Original Article

Efficacy and safety of casirivimab and imdevimab for preventing and treating COVID-19: a systematic review and meta-analysis

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Background: The ongoing global epidemic of coronavirus disease 2019 (COVID-19) has created a serious public health problem. The selection of safe and effective therapeutic agents is of paramount importance. This systematic review aims to evaluate the efficacy and safety of the combination of casirivimab and imdevimab in the treatment of global cases of COVID-19.

Methods: To identify randomized controlled trials (RCTs) investigating the combined administration of casirivimab and imdevimab for COVID-19 management, a comprehensive search was conducted across multiple databases including PubMed, Web of Science, Embase, and the Cochrane Library from their inception to September 10, 2022. Data on the efficacy and safety of casirivimab and imdevimab were extracted. Subgroup analyses and sensitivity analyses were performed.

Results: A total of 851 articles were searched. Twelve studies were finally included in the meta-analysis, with 27,179 participants. Dichotomous and continuous variables were presented as odds ratios (ORs) and weighted mean differences (WMDs) with their 95% confidence intervals (CIs), respectively. Compared to placebo or alternative medications, the combination of casirivimab and imdevimab reduced viral load (WMD: −0.73, 95% CI: −1.09 to −0.38, P<0.01), all-cause mortality (OR =0.90, 95% CI: 0.82–0.99, P=0.03), the incidence of any serious adverse events (OR =0.80, 95% CI: 0.67–0.95, P=0.01), the incidence of Grade 3 or more severe adverse events (OR =0.76, 95% CI: 0.62–0.92, P=0.01), the likelihood of contracting COVID-19, the incidence of hospitalization, emergency room visits, and mortality (OR =0.54, 95% CI: 0.32–0.93, P=0.03).

Conclusions: The monoclonal antibody combination of casirivimab and imdevimab is effective in treating patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as they can reduce viral load, all-cause mortality, infection rates, and the incidence of clinical outcomes of special interest after treatment, while maintaining a favorable safety profile.

Keywords: Coronavirus disease 2019 (COVID-19); casirivimab and imdevimab; monoclonal antibody; antiviral therapy

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Introduction

Ever since its initial identification in 2019, the coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly escalated into a global pandemic, leading to the deaths of millions of lives worldwide (1). The SARS-CoV-2 virus has gradually evolved into new strains, such as Omicron and Delta variants, concurrently generating diverse subvariants (2), characterized by their potent virulence and widespread transmission. Current treatments include vaccination, employment of monoclonal antibodies (anti-SARS-CoV-2 monoclonal antibodies), convalescent plasma therapy, antiviral drugs, and cellular therapy (3). Nevertheless, some studies have underscored the limited efficacy of convalescent plasma therapy, cellular therapy, and antiviral medications in effectively treating COVID-19 (3-6). Challenges surrounding vaccination efforts stem from the persistent mutational shifts of the virus, coupled with the constraints imposed on immunocompromised individuals and patients afflicted with cardiac, pulmonary, and renal conditions, among others. Such individuals constitute a notably higher-risk demographic for developing COVID-19 (7,8). Moreover, hospitalization and mortality rates among these groups after infection are also higher when compared to the healthier population (9). Consequently, an urgent imperative arises to identify universally effective and safe therapies for managing SARS-CoV-2 infections. Research findings have indicated the potential of monoclonal antibodies to serve as a dual-purpose tool—both for preemptive application in uninfected individuals and for treatment across varying degrees of COVID-19 severity (10,11). Furthermore, they offer a viable treatment avenue for patients grappling with chronic medical conditions, without giving rise to safety concerns. The timely administration of COVID-19 antibodies has been shown to mitigate infection rates and enhance recovery rates in those already afflicted (12,13). The isolation of the novel coronavirus monoclonal antibody (anti-SARS-Cov-2 mAb) from the blood of infected patients or its laboratory synthesis (14) has facilitated large-scale production. Working by binding to free viral molecules and neutralizing virus-infected host cells (15), monoclonal antibodies specifically target the SARS-CoV-2 spike protein, which interacts with the angiotensin-converting enzyme 2 receptor on host cell surfaces (16). This interaction triggers an anti-spike effect (17,18), playing a pivotal role in antiviral defense (19,20). Notably, the utilization of monoclonal antibody cocktails can mitigate the risk of viral drug resistance, a common phenomenon associated with the employment of individual antibodies (21). Consequently, the adoption of monoclonal antibody combinations has gained considerable traction in clinical settings. Specifically, the combination of casirivimab and imdevimab has garnered approval from the European Medicines Agency (EMA) for treating severe COVID-19 cases (15). Recent meta-analyses have demonstrated that this combination correlates with reduced hospitalization, mortality, and virus load (3,22,23).

One such meta-analysis (23), investigating the efficacy and safety of casirivimab and imdevimab, revealed their ability to lower mortality rates in patients who were seronegative at baseline, diminish hospitalization rates among the general population, and curtail the incidence of adverse events, while their usage had no impact on mechanical ventilation. Another meta-analysis (22) highlighted that casirivimab and imdevimab brought about decreased mortality in the general population, along with reduced hospitalization rates and viral load. Nonetheless, individuals treated with casirivimab and imdevimab faced comparable risks of encountering adverse events as those receiving the placebo. A distinct meta-analysis (3) indicated a drop in mortality among individuals initially seronegative to SARS-CoV-2 upon receiving the combination of casirivimab and imdevimab. However, this effect did not extend across the entirety of the study population,

Highlight box

Key findings

- The combined analysis showed that the combination of casirivimab and imdevimab reduced viral load, all-cause mortality, the incidence of any serious adverse event, the incidence of grade 3 or more serious adverse events, the likelihood of contracting coronavirus disease 2019 (COVID-19), the incidence of clinical outcomes of special interest.

What is known and what is new?

- Casirivimab and imdevimab are monoclonal antibodies used to prevent and treat SARS-CoV-2 infection.
- The therapy has shown some efficacy and safety in clinical trials.
- The study evaluates the efficacy and safety of casirivimab and imdevimab combination therapy for COVID-19 by systematic review and meta-analysis.

What is the implication, and what should change now?

- These findings may have implications for therapeutic strategies for COVID-19, especially in combination with monoclonal antibody therapy.

failing to improve viral clearance and avert adverse events. Consequently, consensus remains elusive regarding the efficacy and safety of casirivimab and imdevimab. Adding to this complexity, preceding studies predominantly concentrated on specific cohorts, such as the preventive effects in healthy people (13), or the therapeutic efficacy of casirivimab and imdevimab in confirmed COVID-19 cases (12), or in individuals who were seronegative or seropositive at baseline (11). Against this backdrop, the current study undertook a comprehensive meta-analysis of recent randomized controlled trials (RCTs) to evaluate the efficacy and safety of casirivimab and imdevimab within diverse subgroups of individuals. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1604/rc).

Methods

Literature search strategy

The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), CRD42023475640. The comprehensive search spanned databases including PubMed, Web of Science, Embase, and the Cochrane Library, up until September 10, 2022. Keywords used for the literature search were as follows: (imdevimab [Title/Abstract]) AND (Casirivimab [Title/Abstract]) AND (covid-19 [Title/Abstract]). To ensure thoroughness, reference lists of important studies and reviews were also reviewed. In cases of duplication or multiple articles emanating from the same trial exploring an identical population, priority was given to studies yielding the most complete and up-to-date data.

Eligibility criteria

Studies were included in this meta-analysis if they met the following criteria: (I) study subjects encompassed confirmed COVID-19 cases, individuals close to those affected by COVID-19, or individuals in good health; (II) interventions entailed administering casirivimab and imdevimab to subjects in the treatment group, juxtaposed with the delivery of a placebo or alternative medications to subjects in the control group; (III) outcome measures encompassed viral load, deaths, and the need for mechanical ventilation, all-cause mortality, adverse events, infection rates, discharge rates, and the need for additional interventions after treatment; (IV) the study design adhered to the principles of a RCT; (V) publications were available in English.

Exclusion criteria were as follows: (I) reviews, meta-analyses, consensus reviews, conference abstracts, animal experiments, case reports, letters, and so on were excluded; (II) studies devoid of sufficient data for outcome analysis were excluded; (III) studies from which data pertaining to outcome measures were excluded; (IV) duplicate publications were excluded.

Two researchers independently screened, assessed, and extracted data from studies obtained from databases. Disagreements were resolved through deliberation with a third reviewer, eventually arriving at a consensus.

Data extraction

The following information was extracted from each eligible study: first author, year of publication, country, study design, study subjects, information about the treatment group (sample size, drug dosage, and drug administration protocol), details of the control group (sample size, drug dosage, and drug administration protocol), gender distribution, age, duration of follow-up, and trial registration identification. Primary outcome measures encompassed COVID-19 viral load, mortality and the need for mechanical ventilation, all-cause mortality, and adverse event rates. Secondary outcome measures were infection rates, discharge rates, and the need for additional interventions after treatment, including hospitalization, emergency room visits, and mortality.

Quality assessment for the included studies

The Cochrane risk-of-bias tool for randomized trials was utilized to evaluate the quality and potential risk of bias across the incorporated studies. The following seven parameters were considered for quality assessment: (I) random sequence generation; (II) allocation concealment; (III) blinding of participants and personnel; (IV) blinding of outcome reviewers; (V) incomplete outcome data; (VI) selective outcome reporting; and (VII) other sources of bias (24). Each study was rated as having a "high", "low", or "uncertain" risk of bias. The RevMan software (version 5.4) was used for the summary of the risk of bias assessment.

Statistical analysis

Data analysis was conducted using the Stata SE64 software

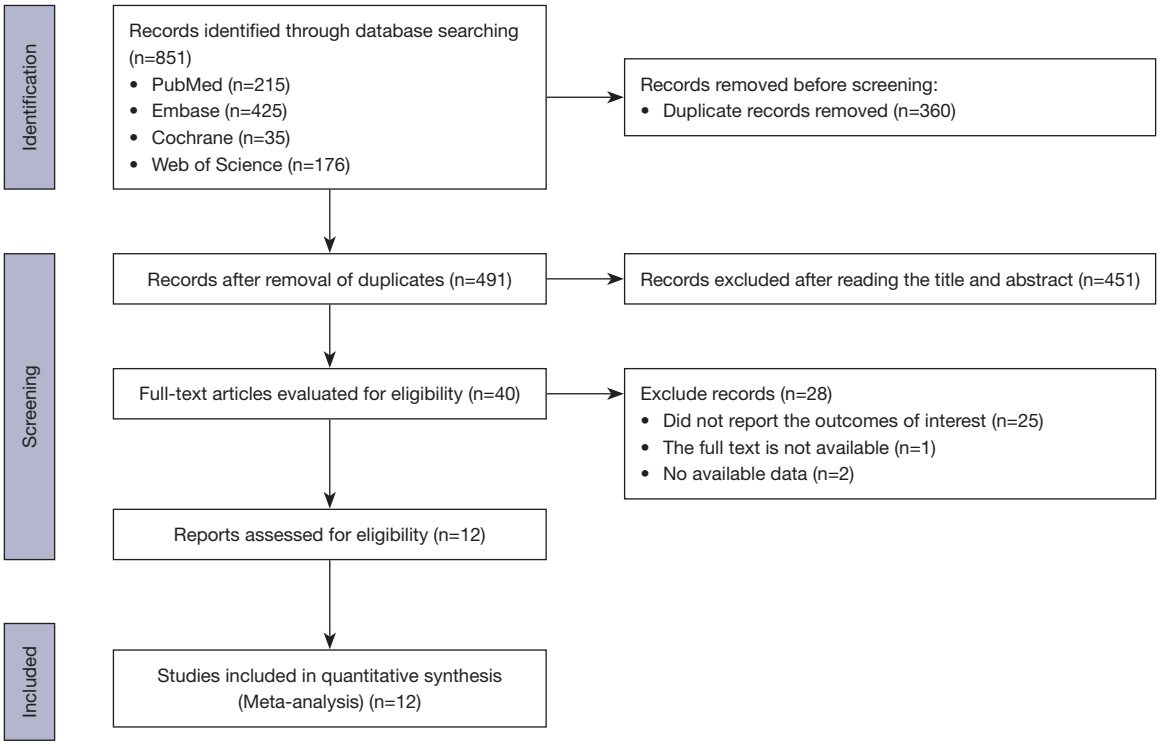


Figure 1 Flow chart of literature screening.

(version 15.1). Continuous variables were expressed as weighted mean differences (WMDs) alongside their corresponding 95% confidence intervals (CIs). Dichotomous variables were summarized as odds ratios (ORs) accompanied by their corresponding 95% CI. Q test and I^2 statistic were used to assess statistical heterogeneity across the incorporated studies, where I^2>50% indicated a significant degree of heterogeneity, warranting the adoption of a random-effects model for data analysis. Otherwise, a fixed-effects model was employed. Subgroup analyses were performed regarding mortality, the need for mechanical ventilation, and discharge rates. Sensitivity analyses were executed to ascertain the stability of the results. The threshold for statistical significance was defined as P<0.05. Funnel plots were used to assess publication bias.

Results

A total of 851 articles were obtained from databases, and 360 of them were removed for duplicate publication. Subsequently, upon a thorough review of titles and abstracts, 451 articles were excluded. Finally, 12 studies were deemed suitable for incorporation into the meta-analysis, following an assessment of full-text articles. Among them, one study (25) was prematurely halted, while another two articles (by Portal-Celhay) were drawn from the same trial (26,27). To ensure the utmost precision in data representation, preference was accorded to the latest and most comprehensive study outcomes (*Figure 1*).

Study and patient characteristics

Twelve RCTs (11-13,15,27-34) were analyzed, involving 27,179 participants in total. Among them, 15,704 participants were administered the combination of casirivimab and imdevimab, whereas 12,105 were given a placebo or alternative medications. Of the twelve studies, nine focused on confirmed COVID-19 cases, while the remaining three centered on healthy people or healthy contacts of SARS-CoV-2-infected individuals. *Table 1* presents the fundamental characteristics of these studies.

Quality assessment

Upon assessment, a substantial portion of the studies exhibited a low risk of bias. Eight studies (11-13,28,30-32,34) had an

Table 1 Characteristics of included studies

Study	Year	Country	Study design	Patient population	Sample size		Intervention		Dose	Gender (male/female)	Meanage (years)		Follow-up (days)	NCT
					EG	CG	EG	CG			EG	CG		
Somersan-Karakaya (12)	2022	USA	RCT	Hospitalized patients with COVID-19	406	393	CAS + IMD	Placebo	2.4 g iv	647/550	61	64	29	04426695
					398				8.0 g iv					
Herman (13)	2022	USA	RCT	Healthy household contacts of SARS-CoV-2-infected individuals	841	842	CAS + IMD	Placebo	1.2 g iv	779/904	43	43.5	240	04452318
Hooper (32)	2022	USA	RCT	Seropositive	57	290	CAS + IMD	Placebo	2.4 g iv	460/361	62.5	66	29	04426695
					53				8.0 g iv					
					213		CAS + IMD	Placebo	2.4 g iv		60	60	29	
					208				8.0 g iv					
RECOVERY Collaborative Group (15)	2022	UK	RCT	Hospital with clinically suspected or laboratory-confirmed SARS-CoV-2 infection	4,839	4,946	CAS + IMD	Usual care	4 g + 4 g iv	6,128/3,657	61.9	61.9	28	04381936
Huang (33)	2022	USA	RCT	Patients with a positive SARS-CoV-2 test result	2,454	1,104	CAS + IMD	Sotrovimab	iv	1,639/1,919	54	53	28	04790786
Isa (34)	2022	USA	RCT	Uninfected adult volunteers	729	240	CAS + IMD	Placebo	1.2 g sc	534/435	48	48	365	04519437
McCreary (31)	2022	USA	RCT	A positive SARS-CoV-2 polymerase chain reaction or antigen test	922	885	CAS + IMD	Bamlanivimab-etesevimab	iv	835/972	55	56	28	04790786
O'Brien (11)	2021	USA	RCT	Not have SARS-CoV-2 infection or seronegativity	753	752	CAS + IMD	Placebo	1.2 g sc	691/814	43.2	42.7	240	04452318
O'Brien (29)	2022	USA	RCT	Seronegativity	101	106	CAS + IMD	Placebo	1.2 g sc	94/113	39.2	42.5	28	04452318
				Seropositive	46	38	CAS + IMD	Placebo	1.2 g sc	47/37	40	39.1	28	
Portal-Celhay (27)	2022	USA	RCT	Outpatients with SARS-CoV-2 infection	80	77	CAS + IMD	Placebo	0.3 g iv	160/199	33.8	35.1	28	04666441
					68				0.6 g iv		33.9			
					72				1.2 g iv		34.1			
					62				2.4 g iv		36.3			
					75	77	CAS + IMD	Placebo	0.6 g sc	102/123	33.5	35.1	28	
					73				1.2 g sc		33.5			
Norton (28)	2021	USA	RCT	SARS-CoV-2-positive nasopharyngeal polymerase chain reaction	266	266	CAS + IMD	Placebo	2.4 g	376/423	42	42	29	04425629
					267				8.0 g		42			
Weinreich (30)	2021	USA	RCT	SARS-CoV-2-positive nasopharyngeal polymerase chain reaction	1,355	1,341	CAS + IMD	Placebo	2.4 g iv	2,005/2,175	50	50	29	04425629
					736	748			1.2 g iv		48.5	48		

EG, experimental group; CG, control group; NCT, National Clinical Trial; RCT, randomized controlled trial; COVID-19, coronavirus disease 2019; CAS, casirivimab; IMD, imdevimab; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figure 2 Risk of bias graph across included studies. (A) Risk of bias graph across included studies; (B) risk of bias summary across included studies. RCG, RECOVERY Collaborative Group.

uncertain risk of bias regarding allocation concealment. Notably, three studies bore a high risk of bias with regard to the blinding of participants and personnel (15,30,33), and four studies had a high risk of bias regarding the blinding of outcome evaluators (15,30,31,33) (*Figure 2A,2B*).

Efficacy outcomes

The analysis of data extracted from the encompassed studies was stratified based on primary and secondary outcome measures. Subgroup analyses were performed in light of the baseline SARS-CoV-2 serology results, which included seropositivity, seronegativity, and uncertain results. Subgroup analyses of patients with or without COVID-19 and patients with or without hospitalization were performed to explore the effectiveness and safety of the drug in patients with different clinical statuses.

Primary outcome measures

Viral load

Five studies reported data on viral load alterations. A random-effects model was used due to the pronounced heterogeneity detected across the dataset (I^2=91.5%, P<0.001). Compared with the placebo, casirivimab and imdevimab administered together significantly reduced viral load in confirmed COVID-19 cases and decreased the increase in the viral load among individuals with no initial infection (WMD: −0.73, 95% CI: −1.09 to −0.38, P<0.01). Subgroup analyses showed that casirivimab and imdevimab

were effective in reducing viral load in COVID-19 patients, non-COVID-19 patients, and in seronegative and seropositive patients at baseline, independent of whether they were hospitalized or not. Regarding the drug dosage, we found that the use of 2.4 g drug was poorly effective (WMD: –0.49, 95% CI: –0.99 to 0.01, P=0.06), and the rest of the therapeutic doses were effective (*Figure 3A-3D*).

All-cause death rates

Seven studies investigated all-cause death rates. A fixed-effects model was used due to the significant heterogeneity across the studies (I^2=46.7%, P=0.04). We found that all-cause death rates decreased in participants who were either confirmed COVID-19 cases or in healthy conditions at baseline. All-cause death rates were treated with the casirivimab and imdevimab antibody cocktail during clinical trials (OR =0.90, 95% CI: 0.82–0.99, P=0.03). However, subgroup analysis results showed that in patients with and without COVID-19, the antibody reduced all-cause mortality (OR =0.90, 95% CI: 0.82–0.99, P=0.03), independent of whether they were hospitalized or not and the specific dose of the drug administered. The mitigation of all-cause death rates owing to casirivimab and imdevimab was evident solely in patients who were seronegative at baseline (OR =0.73, 95% CI: 0.63–0.85, P<0.01) (*Figure 3E-3H*).

Death and mechanical ventilation rates

Three studies provided data on death and mechanical ventilation rates. A random-effects model was used due to the significant heterogeneity across the studies (I^2=72.5%, P=0.001). There was no evidence supporting that casirivimab combined with imdevimab could reduce death and mechanical ventilation rates (OR =0.88, 95% CI: 0.71–1.10, P=0.26). Likewise, subgroup analyses showed that casirivimab and imdevimab did not reduce the death and mechanical ventilation rates of patients with either serologic nature, without statistically significant difference (*Figure 4A*).

Secondary outcome measures

Infection rates

Four studies investigated infection rates. A random-effects model was used due to the significant heterogeneity across the studies (I^2=81.8%, P=0.001). Casirivimab combined with imdevimab significantly lowered the risk of SARS-CoV-2 infection in healthy individuals and those in close contact with infected cases (OR =0.24, 95% CI: 0.13–0.45, P<0.01) (*Figure 4B*).

Discharge rates

Two studies reported discharge rates and a random-effects model was used due to the significant heterogeneity across the studies (I^2=78.6%, P<0.001). The results indicated that casirivimab combined with imdevimab did not increase the discharge rate in individuals with confirmed or suspected COVID-19 (OR =1.15, 95% CI: 0.91–1.46, P=0.23), without significant difference between the treatment group and the control group. Subgroup analyses also found no statistically significant differences between patients with different serological properties (*Figure 4C*).

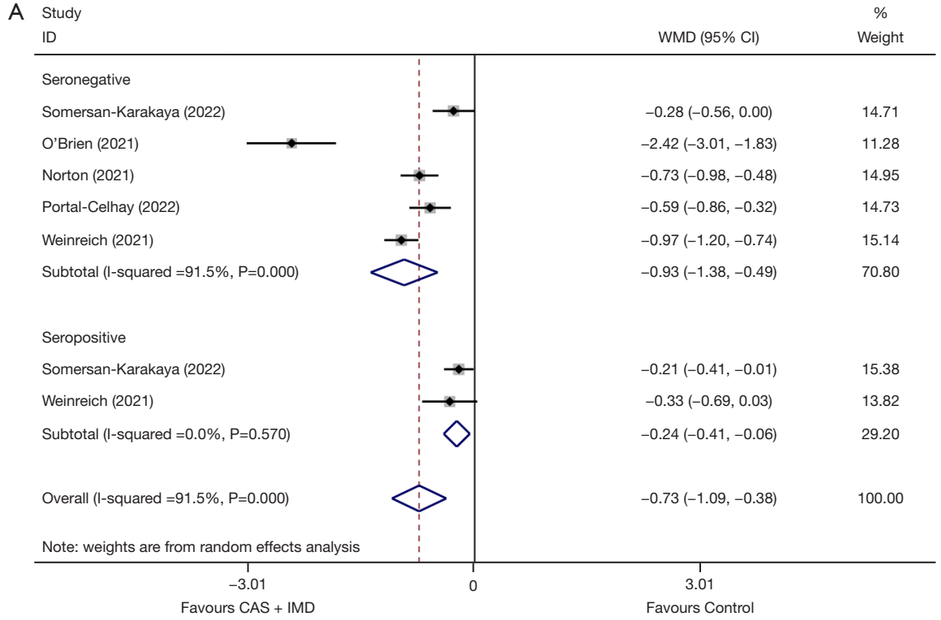
Clinical outcomes of special interest

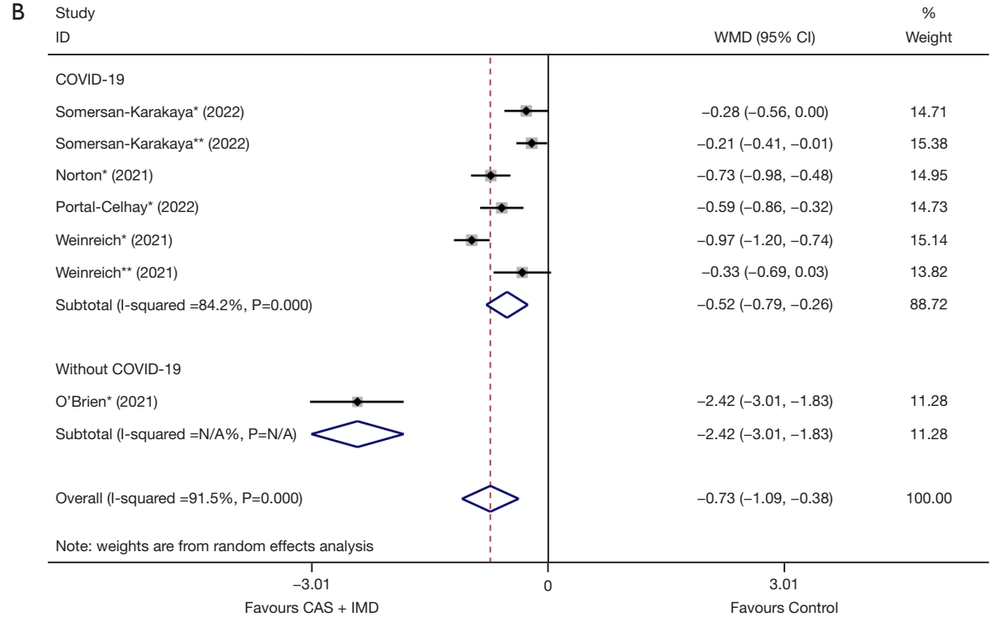
Six studies reported several clinical outcomes of special interest, including hospitalization, emergency room visits, and mortality. A random-effects model was used due to the significant heterogeneity across the studies (I^2=84.4%, P<0.001). The combination of casirivimab and imdevimab reduced the rate of hospitalization, emergency room visits, and mortality among confirmed COVID-19 cases and healthy individuals (OR =0.54, 95% CI: 0.32–0.93, P=0.03). Subgroup analysis demonstrated that casirivimab and imdevimab reduced the occurrence of these clinical outcomes among people who were seronegative at baseline (OR =0.06, 95% CI: 0.01–0.47, P=0.01) (*Figure 4D*).

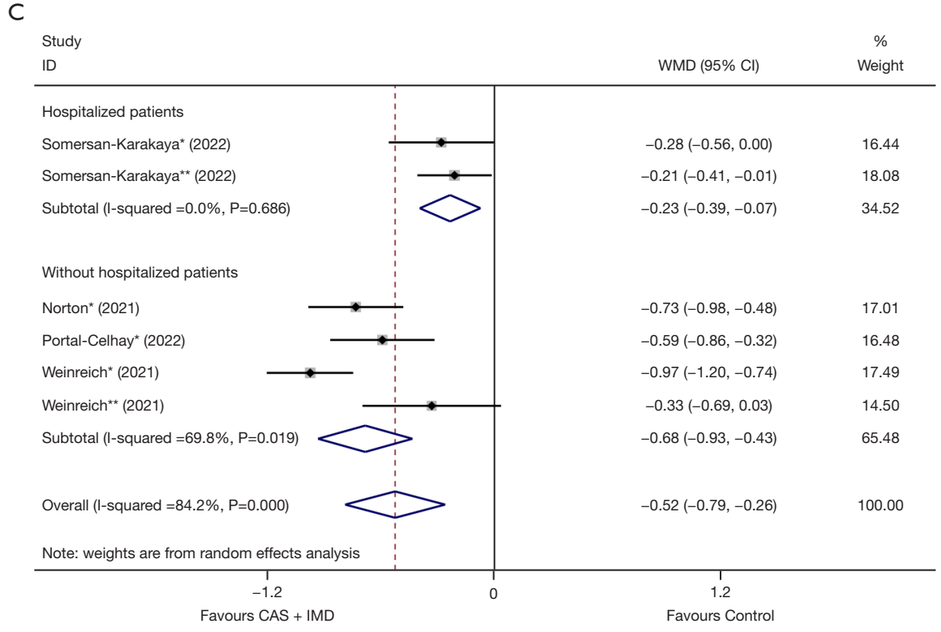
Safety outcomes

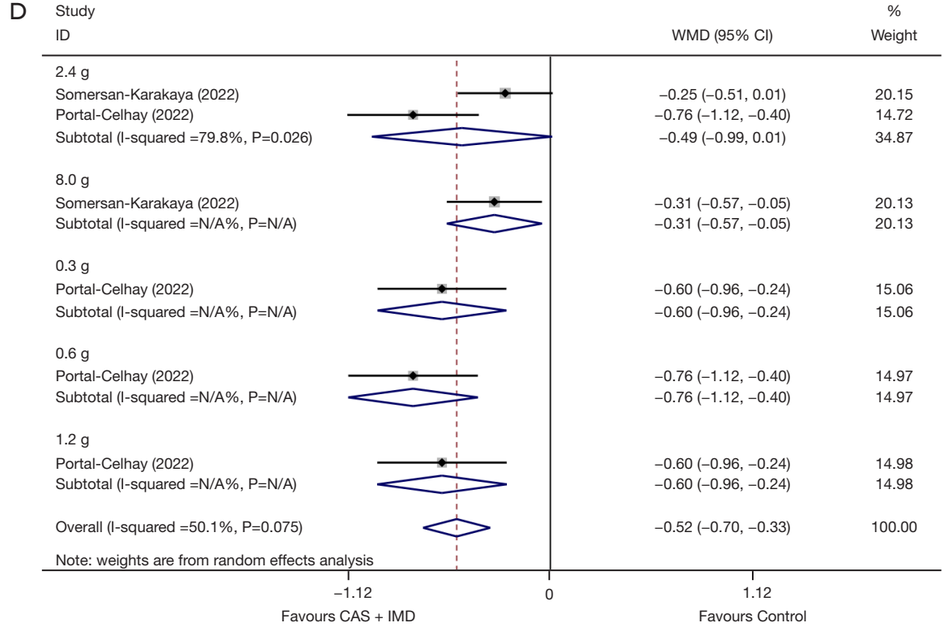
Adverse events

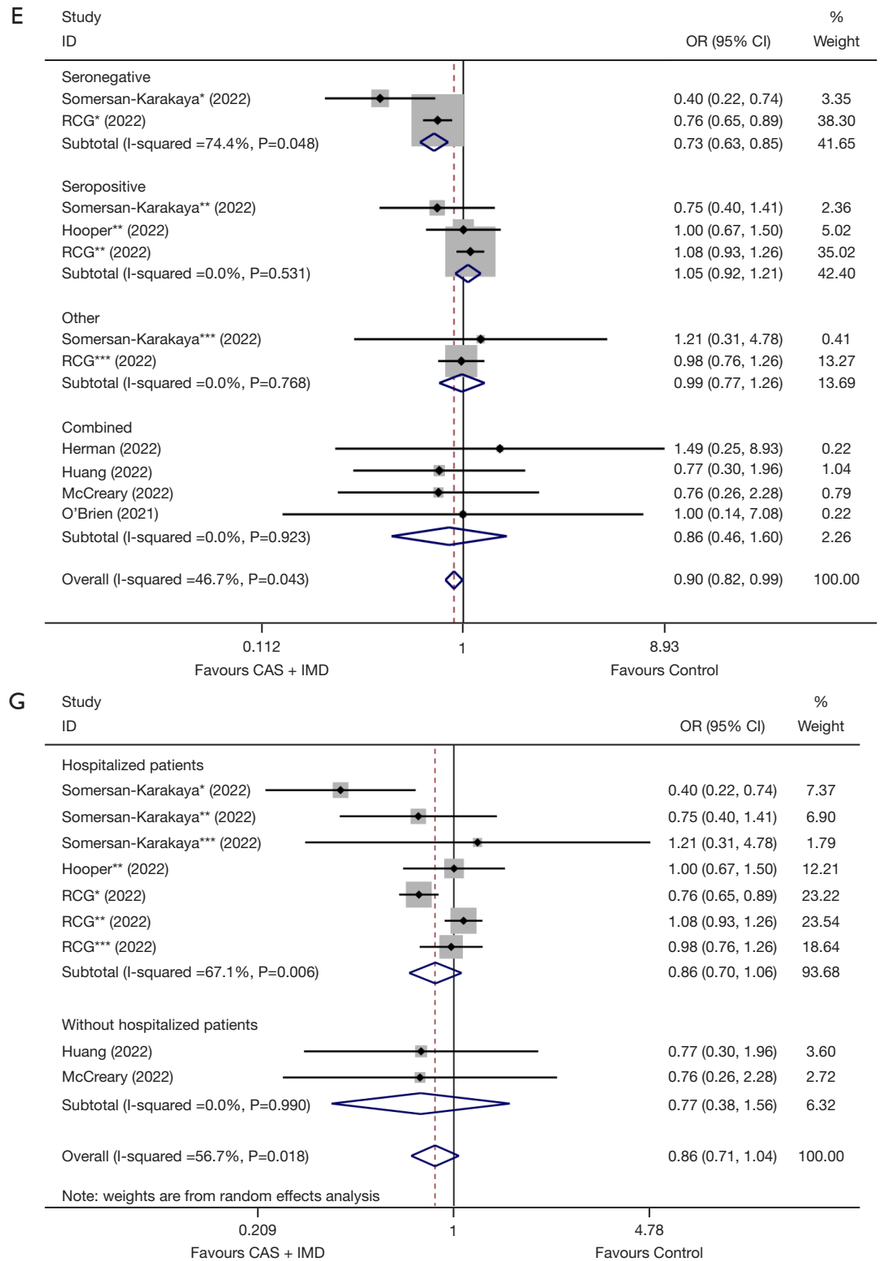
Nine studies reported the incidence of severe adverse events. A random-effects model was used due to the significant heterogeneity across the studies (I^2=62.6%, P=0.003). The results indicated that the incidence of adverse events was significantly reduced among confirmed COVID-19 patients, close contacts, or healthy individuals after treatment with casirivimab and imdevimab compared to the control group, with statistical significance (OR =0.80, 95% CI: 0.67–0.95, P=0.01). Subgroup analyses found that the antibody significantly reduced the rate of any serious adverse events in COVID-19 patients who were not hospitalized (OR =0.64, 95% CI: 0.46–0.87, P=0.01) and those without clear serologic classification (OR =0.69, 95% CI: 0.60–0.81, P<0.01). The drug with a dose of 2.4 g significantly reduced the rate of any serious adverse events (OR =0.80, 95% CI: 0.65–0.98, P=0.03) (*Figure 5A-5D*).











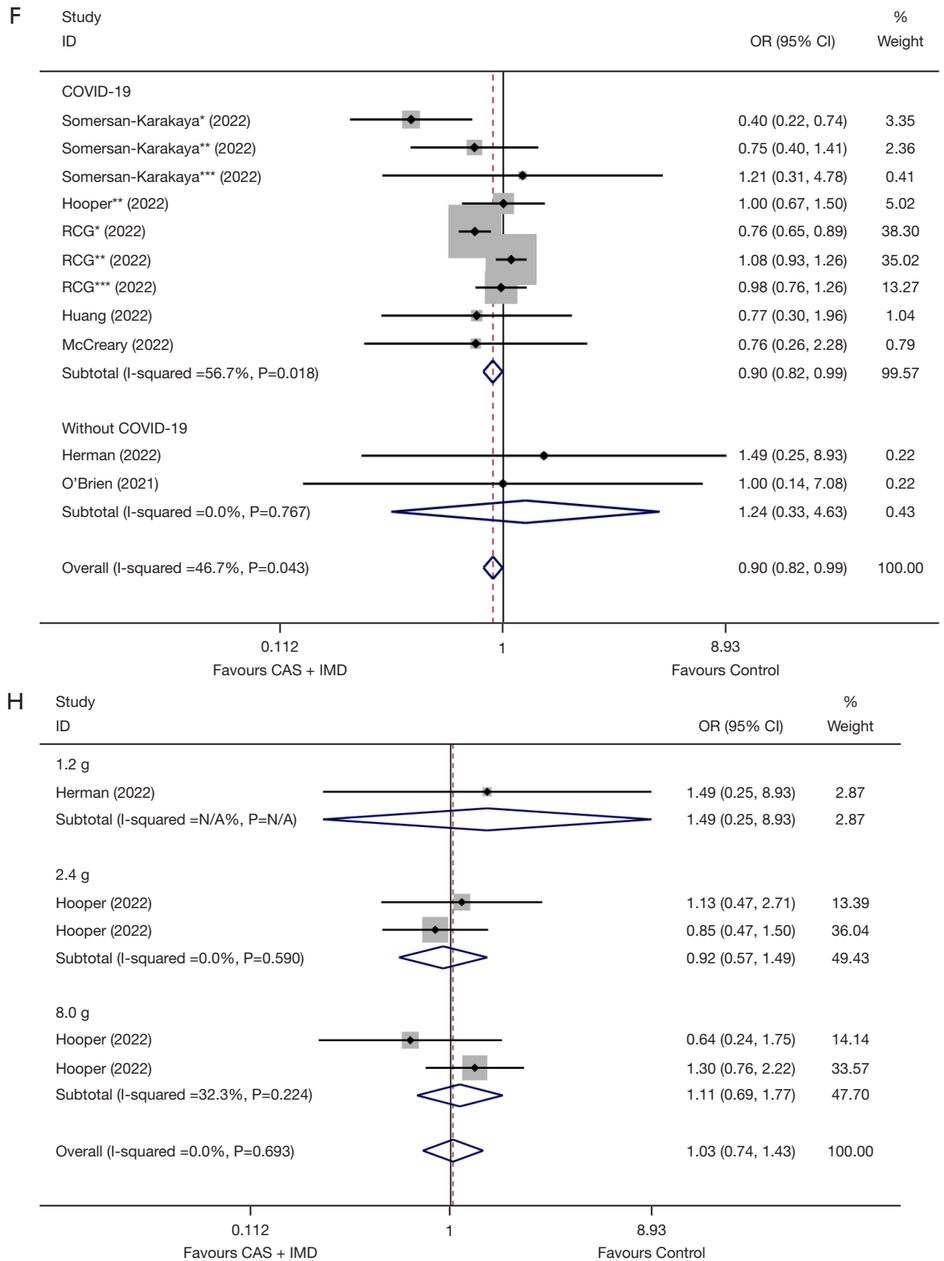
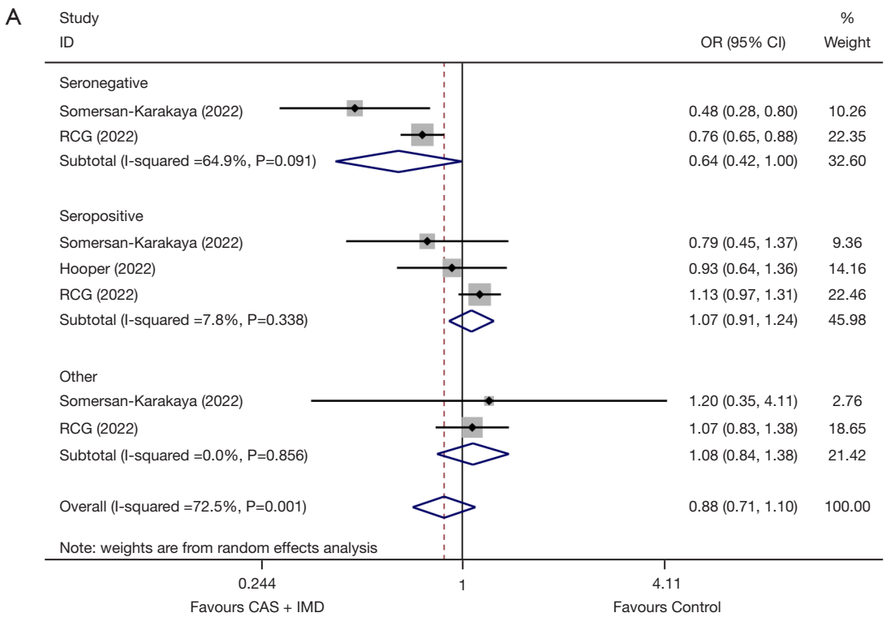
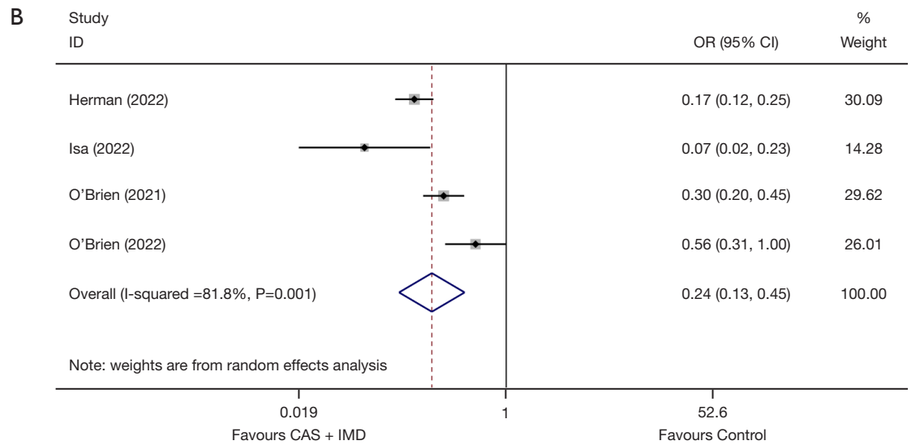
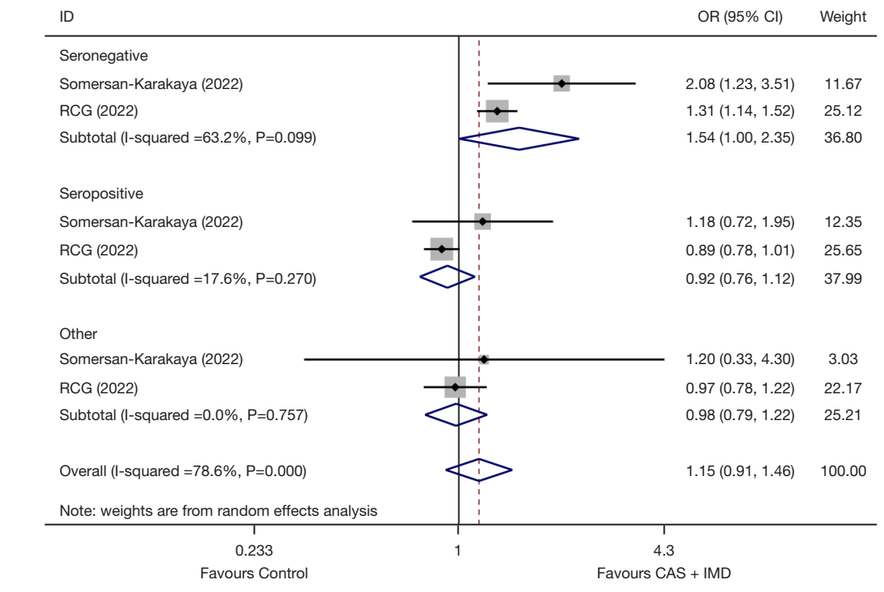


Figure 3 Forest plots of viral load and all-cause mortality. (A) Forest plot of viral load by serological properties. (B) Forest plot of viral load by patients with or without COVID-19 at baseline. (C) Forest plot of viral load by patients with or without need for hospitalization. (D) Forest plot of viral load by dose of antibodies. (E) Forest plot of all-cause mortality by serological properties. (F) Forest plot of all-cause mortality by patients with or without COVID-19 at baseline. (G) Forest plot of all-cause mortality by patients with or without need for hospitalization. (H) Forest plot of all-cause mortality by dose of antibodies. *, seronegative; **, seropositive; ***, other. WMD, weighted mean difference; CI, confidence interval; RCG, RECOVERY Collaborative Group; CAS, casirivimab; IMD, imdevimab; COVID-19, coronavirus disease 2019; OR, odds ratio.







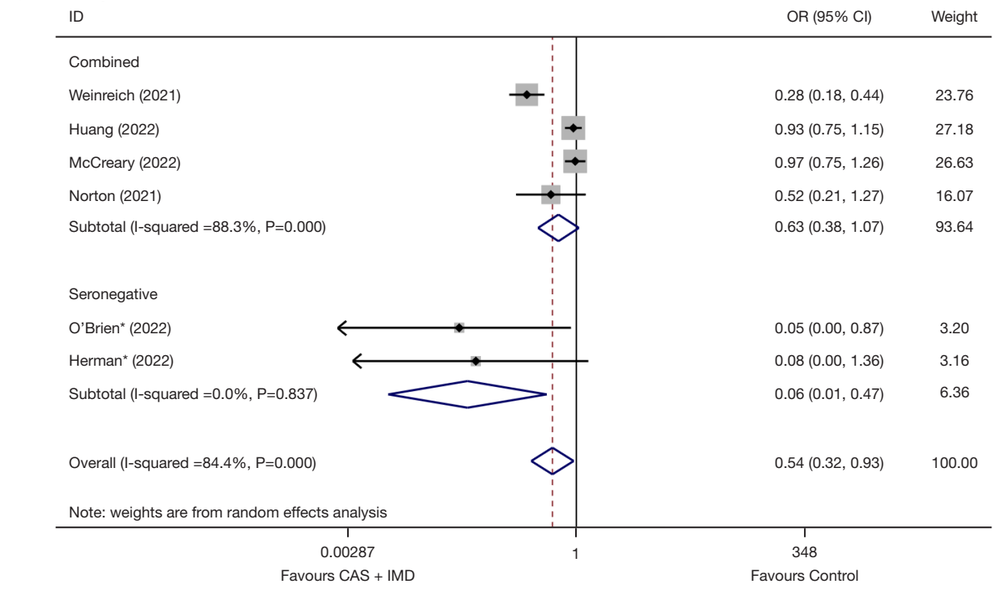
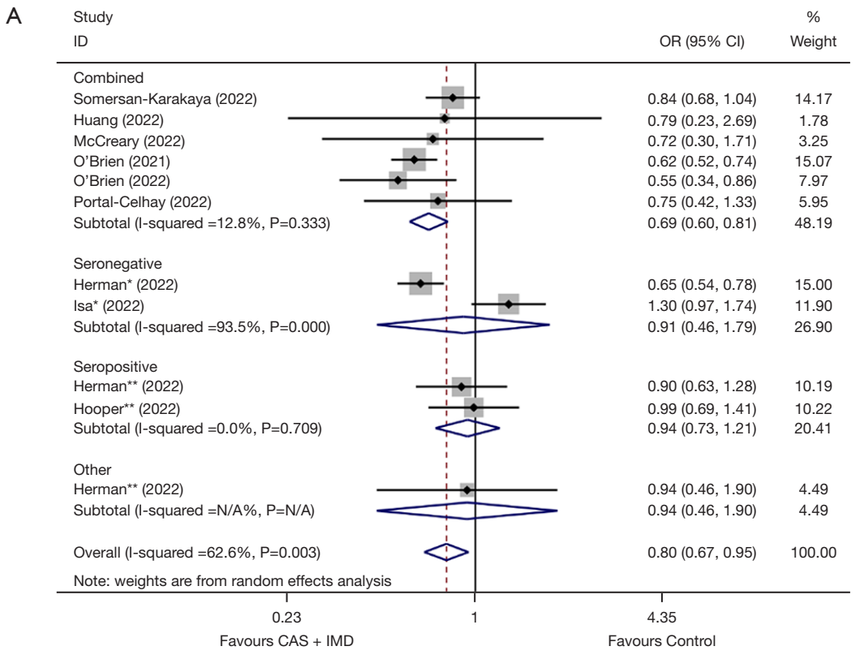
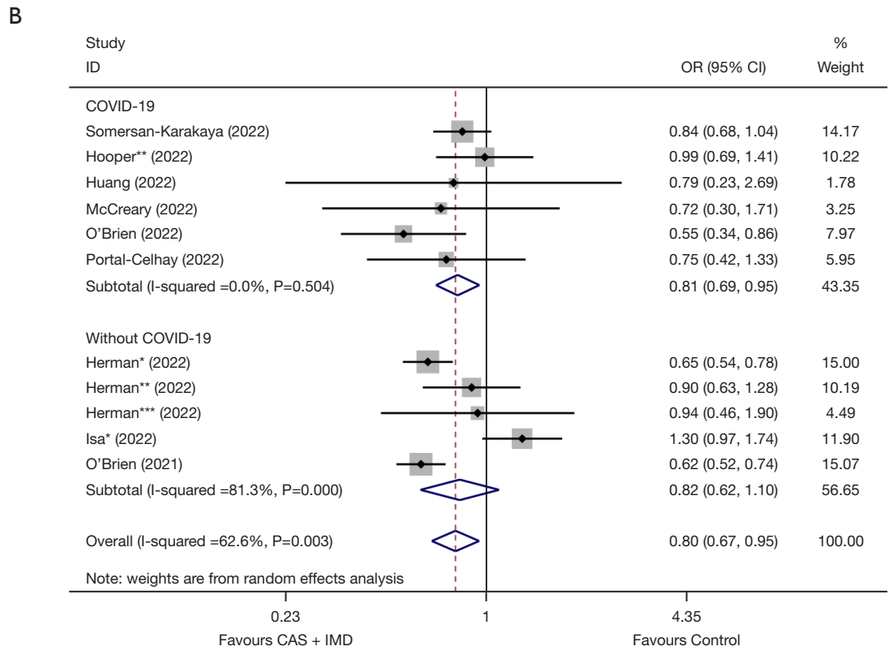
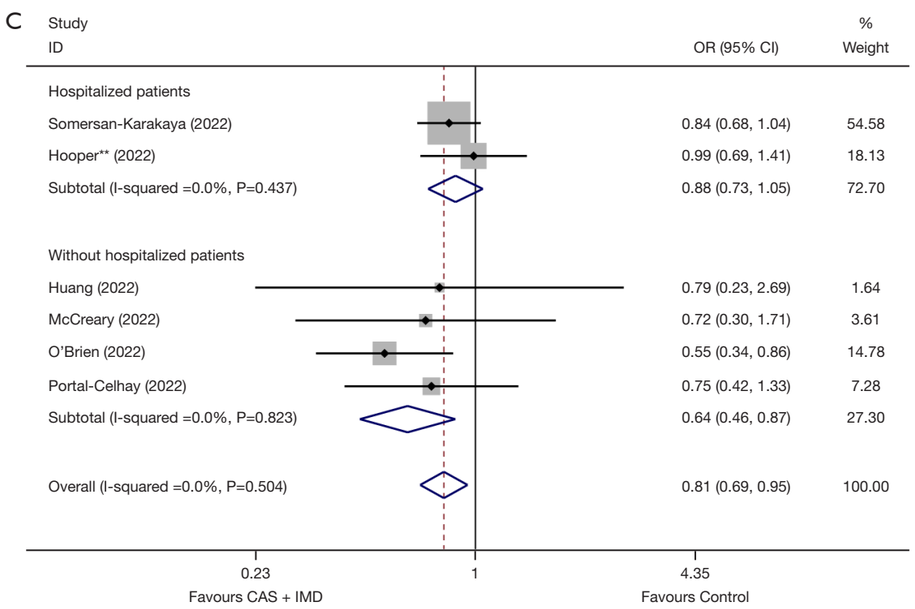
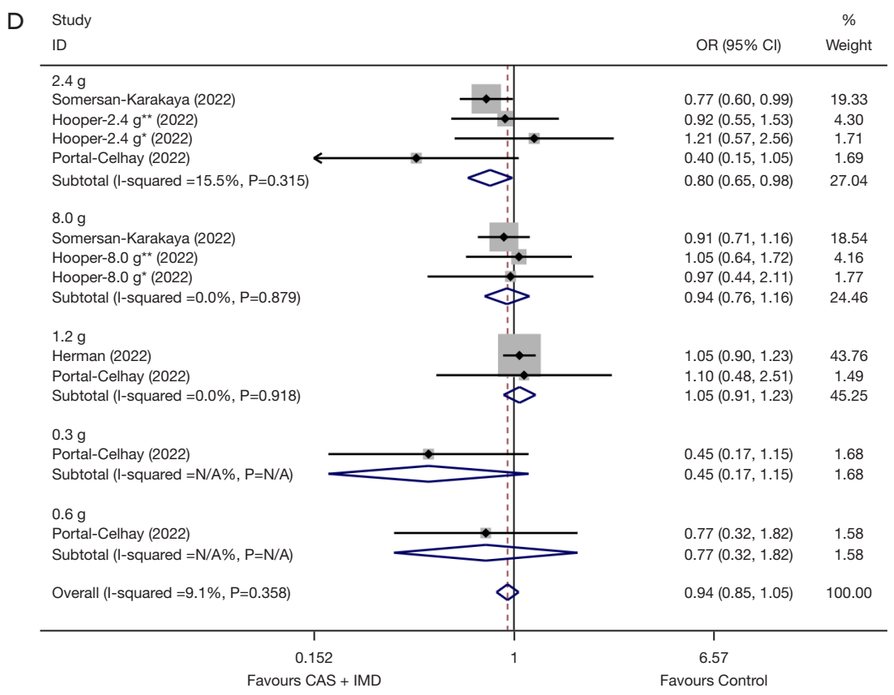


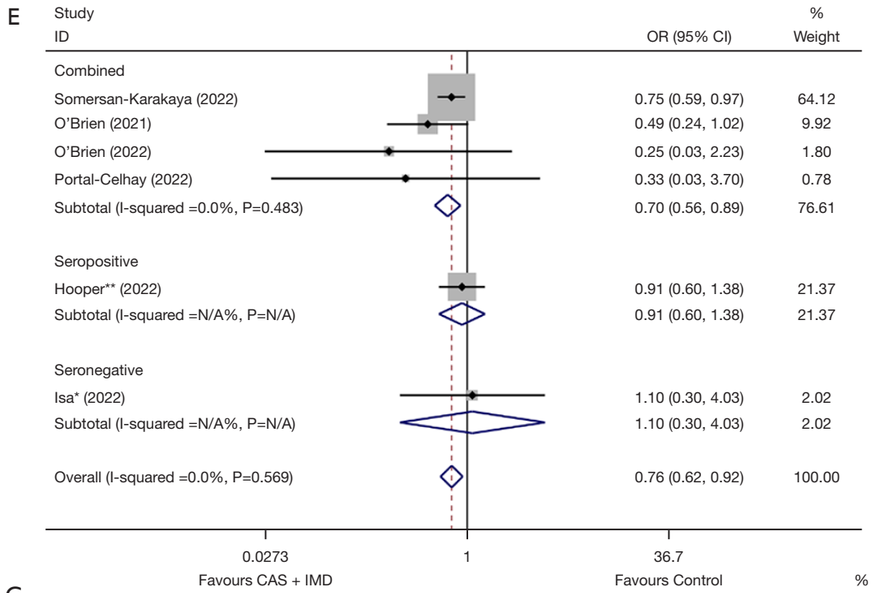
Figure 4 Forest plots of death and mechanical ventilation rates, infection rates, discharge rates and clinical outcomes of special interest. (A) Forest plot of death and mechanical ventilation rates. (B) Forest plot of infection rates. (C) Forest plot of discharge rates. (D) Forest plot of clinical outcomes of special interest. *, seronegative. OR, odds ratio; CI, confidence interval; RCG, RECOVERY Collaborative Group; CAS, casirivimab; IMD, imdevimab.

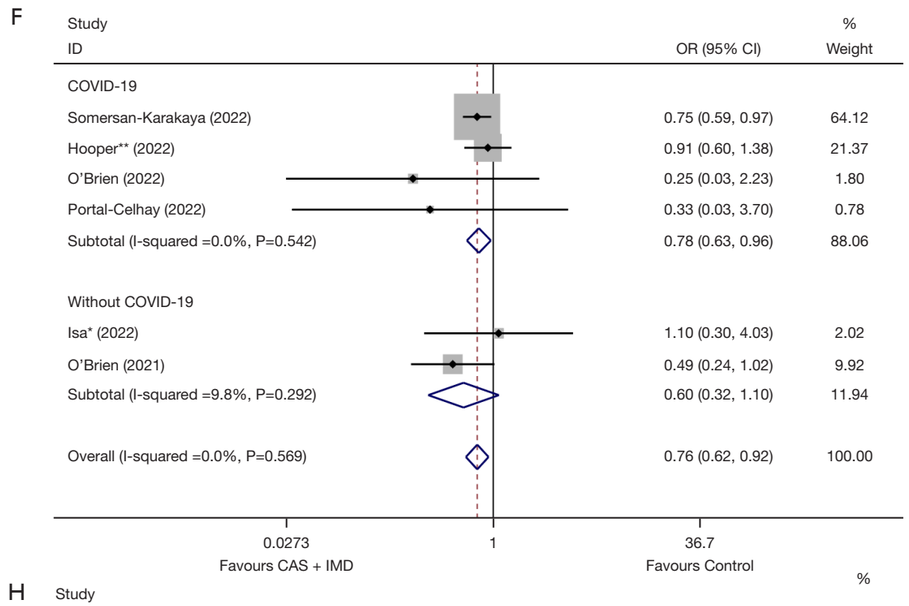


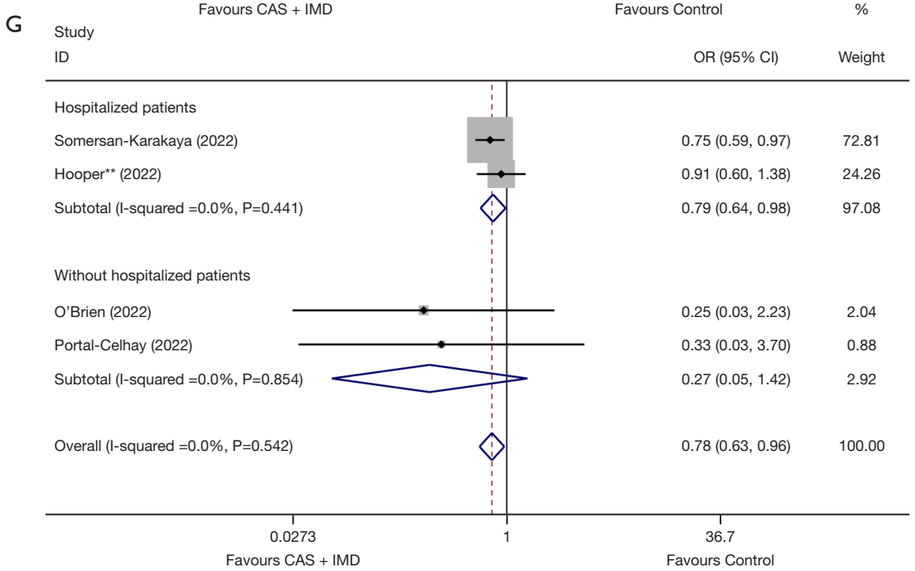












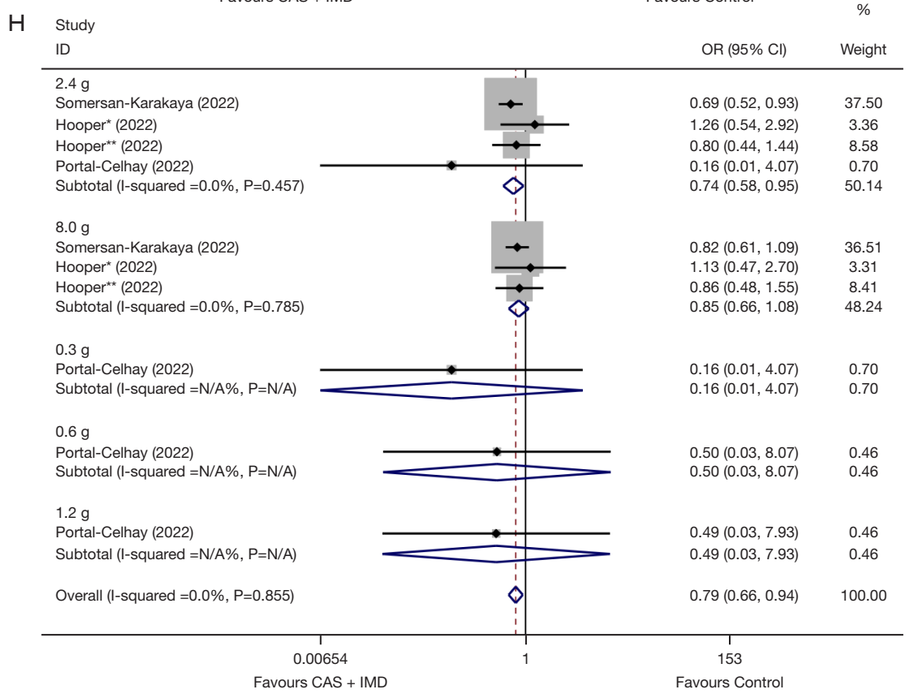


Figure 5 Forest plots of adverse events. (A) Forest plot of severe adverse events by serological properties. (B) Forest plot of severe adverse events by patients with or without COVID-19 at baseline. (C) Forest plot of severe adverse events by patients with or without need for hospitalization. (D) Forest plot of severe adverse events by dose of antibodies. (E) Forest plot of Grade 3 or more severe adverse events by serological properties. (F) Forest plot of Grade 3 or more severe adverse events by patients with or without COVID-19 at baseline. (G) Forest plot of Grade 3 or more severe adverse events by patients with or without need for hospitalization. (H) Forest plot of Grade 3 or more severe adverse events by dose of antibodies. *, seronegative; **, seropositive; ***, other. OR, odds ratio; CI, confidence interval; CAS, casirivimab; IMD, imdevimab; COVID-19, coronavirus disease 2019; RCG, RECOVERY Collaborative Group.

Grade 3 or more severe adverse events were reported in six studies. Due to the significant heterogeneity across the studies (I^2=0.0%, P=0.57), a random-effects model was used, and the analysis results showed that casirivimab combined with imdevimab reduced the incidence of these adverse events among confirmed COVID-19 patients and healthy people (OR =0.76, 95% CI: 0.62–0.92, P=0.01). In subgroup analyses, the drug significantly reduced the incidence of ≥ grade 3 serious adverse events (OR =0.70, 95% CI: 0.56–0.89, P<0.01) in hospitalized COVID-19 patients (OR =0.79, 95% CI: 0.64–0.98, P=0.03) and those without clear serologic classification, and the drug with a dose of 2.4 g also markedly reduced the risk of ≥ grade 3 serious adverse events (OR =0.74, 95% CI: 0.58–0.95, P=0.02) (*Figure 5E-5H*).

Publication bias and sensitivity analysis

Sensitivity analysis was conducted by removing each study in turn, and it was found that the recalculated combined effect size did not change significantly, indicating that the results of this study were relatively stable and the overall outcomes remained largely unaffected by the exclusion of any particular study. As for the assessment of the risk of bias in the included studies, the funnel plot presented a relative symmetry, indicating the absence of significant publication bias (P>0.05).

Discussion

This meta-analysis delved into 12 RCTs to compare the efficacy and safety profiles of casirivimab and imdevimab against those of placebo or alternative medications. The outcomes indicated a significant reduction in viral load among confirmed COVID-19 cases when casirivimab and imdevimab were administered jointly. Furthermore, this antibody combination prevented the increase in viral load among newly infected individuals. Remarkably, the reduction in viral load exhibited heightened significance in individuals who were seronegative at baseline. Notably, a decrease in all-cause mortality was seen across the broader population receiving casirivimab and imdevimab treatment, and this reduction was more significant in those who were seronegative at baseline. Furthermore, the application of this antibody combination was associated with a reduction in infection rates among both healthy people and close contacts, as well as decreased incidence of clinical outcomes of particular interest among subjects who were confirmed COVID-19 cases or in healthy condition at baseline. In contrast, in a subgroup analysis of patients with or without COVID-19 and hospitalized patients, we found that the drug was statistically significant in improving all-cause mortality in COVID-19 patients, independent of whether they were hospitalized or not. Casirivimab and imdevimab were ineffective in reducing mortality and mechanical ventilation rates and improving hospital discharge rates, regardless of serologic properties. In light of adverse events, compared with the control group, the combination of casirivimab and imdevimab was capable of reducing the incidence of any severe adverse event, irrespective of whether applied to confirmed COVID-19 patients, the close contacts of COVID-19 cases, or the healthy population. Additionally, compared with the control group, the incidence of severe adverse events of grade 3 or higher was lower in the infected COVID-19 population and the normal population receiving the treatment, affirming the safety of casirivimab and imdevimab. Based on the above outcome indicators, we believe that casirivimab and imdevimab have obvious strengths in both COVID-19 patients and non-COVID-19 individuals, and in both outpatients and inpatients. Seronegative patients benefit more from this antibody in terms of all-cause mortality, hospitalizations, emergency room visits, and fatal events. COVID-19 patients benefit from this drug in terms of all-cause mortality. Therefore, in clinical practice, we recommend early use of this drug for the prevention and control of COVID-19.

The above findings indicate that casirivimab and imdevimab, which were generally well-tolerated, hold the potential to mitigate the incidence of SARS-CoV-2 infection and increase recovery rates, a pattern previously observed in certain prior studies (23,35). A retrospective cohort study by Cicchitto *et al.* (36) provided evidence that the application of casirivimab and imdevimab led to a reduction in viral load, accompanied by a high level of safety and minimal adverse events. Hegazy *et al.* (37-39) did several studies on COVID-19 antibodies and found that casirivimab and imdevimab had significant advantages over the COVID-19 antibodies Remdesivir and Favipravir in terms of reducing mortality and adverse events, as well as lower oxygen requirements and less invasive mechanical requirements in patients. Casirivimab and imdevimab led to less case progression (presented by lower World Health Organization scale) and better multi-organ functions (presented by lower Sequential Organ Function Assessment score) than remdesivir and favipiravir. Moreover, four

additional retrospective cohort studies (40-43) reported a decline in hospitalization and death rates among the broader population treated with casirivimab and imdevimab, and this efficacy was particularly pronounced in individuals who initiated treatment with a seronegative baseline. This heightened efficacy is closely tied to viral load clearance, with individuals exhibiting high viral loads experiencing the most substantial benefits after treatment (15). Notably, the ability of the anti-spike monoclonal antibody to clear viral load is intricately linked to patients' serological status at baseline (44). Individuals initiating treatment with a seronegative status, lacking an established immune response, might possess higher viral loads compared to those with seropositive status, resulting in more pronounced viral load clearance in the seronegative cohort.

The evaluation of the efficacy and safety of casirivimab and imdevimab across diverse demographic groups remains an unexplored area. Existing studies, whether RCTs or meta-analyses have consistently centered on specific population subsets, leading to a lack of consensus. A prime example is the meta-analysis conducted by Siemieniuk *et al.* (3), which revealed that casirivimab and imdevimab reduced hospitalization rates for less severe COVID-19 cases, yet failed to reduce virus clearance, whereas they increased mortality in severe COVID-19 cases, which is not consistent with the results of the present meta-analysis. This disparity may be related to different study subjects and varying sample sizes. The absence of subgroup analysis in the study by Siemieniuk *et al.* may also lead to these discrepant findings. The current study, in contrast, included a comprehensive spectrum of study subjects encompassing uninfected persons, close contacts, confirmed cases, those seropositive or seropositive at baseline, and individuals with uncertain serostatus. This breadth facilitated robust subgroup analyses. Another meta-analysis (45) with limited study populations only studied the efficacy of casirivimab and imdevimab in COVID-19 patients and showed that the drug reduced the hospitalization rate and mortality rate of COVID-19 patients, consistent with our study. However, the study indicators were more homogeneous, and our study also studied the viral load, death and mechanical ventilation rate, all-cause mortality rate, infection rate, discharge rate, and emergency room visits on this basis. Thus, our study is more comprehensive and more credible. Furthermore, the present study drew upon the latest RCTs for its meta-analysis, enhancing the accuracy of the results compared with previous studies.

Nonetheless, this study does come with certain limitations. Each outcome measure analyzed in this meta-analysis was based on a relatively small number of RCTs, potentially introducing bias to the results. For instance, only three RCTs reported data on death and mechanical ventilation. Moreover, significant differences in serostatus were apparent across the 12 RCTs, and some studies did not provide data on the serostatus of participants, affecting the results of subgroup analyses. Additionally, the predominant ethnic background of study participants in the included RCTs was European and American Caucasians, which may limit the generalizability of findings to other populations. Further research encompassing larger and more diverse samples is imperative. For the subgroup analysis of the dosage, we found that the 2.4 g dose resulted in a small possibility of adverse events, but was poorly effective in clearing viral load, while all other doses were effective in reducing viral load, which was contrary to conventional knowledge. We considered that the conclusions might be biased due to the small number of dose-related studies included and the lack of sufficient sample data. Additional large sample-size studies are needed to further explore the effectiveness and safety of antibody doses in COVID-19 patients.

While preparing this article, China experienced a sharp spike in SARS-CoV-2 cases in 2022, underscoring the urgency of curbing infections, hospitalizations, and fatalities. This outbreak in China is mainly due to the Omicron strain and its subvariants (mainly BA. 5 and BF. 7). A previous meta-analysis of Omicron strains (46) indicated that casirivimab and imdevimab were not so effective for COVID-19 due to their diminished neutralizing activity against these variants. The diverse mutations in the spike receptor-binding domains of the Omicron strain, the main target of monoclonal antibodies have posed challenges to the effectiveness of casirivimab and imdevimab. In light of the rapid revolution of Omicron strains, it is crucial to obtain more comprehensive evidence to ascertain the effectiveness of casirivimab and imdevimab against these variants.

Conclusions

In conclusion, casirivimab and imdevimab demonstrate efficacy in reducing viral load and all-cause mortality compared to conventional treatments or placebos. This efficacy is particularly pronounced in patients seronegative to SARS-CoV-2 at baseline. The safety of casirivimab and imdevimab is affirmed by their association with a lower

incidence of severe adverse events compared to the control group. This study holds implications for COVID-19 prevention and treatment, spanning various infection statuses, with a particular recommendation for patients seronegative to SARS-CoV-2 at baseline.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1604/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1604/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Trougakos IP, Terpos E, Alexopoulos H, et al. Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis. Trends Mol Med 2022;28:542-54.
2. Meo SA, Meo AS, Al-Jassir FF, et al. Omicron SARS-CoV-2 new variant: global prevalence and biological and clinical characteristics. Eur Rev Med Pharmacol Sci 2021;25:8012-8.
3. Siemieniuk RA, Bartoszko JJ, Díaz Martinez JP, et al. Antibody and cellular therapies for treatment of covid-19: a living systematic review and network meta-analysis. BMJ 2021;374:n2231.
4. Şimşek-Yavuz S, Komsuoğlu Çelikyurt FI. An update of anti-viral treatment of COVID-19. Turk J Med Sci 2021;51:3372-90.
5. Deng J, Zhou F, Ali S, et al. Efficacy and safety of ivermectin for the treatment of COVID-19: a systematic review and meta-analysis. QJM 2021;114:721-32.
6. Deng J, Zhou F, Hou W, et al. Efficacy of lopinavir-ritonavir combination therapy for the treatment of hospitalized COVID-19 patients: a meta-analysis. Future Virol 2021.
7. Yan Z, Yang M, Lai CL. COVID-19 Vaccinations: A Comprehensive Review of Their Safety and Efficacy in Special Populations. Vaccines (Basel) 2021;9:1097.
8. Clark A, Jit M, Warren-Gash C, et al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. Lancet Glob Health 2020;8:e1003-17.
9. Ko JY, Danielson ML, Town M, et al. Risk Factors for Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization: COVID-19-Associated Hospitalization Surveillance Network and Behavioral Risk Factor Surveillance System. Clin Infect Dis 2021;72:e695-703.
10. Stein D, Oviedo-Orta E, Kampman WA, et al. Compassionate Use of REGEN-COV® in Patients With Coronavirus Disease 2019 (COVID-19) and Immunodeficiency-Associated Antibody Disorders. Clin Infect Dis 2022;75:e509-15.
11. O'Brien MP, Forleo-Neto E, Musser BJ, et al.

Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. N Engl J Med 2021;385:1184-95.
12. Somersan-Karakaya S, Mylonakis E, Menon VP, et al. Casirivimab and Imdevimab for the Treatment of Hospitalized Patients With COVID-19. J Infect Dis 2022;227:23-34.
13. Herman GA, O'Brien MP, Forleo-Neto E, et al. Efficacy and safety of a single dose of casirivimab and imdevimab for the prevention of COVID-19 over an 8-month period: a randomised, double-blind, placebo-controlled trial. Lancet Infect Dis 2022;22:1444-54.
14. Wang C, Li W, Drabek D, et al. A human monoclonal antibody blocking SARS-CoV-2 infection. Nat Commun 2020;11:2251.
15. RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2022;399:665-76.
16. Walls AC, Park YJ, Tortorici MA, et al. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell 2020;181:281-292.e6.
17. Weisblum Y, Schmidt F, Zhang F, et al. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. Elife 2020;9:e61312.
18. Kreuzberger N, Hirsch C, Chai KL, et al. SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19. Cochrane Database Syst Rev 2021;9:CD013825.
19. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med 2021;384:229-37.
20. Gottlieb RL, Nirula A, Chen P, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA 2021;325:632-44.
21. Baum A, Fulton BO, Wloga E, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science 2020;369:1014-8.
22. Lin WT, Hung SH, Lai CC, et al. The impact of neutralizing monoclonal antibodies on the outcomes of COVID-19 outpatients: A systematic review and meta-analysis of randomized controlled trials. J Med Virol 2022;94:2222-9.
23. Deng J, Heybati K, Ramaraju HB, et al. Differential efficacy and safety of anti-SARS-CoV-2 antibody therapies for the management of COVID-19: a systematic review and network meta-analysis. Infection 2023;51:21-35.
24. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
25. Mazzaferri F, Mirandola M, Savoldi A, et al. Exploratory data on the clinical efficacy of monoclonal antibodies against SARS-CoV-2 Omicron variant of concern. Elife 2022;11:e79639.
26. Portal-Celhay C, Forleo-Neto E, Eagan W, et al. Phase 2 dose-ranging study of the virologic efficacy and safety of the combination COVID-19 antibodies casirivimab and imdevimab in the outpatient setting. medRxiv 2021. doi: 10.1101/2021.11.09.21265912
27. Portal-Celhay C, Forleo-Neto E, Eagan W, et al. Virologic Efficacy of Casirivimab and Imdevimab COVID-19 Antibody Combination in Outpatients With SARS-CoV-2 Infection: A Phase 2 Dose-Ranging Randomized Clinical Trial. JAMA Netw Open 2022;5:e2225411.
28. Norton T, Ali S, Sivapalasingam S, et al. REGEN-COV Antibody Combination in Outpatients With COVID-19 - Phase 1/2 Results. medRxiv 2021. doi: 10.1101/2021.06.09.21257915
29. O'Brien MP, Forleo-Neto E, Sarkar N, et al. Effect of Subcutaneous Casirivimab and Imdevimab Antibody Combination vs Placebo on Development of Symptomatic COVID-19 in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Clinical Trial. JAMA 2022;327:432-41.
30. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19. N Engl J Med 2021;385:e81.
31. McCreary EK, Bariola JR, Minnier TE, et al. The comparative effectiveness of COVID-19 monoclonal antibodies: A learning health system randomized clinical trial. Contemp Clin Trials 2022;119:106822.
32. Hooper AT, Somersan-Karakaya S, McCarthy SE, et al. Casirivimab and Imdevimab Treatment Reduces Viral Load and Improves Clinical Outcomes in Seropositive Hospitalized COVID-19 Patients with Nonneutralizing or Borderline Neutralizing Antibodies. mBio 2022;13:e0169922.
33. Huang DT, McCreary EK, Bariola JR, et al. Effectiveness of Casirivimab-Imdevimab and Sotrovimab During a SARS-CoV-2 Delta Variant Surge: A Cohort Study and Randomized Comparative Effectiveness Trial. JAMA Netw Open 2022;5:e2220957.
34. Isa F, Forleo-Neto E, Meyer J, et al. Repeat subcutaneous administration of casirivimab and imdevimab in adults is

well-tolerated and prevents the occurrence of COVID-19. Int J Infect Dis 2022;122:585-92.
35. Liu L, Wang P, Nair MS, et al. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. Nature 2020;584:450-6.
36. Cicchitto G, Cardillo L, de Martinis C, et al. Effects of Casirivimab/Imdevimab Monoclonal Antibody Treatment among Vaccinated Patients Infected by SARS-CoV-2 Delta Variant. Viruses 2022;14:650.
37. Hegazy SK, Tharwat S, Hassan AH. Clinical study to compare the efficacy and safety of casirivimab & imdevimab, remdesivir, and favipravir in hospitalized COVID-19 patients. J Clin Virol Plus 2023;3:100151.
38. Hegazy SK, Tharwat S, Hassan AH. Comparing the efficacy of regen-cov, remdesivir, and favipiravir in reducing invasive mechanical ventilation need in hospitalized COVID-19 patients. World J Clin Cases 2023;11:6105-21.
39. Hegazy SK, Tharwat S, Hassan AH. Study to compare the effect of casirivimab and imdevimab, remdesivir, and favipiravir on progression and multi-organ function of hospitalized COVID-19 patients. Open Med (Wars) 2023;18:20230768.
40. Bierle DM, Ganesh R, Razonable RR. Breakthrough COVID-19 and casirivimab-imdevimab treatment during a SARS-CoV-2 B1.617.2 (Delta) surge. J Clin Virol 2021;145:105026.
41. Al-Obaidi MM, Gungor AB, Nematollahi S, et al. Effectiveness of Casirivimab-Imdevimab Monoclonal Antibody Treatment Among High-Risk Patients With Severe Acute Respiratory Syndrome Coronavirus 2 B.1.617.2 (Delta Variant) Infection. Open Forum Infect Dis 2022;9:ofac186.
42. Hussein M, Wei W, Mastey V, et al. Real-world effectiveness of casirivimab and imdevimab among patients diagnosed with COVID-19 in the ambulatory setting: a retrospective cohort study using a large claims database. BMJ Open 2022;12:e064953.
43. Jalbert JJ, Hussein M, Mastey V, et al. Effectiveness of Subcutaneous Casirivimab and Imdevimab in Ambulatory Patients with COVID-19. Infect Dis Ther 2022;11:2125-39.
44. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med 2021;384:238-51.
45. Gao M, Ao G, Hao X, et al. Casirivimab-imdevimab treatment is associated with reduced rates of mortality and hospitalization in patients with COVID-19: A systematic review with meta-analysis. J Infect 2023;87:82-4.
46. Tao K, Tzou PL, Kosakovsky Pond SL, et al. Susceptibility of SARS-CoV-2 Omicron Variants to Therapeutic Monoclonal Antibodies: Systematic Review and Meta-analysis. Microbiol Spectr 2022;10:e0092622.

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