.72–1.47)	Age, sex, race, Charlson Comorbidity Index, obesity	7

CI confidence interval *COVID-19* coronavirus disease 2019 *HR* hazard ratio *NOS* Newcastle-Ottawa Scale *OR* odds ratio

Our literature search yielded 483 unique abstracts. After deduplication and application of the eligibility criteria, eighteen relevant articles were shortlisted for inclusion through full-text examination. Of these, six studies were excluded since they reported no adjusted measures of association. Eventually, 12 studies [9, 11–21] were included for this meta-analysis; 6 studies [9, 17–21] investigated the effect of antiplatelets, and 6 studies [11–16] investigated the effect of aspirin alone. Study characteristics are depicted in Table 1. Across the 6 studies [11–16] which investigated the effect of antiplatelets in patients with COVID-19, all [9, 17, 19–21] but one studies [18] were retrospective in design, with one multicentered study [19] and four database reviews [17, 18, 20, 21]; the remaining one study [18] was a prospective multicentered study. On the other hand, all the 6 studies [11–16] that investigated the effect of aspirin in patients with COVID-19 were retrospective in nature, with two multicentered studies [12, 15], two single-centered studies [11, 16], and two database reviews [13, 14]. The included studies were originated from the United Kingdom [17, 18], the United States [9, 12–15, 21], Italy [19], Germany [20], and China [11, 16], and they are deemed moderate-to-high quality with Newcastle-Ottawa Scale ranging from 6 to 8 (Table 1).

The meta-analysis of 5 studies [9, 17–20] which reported the effect measures in odds ratio/relative risk revealed no significant difference in the odds for the development of a fatal course of COVID-19 between antiplatelet users and non-antiplatelet users (Fig. 1a; pooled odds ratio = 0.81; 95 % confidence interval 0.54–1.23). The remaining one study [21] which reported the effect measure in hazard ratio (and thus unable to be included in the meta-analysis) reported consistent findings with the meta-analysis in which no significant difference in the risk for the development of a fatal course of COVID-19 between the two groups (hazard ratio = 1.03; 95 % confidence interval 0.72–1.47). However, we observed a significantly reduced risk of a fatal course of COVID-19 with the use of aspirin in patients with COVID-19 relative to non-use of aspirin (Fig. 1b; pooled odds ratio = 0.50; 95 % confidence interval 0.32–0.77 and Fig. 1c; pooled hazard ratio = 0.50; 95 % confidence interval 0.36–0.69). These preliminary findings with the use of aspirin in patients with COVID-19 suggest aspirin to be potentially therapeutic in this patient population and support the intention for its repurposing. Although antiplatelet agents have systemic antithrombotic effects, the fact that the use of aspirin was associated with mortality benefits, but not antiplatelet agents as a whole, may be related to aspirin's antiviral effects and anti-inflammatory effects, which are not found in other antiplatelet agents [4]. Nevertheless, the studies included in our meta-analysis are mostly of retrospective design, and thus generalizability of the findings may be limited. There were at least seven ongoing randomized

controlled trials (Table S1) investigating the mortality outcomes with the use of antiplatelets as standalone or combination therapy in patients with COVID-19 which could clarify their potential risks and benefits in this patient population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11239-021-02436-0.

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Declarations

Conflict of interest Chia Siang Kow and Syed Shahzad Hasan declare that they have no potential conflicts of interest that might be relevant to the contents of this article.

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