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Original Article

Clinical efficacy and safety of SARS-CoV-2-neutralizing monoclonal antibody in patients with COVID-19: A living systematic review and meta-analysis

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Abstract This study evaluated the efficacy and safety of neutralizing monoclonal antibodies (mAbs) with usual care in patients with coronavirus disease 2019 (COVID-19). Randomized controlled trials comparing the efficacy and safety of neutralizing mAb treatment in patients with COVID-19 were identified using electronic database searches through March 10, 2023. This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Overall, 13 trials (23 articles) involving 25,646 patients were included in this systematic review. Compared with usual care, neutralizing mAbs were associated with significantly reduced all-cause mortality in outpatients with COVID-19 (pooled risk ratios [RR], 0.41; 95% confidence interval (CI), 0.20–0.83; 12 studies), but not in

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inpatients. In the subgroup analysis, only outpatients infected prior to the emergence of Delta variant or those with mAb—VOC match had significantly reduced mortality, while no significant benefit was observed in patients infected with Delta and post—Delta variants or mAb—VOC mismatch. Moreover, the rate of hospitalization and number of hospital visits had significantly reduced only in outpatients infected prior to the emergence of the Delta variant and those with mAb—VOC match. Our systematic review used majority of the high-certainty evidence. Our study found neutralizing mAbs were beneficial for outpatients infected prior to Delta variant or mAb—VOC match. In the face of the continuous emergence of new COVID-19 variants, additional clinical data are needed to determine whether neutralizing mAb treatment will be effective for the newly emerging variants.

Introduction

Over 650 million confirmed coronavirus disease (COVID)-19 cases and approximately 6.6 million fatalities have been reported globally as of 31 December 2022 since the first case was reported in Wuhan in December 2019.[1] Vaccination is still one of the greatest strategies in the era of COVID-19 to combat infection and disease progression.[2] However, a number of barriers, such as vaccination reluctance, supply constraints, and lack of access in low- and middle-income countries, continue to impede its widespread use.[3]

Many patients have mild or moderate disease, whereas older adults and those with comorbidities such as diabetes, obesity, and immunosuppression are more likely to present with unusual symptoms, have inconsistent vaccination immunity, and remain at a high risk of hospitalization and mortality.[3] With the emergence of new variants of concern (VOC), those who have received all recommended vaccinations have reported breakthrough cases.[4] Therefore, major critical concerns remain disease progression and hospitalization in patients with mild or moderate COVID-19. Hence, various SARS-CoV-2 neutralizing monoclonal antibodies (mAbs) have been developed and are being used to treat non-hospitalized patients with COVID-19 with mild to moderate infection and at high risk for progression to severe disease.[5]

Etesevimab, bamlanivimab, casirivimab, and imdevimab are some of the mAbs that particularly target the SARS-CoV-2 surface spike protein receptor-binding domain (RBD). While casirivimab and imdevimab attach to the RBD's non-overlapping epitopes, bamlanivimab and etesevimab bind to its overlapping epitope.[6] Recombinant human IgG1k monoclonal antibodies such as sotrovimab, bebtelovimab, tixagevimab, and cilgavimab act by attaching to a conserved epitope on the spike protein RBD of SARS-CoV-2. Preclinical investigations have shown that the antibodies offer a strong barrier against viral escape and maintain antiviral activity against newer SARS-CoV-2 variants, including the Omicron variant, which is linked to increased transmissibility and immune invasion.[7—9]

To date, the impact of the early use of neutralizing mAbs on the likelihood of progression to severe COVID-19 in terms of hospital admission and the risk of mortality has been evaluated in a number of randomized controlled trials (RCTs).[3,10—23] Several previous systematic reviews have studied the effect of neutralizing mAbs in treatment of patients with COVID-19.[24—27] However, the current data is insufficient to draw meaningful conclusions in the era of emerging new VOCs, and data is being updated. Therefore, in this systematic review and meta-analysis we aimed to comprehensively summarize the available data based on the latest articles.

Methods

A systematic review of RCTs was conducted with a meta-analysis in accordance with the recommendations of the Cochrane Handbook and the preferred reporting items for systematic review and meta-analysis (PRISMA) statement.[28] The protocol for this review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42022358681.

Search strategy

We performed a living systematic review by searching the databases and then regularly updating the search to obtain new evidence on the treatment for COVID-19 using neutralizing mAbs. First, we systematically searched PubMed, Ovid-EMBASE, CENTRAL, and the Korean databases (KMBASE) through June 14, 2021. A manual search using reference lists of relevant primary and review articles was also performed for completeness. Additionally, the search was updated every month from August 2021 to March 10, 2023, using Ovid-MEDLINE. The complete electronic search strategy for each database is presented in Supplementary Material 1.

Eligibility criteria and study selection

Articles that met the following requirements were included in the study: 1) patients were adults with COVID-19; 2) interventions using neutralizing mAbs; 3) the comparator was a placebo or standard of care treatment; and 4) outcomes included primary or secondary outcomes (the primary outcomes included all-cause mortality at 28 days and hospitalization or hospital visit. Clinical recovery, ICU admission, mechanical ventilation, hospital discharge, and serious adverse events were classified as secondary outcomes.); 5)

The study was a RCT. Only English and Korean studies were included in this meta-analysis. Two review authors independently and in duplicate evaluated publications for inclusion based on title and abstract and then reviewed relevant full-text articles. Disagreements during the review process were addressed by consensus, with the involvement of a third review author.

Risk of bias assessment, data extraction, and certainty of evidence

Authors independently assessed the quality of the selected studies using the Cochrane risk of bias tool.[29] Disagreements were resolved by consensus with the participation of a third review author.

Two review authors extracted the information from each included trial. These evaluations were performed independently and yielded separate results. Disagreements were resolved by discussion and third opinion. The following information was included in the data extraction form: first author, publication date, study design, characteristics of the study participants, ingredients of neutralizing mAbs, and pre-defined outcomes.

To align the included research as a single figurative criterion, some data were collected from supplementary materials or, when possible, using the intention-to-treat (ITT) principle (if not defined in the original article). To obtain additional information, we contacted the corresponding authors of included trials with insufficient information.

The certainty of evidence was graded using the grading of recommendations, assessment, development, and evaluation (GRADE) approach for primary and secondary outcomes[30].

Data synthesis and statistical analysis

For each included trial, continuous outcomes were presented as mean differences or hazard ratios (HR) with inverse-variance random-effects analysis and dichotomous outcomes as risk ratios (RR) with Mantel-Haenszel random-effects analysis and 95% confidence intervals (CIs) for all outcome measures. Heterogeneity among trials was evaluated using forest plots and calculating Higgins I^2 statistics.

We conducted the following pre-planned subgroup analyses:[1] hospitalization status (outpatient vs. inpatient),[2] VOC (pre-Delta variant vs. Delta and post–Delta variants),[3] serum antibody status (seronegative vs. seropositive), and[4] *in-vitro* efficacy of mAbs against SARS-CoV-2 VOCs (mAb–VOC match vs. mAb–VOC mismatch).[5,31] Statistical analyses were performed using Review Manager Software version 5.4 and R 4.2.1. For studies in which no events were observed in one or both arms, these computations often involve dividing by a zero count, which yields a computational error. Therefore, we added a fixed value of 0.5 to all cells in the study results tables with this issue, according to the Cochrane Handbook.[32]

Publication bias for the primary endpoint was assessed by visual inspection of funnel plots. Egger's linear regression test was also performed for the data with an asymmetric funnel plot (Stata version 14).

Results

Description of included studies

A total of 872 articles were retrieved from the databases after excluding duplicates. According to the selection criteria, 170 articles were selected for the full-text review. Overall, 23 published articles with 13 RCTs were included in this systematic review.[3,10–23,33–40] The details of the study selection and flowchart of the review are shown in Fig. 1. The timing of patient enrolment was different across the included studies, ranging from May of 2020 to September of 2021. Of the 23 final selected articles, three included patients infected with the Delta variant of COVID-19,[10,11,33] and the rest were conducted before the emergence of the Delta variant. In these three studies, 51.0%, 49.8%, and 15% of the patients were infected with the Delta variant of the SARS-CoV-2, respectively. Additionally, regarding hospitalization status, 14 articles reported treatment for outpatients[3,10–22] and 9 for inpatients.[23,33–40] Previous studies have used bamlanivimab,[12–14,35,37,38] bamlanivimab/etesevimab,[14–16,23] sotrovimab,[3,17,34] etesevimab,[36] regdanvimab,[18,20] bebtelovimab,[10] amubaryvimab/romlusevimab,[34] casirivimab/imdevimab,[19,21,22,39,40] tixagevimab/cilgavimab,[11,33] and bebtelovimab/bamlanivimab/etesevimab[10] as neutralizing mAb treatment.

The specific characteristics of the included studies are presented in Table 1. The results of the risk of bias summary are presented in Supplementary Material 2. Most studies showed a low risk of bias. The GRADE evidence profiles and a summary of the findings are presented in Table 2.

Primary outcomes

All-cause mortality at day 28

A total of 19 articles were used for meta-analysis of all-cause 28-day mortality using 25,235 participants, excluding duplicates. Neutralizing mAbs significantly reduced the all-cause 28-day mortality in outpatients (RR = 0.40, 95% CI 0.20–0.79; I^2 0%; 12 studies; high certainty evidence). Subgroup analysis with virus variants and mAb–VOC match were also performed. The neutralizing mAbs had a significant effect on the mortality rate of the outpatients infected prior to the emergence of the Delta variant and in those with mAb–VOC match (RR = 0.22, 95% CI, 0.09–0.53 and RR = 0.39, 95% CI, 0.19–0.78, respectively), but not in outpatients infected with Delta and post–Delta variants or in those with mAb–VOC mismatch (RR = 0.95, 95% CI, 0.32–2.79 and RR = 0.99, 95% CI, 0.02–49.77, respectively) (Fig. 2).

In inpatients, the effect of neutralizing mAbs was uncertain in the base-analysis (RR = 0.83, 95% CI 0.67–1.02; I^2 34%; seven studies; high-certainty evidence) (Table 2). However, neutralizing mAbs showed differential effects on mortality according to the immunity of inpatients. The seronegative group had a significantly lower mortality rate than the seropositive group (seronegative, RR = 0.67, 95% CI, 0.50–0.90; seropositive, RR = 1.00, 95% CI, 0.72–1.39). Meanwhile, in the sub-group analysis with VOCs and

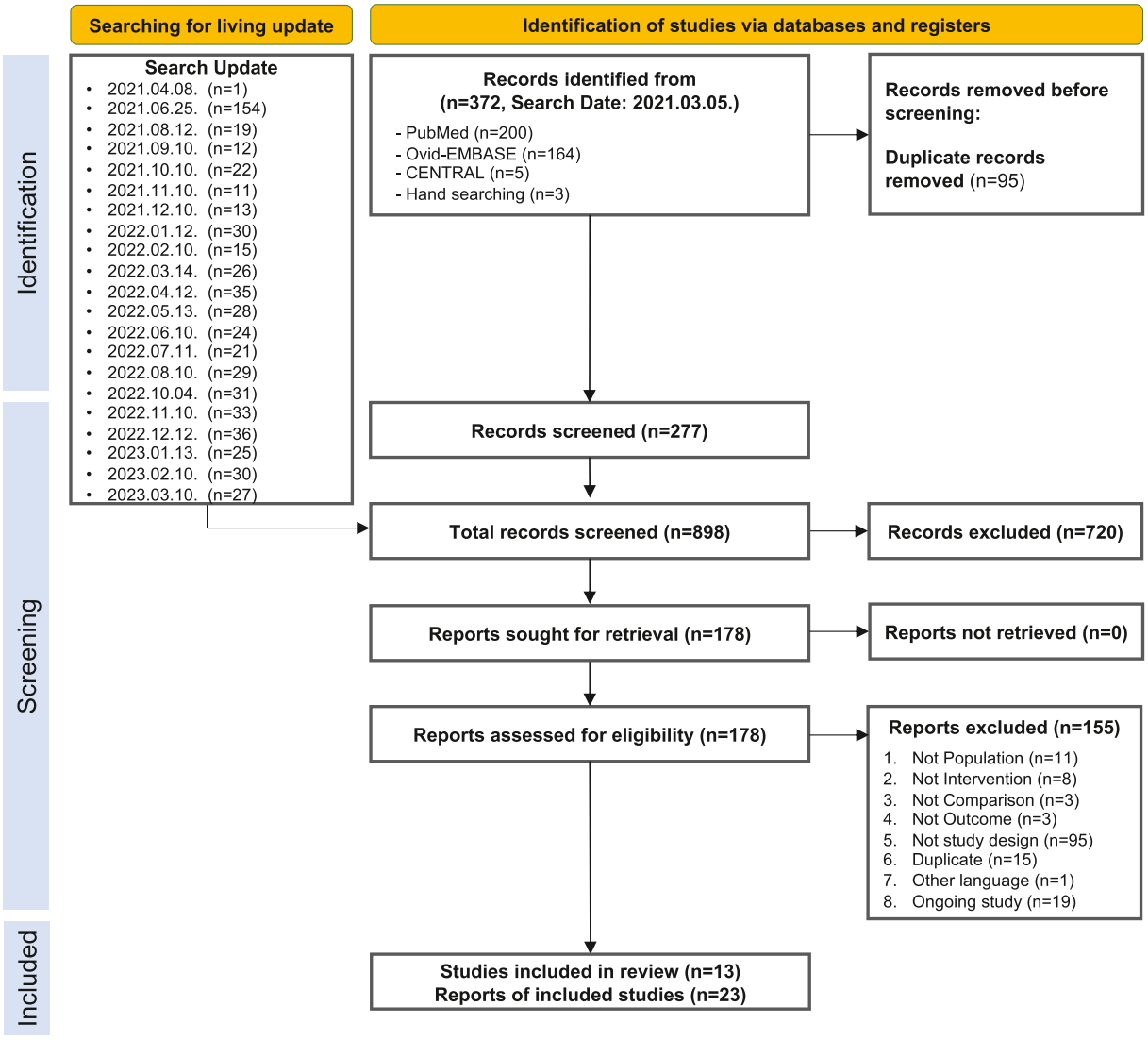

Figure 1. Preferred reporting items for systematic reviews and meta-analyses study flowchart.

mAb—VOC match, no significant differences in the effect of neutralizing mAbs were observed between the sub-groups (Fig. 3).

The publication bias of the included studies was assessed to be low risk with respect to mortality. Although the funnel plot was asymmetric, Egger's test did not reveal statistically significant publication bias (P = 0.0844) (Supplementary Material 3).

Hospitalization or hospital visits

Hospitalization or hospital visits were reported in 10 articles with all outpatient participants. Neutralizing mAbs were significantly associated with reduced hospitalization or hospital visits in outpatients than the control group (RR = 0.33, 95% CI, 0.24—0.43; I^2, 28%; high certainty evidence; Table 2). Subgroup analysis with virus variants and mAb—VOC match was followed by hospitalization or hospital visits. Outpatients infected prior to the spread of Delta variant and the mAb—VOC match group had significantly lower hospitalization rates or hospital visits after treatment with neutralizing mAbs than the control group (RR = 0.29, 95% CI, 0.22—0.39 and RR = 0.31, 95% CI, 0.23—0.41, respectively), while patients infected with VOCs, including the Delta variant, or those with mAb—VOC mismatch, treatment with neutralizing mAbs showed no significant effect (Fig. 4).

Secondary outcomes

A meta-analysis was performed for secondary outcomes (Table 2, Supplementary Material 4). In the case of clinical recovery, ICU admission, mechanical ventilation, and serious adverse events, neutralizing mAbs had a significant positive effect on outpatients, but not on inpatients. The RR of neutralizing mAbs for treatment of outpatients as compared to the control group are 1.12 (95% CI, 1.07—1.18, I^2 34%, six studies%; high certainty evidence) in clinical

Table 1 Baseline study characteristics of included randomized controlled trials of monoclonal antibodies.

Trial name Trial number	First author Year (Study phase)	Treatment dose (g)	Control	Patients at randomization [N]	Enrolment period	Country [N of study site]	Patient age (mean, median) (Treatment, Control)	Serum antibody status, positive (Treatment, Control)	Variants of concern (match[a])	Inpatient/ Outpatient	Published date
ACTIV-2/A5401 NCT04518410	Chew 2022[9] (Phase 2)	Bamlanivimab (7)	Placebo	94	Aug 19 – Nov 17, 2020	USA	T: 46 C: 42	N/A	Pre-Delta (mismatch)	Outpatients	Nature Aug 22, 2022
		Bamlanivimab (0.7)	Placebo	223			T: 46 C: 49	N/A			
ACTIV-3/TICO NCT04501978	Lundgren 2021[32] (Phase 3)	Bamlanivimab (7)	Placebo	314	Aug 5 – Oct 13, 2020	USA (23) Denmark (7) Singapore (1)	T: 63 C: 59	T: 50.9% C: 45.7%	Pre-Delta (mismatch)	Inpatients	NEJM Mar 11, 2021
	Lundgren 2022[33] (Phase 3)	Bamlanivimab (7)	Placebo	314	Aug 5 – Oct 13, 2020	USA (23) Denmark (7) Singapore (1)	T: 63 C: 59	T: 50.9% C: 45.7%		Inpatients	NEJM Dec 22, 2020
	ACTIV-3/ TICO Study Group 2022[29] (Phase 3)	Sotrovimab (0.5) Amubarvimab (1) + Romlusevimab (1)	Placebo	536	Dec 16, 2020– Mar 1, 2021	USA, Denmark, Switzerland, Poland (43)	S: 61 A + R: 61 C: 60	T: 38.0% C: 42.7%	Pre-Delta (match)	Inpatients	Lancet Infect Dis Dec 23, 2021
	ACTIV-3-TICO Study Group 2022[28] (Phase 3)	Tixagevimab (1) + Cilgavimab (1)	Placebo	1417	Feb 10 – Sept 30, 2021	USA (66) Uganda (5) UK (3) Greece (2) Spain (2) Singapore (1) Denmark (1) Switzerland (1)	T: 55 C: 55	T: 53.5% C: 47.9%	Delta 51.0% Non-Delta 49.0% (match)	Inpatients	Lancet Respir Med Jul 8, 2022
BLAZE-1 NCT04427501	Chen 2021[8] (Phase 2)	Bamlanivimab (0.7, 2.8, 7)	Placebo	452	Jun 17 – Aug 21, 2020	USA (41)	T: 0.7g, 39; 2.8g, 45; 7g, 46 C: 46	N/A	Pre-Delta Pre-Delta (match)	Outpatients	NEJM Jul 14, 2021
	Gottlieb 2021[10] (Phase 2)	Bamlanivimab (0.7, 2.8, 7)	Placebo	577	Jun 17 – Aug 21, 2020	USA	T: 0.7g, 39; 2.8g, 45; 7g, 46 C: 46	N/A		Outpatients	JAMA February 16, 2021
		Bamlanivimab (2.8)+ Etesevimab (2.8)		577				N/A			
	Dougan 2021[19] (Phase3)	Bamlanivimab (2.8)+ Etesevimab (2.8)	Placebo	1035	Sep 4 – Dec 8, 2020	USA	B + E: 54 C: 53	N/A		Inpatients	NEJM Oct 7, 2021
	Chen 2022[11] (Phase3)	Bamlanivimab (0.7)+ Etesevimab (1.4)	Placebo	769	Dec 9, 2020– Jan 7, 2021	USA (104)	B + E: 57 C: 55	N/A		Outpatients	Open Forum Infectious Diseases Apr 7, 2022
	Dougan 2022[12] (Phase3)	Bamlanivimab (0.7)+ Etesevimab (1.4)	Placebo	769	Dec 9, 2020– Jan 7, 2021	USA	B + E: 57 C: 55	N/A		Outpatients	Clin Infect Dis Augt 24, 2022
BLAZE-4 J2X-MC-PYAH NCT04634409	Dougan 2022[6] (Phase 2)	Bebtelovimab (0.175) Bebtelovimab (0.175) + Bamlanivimab (0.7) + Etesevimab (1.4)	Placebo	380	May 7 – Jul 21, 2021	USA	B: 34 B + B + E: 37 C: 34	T: 8.3% C: 14.1%	Delta 49.8% Alpha 28.6% (match)	Outpatients	medRxiv Mar 12, 2022
J2W-MC-PYAA NCT04411628	Chen 2021[30] (Phase 1)	Bamlanivimab (0.7, 2.8, 7)	Placebo	24	May 29 – Jun 28, 2020	USA	T: 0.7g, 57; 2.8g, 49; 7g: 67 C: 43	N/A	Pre-Delta (match)	Inpatients	Clin Pharmacol Ther Dec, 2021
NCT04425629	Weinreich 2021[17]	Casirivimab	Placebo	275	Jun 16 –	USA	T: 2.4g, 43;	T: 41.8%	Pre-Delta	Outpatients	NEJM

(*continued on next page*)

Table 1 (*continued*)

Trial name Trial number	First author Year (Study phase)	Treatment dose (g)	Control	Patients at randomization [N]	Enrolment period	Country [N of study site]	Patient age (mean, median) (Treatment, Control)	Serum antibody status, positive (Treatment, Control)	Variants of concern (match[a])	Inpatient/ Outpatient	Published date
	(Phase 1/2)	+ Imdevimab (2.4, 8)			Aug 13, 2020		8g, 44 C: 45	C: 50.5%	(match)		Jan 21, 2021
	Weinreich 2021[18] (Phase 3)	Casirivimab + Imdevimab (1,0.2, 2.4, 8)	Placebo	4057	Sept 24, 2020– Jan 17, 2021	USA	T: 1.2g, 49; 2.4g, 50 C: 1.2g,: 48; 2.4g, 50	T: 24.4% C: 22.1%		Outpatients	NEJM Dec 2, 2021
NCT04666441	Portal-Celhay 2022[15] (Phase 2)	Casirivimab + Imdevimab (0.3,.0.6, 1.2, 2.4)	Placebo	507	Dec 15, 2020– Feb 26, 2021	USA (47)	T IV: 34.6, SC: 34.1 C: 35.1	N/A	Pre-Delta (match)	Outpatients with low risks	JAMA Aug 15, 2022
RECOVERY NCT04381936	Recovery Collaborative Group 2022[35] (Phase 2/3)	Casirivimab (4) + Imdevimab (4)	Usual care	9785	Sept 18 – May 22, 2021	UK (127)	T: 61.9 C: 61.9	T: 54.5% C: 53.3%	Pre-Delta (match)	Inpatients	Lancet Feb 12, 2022
NCT04426695	Somersan- Karakaya 2022[34] (Phase 3)	Casirivimab (1.2) + Imdevimab (1.2) Casirivimab (4) + Imdevimab (4)	Placebo	1197	Jun 10, 2020– Apr 9, 2021	USA, Brazil, Chile, Mexico, Moldova, Romania (103)	T 1.2g: 60, 4g: 62 C: 64	T: 45.9% C: 51.1%	Pre-Delta (match)	Inpatients	J Infect Dis Jul 27, 2022
COMET-ICE NCT04545060	Gupta 2021[3] (Phase 3)	Sotrovimab (0.5)	Placebo	583	Aug 27, 2020– March 4, 2021	USA, Canada, Brazil, and Spain (37)	S: 53.0 C: 52.5	N/A	Pre-Delta (match)	Outpatients	NEJM Nov 18, 2021
	Gupta 2022[13] (Phase 3)	Sotrovimab (0.5)	Placebo	1057	Aug 27, 2020– Mar 11, 2021	Brazil, Canada, Peru, Spain, USA (57)	T: 53 C: 53	N/A		Outpatients	JAMA Mar 14, 2022
NCT04602000	Streinu-Cercel 2022[16] (Phase 2)	Regdanvimab (40 mg/kg) Regdanvimab (80 mg/kg)	Placebo	327	Oct 7 – Nov 21, 2020	South Korea, Romania, Spain, USA (23)	T 40 mg/kg; 51.0, 80 mg/kg: 51.0 C: 52.0	N/A	Pre-Delta (match)	Outpatients	OFID Feb 2022
	Kim 2022[14] (Phase 3)	Regdanvimab (40 mg/kg)	Placebo	1315	Jan 18 – Apr 24, 2021	South Korea, Romania, Spain, USA, Servia, Romania, Hungary, Poland, Peru, Mexico, Macedonia, Italy, Maldova, Ireland, Ukraina (60)	T: 49.0 C: 47.0	T: 11.6% C: 10.9%		Outpatients	OFID Aug 2022
NCT04931238	Dong 2022[31] (Phase 2/3)	Etesevimab (50 mg/kg)	Placebo	197	Jan 18 – Feb 2, 2021	China	T: 58 C: 59	N/A	Pre-Delta (match)	Inpatients	AAC.ASM Mar 15, 2022
TACKLE NCT04723394	Montgomery 2022[7] (Phase 3)	Tixagevimab (0.3) + Cilgavimab (0.3)	Placebo	903	Jan 28 – Jul 22, 2021	USA, Latin America, Europe, Japan (95)	T: 46.3 C: 45.9	T: 13.3% C: 14.9%	Alpha 60% Gamma 20% Delta 15% Lambda 5% Mu 1% Beta <1% (match)	Outpatients	Lancet Jun 7, 2022

[a] In-vitro efficacy of mAbs against SARS-CoV-2 variants of concern[5,31].

Table 2 GRADE summary of findings table of primary and secondary outcomes.

Outcomes	Subgroups	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
		Risk with standard of care/placebo	Risk with Neutralizing monoclonal antibody			
All-cause mortality at day 28	Outpatient	6 per 1000	2 per 1000 (1–5)	RR 0.41[a] (0.20–0.83)	12,176 (12 studies)	⨁⨁⨁⨁ High
	Inpatient	183 per 1000	155 per 1000 (128–186)	RR 0.85 (0.72–1.01)	13,470 (7 studies)	⨁⨁⨁⨁ High
Hospitalization or hospital visit	Outpatient	55 per 1000	18 per 1000 (13–25)	RR 0.33[a] (0.24–0.43)	10,614 (9 studies)	⨁⨁⨁⨁ High
Clinical recovery	Outpatient	605 per 1000	677 per 1000 (647–713)	RR 1.12[a] (1.07–1.18)	7336 (6 studies)	⨁⨁⨁⨁ High
	Inpatient	851 per 1000	868 per 1000 (843–902)	RR 1.02 (0.99–1.06)	2267 (3 studies)	⨁⨁⨁⨁ High
Admission to ICU	Outpatient	16 per 1000	4 per 1000 (2–8)	RR 0.27[a] (0.14–0.49)	6399 (5 studies)	⨁⨁⨁⨁ High
	Inpatient	0 per 1000	0 per 1000 (0–0)	RR 1.11 (0.05–24.07)	24 (1 study)	⨁⨁◯◯ Low[b]
Mechanical ventilation	Outpatient	6 per 1000	1 per 1000 (0–4)	RR 0.23[a] (0.07–0.75)	5565 (4 studies)	⨁⨁⨁⨁ High
	Inpatient	83 per 1000	85 per 1000 (76–95)	RR 1.03 (0.92–1.15)	13,467 (7 studies)	⨁⨁⨁⨁ High
Hospital discharge	Inpatient	715 per 1000	723 per 1000 (701–744)	RR 1.01 (0.98–1.04)	12,029 (5 studies)	⨁⨁⨁⨁ High
Serious adverse events	Outpatient	36 per 1000	21 per 1000 (14–31)	RR 0.57[a] (0.39–0.84)	13,260 (12 studies)	⨁⨁⨁⨁ High
	Inpatient	30 per 1000	26 per 1000 (21–31)	RR 0.86 (0.70–1.04)	13,486 (6 studies)	⨁⨁⨁⨁ High

[a] Statistically significant: GRADE Working Group grades of evidence.
[b] Imprecision downgraded by two level due to low number of sample size and a wide confidence interval consistent with the possibility for benefit and the possibility for harm.
Abbreviation: GRADE, Grading of Recommendations, Assessment, Development and Evaluations; CI, Confidence Interval; RR, Risk Ratio.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

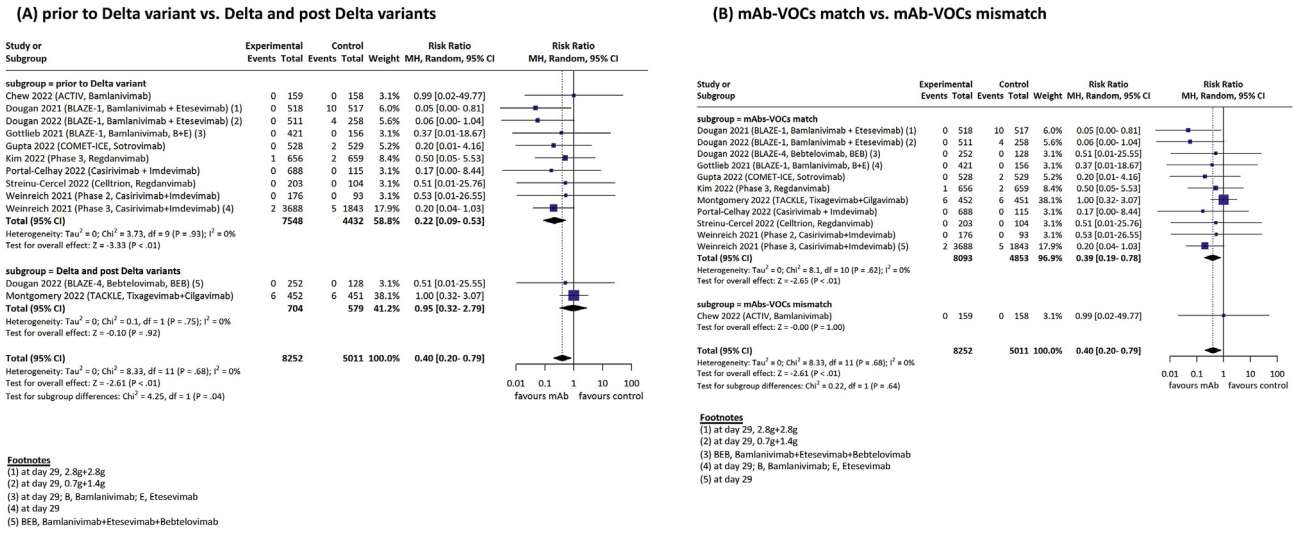

Figure 2. Meta-analysis of all-cause 28-day mortality for outpatients with COVID-19 infection.

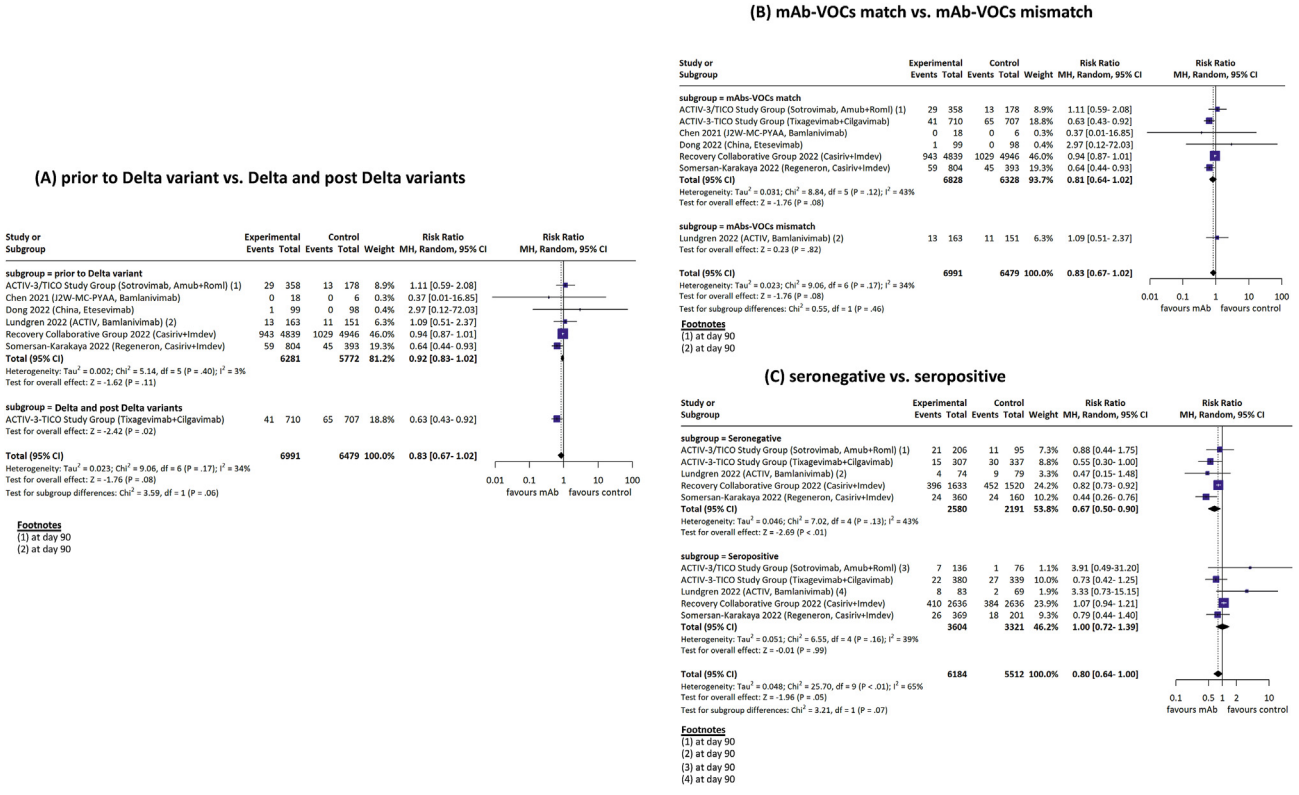

Figure 3. Meta-analysis of all-cause 28-day mortality for inpatients with COVID-19 infection.

recovery, 0.27 (95% CI, 0.14—0.49, I^2 0%, five studies%; high certainty evidence) in admission to ICU, 0.23 (95% CI, 0.07—0.75, I^2 0%, four studies%; high certainty evidence) in mechanical ventilation, and 0.57 (95% CI, 0.39—0.84, I^2 35%, 12 studies%; high certainty evidence) in serious adverse events. However, hospital discharge was not significantly improved with the treatment using neutralizing mAbs (RR = 1.01, 95% CI, 0.98—1.04, I^2 49%; five studies; high certainty evidence).

Discussion

In this meta-analysis, 23 published articles with 13 RCTs were reviewed to investigate the clinical efficacy and safety of neutralizing mAbs including bamlanivimab, etesevimab, bamlanivimab/etesevimab, casirivimab/imdevimab, regdanvimab, sotrovimab, bebtelovimab, sotrovimab, amubaryvimab/romlusevimab, tixagevimab/cilgavimab, and bebtelovimab/bamlanivimab/etesevimab. Our

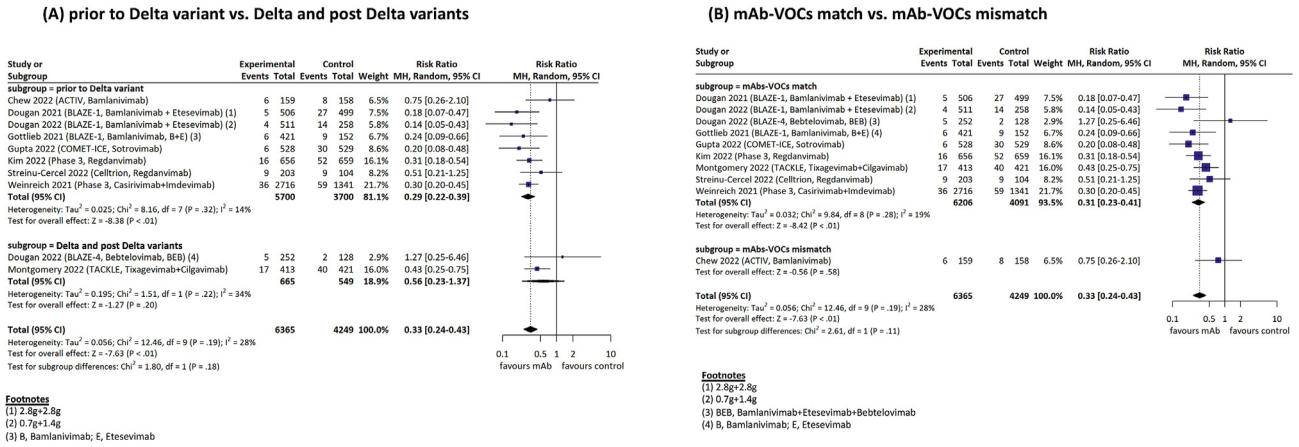

Figure 4. Meta-analysis of hospitalization or hospital visit for outpatients with COVID-19 infection.

systemic review and meta-analysis were based on the majority of high certainty of evidence, and our study showed that the administration of neutralizing mAbs significantly reduced all-cause 28-day mortality in outpatients with COVID-19, especially among patients infected prior to the Delta variant. Moreover, there was a significant reduction in hospitalization and hospital visits among outpatients infected prior to the Delta variant.

Consistent with other meta-analyses of RCTs evaluating the clinical efficacy in patients with COVID-19,[24–27] our study reports that the administration of neutralizing mAbs was beneficial for outpatients, but not inpatients. In the BLAZE 1 trial, bamlanivimab/etesevimab significantly reduced the rates of COVID-19 related hospitalization by day 29 when compared with the placebo group (0.8% vs. 5.4%; RR 0.14; 95% CI. 0.05–0.43, $p < 0.001$).[15] Casirivimab/imdevimab significantly reduced COVID-19 related hospitalization or death from any cause (1.3% vs. 4.6%; relative risk reduction, 71.3%; 95% CI, 51.7–82.9; $p < 0.001$).[22] Omicron VOC and their subvariants have significantly decreased *in vitro* susceptibility to these mAbs, which has caused the distribution of bamlanivimab/etesevimab and casirivimab/imdevimab to halt in the United States (US).[41]

In a RCT that included 1057 non-hospitalized patients with symptomatic, mild to moderate COVID-19, sotrovimab significantly reduced all-cause hospitalization lasting more than 24 h or fatalities (6/528 [1%] for sotrovimab vs 30/529 [6%] for placebo). Sotrovimab reduced the risk of emergency department visit, hospitalization, or mortality (13/528 [2%] for sotrovimab vs 39/529 [7%] for placebo; adjusted RR, 0.34 [95% CI, 0.19 to 0.63]; absolute difference, −4.91% [95% CI, −7.50% to −2.32%]; $p < 0.001$), and the progression to severe or critical respiratory failure due to COVID-19 (7/528 [1%] for sotrovimab vs 28/529 [5%] for placebo; adjusted RR, 0.26 [95% CI, 0.12 to 0.59]; absolute difference, −3.97% [95% CI, −6.11% to −1.82%]; $p = 0.002$); four of the five secondary outcomes that had statistically significant favoring outcomes.[17] In the BLAZE-4 trial, 90.2% of the samples were aligned with a VOC, with the majority patients infected with Alpha (28.6%) or Delta (49.8%) variants. By day 29, the COVID-19-related hospitalization or all-cause mortality rates in the low-risk population were similar to that of the placebo group. In this study, all patients at high risk for severe COVID-19 were treated with mAbs via open-label; therefore, the clinical efficacy of mAbs in the high-risk population compared to placebo was not evaluated.[10] Sotrovimab retained *in vitro* neutralization activity against the Omicron VOCs BA.1 and BA.1.1; however, the activity against BA.2, BA.4, and BA.5 subvariants was substantially reduced. Thus, sotrovimab is not expected to be effective in patients infected with these subvariants. The distribution of sotrovimab has halted as the Omicron BA.2 subvariant has become the predominant circulating subvariant in all areas of the US.[42]

With the emergence of VOC, the clinical efficacy of many neutralizing mAbs has decreased, but there has been no systematic review and meta-analysis comparing the efficacy of neutralizing mAbs before and after the emergence of VOC. The susceptibility of these new Omicron subvariants (BA.2.11, BA.2.12.1, and BA.4/5) to eight therapeutic monoclonal antibodies was assessed in *in vitro* investigation (bamlanivimab, bebtelovimab, casirivimab, cilgavimab, etesevimab, imdevimab, sotrovimab and tixagevimab). While BA.2 S containing the R493Q alteration was only partially susceptible to casirivimab and tixagevimab, the other antibodies, i.e., bamlanivimab, etesevimab, and imdevimab, were less effective against the novel Omicron subvariants.[43] Bebtelovimab was 2 times more effective against BA.2 and all omicron subvariants than against the ancestral strain43.

Owing to their recent approval and limited clinical application, the safety of these neutralizing mAbs may be a cause for concern. According to our research, neutralizing mAbs did not increase the probability of any adverse events (AEs) or significant AEs compared to placebo. In another study, the percentage of patients who had treatment-emergent AEs while receiving bebtelovimab or bebtelovimab/bamlanivimab/etesevimab was 9.7% in low-risk patients and 14.7% in high-risk patients; the majority of AEs were rated as mild to moderate in severity. One fatality (cerebrovascular accident) and two significant AEs were recorded in 2.1% of high-risk patients; no serious AEs were reported in low-risk patients.[10]

Our study had several limitations. First, the participants included in each study had different demographic and

clinical characteristics. However, the heterogeneity of the study participants was minimized by stratification of outpatients and inpatients, and the random-effects model was used for all analyses to generate conservative effect estimates. Second, the type and dosage of mAbs used were heterogeneous in each included study. Although various RCTs of different mAbs have been conducted, the endpoints of primary and secondary outcomes were similar between trials. Third, we performed subgroup analysis by VOCs. However, we could not analyze outcomes specific to different VOCs as the trials included in our study did not provide event numbers categorized by VOCs. Fourth, we were unable to assess the impact of neutralizing mAbs on Omicron variants owing to a lack of data. Further evidence on their potential impact as a confounder in management of COVID-19 is needed.

Nevertheless, our study had two strengths. First, our systematic review included a large number of patients (25,235 patients and 18 studies for mortality analysis) and up-to-date evidence including publications until March 10 2023. The latest evidence leads to robust conclusions regarding the efficacy and safety of mAbs. Second, we performed subgroup analyses to stratify patients across different COVID-19 variants (pre-Delta vs. Delta and post—Delta variants) and the mAb—VOC match. We found that mAbs were less effective in treating patients with COVID-19 in the Delta and post—Delta period or those with mAb—VOC mismatch. It should be noted that many neutralizing mAbs that were eventually made available did not prove to be effective against SARS-CoV-2 within a short period of time after their introduction because the virus quickly escaped their restricted specificity with the generation of monoclonal antibody-resistant variants.[5] In terms of the immunity of inpatients, the seronegative group had significantly lower mortality than the seropositive group. However, in the sub-group analysis with VOCs and mAb—VOC match, there were no significant differences in the effect of neutralizing mAbs between the sub-groups. For this reason, the COVID-19 treatment guidelines in some countries conditionally recommend that casirivimab/imdevimab be administered only to seronegative adults hospitalized with COVID-19,[44,45] but the guideline development group strongly recommended against the use of casirivimab/imdevimab for all patients with COVID-19 after the emergence of the new VOCs.[46]

In conclusion, neutralizing mAbs are effective for reducing the risk of all-cause mortality, hospitalization rate, and hospital visits of outpatients infected prior to the emergence of Delta variant and those with mAb—VOC match. Considering that the neutralization activity of existing mAbs is decreasing owing to the worldwide prevalence of diverse Omicron variants, COVID-19 treatment guidelines in the US recommend nirmatrelvir/ritonavir and remdesivir over mAbs.[41,47] Based on the continuous emergence of new COVID-19 variants, additional clinical data are needed to determine the effectiveness of neutralizing mAb treatment for the newly emerging variants, and the potential of neutralizing mAb acting as a very specific binding reaction to SARS-CoV-2; thus, it should be considered carefully.

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Conflicts of interest

None of the authors have conflicts of interest associated with this manuscript to declare.

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Appendix A. Supplementary data

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