




The use of neutralizing monoclonal antibodies and risk of hospital admission and mortality in patients with COVID-19: a systematic review and meta-analysis of randomized trials

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ABSTRACT

Aim: Several randomized trials have evaluated the effect of neutralizing monoclonal antibodies on the risk of hospital admission and risk of mortality in patients with COVID-19. We aimed to summarize the overall evidence in the form of a systematic review and meta-analysis.

Methods: A systematic literature search with no language restriction was performed in electronic databases and preprint repositories to identify eligible studies published up to 29 June 2021. The outcomes of interest were hospital admission and all-cause mortality. A random-effects model was used to estimate the pooled odds ratio (OR) for outcomes of interest with the use of neutralizing monoclonal antibodies relative to nonuse of neutralizing monoclonal antibodies, at 95% confidence intervals (CI).

Results: Our systematic literature search identified nine randomized controlled trials. Three trials had an overall low risk of bias, while four trials had some concerns in the overall risk of bias. The meta-analysis revealed no statistically significant difference in the odds of mortality (pooled OR = 0.69; 95% CI 0.33–1.47), but a statistically significant reduction in the odds of hospital admission (pooled OR = 0.29; 95% CI 0.21–0.42), with the administration of a neutralizing monoclonal antibody among patients with COVID-19, relative to non-administration of a neutralizing monoclonal antibody, at the current sample size.

Conclusion: The reduced risk of hospital admission with neutralizing monoclonal antibodies use suggests that the timing of neutralizing antibodies administration is key in preventing hospital admission and, ultimately, death. Future randomized trials should aim to determine if the clinical outcomes with neutralizing monoclonal antibodies differ based on serostatus.

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Introduction

Since the outbreak of coronavirus disease 2019 (COVID-19) in late December 2019, morbidity and mortality continue to increase worldwide, with more than 240 million cases have been reported, and over 4.9 million people lost their lives due to this highly contagious disease, and even with numerous reports of re-infection [1,2]. The spectrum of COVID-19 severity ranges from asymptomatic to critical, though; most cases are of mild-to-moderate severity. While many therapeutic options such as corticosteroids and tocilizumab target those who develop severe-to-critical illness, treating those who have a mild-to-moderate illness is equally important, in order to prevent disease progression [3]. In fact, since those with mild-to-moderate illness constitute the largest proportion of patients with COVID-19, effective treatment for this subpopulation of patients with COVID-19 to prevent worsening of disease has the potential to conserve the limited health care resources during the pandemic.

Despite extensive efforts to discover an effective therapeutic intervention for COVID-19, no therapeutic agent has been thus far licensed for the treatment of COVID-19. Several vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed and being utilized in mass vaccination campaigns [4,5], but the unequal distribution of the vaccines and emergence of variants had led to waves of COVID-19 cases still being observed in many countries [6]. In addition, the vaccinees are not fully protected from the acquisition of SARS-CoV-2; breakthrough cases have been reported among those who are fully vaccinated [7]. Therefore, new treatment modalities are still an urgent requirement and the major agenda to tackle this pandemic, in addition to a safe and effective vaccination.

Monoclonal antibodies are a type of passive immunotherapy that could be an effective therapeutic intervention against a specific disease [8]. A monoclonal antibody is a laboratory-created molecule that mimics or improves the body's natural immune response to an invader, such as

tumors or infections. Since monoclonal antibodies are engineered to target an important portion of the infectious process directly, they offer an advantage over conventional methods of antiviral treatment. A monoclonal antibody is made by exposing a white blood cell to a specific viral protein and cloning it to mass generate antibodies against a particular virus. Monoclonal antibodies have been developed even before the COVID-19 pandemic, where they are used to treat various viral illnesses, including Ebola and rabies [9]. Since SARS-CoV-2 utilizes its spike protein to bind to the ACE2 receptors to enter human cells, various neutralizing monoclonal antibodies have been produced that target the spike protein in an attempt to prevent the virus from infecting human cells [10].

The United States Food and Drug Administration has granted Emergency Use Authorization for three neutralizing monoclonal antibodies for the treatment of selected non-hospitalized patients with COVID-19, namely LY-CoV555 (bamlanivimab ± etesevimab), REGEN-COV (casirivimab + imdevimab), and sotrovimab. They are recombinant neutralizing human monoclonal antibodies to the spike protein of SARS-CoV-2. These neutralizing monoclonal antibodies require only a single intravenous infusion, which can be conveniently administered to outpatients with COVID-19 at an emergency department, an infusion center, or another outpatient environment (such as the patient's home or nursing home). To date, there have been several randomized trials evaluating the effect of early use of neutralizing monoclonal antibodies on the risk of progression to severe COVID-19 in terms of hospital admission as well as the risk of mortality, and therefore we aimed to summarize the overall evidence in the form of a systematic review and meta-analysis.

Methods

This study was conducted according to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. Two investigators (CSK and SSH) independently conducted systematic literature searching in electronic databases, including PubMed, Cochrane Central Register of Controlled Trials, Google Scholar, and preprint repositories (SSRN and medRxiv), up to 29 June 2021, with the following keywords and their MeSH terms: 'COVID-19', 'SARS-CoV-2', 'novel coronavirus disease', 'monoclonal antibody', 'neutralizing antibody', 'REGEN-COV', 'casirivimab', 'imdevimab', 'sotrovimab', 'bamlanivimab', 'LY-Cov555', 'tixagevimab', 'cilgavimab', 'AZD7442', 'randomized', 'controlled trial', and 'clinical trial', without language restrictions. The Clinical Trial Registries of the United States (clinicaltrials.gov) were also searched for ongoing registered clinical trials of neutralizing monoclonal antibodies for the treatment of COVID-19, which had released their findings. In addition, we hand-searched the reference lists of relevant articles to identify additional studies. The inclusion criteria of studies for this systematic review and meta-analysis were randomized controlled trials comparing the clinical outcomes between any neutralizing monoclonal antibodies which

target the receptor-binding domain of the spike glycoprotein of SARS-CoV-2 and its comparators for the treatment of patients with COVID-19. We excluded single-arm trials, non-randomized trials, and trials that did not report clinical outcomes.

The outcomes of interest were hospital admission and all-cause mortality. Two investigators (CSK and SSH) independently evaluated each study, and also extracted the study characteristics. Study characteristics extracted included first author's surname, year of publication, trial design, the country where the trial was performed, disease severity of median age of patients, regimen/median age of patients, regimen of neutralizing monoclonal antibodies, regimen of comparative therapies, number of deaths in the intervention arm(s), number of deaths in the control arm, number of hospital admission in the intervention arm (s), and number of hospital admission in the control arm. In addition, two investigators (CSK and DSR) assessed the risk of bias of the trials included with Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), which is a standardized method for assessing potential bias in reports of randomized interventions [12]. RoB 2 is structured into a fixed set of bias domains, which include 'randomization', 'deviations from intervention', 'missing outcome data', 'measurement of the outcome', and 'selection of the reported results'. A proposed judgment about the risk of bias arising from each domain is generated by an algorithm, where judgment can be 'Low' or 'High' risk of bias or express 'Some concerns'.

A random-effects model meta-analysis was used to estimate the pooled odds ratio for outcomes of interest with the use of neutralizing monoclonal antibodies, relative to nonuse of neutralizing monoclonal antibodies, at 95% confidence intervals. We examined the heterogeneity across studies using the I^2 statistics and the χ^2 test, with substantial heterogeneity being considered at 50% and at $p < .10$, respectively. We examined for the existence of publication bias using the funnel plot with a triangle centered on a fixed effect summary estimate and extending 1.96 standard errors on either side. All analyses were performed using Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

Results

Our systematic literature search retrieved 644 hits, of which 241 were unique. After screening, nine randomized controlled trials [13–21] were included (Figure 1), with a total of 9565 patients who were randomized to the intervention arm and received a neutralizing monoclonal antibody and 7749 patients who were randomized to the control arm and did not receive a neutralizing monoclonal antibody. Five of the included trials [15,17–20] assessed mortality outcomes (with non-zero mortality events), while seven of the included trials [13–17,20,21] assessed outcomes on hospital admission. Four of the included trials [15–18] were performed in multiple countries, whereas the remaining five randomized trials were originated from the United States ($n=3$) [13,14,20], the United Kingdom [19], and Korea [21], respectively.

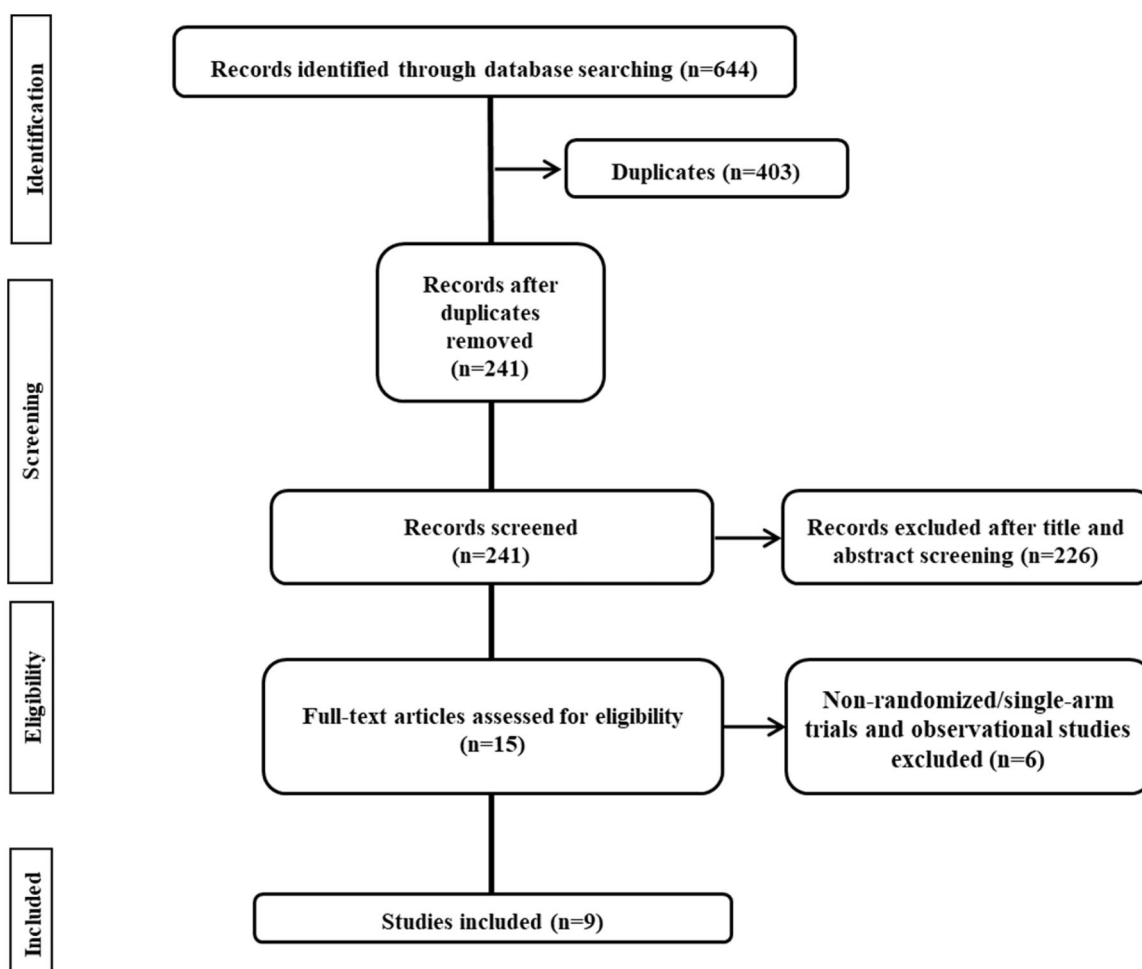


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram of process of study selection.

Characteristics of the included randomized trials are shown in Table 1.

The individual neutralizing monoclonal antibodies administered differed across the nine included trials: in both the trials by Lundgren et al. [18] and Chen et al. [13] respectively, LY-CoV555 (bamlanivimab) was administered as single intravenous infusion at a dose of 7000 mg in the former [18] and at doses of either 700 mg, 2800 mg, or 7000 mg in the latter [13]; in both the trials by Gottlieb et al. [14] and Dougan et al. [21] respectively, LY-CoV555 (bamlanivimab) was administered as single intravenous infusion at doses of either 700 mg, 2800 mg, 7000 mg, or 2800 mg in combination with etesevimab 2800 mg; in the trials by Weinreich et al. [15], O'Brien et al. [16], and Horby et al. [19] respectively, REGENCOV (casirivimab and imdevimab) was administered as single intravenous/subcutaneous infusion at doses of either 1200 mg, 2400 mg, or 8000 mg in the former two trials [15,16] and at a dose of 8000 mg in the latter trial [19]; in the trial by Gupta et al. [17], sotrovimab was administered as single intravenous infusion at a dose of 500 mg; and in the trial by Eom et al. [21], CT-P59 was administered as single intravenous infusion at doses of either 40 mg/kg or 80 mg/kg.

The overall risk of bias assessed by RoB 2 is presented in Table 1. The trials by Gupta et al. [17], Lundgren et al. [18], Gottlieb et al. [14], and Eom et al. [21], respectively, had an

overall low risk of bias (low risk of bias in all the domains assessed). The remaining four trials [13,15,16,19] had some concerns in the overall risk of bias; the trial by Chen et al. [13] had some concerns of bias in the domain of deviations from intervention due to a lack of information on the blinding of physicians/carers as well as on the administration of co-interventions of interest such as antivirals and corticosteroids; the trial by Weinreich et al. [15] had some concerns of bias in the domain of randomization due to a lack of information on randomization as well as on allocation concealment, in the domain of missing outcome data since the data was not available for every participants randomized (4507 participants randomized but only 4057 participants were analyzed), and in the domain of selection of the reported results since the trial was probably not analyzed as pre-specified (the outcome on hospital admission was added retrospectively); the trial by O'Brien et al. [16] had some concerns of bias in the domain of randomization due to a lack of information on allocation concealment; the trial by Horby et al. [19] had some concerns of bias in the domain of deviations from intervention due to open-label design of the trial; and the trial by Dougan et al. [20] had some concerns of bias in the domain of missing outcome data since the data was not available for every participants randomized (1,049 participants randomized but only 973 participants were analyzed).

Table 1. Characteristic of included studies.

Study (year)	Study design	Country	Age (median/mean)	Proportion of participants with different baseline severity of COVID-19 (%)	Regimen of NAb in the intervention group	Regimen of comparator intervention in the control group	Hospital admission		Mortality		Risk of bias ¹
							NAB users (n/N; %)	Non-NAB users (n/N; %)	NAB users (n/N; %)	Non-NAB users (n/N; %)	
Chen et al. [13] (2021)	Randomized, double-blind, placebo-controlled trial	United States	NAB users = 45.0 Non-NAB users = 46.0	Mild: NAB users = 75.1 Non-NAB users = 79.0 Moderate: NAB users = 24.9 Non-NAB users = 21.0	LY-CoV555 (single intravenous infusion at doses of 700 mg, 2800 mg, and 7000 mg)	Placebo	5/309; 1.6	9/143; 6.3	N/A	N/A	Some concerns
Gottlieb et al. [14] (2021)	Randomized, double-blind, placebo-controlled trial	United States	NAB users = 39.0 (700 mg)- 46.0 (7000 mg) Non-NAB users = 46.0	Mild: NAB users = 77.0 Non-NAB users = 80.1 Moderate: NAB users = 23.0 Non-NAB users = 19.9 N/A	LY-CoV555 (single intravenous infusion at doses of 700 mg, 2800 mg, 7000 mg, and 2800 mg in combination with etesevimab 2800 mg)	Placebo	6/421; 1.4	9/156; 5.8	N/A	N/A	Low
Weinreich et al. [15] (2021)	Randomized, double-blind, placebo-controlled trial	Global (2 countries)	NAB users = 48.0 (1200 mg)- 51.0 (8000 mg) Non-NAB users = 50.0	N/A	REGEN-COV (single intravenous infusion at doses of 1200 mg, 2400 mg, or 8000 mg)	Placebo	36/2716; 1.3	59/1341; 4.4	2/2716; 0.1	3/1341; 0.2	Some concerns
O'Brien et al. [16] (2021)	Randomized, double-blind, placebo-controlled trial	Global (3 countries)	NAB users = 39.2 Non-NAB users = 42.5	All participants were asymptomatic	REGEN-COV (single subcutaneous infusion at doses of 1200 mg or 2400 mg)	Placebo	3/104; 2.9	0/100; 0	N/A	N/A	Some concerns
Gupta et al. [17] (2021)	Randomized, double-blind, placebo-controlled trial	Global (4 countries)	NAB users = 53.0 Non-NAB users = 52.5	All participants were with mild-to-moderate COVID-19; no breakdown on the proportion of mild versus moderate cases	Sotrovimab (single intravenous infusion at a dose of 500 mg)	Placebo	3/291; 1.0	21/292; 7.2	0/291; 0	1/292; 0.3	Low
Lundgren et al. [18] (2021)	Randomized, double-blind, placebo-controlled trial	Global (3 countries)	NAB users = 63.0 Non-NAB users = 59.0	N/A	LY-CoV555 (single intravenous infusion at a dose of 7000 mg) + supportive care	Placebo + supportive care (remdesivir and, when indicated, supplemental oxygen and glucocorticoids)	N/A	N/A	6/163; 3.7	4/151; 2.6	Low
Horby et al. [19] (2021)	Open label, randomized controlled trial	United Kingdom	NAB users = 61.9 Non-NAB users = 61.9	N/A	REGEN-COV (single intravenous infusion at a dose of 8000 mg) + usual care	Usual care (glucocorticoids, azithromycin, tocilizumab/sarilumab, aspirin, colchicine, and remdesivir)	N/A	N/A	944/4839; 19.5	1026/4946; 20.7	Some concerns
Dougan et al. [20] (2021)	Randomized, double-blind, placebo-controlled trial	United States	NAB users = 54.3 Non-NAB users = 53.3	Mild: NAB users = 76.6 Non-NAB users = 77.9 Moderate: NAB users = 23.4 Non-NAB users = 22.1	LY-CoV555 (single intravenous infusion at a dose of 2800 mg) in combination with etesevimab 2800 mg	Placebo	0/518; 0	10/517; 1.9	11/518; 2.1	36/517; 6.7%	Some concerns
Eom et al. [21] (2021)	Randomized, double-blind, placebo-controlled trial	Korea	NAB users = 51.0 Non-NAB users = 52.0	Mild: NAB users = 40.3 Non-NAB users = 45.9 Moderate: NAB users = 59.7 Non-NAB users = 54.1	CT-P59 (single intravenous infusion at doses of 40 mg/kg or 80 mg/kg)	Placebo	9/204; 4.4	9/103; 8.7	N/A	N/A	Low

COVID-19: coronavirus disease 2019; NAB: Neutralizing antibody.

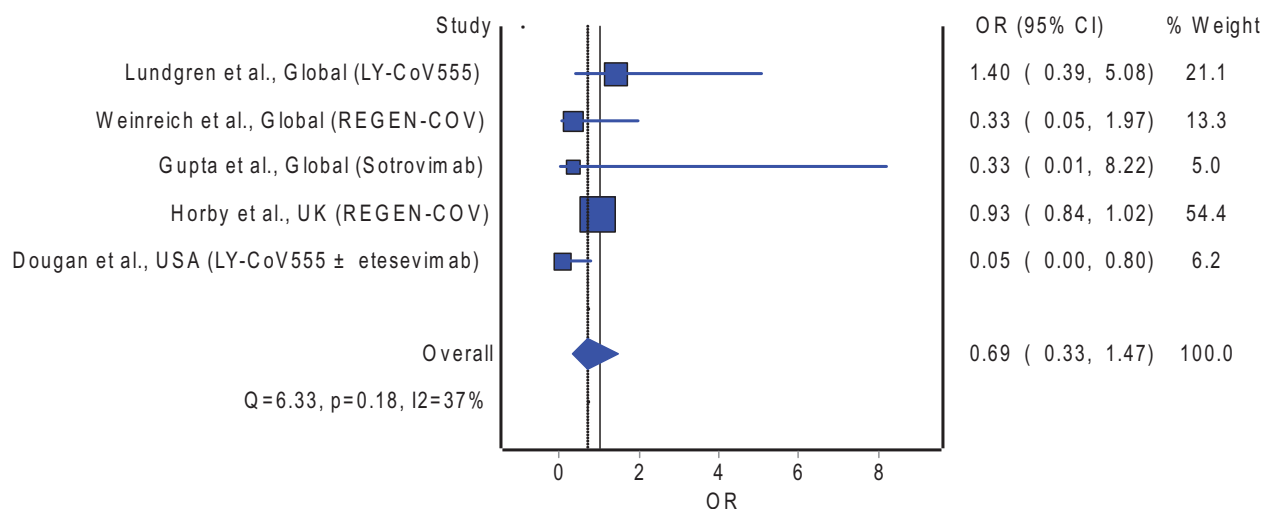


Figure 2. Pooled odds ratio for mortality with the administration of a neutralizing monoclonal antibody relative to non-administration of a neutralizing monoclonal antibody in patients with COVID-19.

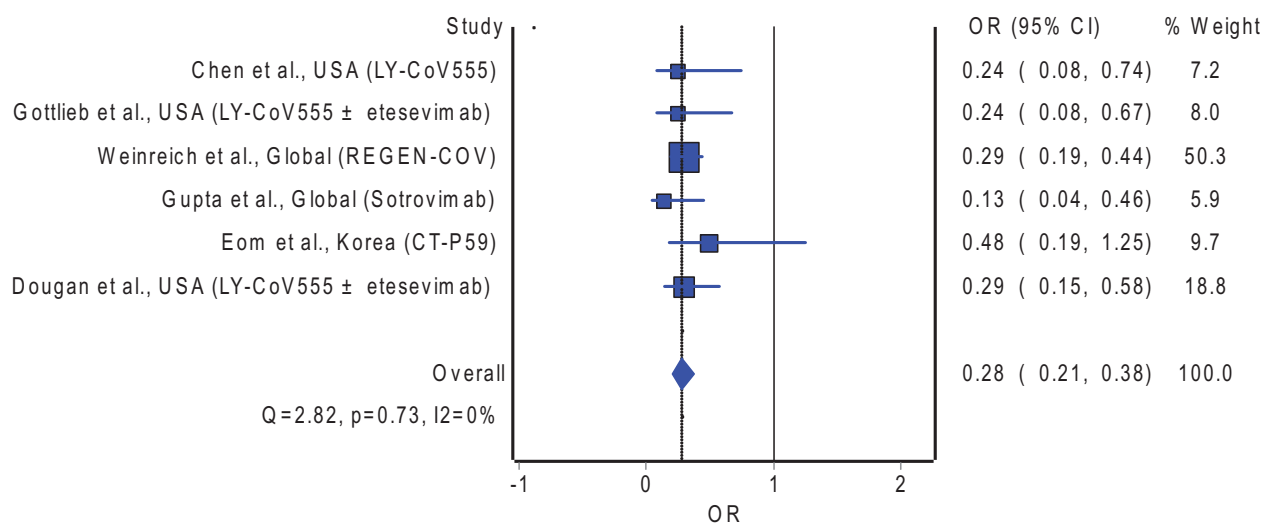


Figure 3. Pooled odds ratio for the risk of hospital admission with the administration of a neutralizing monoclonal antibody relative to non-administration of a neutralizing monoclonal antibody in patients with COVID-19.

The meta-analysis of five trials [15,17–20] revealed no statistically significant difference in the odds of mortality with the administration of a neutralizing monoclonal antibody among patients with COVID-19 relative to non-administration of a neutralizing monoclonal antibody; the estimated effect though indicated mortality benefits (Figure 2; pooled odds ratio = 0.69; 95% confidence interval 0.33–1.47), but is without adequate evidence to refute the null hypothesis of ‘no significant difference’, at the current sample size. On the other hand, the meta-analysis of seven trials [13–17,20,21] revealed a statistically significant reduction in the odds of hospital admission with the administration of a neutralizing monoclonal antibody among outpatients with COVID-19 relative to non-administration of a neutralizing monoclonal antibody; the estimated effect indicated reduction in hospital admission (Figure 3; pooled odds ratio = 0.29; 95% confidence interval 0.21–0.42), and with adequate evidence to refute the null hypothesis of ‘no significant difference’, at the current sample size. Re-analysis of the odds of hospital admission with the administration of a neutralizing

monoclonal antibody after removal of the outlier (O’Brien et al. [16]) also revealed consistent findings (pooled odds ratio = 0.28; 95% confidence interval 0.21–0.38). A funnel plot (or scatter plot) of the effect estimates from individual studies revealed no or limited publication bias. Except for one study, all studies are located in either side (extending 1.96 standard errors) of the triangle centered on a fixed effect summary estimate.

Discussion

To the best of the authors’ knowledge, this is the first reported systematic review and meta-analysis that analyzed the overall evidence on the clinical outcomes with the administration of neutralizing monoclonal antibodies among patients with COVID-19. Our study indicated no mortality benefits with the administration of neutralizing monoclonal antibodies among patients (both hospitalized and non-hospitalized) with mild-to-moderate COVID-19, but a significant reduction in hospital admission among outpatients with

COVID-19. However, the mortality outcomes narrowly missed statistical significance; most of the included trials might not be adequately powered to assess mortality outcomes. Therefore, our findings suggest that future, larger scale, adequately powered randomized trials, may be able to overturn the pooled findings on mortality outcomes.

Nevertheless, a significant reduction in hospital admission with the administration of neutralizing monoclonal antibodies among outpatients with COVID-19 should not be considered of low importance, since it suggests that neutralizing monoclonal antibodies can prevent disease progression/or accelerate clinical improvement in this patient population. By diverting more patients with COVID-19 away from the hospital, the limited health care resources could be better conserved during the pandemic. This would facilitate better care for the remaining patients with severe-to-critical COVID-19 who would require hospitalization and patients with other acute illnesses such as myocardial infarction or stroke, who generally would require inpatient management.

An important additional practical consideration is that the resources and supporting infrastructure required for the administration of neutralizing monoclonal antibodies may consume the resources from other COVID-19 management efforts. Therefore, resource-rich communities may be prioritized for neutralizing monoclonal antibody therapy over resource-limited communities. Thus, it is of utmost importance to ensure equitable access to these treatments in such a manner that the population can benefit as a whole. Furthermore, it should be noted that all the included trials [13–17], which assessed outcome on hospital admission among outpatients with COVID-19, administered the neutralizing monoclonal antibodies at a median of not more than seven days after symptom onset. Therefore, to maximize their efficacy, neutralizing monoclonal antibody treatment should be given to outpatients with COVID-19 as soon as possible after diagnosis and within seven days of symptom onset.

The safety of these neutralizing monoclonal antibodies can be a concern since they are newly approved agents with limited clinical experience of use. We observed that infusion-related reactions were reported more frequently among patients in the intervention group than the control group in the majority of the included trials [13–16,18,19]. In the trial by Chen et al. [13], the authors reported that most of these events which occurred during the infusion, including pruritus, flushing, rash, and facial swelling, were reported as mild in severity. In the trial by Gupta et al. [17], one patient receiving sotrovimab had an infusion-related reaction (moderate dyspnea) that was considered related to study treatment. In the trial by Gottlieb et al. [14], immediate hypersensitivity reactions that could have been infusion-related were reported as mild in severity and not dose-related, including pruritus, flushing, rash, and facial swelling. The other included trials did not describe in detail the nature of infusion-related reactions.

Our study was limited because we could not perform subgroup analyses to stratify patients according to serostatus (seropositive or seronegative). In the trial by Horby et al.

[19], the monoclonal antibody combination of casirivimab and imdevimab (REGEN-COV) reduced 28-day mortality among seronegative patients (relative risk = 0.80; 95% confidence interval 0.70–0.91) but not those with seropositive at baseline (relative risk = 1.09; 95% confidence interval 0.95–1.26). The mortality benefits with neutralizing monoclonal antibodies may be limited only to patients with COVID-19 who are seronegative, though we need more confirmation from future clinical trials. In addition, we were not able to stratify our analyses based on the individual neutralizing monoclonal antibodies administered in the included trials due to the limited number of trials available. We have pooled the data from studies using different neutralizing monoclonal antibodies formulations, but all of them target SARS-CoV-2. However, all but one included trial [13–15,17] individually observed a significant reduction in hospital admission with the administration of neutralizing monoclonal antibodies among outpatients with COVID-19 relative to non-administration of neutralizing monoclonal antibodies.

Conclusion

Our systematic review and meta-analysis indicates that neutralizing monoclonal antibodies can reduce the risk of hospital admission among outpatients with COVID-19. Future randomized trials should aim to determine if the clinical outcomes with neutralizing monoclonal antibodies differ based on serostatus and likewise to determine if the efficacy of neutralizing monoclonal antibodies extends to different variants of concern of SARS-CoV-2 as well.

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