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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Letter to the Editor

Lack of efficacy for sotrovimab use in patients with COVID-19: A meta-analysis

Dear Editor,

We read with great interest the article in this journal by Luo et al. regarding the use of tocilizumab in patients with COVID-19 infection[1]. As the global cases of COVID-19 continue to rise and the virus continues to mutate, monoclonal antibodies have emerged as a novel option with potential therapeutic and prophylactic applications.

Sotrovimab is a neutralizing monoclonal antibody targeting the conserved epitope on the spike protein receptor of SARS-CoV-2. It was granted emergency use authorization by the United States Food and Drug Administration in May 2021 with several countries closely following suit[2]. Given as a single 500 mg IV infusion, sotrovimab inhibits the fusion of viral and cell membranes to decrease viral internalization[2]. In addition, it was reported that the Omicron spike was resistant against most therapeutic antibodies but remained susceptible to inhibition by sotrovimab[2,3]. However, on March 25, 2022, the FDA revised the authorization for sotrovimab to limit its use for the treatment of COVID-19 in certain U.S. regions with high frequency of the omicron BA.2 subvariant. Currently, there were a few studies that evaluated the effect of sotrovimab on clinical outcomes in patients with mildto-moderate COVID-19. Thus, we aim to perform a meta-analysis to evaluate the effect of sotrovimab in patients with COVID-19.

An electronic search was performed in (PubMed, Embase, Cochrane Library databases, Scopus and medRxiv) from December 1 2019 to March 20th, 2022. No language, year, or publication restrictions were applied. The following medical subject Heading Terms (MeSH) and key words were searched: ("2019-nCoV or coronavirus disease 2019 or COVID-19 or SARS-CoV-2 or novel coronavirus") AND (sotrovimab or VIR-7831).

The inclusion criteria were defined as follows: (1) patients with confirmed COVID-19; (2) comparison for clinical outcomes between sotrovimab treatment (administered alone) and control groups (standard care, placebo) was reported. Following studies were excluded (1) reviews, letters, editorials, conference abstracts, and case reports; and (2) duplicated publications. We also extracted information on baseline characteristics of the studies and participants, including first author's name, year of publication, study design, country of origin, age, gender, number of participants, usage of sotrovimab, outcomes of interest (mortality and disease severity).

The statistical analysis was performed using Review Manager, version 5.2 (Cochrane Collaboration, Oxford). Dichotomous variables were analyzed using the odds ratio (OR) with a 95% confidence interval (95% CI). We assessed the heterogeneity using Cochran's Q test and the I^2 statistic. A P value <0.05 is considered to be statistically significant. This meta-analysis is registered with the PROSPERO international prospective register of systematic reviews (registration number CRD42022322696).

The electronic literature search identified a total of 4 studies[4-7] comprising of 3866 adult patients with COVID-19, including 1040 in the sotrovimab (administered alone) and 2826 in the control group arm, were included in this meta-analysis. The patient demographics and baseline disease characteristics of the study population are shown in Table 1. Three studies were from USA and one from Singapore. Two studies were RCTs, one study was retrospective and one study was prospective cohort study. Most studies included mild to severe COVID-19 patients. Sotrovimab was intravenously administered in the included studies. The four studies were published between 2021 and 2022 with different sample patient sizes that ranged from 94 to 2357 patients with COVID-19.

The meta-analysis showed the overall mortality was not statistically different between the sotrovimab group and control group (OR=0.36, 95%CI: 0.08 to 1.66, $P = 0.19$; I^2=57%) (Fig.1A). In addition, sotrovimab treatment was not associated with developing severe COVID-19 disease (OR=0.40, 95%CI: 0.10 to 1.60, $P = 0.19$; I2=60%) (Fig.1B) compared with control group.

In this study, we find that sotrovimab administration in patients with COVID-19 infection does not have a significant benefit with either mortality rate or severity of disease. Since most of the patients in our study were mild to moderate COVID-19, an alternative view of this result is that sotrovimab may not significantly improve the mortality or severity among non-severe COVID-19 patients because the risk of death is very low regardless of the interventions used[8].

The level of effectiveness of sotrovimab in patient with COVID-19 is most likely multifactorial. While the studies by Gupta et al. and Huang et al. investigated the use of sotrovimab in non-hospitalized patients, the other studies had hospitalized patients in their inclusion criteria. These populations have differing baseline risks for severity and mortality following COVID-19 infection[9]. As such, further investigation is needed to probe the effectiveness separately between inpatient and outpatient settings. Emerging evidence has also suggested that the use of neutralizing monoclonal antibody therapy may not as effective in patients with endogenous anti-SARS-CoV-2 antibodies as compared to those without[10]. While one included study attempted to correct through randomization, the others did not test for presence of anti-SARS-CoV-2 antibodies. As such, it is possible that monoclonal antibody therapy may have a higher indication for use in patients without a past COVID-19 infection history or with lower levels of endogenous anti-SARS-CoV2 antibodies.

SARS-CoV-2 continues to develop mutations creating new variant of concerns (VOC) with differing susceptibilities to medication treatment and differing immune escape properties. While Huang et al. only included the delta variant, the other studies did not use

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Table 1
Characteristics of included studies.

Study	Region	Sotrovimab		No Sotrovimab		Study design	Sample size	Patients included	Usage of sotrovimab
		Age[a]	Male (%)	Age[a]	Male (%)				
Gupta[4] 2022	USA	53 (41.5–62)	229 (43)	53 (43–63)	256 (48)	RCT	1057	Non-hospitalized patients with mild to moderate COVID-19	A single intravenous infusion with 500 mg of sotrovimab
Huang[5] 2021	USA	NR	NR	52.8 ± 19.5	889 (43.4)	Prospective cohort study	2357	Non-hospitalized patients with mild to moderate COVID-19	Intravenously sotrovimab
Ong[6] 2022	Singapore	81 (75–88)	14(73.7)	70 (59–80)	45 (60)	Retrospective cross-sectional study	94	Hospitalized patients with mild-to-moderate COVID-19	A single dose of sotrovimab
Self[7] 2021	USA	61 (50–74)	107 (59)	60 (49–70)	103 (58)	RCT	358	Adults hospitalized with COVID-19 without organ failure	Intravenously sotrovimab 500 mg

[a] Age data presented as median (IQR) or mean (SD); RCT: randomized controlled trial; NR: not reported.

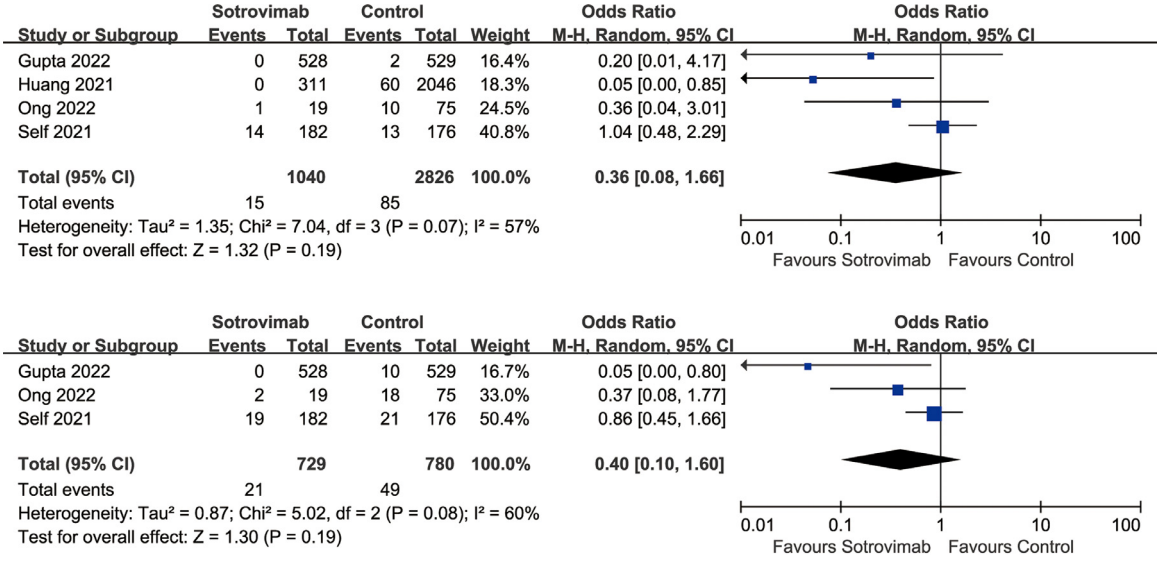

Fig. 1. A Association between sotrovimab treatment and mortality. Figure 1B Association between sotrovimab treatment and developing severe COVID-19.

the VOC as exclusion criteria. In addition, Ong et al. excluded fully vaccinated patients, while the other studies did not consider vaccination status in their inclusion criteria. These results thus may not be completely applicable to new and emerging VOCs, including the Omicron subvariant BA.2 which has recently been documented as displaying considerable resistance to sotrovimab[11]. Thus, sotrovimab is no longer authorized by the FDA to treat COVID-19 in eight states and two territories.

Our study has several limitations that should be noted. There was a small sample size of included articles for use in meta-analysis of four studies. Both the mortality and severity analysis results also had significant heterogeneity (I^2>50%). Furthermore, the studies had differing patient populations, including healthcare setting, type of VOC, and vaccination status. Despite these limitations, our study offers considerable value as the first meta-analysis to investigate the impact of sotrovimab treatment in patients with COVID-19 infection.

More studies are needed to explore the association between treatment with sotrovimab and outcomes of patients with COVID-19 to better understand the factors involved in the effectiveness of medication, including inpatient versus outpatient settings, the severity of COVID-19 infection, the time of medication administration, and the presence or absence of endogenous anti-SARS-CoV-2 antibodies.

In conclusion, the use of sotrovimab to treat patients with COVID-19 infection does not have a significant benefit in either the mortality rate or severity of illness. Additional research is needed to corroborate these findings.

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Declaration of Competing Interest

The authors declare that they have no competing interest.

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