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The use of neutralizing monoclonal antibody in patients with COVID-19: a systematic review and meta-analysis

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INTRODUCTION

Neutralizing monoclonal antibody (mAb) therapies targeting with high specificity to SARS-CoV-2 has been considered as one of the potential therapies for COVID-19 since the beginning of the pandemic. Preclinical studies demonstrated a marked reduction in viral loads in the upper and lower respiratory tract with the use of neutralizing mAbs[1].

The mAbs have the ability to coordinate the immune defense to link to the virus and control the virus load. The mAbs are defined as an antibody derived from a single B-cell clone and recognize a single and unique epitope that can link to their specific epitope on target antigens and can mediate multiple effects such as disruption of the function and eliminate cells or pathogens[2]. These mAbs for COVID-19 are fully human and were discovered from COVID-19 patient' donors, and one of their targets is to block the S protein of the SARS-CoV-2, preventing viral entry into host cells[3].

The U.S. Food and Drug Administration (FDA) issued an emergency use authorization for mAbs to be used as pre-exposure prophylaxis and mild-moderate COVID-19. However, given to the Omicron variant, the FDA did not recommend using casirivimab+imdevimab. In Brazil, mAbs were approved by the Brazilian regulatory agency, i.e., The National Health Surveillance Agency (ANVISA), for use in patients with mild- to-moderate nonhospitalized COVID-19 patients and for the prevention of COVID-19 infection.

This systematic review aimed to identify, describe, evaluate, and synthesize evidence of effectiveness of mAbs in clinical outcomes in COVID-19 patients.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations[4].

Eligibility criteria

The study protocol followed the patients of interest, intervention to be studied, comparison of interventions, and outcome of interest (PICO) methodology. With the use of a mAb as the main study point, the PICO framework was as follows: patients, adult COVID-19 patients; intervention, use of an mAb (casirivimab+imdevimab, bamlanivimab, bamlanivimab+etesevimab, sotrovimab, regdanvimab, and tixagevimab+cilgavimab); comparison between the standard of care (SOC) and placebo; and outcome, symptomatic COVID-19 infection, symptom resolution, adverse event, severe adverse event, hospitalization, and the mortality rate due to any cause in 29 days. The protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews: CRD42022320972.

All phase 3 randomized controlled trials (RCTs) on the topic were included. No restrictions were imposed with regard to the date of publication, language, or availability of the full text of the article.

Information sources and search strategy

Two authors developed a search strategy that was revised and approved by the team, selected information sources, and systematically searched MEDLINE, EMBASE, Central Cochrane, and ClinicalTrials.gov. Specific search strategies were used for each database: ("COVID-19" OR "COVID" OR "coronavirus" OR

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"SARS-CoV-2") AND ("casirivimab and imdevimab" OR "regn-cov2" OR "bamlanivimab etesevimab" OR "Bamlanivimab" OR "Regdanvimab" OR "CT-p59" OR "Sotrovimab" OR "VIR-7831" OR "Tixagevimab and Cilgavimab" OR "Evusheld" OR "AZD7442") AND (therapy/narrow[filter] OR prognosis/narrow [filter] OR comparative study OR comparative studies). Central Cochrane: (COVID-19 OR COVID OR CORONAVIRUS OR SARS-CoV-2) AND (monoclonal antibody).

Study selection

Two researchers independently selected and extracted data from the included studies. First, articles were selected based on their titles and abstracts. Then, the full texts were evaluated to decide whether to include or exclude the studies, and disagreements were resolved by consensus or following a discussion with a third researcher. We performed selection separately by each class of mAbs.

Data collection and investigated outcomes

Data regarding authorship, year of publication, patient description, interventions (anticoagulant and control), absolute numbers of each outcome, and follow-up duration were extracted from the studies by two researchers independently, and the extracted values were compared.

Risk of bias and quality of evidence

The risk of bias for RCTs was assessed using the Cochrane risk of bias (RoB 2) tool[5,6], as were other fundamental elements, and was expressed as very serious, serious, or non-serious. The risk of bias assessment was conducted by two reviewers independently, and in case of disagreement, a third reviewer deliberated the assessment. The quality of the evidence was extrapolated from the risk of bias based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) terminology as very low, low, or high; for meta-analyses, the GRADEpro Guideline Development Tool ([GDT]; McMaster University, Hamilton, ON, Canada) gives outcomes of very low, low, moderate, or high[7,8].

Synthesis of results and analysis

Categorical outcomes were expressed by group (mAb and control), the number of events, and calculated risk (in %) for each group (by dividing the number of events by the total number of patients in each group). If the risk difference between the groups was significant, a 95% confidence interval (CI) was expressed based on the number needed to treat (NNT) or the number needed to harm. We analyzed separate RCTs that assessed outpatients infected or noninfected COVID-19 patients and hospitalized patients. We analyzed the mAbs separately by molecular type.

We used fixed-effect or random meta-analysis to evaluate the effect of mAbs versus control on the outcomes when these data were available in at least two RCTs. The effects were reported as risk differences (RDs) and corresponding 95%CIs; a 95%CI which encompassed the value 0 in its range indicated that there was no difference in the outcome effect between the mAbs and control arms. RD shows the absolute effect size in the meta-analysis when compared with the relative risk or odds ratio, and this technique can be used when the binary outcome is zero in both study arms. The heterogeneity of the effects among studies was quantified using the I^2 statistic (I^2>50% indicates high heterogeneity). For the meta-analysis, we used Review Manager software, version 5.4 (RevMan 5; Cochrane Collaboration, Oxford, UK)[9].

RESULTS

All characteristics of each study included in this systematic review are presented in Table 1.

Casirivimab+Imdevimab

In total, 103 studies were retrieved from the selected databases. After eliminating duplicates and including studies that met the eligibility criteria, five studies were selected for the assessment of the full texts. Of these, one was excluded (Figure 1). Therefore, four RCTs[10-13] were selected. The characteristics of each study, risk of bias, and quality of evidence are presented in Table 2. We could not perform a meta-analysis regarding the different populations included in each study.

Prevention of COVID-19 infection among previously uninfected household contacts of infected persons

The study randomized 2475 participants (i.e., 1235 in the placebo group and 1240 in the intervention group)[10]. All participants were negative for RT-qPCR with exposure to household index infected persons within 96 h after collection of the index patient's positive COVID-19 test. In the end, 751 participants in the placebo group and 748 participants in the intervention group finalized the study protocol. The intervention group received 1200 mg subcutaneous casirivimab+imdevimab and was stratified by age. The primary end point was the percentage of participants who were symptomatic RT-qPCR during the 28-day efficacy assessment period; the RT-qPCR was collected weekly over 28 days. The RD of the use of casirivimab+imdevimab reduces in 4% the risk of symptomatic and 2% of asymptomatic infection. The adverse event showed an RD reduction in 13% to the casirivimab+imdevimab group compared to placebo (Table 3). The risk of bias was moderate (Table 2) with low quality of evidence.

Table 1. Characteristics of each study included in systematic review.

Study	Design	Population	Intervention (n)	Comparator (n)	Outcome	Time
O'Brien et al.[10]	RCT Double-blind	Adults nonhospitalized without COVID-19 post-exposure	n=748 1200 mg subcutaneous casirivimab+imdevimab	n=751 Placebo	Positive RT-qPCR asymptomatic Positive RT-qPCR symptomatic Adverse event Serious adverse event	28 days
O'Brien et al.[11]	RCT Double-blind	Adults nonhospitalized with early asymptomatic positive COVID-19	n=156 1200 mg subcutaneous casirivimab+imdevimab after 96 h after a collection of the index case's positive	n=158 Placebo	Positive RT-qPCR symptomatic Hospitalization Adverse event Serious adverse event	28 days
Weinreich et al.[12]	RCT Double-blind	Adults non-hospitalized symptomatic positive COVID-19 and risk factors	n=838 Casirivimab+imdevimab (1200 mg) n=1529 Casirivimab+imdevimab (2400 mg)	n=840 Placebo n=1500 Placebo	Hospitalization or death Hospitalization Adverse event Serious adverse event	29 days
Recovery[13]	RCT Open-label	Adults hospitalized in ward with COVID-19 (without of need of respiratory support or cardiac support)	n=2636 Casirivimab 4 g and imdevimab 4 g	n=2636 Standard of care	Death Mechanical ventilation Adverse event	28 days
Cohen et al.[14]	RCT Double-blind	Adults non-hospitalized with negative COVID-19 in skilled nursing and assisted living facility residents and staff	n=484 bamlanivimab 4200mg intravenously	n=482 Placebo	Symptomatic infection Adverse event Death	21 days
Gottlieb et al.[15]	RCT Double-blind	Adults non-hospitalized with COVID-19 with 3 days of onset symptoms	n=104 Bamlanivimab 700 mg n=109 Bamlanivimab 2800 mg n=104 Bamlanivimab 7000 mg n=114 Bamlanivimab 2800 mg +etesevimab 2800 mg intravenously	n=161 Placebo	Symptom improvement Symptom resolution Hospitalization Adverse event Serious adverse event Death	29 days
Dougan et al.[16]	RCT Double-blind	Adults nonhospitalized with COVID-19 and risk factors	n=518 Bamlanivimab 700 mg + etesevimab 1400 mg single dose intravenously	n=517 Placebo	Hospitalization Death Severe adverse event	29 days
Dougan et al.[17]	RCT Double-blind	Adults nonhospitalized with COVID-19 and risk factors	n=520 Bamlanivimab 2800 mg + etesevimab 2800 mg	n=262 Placebo	Hospitalization Death Severe adverse event	29 days
Gupta et al.[18]	RCT Double-blind	Adults non-hospitalized with COVID-19 with 5 days of onset symptoms	n=291 Sotrovimab 500 mg intravenously	n=292 Placebo	Hospitalization Death Severe adverse event	29 days

Development of symptomatic COVID-19 in early asymptomatic COVID-19

The study included 314 asymptomatic with positive RT-qPCR: 156 patients were randomized to receive 1200 mg subcutaneous casirivimab+imdevimab after 96 h after a collection of the index case's positive COVID-19 test sample, and 158 patients were randomized to receive placebo[11]. The primary end point was the proportion of participants who developed signs and symptoms (broad-term) of COVID-19 within 14 days of a positive RT-qPCR at baseline or during the 28-day efficacy assessment period. The RD of the use of casirivimab+imdevimab reduces in 9% the risk of symptomatic infection and 4% of hospitalization. The adverse event showed an RD reduction in 26% to the

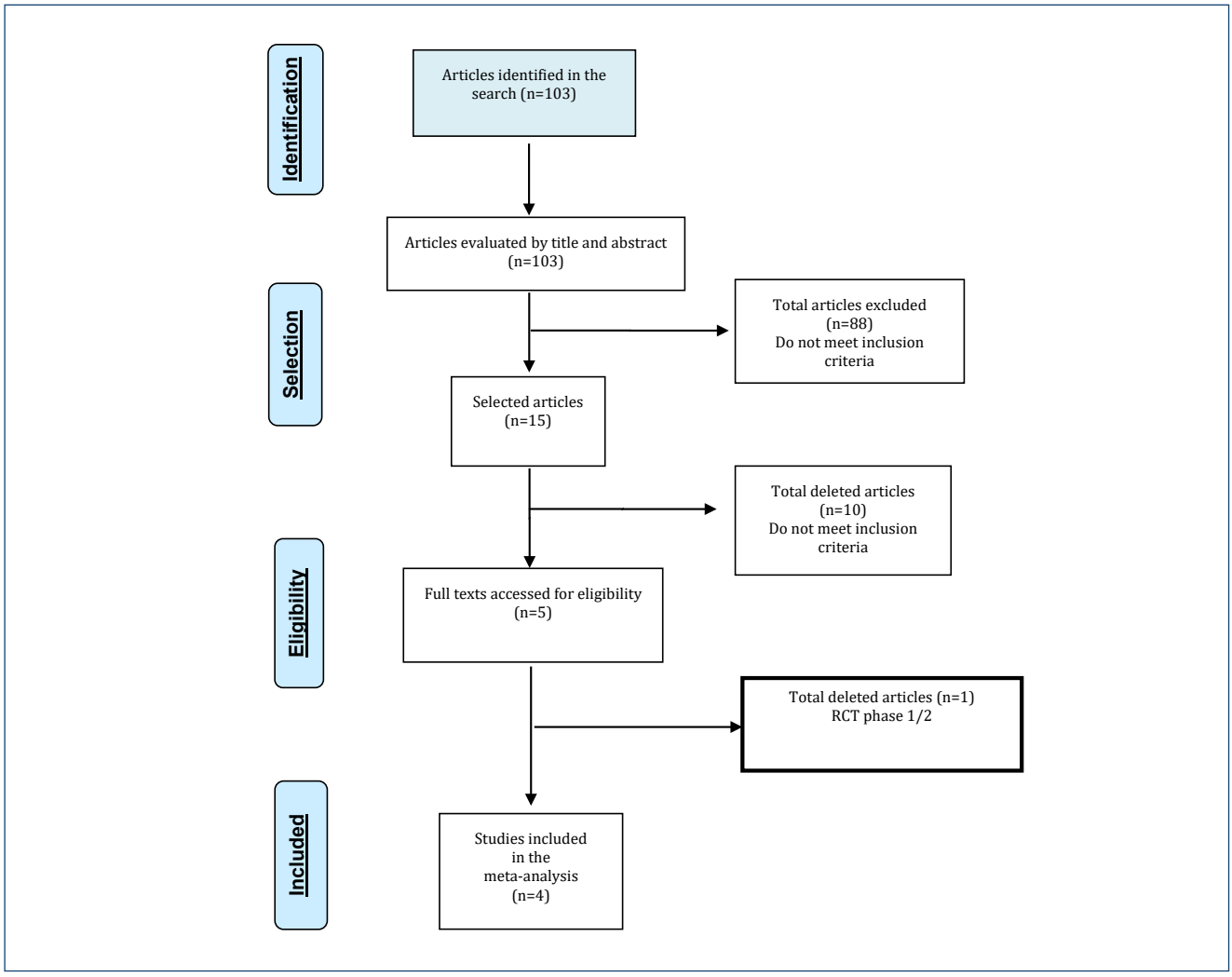

Figure 1. PRISMA flow diagram for casirivimab+imdevimab.

Table 2. Outcomes related to the use of casirivimab+imdevimab compared to placebo in uninfected household contacts of the infected person.

	Placebo n=1235	Casirivimab+imdevimab n=1240	Risk difference (95% confidence interval)
Symptomatic infection	59	11	-0.04 [-0.05; -0.03]
Asymptomatic infection	48	25	-0.02 [-0.03; -0.01]
Adverse event	709	556	-0.13 [-0.16; -0.09]
Serious adverse event	17	14	-0.00 [-0.01; 0.01]

Table 3. Outcomes related to the use of casirivimab+imdevimab compared to placebo in asymptomatic COVID-19-infected person.

	Placebo n=158	Casirivimab+imdevimab n=156	Risk difference (95% confidence interval)
Symptomatic infection in 14 days	44	29	-0.09 [-0.19; 0.00]
Hospitalization	6	0	-0.04 [-0.07; -0.01]
Adverse event	109	67	-0.26 [-0.37; -0.15]
Serious adverse event	4	0	-0.03 [-0.05; 0.00]

casirivimab+imdevimab group compared to placebo (Table 4). The risk of bias was low (Table 2) with low quality of evidence.

Risk of hospitalization or death in outpatients COVID-19-infected persons

This study included outpatients with COVID-19 infection and risk factors. The confirmation of the COVID-19 test needed to be no more than 72 h before randomization with the onset of any COVID-19 symptom no more than 7 days before randomization[12]. The list of risk factors included age >50 years, obesity with body mass index >30 kg/m^2, immunocompromised, diabetes, and liver, kidney, cardiovascular, or lung dysfunction. The casirivimab+imdevimab was administered intravenously, and the primary end point was the percentage of patients with at least one COVID-19-related hospitalization or death from any cause through day 29. The original phase 3 portion of the trial included 3088 patients, with or without risk factors for severe COVID-19, who were randomly assigned to receive a single intravenous dose of casirivimab+imdevimab (8000 or 2400 mg) or placebo. In the amended phase 3 portion of the trial, an additional 2519 patients with at least one risk factor for severe COVID-19 were randomly assigned to receive a single dose of casirivimab+imdevimab (2400 or 1200 mg). The total placebo group was 1500 patients, casirivimab+imdevimab 1200 mg was 838 patients, and casirivimab+imdevimab 2400 mg was 1529 patients randomized. Both doses of 1200 and 2400 mg of casirivimab+imdevimab presented a reduction of hospitalization and death (Table 5) with low risk of bias (Table 2) and low quality of evidence.

Risk of death and mechanical ventilation in hospitalized COVID-19 patients

This study RECOVERY is a randomized, controlled, open-label platform trial comparing several possible treatments with usual care in patients admitted to hospital with COVID-19[13]. Patients admitted to the hospital were eligible for the study if they had clinically suspected or laboratory-confirmed COVID-19 infection. They were assigned (1:1:1) to either the usual standard of care, the usual standard of care plus casirivimab+imdevimab, or the usual standard of care plus convalescent plasma (until January 15, 2021). The intervention group received intravenously casirivimab 4 g and imdevimab 4 g. The primary outcome was 28-day all-cause mortality. Secondary outcomes were time to discharge from hospital and, in patients not on invasive mechanical ventilation at randomization, the composite outcome of invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death. Concomitant medication was predominantly of a systemic corticosteroid, 94% of the total included population, 24% used remdesivir, 14% tocilizumab, and, 9% in both groups used baricitinib. The

Table 4. Outcomes related to the use of casirivimab+imdevimab compared to placebo in outpatient symptomatic COVID-19-infected person.

	Placebo Compare 1200 mg n=840	Casirivimab+imdevimab 1200 mg n=838	Risk difference (95% confidence interval)	Placebo Compare 2400 mg n=1500	Casirivimab+imdevimab 2400 mg n=1529	Risk difference (95% confidence interval)
Hospitalization or death	24	7	-0.02 [-0.03; -0.01]	62	18	-0.03 [-0.04; -0.02]
Hospitalization	23	6	-0.02 [-0.03; -0.01]	59	17	-0.03 [-0.04; -0.02]
Death	1	1	0.00 [-0.00; 0.00]	3	1	-0.00 [-0.00; 0.00]
Adverse event	–	59	–	189	142	-0.03 [-0.06; -0.01]
Serious adverse event	–	9	–	74	24	-0.03 [-0.05; -0.02]

Table 5. Outcomes related to the use of casirivimab+imdevimab compared to placebo in hospitalized COVID-19-infected person.

	Placebo Total n=4946 COVID-19 positive n=2636	Casirivimab+imdevimab Total n=4839 COVID-19 positive n=2636	Risk difference (95% confidence interval)
Death	384	410	0.01 [-0.01; 0.03]
Mechanical ventilation or death	416	459	0.02 [-0.00; 0.04]
Adverse event in positive and negative COVID-19	1715	1792	0.02 [0.00; 0.04]

use of casirivimab+imdevimab increased the risk of mechanical ventilation or death by 2% (Table 6). The risk of bias was high (Table 2) with very low quality of evidence.

Bamlanivimab with or without Etesevimab

In total, 210 studies were retrieved from the selected databases. After eliminating duplicates and including studies that met the eligibility criteria, eight studies were selected for the assessment of the full texts. Of these, three were excluded by the same population, one used combined therapy, and one was phase 2 RCT (Figure 2). Therefore, four RCTs (14-17) were selected. The risk of bias is presented in Table 7. We stratified studies according to the use of the different interventions, such as bamlanivimab isolate or combined to etesevimab.

Bamlanivimab

For the bamlanivimab used alone, we identified two studies[14-15]. We could not perform a meta-analysis regarding the different populations included in each study.

Prevention of COVID-19 infection among previously uninfected contacts of infected persons

The study randomized 1175 participants to evaluate the efficacy of bamlanivimab (4200 mg intravenously – single dose) in skilled nursing and assisted living facility residents and staff (i.e., 587 in the placebo group and 588 in the intervention group) after one positive COVID-19 case at the facility (Cohen JAMA). Within 7 days of a reported confirmed SARS-CoV-2 case at a facility, residents and staff of the facility were screened for enrollment, all participants collected RT-PCR and were randomized to receive intervention or placebo before knowing the results of RT-PCR. The primary end point was the cumulative incidence within 8 weeks of randomization of COVID-19 and the presence of mild or worse disease severity within 21 days of detection. The intervention group and control group with previous negative RT-PCR test was 484 and 482 patients, respectively.

The RD of the use of bamlanivimab reduces in 7% the risk of symptomatic infection. The adverse event or death did not show an RD reduction in the bamlanivimab group compared to placebo (Table 8). The risk of bias was moderate (Table 7) with low quality of evidence.

Risk of hospitalization in outpatients COVID-19-infected persons

This phase 2/3, randomized, double-blind, placebo-controlled, single-infusion study included patients with recently diagnosed mild or moderate COVID-19 in the outpatient setting[15]. All patients were aged 18 years or older, who were tested positive for COVID-19 infection 3 days before randomization with one or more mild-to-moderate symptoms. The main outcome was the SARS-CoV-2 log viral load from baseline to 11 days. The secondary outcomes were time to symptom improvement, time to symptom resolution, the proportion of patients with a COVID-19-related hospitalization, emergency department visit, or death at day 29. Three different doses of bamlanivimab intravenously single dose were used: 700 mg (104 randomized patients), 2800 mg (109 randomized patients), and 7000 mg (104 randomized patients). The placebo group was compound with 161 randomized patients. The proportion of symptom improvement, resolution, hospitalization, and adverse events are presented in Table 9. The use of bamlanivimab reduced by 4% in the hospitalization rate (-0.08 to -0.00). The risk of bias was low (Table 7) with low quality of evidence.

Bamlanivimab+Etesevimab

Risk of hospitalization or death in outpatients COVID-19-infected persons

Three studies assessed this population. One study was phase 2/3, randomized, double-blind, placebo-controlled, single-infusion study that included patients with recently diagnosed mild or moderate COVID-19 in the outpatient setting[15]. All patients aged 18 years or older and were tested positive for

Table 6. Risk of bias of the casirivimab+imdevimab studies included in the systematic review.

RoB 2 Risk of bias from RCT										
Study	Randomization	Allocation	Double blind	Observer	Looses	Charac Prog	Outcome	ITT	Sample size calculation	Early stop trial
O'Brien et al.[10]										
O'Brien et al.[11]										
Weinreichet al.[12]										
Recovery[13]										

RoB 2: Cochrane risk of bias; RCT: Randomized control trial; Charact Prog: Characteristic Prognosis; ITT: Intention to treat.

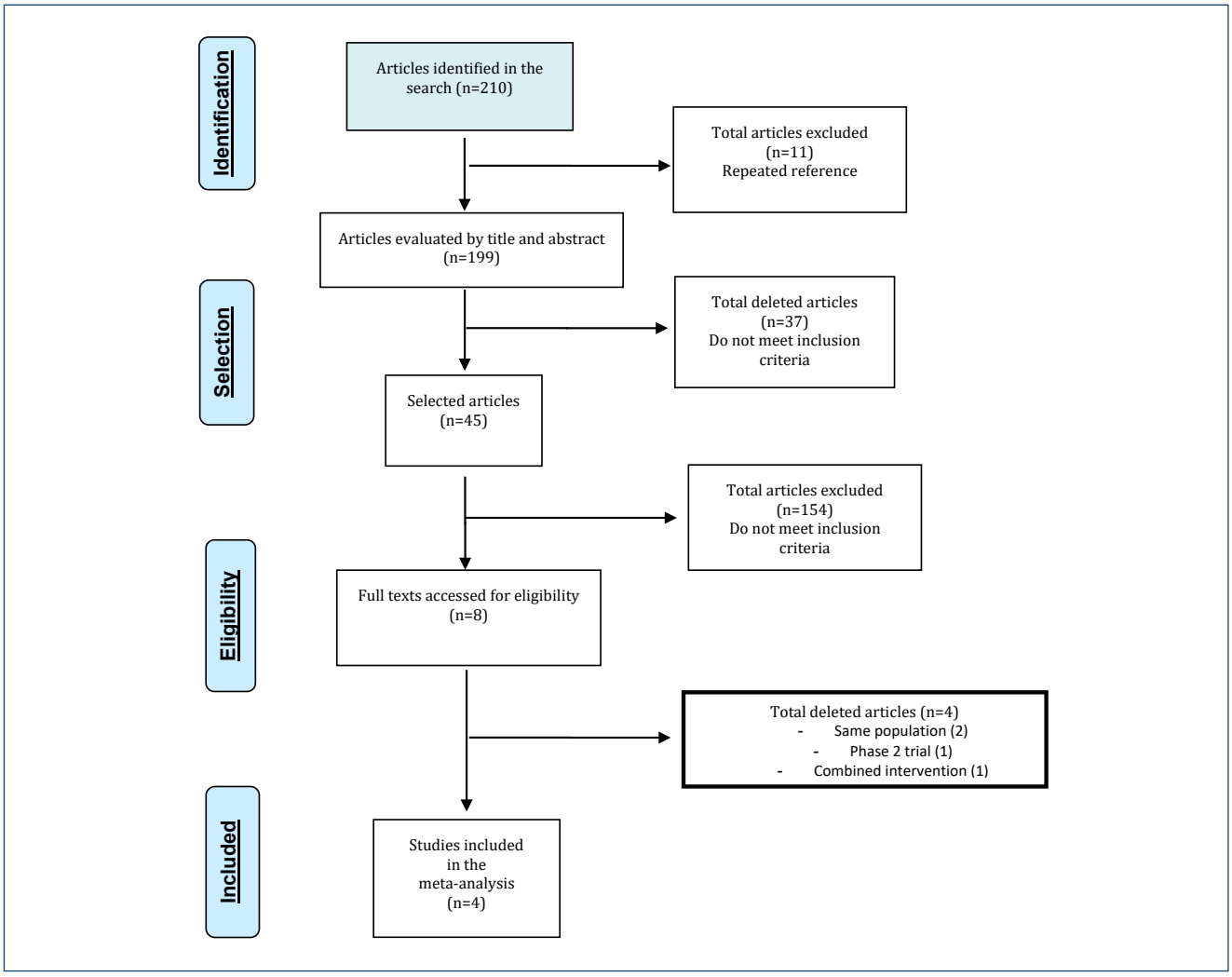

Figure 2. PRISMA flow diagram for bamlanivimab+etesevimab.

Table 7. Outcomes related to the use of prophylaxis bamlanivimab compared to placebo.

	Placebo N=482	Bamlanivimab N=484	Risk difference (95% confidence interval)
Symptomatic infection	73	41	-0.07 [-0.11; -0.03]
Adverse event	86	97	0.02 [-0.03; 0.07]
Death	6	5	-0.00 [-0.02; 0.01]

Table 8. Outcomes related to the use of bamlanivimab in different doses compared to placebo in outpatient symptomatic COVID-19-infected person.

	Placebo N=161	Bamlanivimab 700 mg+2800 mg+7000 mg N=317	Risk difference (95% confidence interval)
Symptom improvement at day 22	96	210	0.07 [-0.03; 0.16]
Symptom resolution at day 22	88	193	0.06 [-0.03; 0.16]
Hospitalization in 29 days	9	5	-0.04 [-0.08; -0.00]
Adverse event	42	75	-0.02 [-0.11; 0.06]
Serious adverse event	1	0	-0.01 [-0.02; 0.01]
Death	0	0	0.00 [-0.01; 0.01]

COVID-19 infection 3 days before randomization with one or more mild-to-moderate symptoms. The main outcome was the SARS-CoV-2 log viral load from baseline to 11 days. The secondary outcomes were time to symptom improvement, time to symptom resolution, the proportion of patients with a COVID-19-related hospitalization, emergency department visit, or death at day 29. The intervention group used bamlanivimab 2800 mg+etesevimab 2800 mg intravenously single dose and compared to placebo. No deaths occurred during the RCT period. We observed the RD of the use of bamlanivimab+etesevimab compared to placebo in outpatient symptomatic COVID-19-infected persons in the recovery of symptom, adverse event, and hospitalization risk.

Other two RCTs[16-17] were performed in outpatients who were 12–17 years of age and who had at least one of the following risk factors at the time of screening: a BMI in at least the 85th percentile for age and sex; sickle cell disease; congenital or acquired heart disease; neurodevelopmental disorders such as cerebral palsy; dependence on a medical-related mechanical device or procedure such as tracheostomy, gastrostomy, or positive-pressure ventilation (not related to COVID-19); asthma, a reactive airway, or another chronic respiratory disease; type 1 or type 2 diabetes mellitus; and an immunocompromised condition or receipt of immunosuppressive treatment. Outpatients who were at least 18 years of age and who presented with at least one of the following risk factors were also included: age of at least 65 years, a BMI of at least 35 kg/m^2, chronic kidney disease, type 1 or type 2 diabetes mellitus, immunosuppressive disease or receipt of immunosuppressive treatment, and an age of at least 55 years with cardiovascular disease, hypertension, or chronic obstructive pulmonary disease or another chronic respiratory disease. All patients had mild or moderate COVID-19 infection confirmed by RT-PCR within 3 days after they had tested positive. The primary outcome was hospitalization (acute care for ≥24 h) or death from any cause by day 29. The difference between studies was the doses of bamlanivimab+etesevimab. One RCT used bamlanivimab 700 mg + etesevimab 1400 mg single dose intravenously, and other RCT used bamlanivimab 2800 mg + etesevimab 2800 mg.

The risk of hospitalization or death was statistically different between groups, with an RD of 5% (95%CI -0.09 – -0.01, p<0.0001, I^2=0%) and NNT=20 in bamlanivimab+etesevimab group (Figure 3A). The risk of bias was low with moderate quality of evidence. Death showed an RD of 2% (95%CI -0.02 – -0.01, p<0.0006, I^2=56%) and NNT=50 in bamlanivimab+etesevimab group (Figure 3B). The risk of bias was low with low quality of evidence. Adverse events or severe adverse events did not demonstrate a difference between groups (Figure 3C and D). The risk of bias was low with low quality of evidence (Table 7).

Sotrovimab

In total, 60 studies were retrieved from the selected databases. After eliminating duplicates and including studies that met the eligibility criteria, two studies were selected for the assessment of the full texts. Of these, one was excluded by using combined therapy intervention (Figure 4).

The RCT included[18] was a double-blind, randomized, for outpatients with symptomatic COVID-19 with ≤5 days after the onset of symptoms, and at least one risk factor for disease progression to receive a single infusion of sotrovimab at a dose of 500 mg or placebo. Patient's high risk for progression of COVID-19 was considered when they presented: older age (≥55 years) or because they had at least one of the following risk factors: diabetes for which medication was warranted, obesity (>30 kg/m^2), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, and moderate-to-severe asthma. The primary efficacy outcome was hospitalization (for >24 h) for any cause or death within 29 days after randomization. The RCT had an early stop trial, because of efficacy, with 583 patients who completed the trial. The safety was performed with 868 patients who were under the protocol at the stop trial. The hospitalization was RD of 6% (95%CI -0.09 – -0.03) and NNT=16.7 of sotrovimab use compared to the placebo group, and severe adverse event RD of 4% (95%CI -0.07 – -0.02) and NNT=25 (Table 10), with the risk of bias moderate with low quality of evidence (Table 11).

Regdanvimab

In total, 30 studies were retrieved from the selected databases. After eliminating duplicates and including studies that met the eligibility criteria, no one study was selected for the assessment of the full texts (Figure 5). We have not identified RCT available at the moment with the eligibility criteria proposed in this systematic review that would support the assessment of the efficacy of regdanvimab in COVID-19 patients.

Tixagevimab+Cilgavimab

In total, 25 studies were retrieved from the selected databases. After eliminating duplicates and including studies that met the eligibility criteria, no one study was selected for the assessment of the full texts (Figure 6). We have not identified RCT available at the moment with the eligibility criteria proposed in this systematic review that would support the assessment of the efficacy of tixagevimab+cilgavimab in COVID-19 patients.

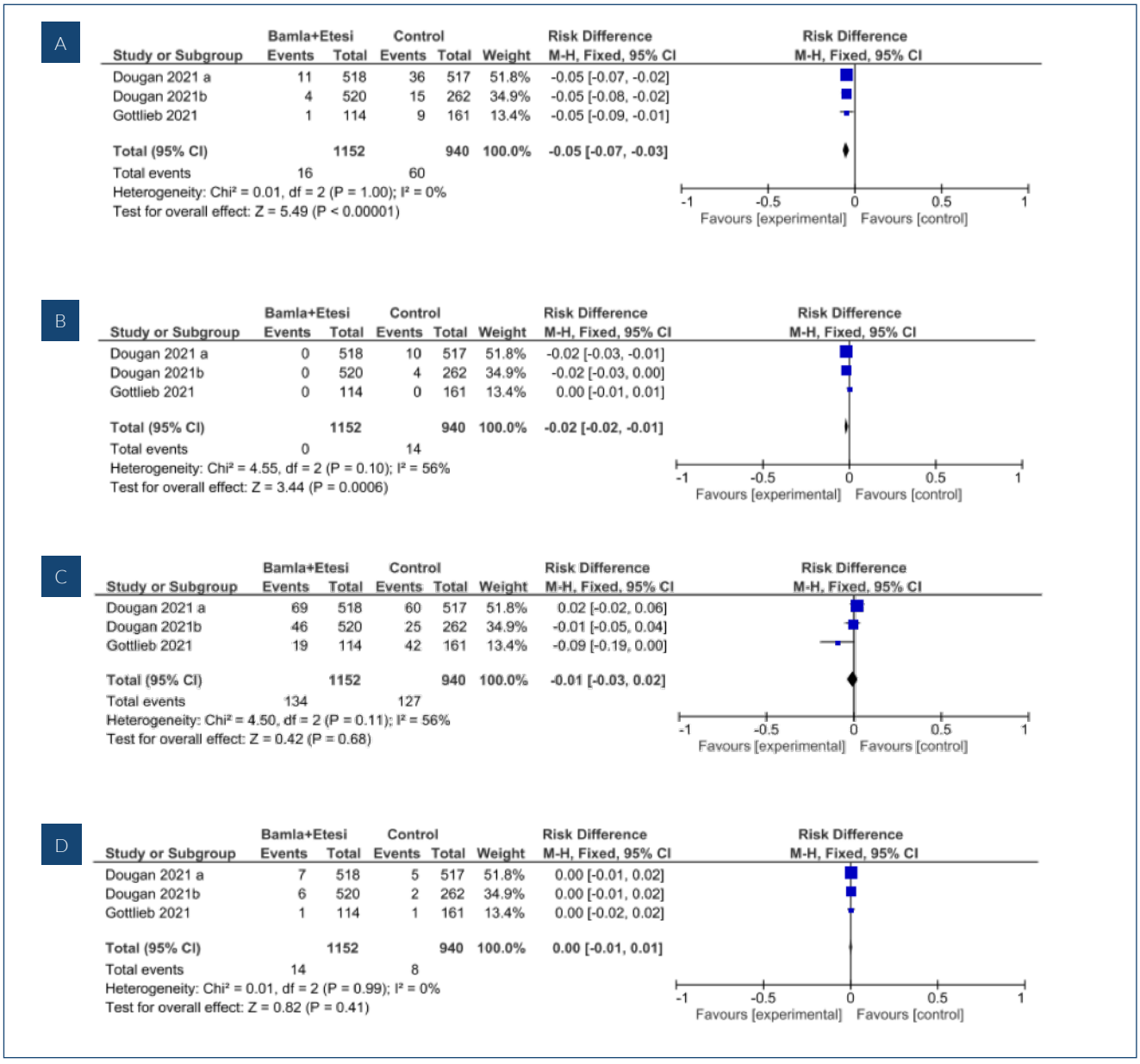

Figure 3. Forest plot of comparison: bamlanivimab+etesevimab versus placebo/SOC (control), with outcome (**A**): hospitalization or mortality in 29 days, (**B**) mortality in 29 days, (**C**) adverse events, and (**D**) severe adverse events.

Recommendations

In patients nonhospitalized without COVID-19:

- The use of casirivimab+imdevimab reduces in 4% the risk of symptomatic COVID-19 infection.
- The use of bamlanivimab reduces in 7% the risk of symptomatic COVID-19 infection.

In patients nonhospitalized with asymptomatic COVID-19:

- The use of casirivimab+imdevimab reduces in 9% the risk of symptomatic infection, 4% of hospitalization, and 26% of the adverse event.

In patients nonhospitalized with symptomatic COVID-19:

- Both doses of 1200 and 2400 mg of casirivimab+imdevimab presented a reduction in hospitalization and death.

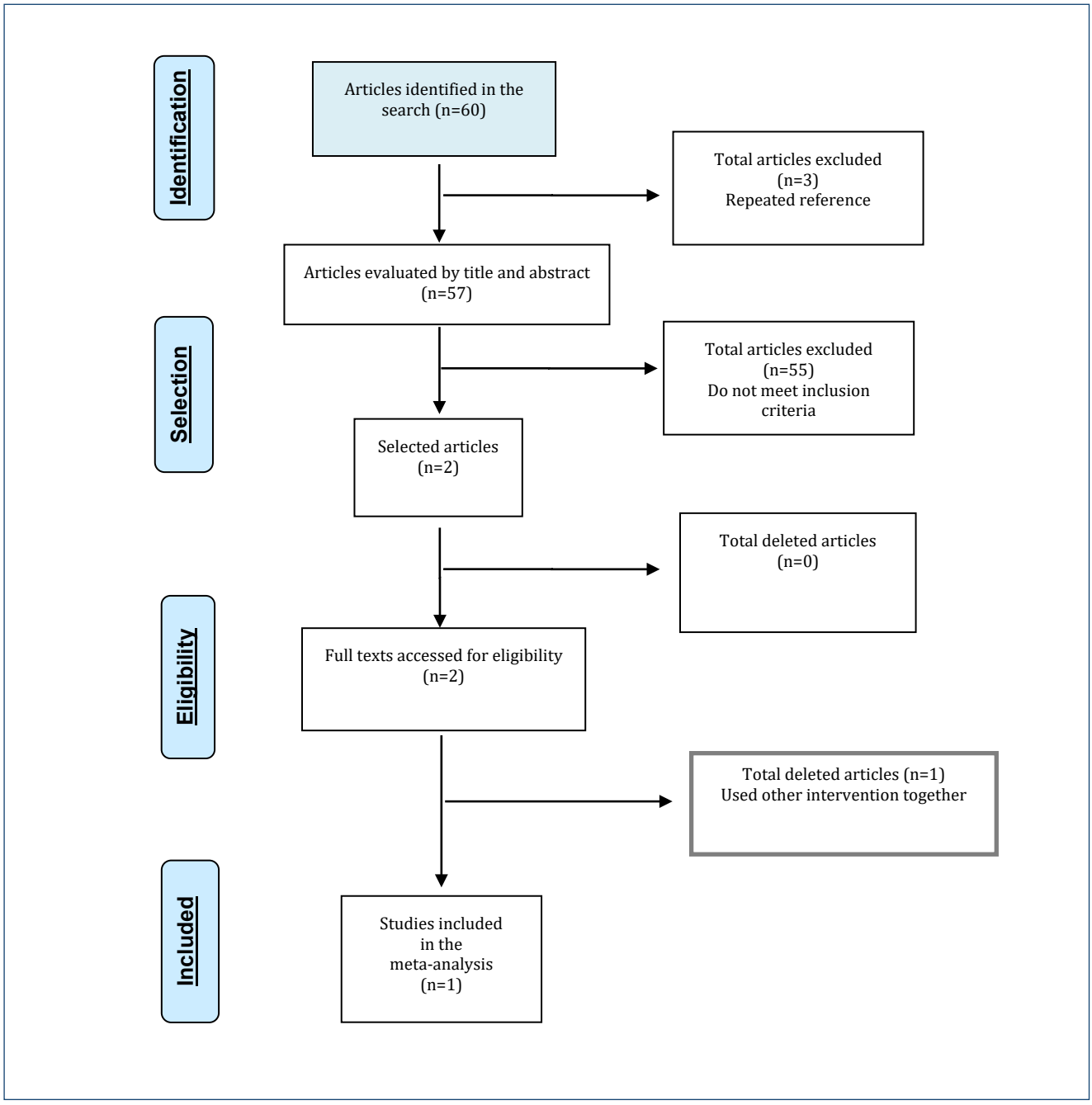

Figure 4. PRISMA flow diagram for sotrovimab.

Table 9. Risk of bias of the bamlanivimab+etesevimab studies included in the systematic review.

RoB 2 Risk of bias from RCT										
Study	Randomization	Allocation	Double blind	Observer	Looses	Charac Prog	Outcome	ITT	Sample size calculation	Early stop trial
Cohen et al.[14]										
Gottlieb et al.[15]										
Dougan et al.[16]										
Dougan et al.[17]										

RoB 2: Cochrane risk of bias; RCT: Randomized control trial; Charact Prog: Characteristic Prognosis; ITT: Intention to treat.

Table 10. Outcomes related to the use of prophylaxis sotrovimab compared to placebo.

	Placebo N=292	Sotrovimab N=291	Risk difference (95% confidence interval)
Hospitalization	21	3	-0.06 [-0.09; -0.03]
Death	1	0	-0.00 [-0.01; 0.01]
Adverse event	85/438	73/430	-0.02 [-0.08; 0.03]
Severe adverse event	26/438	7/430	-0.04 [-0.07; -0.02]

Table 11. Risk of bias of the sotrovimab studies included in the systematic review.

RoB 2 Risk of bias from RCT										
Study	Randomization	Allocation	Double blind	Observer	Looses	Charac Prog	Outcome	ITT	Sample size calculation	Early stop trial
Gupta et al.[18]										

RoB 2: Cochrane risk of bias; RCT: Randomized control trial; Charact Prog: Characteristic Prognosis; ITT: Intention to treat.

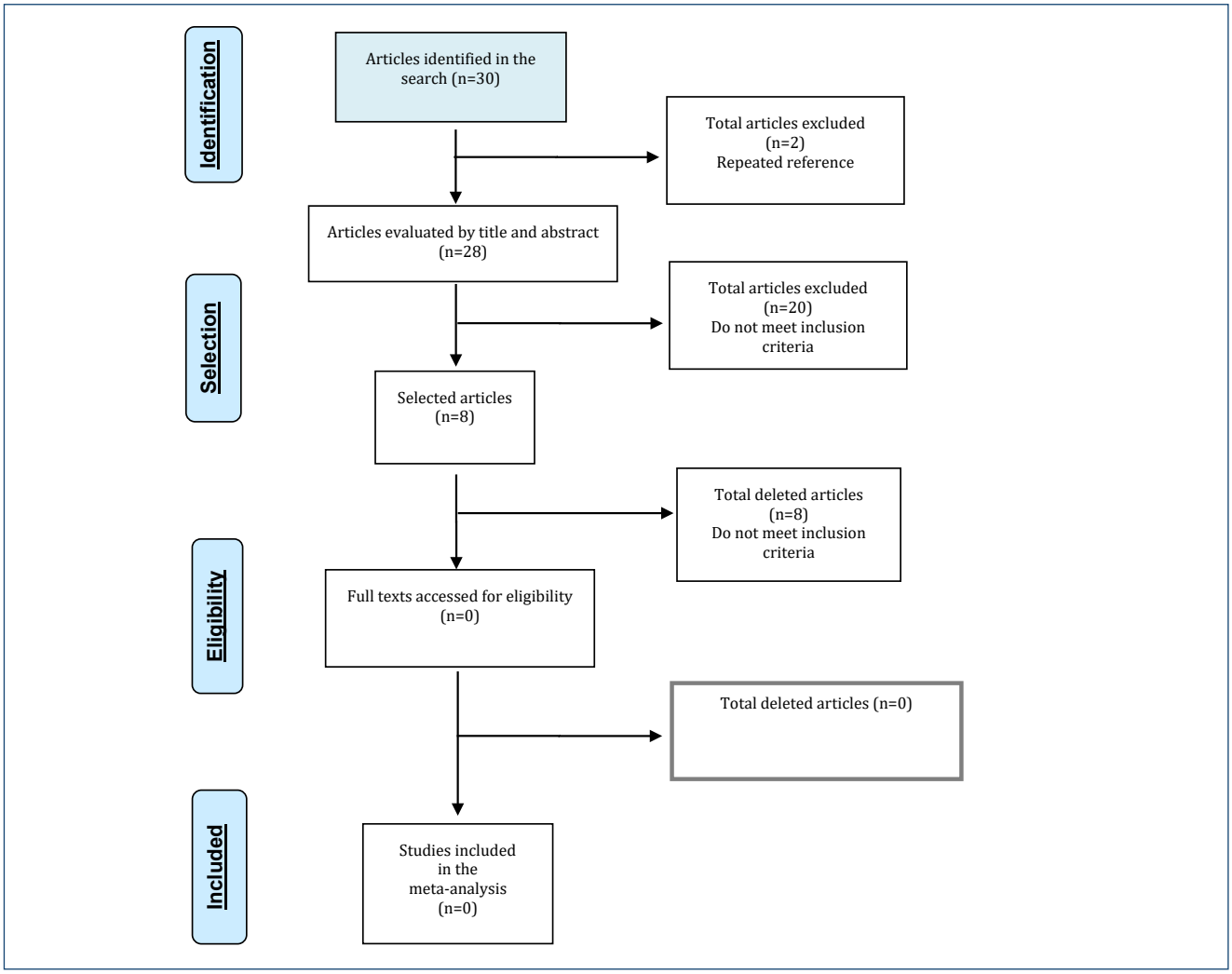

Figure 5. PRISMA flow diagram for regdanvimab.

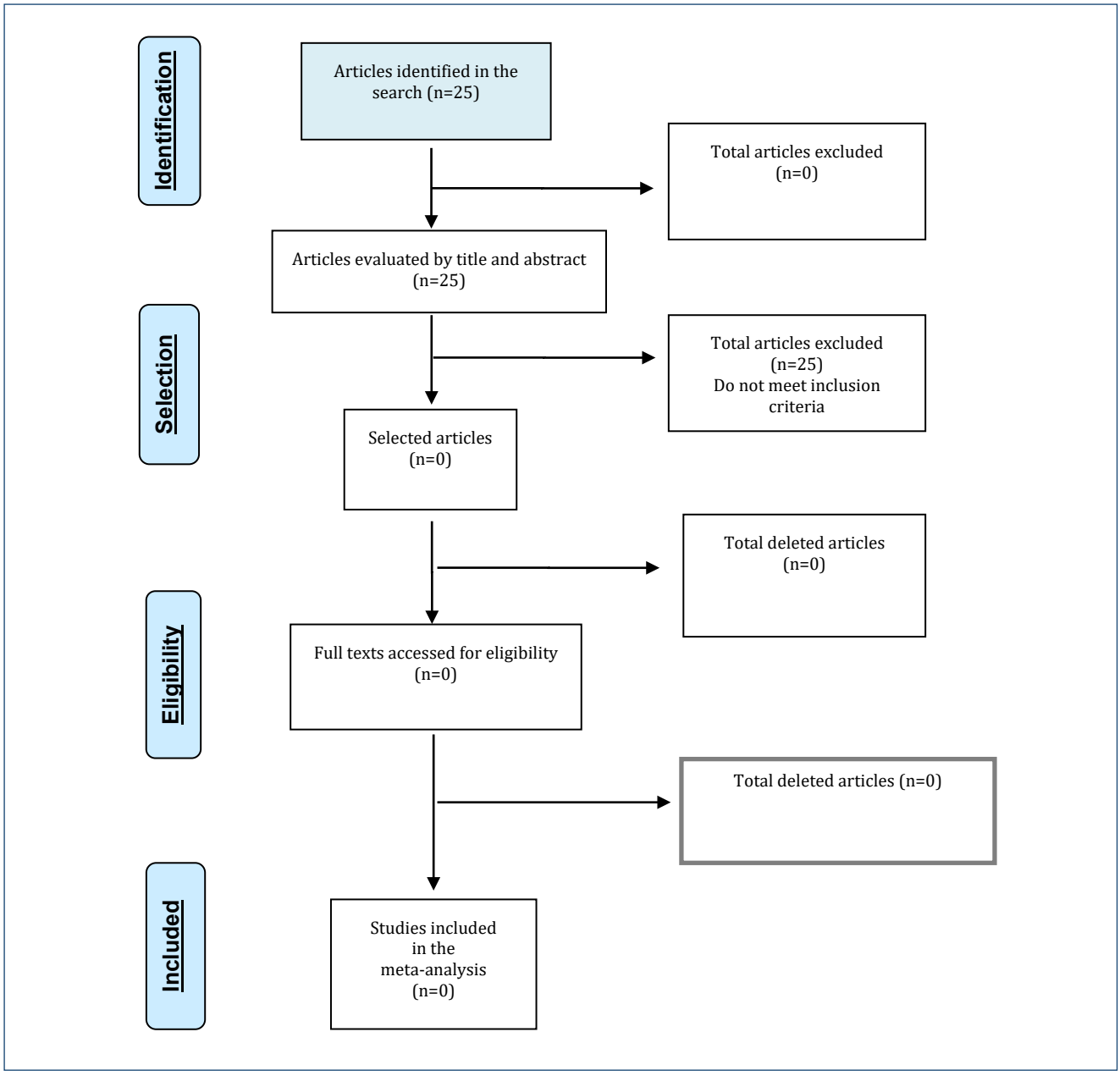

Figure 6. PRISMA flow diagram for tixagevimab+cilgavimab.

- The use of bamlanivimab reduced the hospitalization rate by 4%.
- The use of bamlanivimab+etesevimab reduces mortality risk by 2%.
- The use of sotrovimab reduced hospitalization risk by 6% and 4% of severe adverse event.

In hospitalized COVID-19 patients:

- The use of casirivimab+imdevimab increased the risk of mechanical ventilation or death by 2%.

The quality of evidence to support these recommendations is low.

AUTHORS' CONTRIBUTIONS

SET: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **HB:** Conceptualization, Writing – review & editing. **ANB:** Conceptualization, Writing – review & editing. **WMB:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **SET:** Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **DRB:** Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

REFERENCES

1. Baum A, Ajithdoss D, Copin R, Zhou A, Lanza K, Negron N, et al. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Science. 2020;370(6520):1110-5. https://doi.org/10.1126/science.abe2402
2. Corti D, Purcell LA, Snell G, Veesler D. Tackling COVID-19 with neutralizing monoclonal antibodies. Cell. 2021;184(12):3086-108. https://doi.org/10.1016/j.cell.2021.05.005
3. Du L, Yang Y, Zhang X. Neutralizing antibodies for the prevention and treatment of COVID-19. Cell Mol Immunol. 2021;18(10):2293-306. https://doi.org/10.1038/s41423-021-00752-2
4. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
5. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
6. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021;12(1):55-61. https://doi.org/10.1002/jrsm.1411
7. Grade working group. GRADE working group from evidence to recommendations – transparent and sensible [Internet]. [cited on Mar 20, 2022]. Available from: https://www.gradeworkinggroup.org/
8. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2020 (developed by Evidence Prime, Inc.). [cited on Mar 20, 2022]. Available from: gradepro.org.
9. Review Manager (RevMan) [Computer Program]. version 5.4. The Cochrane Collaboration, 2020.
10. O'Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan KC, Sarkar N, et al. COVID-19 phase 3 prevention trial team. subcutaneous REGEN-COV antibody combination to prevent COVID-19. N Engl J Med. 2021;385(13):1184-95. https://doi.org/10.1056/NEJMoa2109682.
11. O'Brien MP, Forleo-Neto E, Sarkar N, Isa F, Hou P, Chan KC, et al; COVID-19 Phase 3 prevention trial team. 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(5):432-41. https://doi.org/10.1001/jama.2021.24939
12. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al; Trial investigators. REGEN-COV antibody combination and outcomes in outpatients with COVID-19. N Engl J Med. 2021;385(23):e81. https://doi.org/10.1056/NEJMoa2108163
13. 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(10325):665-76. https://doi.org/10.1016/S0140-6736(22)00163-5
14. Cohen MS, Nirula A, Mulligan MJ, Novak RM, Marovich M, Yen C, et al. Effect of Bamlanivimab vs placebo on incidence of COVID-19 among residents and staff of skilled nursing and assisted living facilities: a randomized clinical trial. JAMA. 2021;326(1):46-55. https://doi.org/10.1001/jama.2021.8828
15. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, 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(7):632-44. https://doi.org/10.1001/jama.2021.0202
16. Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, et al.; BLAZE-1 investigators. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. N Engl J Med. 2021a;385(15):1382-92. https://doi.org/10.1056/NEJMoa2102685
17. Dougan M, Azizad M, Mocherla B, Gottlieb RL, Chen P, Hebert C, et al.; BLAZE-1 investigators. A randomized, placebo-controlled clinical trial of Bamlanivimab and Etesevimab together in high-risk ambulatory patients with COVID-19 and validation of the prognostic value of persistently high viral load. Clin Infect Dis. 2021b;ciab912. https://doi.org/10.1093/cid/ciab912
18. Gupta A, Gonzalez-Rojas Y, Juarez E, Casal MC, Moya J, Falci DR, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. N Engl J Med. 2021;385(21):1941-50. https://doi.org/10.1056/NEJMoa2107934