Review Article

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Bebtelovimab for COVID-19: A Systematic Review and Meta-Analysis

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Abstract

Background: Bebtelovimab is a monoclonal antibody used for treating mild-to-moderate COVID-19 in high-risk outpatients. This study assessed its effectiveness on the mortality, the hospitalization, the composite outcome of hospitalization or death, and the ICU admission.

Methods: The authors searched PubMed, Cochrane Library, Web of Science, Scopus, Embase, medRxiv, and Google Scholar up to April 1, 2025, per PRISMA 2020 checklist. Reference lists of selected studies were also reviewed to identify additional records. Study quality was assessed using the Cochrane Risk of Bias tool. Data analysis was conducted with Comprehensive Meta-Analysis (CMA) software.

Results: Twelve studies, involving [1 Randomized Controlled Trials (RCT), 11 observational; 59203 patients] patients, were included. The meta-analysis revealed no significant differences between the Bebtelovimab and control groups in mortality rate [Odds Ratio (OR) =0.69; 95% Confidence Interval (CI): 0.30-1.59, p=0.391], hospitalization rate (OR=0.87; 95%CI: 0.63-1.21, p=0.431), death or hospitalization rate (OR=0.93; 95%CI: 0.58–1.48, p=0.775), and ICU admission (OR=0.61; 95%CI: 0.36-1.03, p=0.068). Subgroup analysis indicated no significant difference in mortality rate (OR=1.13; 95%CI: 0.79-1.63, p=0.480).

Conclusion: The findings indicate that Bebtelovimab does not have a statistically significant effect on reducing mortality, hospitalization, ICU admission, and death or hospitalization rate compared to the control group. Given the moderate heterogeneity and the predominance of observational studies, results should be interpreted cautiously. Further studies with larger RCTs are needed to assess Bebtelovimab's efficacy more accurately, particularly against evolving SARS-CoV-2 variants.

Keywords: Bebtelovimab, COVID-19, Efficacy, SARS-CoV-2

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Introduction

The global impact of Coronavirus disease 2019 (COVID-19), caused by *SARS-CoV-2*, continues to challenge healthcare systems worldwide (1-4). Despite extensive vaccination efforts, the emergence of new *SARS-CoV-2* variants poses significant hurdles to controlling the pandemic (5-7). Vaccines remain the cornerstone of defense against COVID-19, but their effectiveness against emerging variants and global accessibility are not always assured (8-10). These challenges highlight the urgent need for effective therapeutic options, particularly for high-risk patients with mild-to-moderate disease (2,11).

Monoclonal antibodies (mAbs) have emerged as a promising therapeutic strategy for managing mild-to-moderate COVID-19 in high-risk outpatients (2,12,13). Among the therapeutic options for COVID-19, Bebtelovimab, a neutralizing IgG1 monoclonal antibody, targets the spike protein of *SARS-CoV-2*, preventing viral attachment and entry into host cells (14). Authorized by the U.S. Food and Drug Administration (FDA) in 2022 for emergency use in high-risk patients with COVID-19, its real-world effectiveness remains under evaluation (15). Rapid evolution of *SARS-CoV-2* variants, particularly Omicron subvariants, necessitates a rigorous assessment of Bebtelovimab's efficacy to guide clinical decision-making and public health strategies. Prior studies, such as Liew *et al* (16) and Luo *et al* (17), have reported conflicting findings regarding Bebtelovimab's impact on mortality and clinical outcomes. These inconsistencies, coupled with the emergence of resistant variants, underscore the need for a comprehensive systematic review and meta-analysis to synthesize existing evidence and clarify Bebtelovimab's role in COVID-19 treatment.

This study aims to evaluate the effectiveness of Bebtelovimab in patients with mild-to-moderate COVID-19, providing robust evidence to optimize treatment protocols and inform public health policies. Given the ongoing global impact of the pandemic and the critical need for evidence-based therapeutic options, this meta-analysis seeks to address gaps in current knowledge and offer guidance for clinicians and policymakers.

Materials and Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (2020 version) (18), with a completed PRISMA checklist provided in table S1.

Table S1. PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Title	1	Bebtelovimab for COVID-19: A systematic review and meta-analysis	1
Abstract	2	See the PRISMA 2020 for Abstracts checklist	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge	2 and 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses	2 and 3
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	3
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used	3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process	3

Contd. table S1.

Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process	3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect	3
	10b	List and define all other variables for which data were sought (*e.g.* participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process	4
Effect measures	12	Specify for each outcome the effect measure(s) (*e.g.* risk ratio, mean difference) used in the synthesis or presentation of results	4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (*e.g.* tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5))	4 and 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions	4 and 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	4 and 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used	4 and 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (*e.g.* subgroup analysis, meta-regression).	4 and 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results	4 and 5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	4
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram	6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	6
Study characteristics	17	Cite each included study and present its characteristics	6
Risk of bias in studies	18	Present assessments of risk of bias for each included study	6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (*e.g.* confidence/credible interval), ideally using structured tables or plots.	6 - 8

Contd. table 1S.

Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	6 - 8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (*e.g.* confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	6 - 8
	20c	Present results of all investigations of possible causes of heterogeneity among study results	6 - 8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results	6 – 8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	6 - 8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	6 - 8
Discussion	23a	Provide a general interpretation of the results in the context of other evidence	10
	23b	Discuss any limitations of the evidence included in the review	12
	23c	Discuss any limitations of the review processes used	12
	23d	Discuss implications of the results for practice, policy, and future research	12
Other information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	13
Competing interests	26	Declare any competing interests of review authors	13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	13

Literature search strategy

A systematic literature search was conducted across PubMed, Embase, Cochrane Library, Web of Science, Scopus, medRxiv, and Google Scholar, covering records up to April 1, 2025. To maximize the identification of pertinent studies, the reference lists of all studies selected for inclusion were manually reviewed to uncover additional relevant publications that might not have appeared in the initial database searches. The search strategy was designed to be both sensitive and specific, utilizing a combination of Medical Subject Headings [MeSH] terms and and keywords such as "COVID-19", "SARS-CoV-2", "Bebtelovimab", and "LY-CoV1404". Reference lists of included studies were manually reviewed to identify additional relevant publications.

Study selection

Duplicate records were removed using reference management software to streamline screening.

Studies were eligible if they included patients with mild-to-moderate COVID-19, confirmed by Polymerase Chain Reaction (PCR) testing, and compared Bebtelovimab to Standard of Care (SOC), placebo, or other treatments (*e.g.*, Paxlovid, Sotrovimab). Eligible studies reported at least one outcome: all-cause mortality, hospitalization, composite outcome of hospitalization or death, or ICU admission. Randomized Controlled Trials (RCTs) and observational studies (cohort, case-control) were included to balance rigorous evidence with real-world applicability. Exclusion criteria included animal studies, case reports, case series, studies without comparative data, or those lacking methodological detail (*e.g.*, unclear intervention protocols). Studies on severe COVID-19 or irrelevant outcomes were also excluded to ensure focus on the target population and outcomes. Two independent reviewers screened titles, abstracts, and full texts, with discrepancies resolved by a third reviewer.

Quality assessment

The methodological quality and risk of bias of included studies were evaluated using standardized tools tailored to their designs to ensure a robust assessment of evidence reliability and potential biases. This process informed the interpretation of meta-analysis results and addressed limitations in study quality.

RCTs: For the single RCT, the Cochrane Collaboration's Risk of Bias 2 (RoB 2) tool was applied (19). This tool assesses bias across five domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. Each domain was rated as low risk, some concerns, or high risk, with an overall risk of bias judgment. For example, inadequate blinding of outcome assessors for hospitalization decisions was noted as a potential source of bias, leading to a rating of "some concerns" for the RCT.

Non-randomized studies: The ROBINS-I tool is a comprehensive framework designed to assess the risk of bias in non-randomized studies, such as cohort and case-control studies, by comparing their methodological rigor to that of an idealized randomized trial (20). ROBINS-I evaluates seven domains of bias: (1) bias due to confounding, (2) bias in selection of participants, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of the reported result. Each domain was assessed using signaling questions, with ratings of low, moderate, serious, critical, or no information. For instance, studies adjusting for confounders like age, comorbidities, and vaccination status via propensity score matching were rated low risk for confounding, while those with unclear Bebtelovimab protocols risked bias in intervention classification.

Two independent reviewers conducted the assessments, recording detailed justifications for each judgment in a standardized form. Discrepancies were resolved through discussion or consultation with a third reviewer. Results were summarized in table S2, with most observational studies rated low to moderate risk.

Data extraction process

Two independent reviewers extracted data from the included studies. Extracted data encompassed study characteristics (*e.g.*, first author, publication year, study location, design, COVID-19 vaccination rates, SARS-CoV-2 variant, and disease severity), participant details (*e.g.*, sample size and sex), intervention and control group details (*e.g.*, sample size, treatment dosage, and duration), and efficacy outcomes.

Data analysis

The efficacy of Bebtelovimab compared to control groups was analyzed using Comprehensive Meta-Analysis (CMA) software. Dichotomous outcomes were expressed as Odds Ratios (OR) with 95% Confidence Intervals (CI). For these outcomes, the number of events and total participants in both intervention and control groups were recorded. Heterogeneity was assessed using the I^2 statistic, with $I^2 > 50\%$ and $p < 0.1$ indicating significant heterogeneity. Fixed-effect models were used for $I^2 < 50\%$, and random-effects models for $I^2 > 50\%$. Subgroup analyses were performed based on study design (RCTs *vs.* observational studies), and control

type (SOC, placebo, or other treatments). Sensitivity analyses were conducted using the leave-one-out method to ensure the robustness of the meta-analysis results. This approach involved systematically removing one study at a time from the pooled analysis and recalculating the summary effect size to assess the influence of each individual study on the overall findings. Publication bias was assessed using Begg's and Egger's tests, with caveats noted for outcomes with fewer than 10 studies.

Ethical considerations

No patient-level data were directly analyzed; only aggregated data from published studies were used. Ethical approval was not required.

Results

Study characteristics

The process of identifying and screening relevant literature is illustrated in the flow diagram provided in figure 1. Initially, a total of 136 studies were retrieved from the searched databases. After eliminating duplicate entries, the titles and abstracts of the remaining studies were carefully reviewed for relevance. This screening process narrowed the selection down to 14 studies, for which the full texts were thoroughly evaluated to determine their eligibility for inclusion. Ultimately, twelve studies (14,21-31), encompassing a total of 59203 patients, met the inclusion criteria and were incorporated into the meta-analysis. Among these twelve studies,

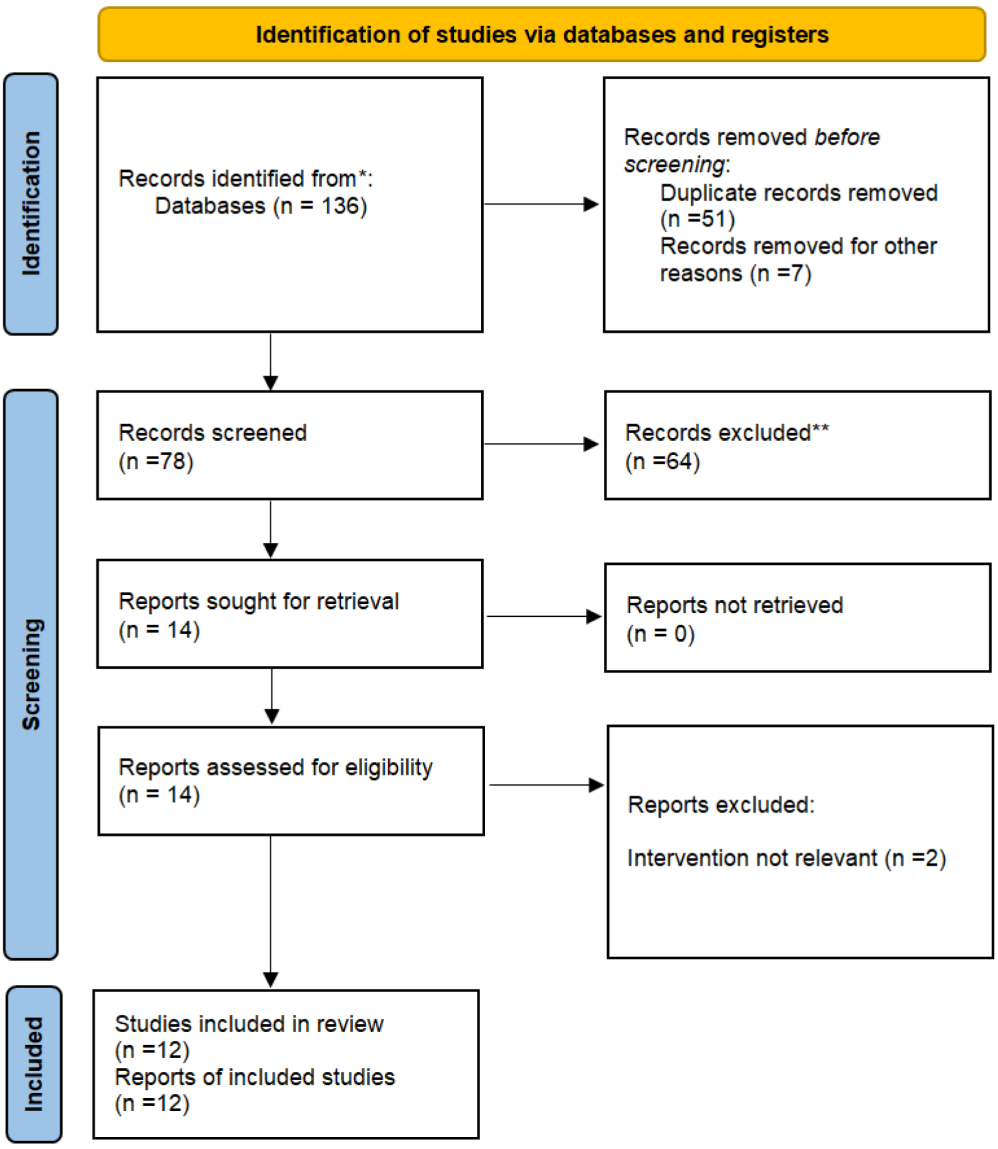


Figure 1. Flow diagram of PRISMA 2020.

one was a RCT, while the other eleven utilized observational study designs. The key characteristics and details of the included studies, such as study design, population, and outcomes, are systematically summarized in table 1 for reference. Most studies focused on Omicron variants, with vaccination rates ranging from 17.4 to 95.5%.

Risk of bias assessment

The single RCT (21) showed high risk of bias in randomization, allocation concealment, and blinding of participants and outcome assessors, limiting its reliability, though it had low risk in incomplete outcome data and selective reporting (Table S2). All eleven included studies were judged to be at moderate risk of bias using the ROBINS-I tool. The most frequent concerns were confounding (seven studies at moderate risk due to incomplete adjustment for key prognostic factors) and missing data (all eleven studies at moderate risk owing to loss to follow-up without sensitivity analysis). No study was rated serious or critical in any domain. Measurement of interventions was rated moderate in four studies because of potential exposure misclassification (Table S3). These quality issues, particularly the RCT's limitations and potential unmeasured confounding in observational data, require cautious interpretation of meta-analysis results. Sensitivity analyses confirmed result robustness despite these limitations.

Outcomes

Mortality rate: A meta-analysis of 10 studies

Table 1. Characteristics of studies included in the systematic review and meta-analysis

First author	Year	Country	Sample size	Male	Design	Bebtelovimab			Control			Follow-up (days)
						No.	Mean age	COVID-19 vaccination%	No.	Mean age	COVID-19 vaccination%	
Dougan (21)	2022	USA	253	118	RCT	125	NR	NR	128	NR	NR	28
Dryden-Peterson (22)	2022	USA	754	350	RCS	377	NR	95.5	377	NR	95.2	28
Kip (23)	2023	USA	314	NR	Cohort	NR	NR	NR	NR	NR	NR	28
McCreary (14)	2022	USA	1860	714	RCS	930	61.2	95.4	930	62.2	97.2	28
Molina (24)	2023	USA	9162	3745	Retro-spective	3739	NR	84.5	5423	NR	82.4	28
Razonable a (25)	2022	USA	3607	1501	Retro-spective	2833	66.7	92.6	370	62.2	92.5	30
Razonable b (26)	2022	USA	3872	1590	Retro-spective	1690	65.4	92.9	2182	60.4	86.3	30
Rowan (27)	2025	USA	11654	4622	Cohort	5827	62.1	17.4	5827	62.1	17.4	30
Salto-Alejandre (28)	2024	USA	90	60	Retro-spective	60	58	90.7	30	60	84.8	30
Sridhara (29)	2022	USA	2182	943	Retro-spective	1091	64	68.6	1091	64	68.6	30
Wang (30)	2023	USA	24937	9302	Retro-spective	1337	65.1	68	23600	54.7	49	90
Yetmar (31)	2022	USA	361	222	Retro-spective	92	59.7	85.9	269	56.9	87	30

NR: Not Reported.

Table S2. Risk of bias of included RCT

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Dougan 2022	High	High	High	High	Low	Low

Table S3. ROBINS-I tool results for non-randomized studies

Study	Confounding	Selection	Measurement of intervention	Deviations from Intended interventions	Missing data	Measurement of outcomes	Reported result	Overall
Dryden-Peterson	Moderate	Low	Moderate	Low	Low	Moderate	Low	Moderate
Kip	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
McCreary	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Molina	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Razonable a	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Razonable b	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Rowan	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Salto-Alejandre	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Sridhara	Low	Low	Moderate	Low	Low	Moderate	Low	Moderate
Wang	Moderate	Low	Moderate	Low	Low	Moderate	Low	Moderate
Yetmar	Moderate	Low	Moderate	Low	Low	Moderate	Low	Moderate

Note: Moderate= the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial; Low=the study is comparable to a well-performed randomized trial with regard to this domain.

(14,22,24-31) found no significant difference in mortality rates between the Bebtelovimab and control groups (OR = 0.69; 95%CI: 0.30-1.59, p=0.391, I^2 =58%) (Figure 2). Subgroup analyses also revealed no significant differences in mortality rates for the following comparisons: Bebtelovimab *vs.* SOC (OR=1.13; 95%CI: 0.79-1.63, p=0.480, I^2=68%), Bebtelovimab versus Paxlovid (OR=4.99; 95%CI: 0.90-27.50, p=0.064, I^2=0), Bebtelovimab versus Sotrovimab (OR=0.77; 95%CI: 0.26-2.30, p=0.646, I^2=60%) (Figure S1). The forest plot (Figure 2) shows most studies' point estimates favor Bebtelovimab (OR<1), but the wide confidence intervals and non-significant p-value indicate no clear mortality benefit, with moderate heterogeneity (I^2=58%) suggesting variability across studies; subgroup analyses (Figure S1) confirm this lack of effect across control types, though high heterogeneity in SOC comparisons (I^2=68%) and low power in Paxlovid comparisons warrant cautious interpretation.

Hospitalization rate

Nine studies (14,21,22,24,25,27-30) were included to evaluate hospitalization rates. Meta-analyses stratified by study design showed no significant differences between Bebtelovimab and control groups in retrospective studies (OR=0.87; 95%CI: 0.63-1.21, p=0.431, I^2=72%) or RCTs (OR=1.02; 95%CI: 0.14-7.38, p=0.981, I^2=0) (Figure 3). Subgroup analyses based on control group treatment also indicated no significant differences for Bebtelovimab *vs.* SOC (OR=1.05; 95%CI: 0.91-1.21, p=0.475, I^2=82%),

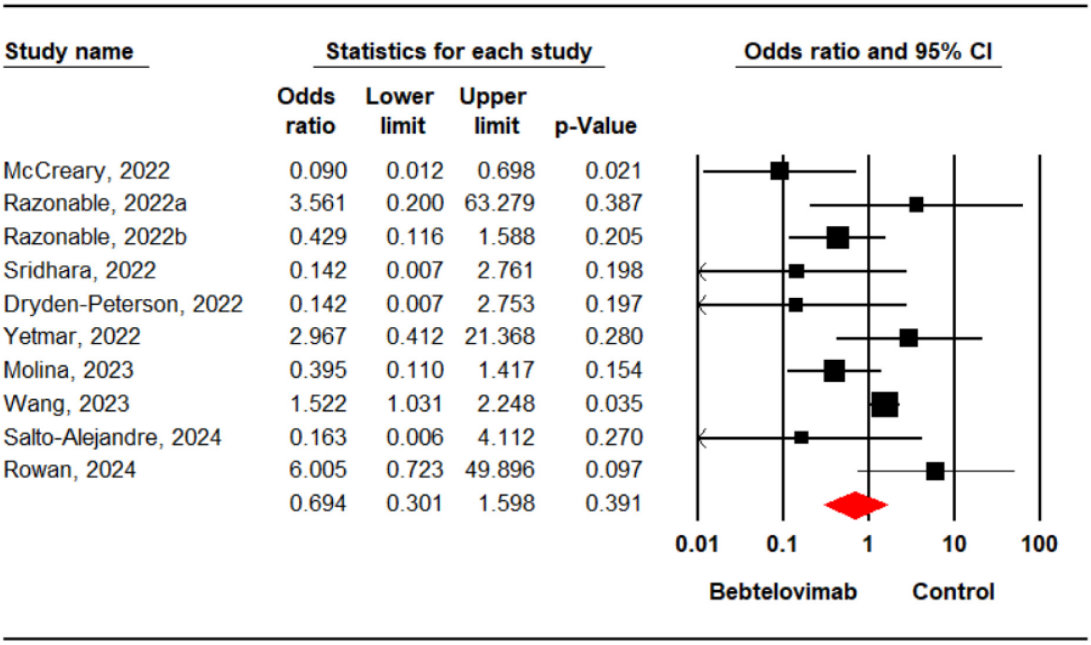


Figure 2. Forest plot of mortality rate between the Bebtelovimab and control groups.

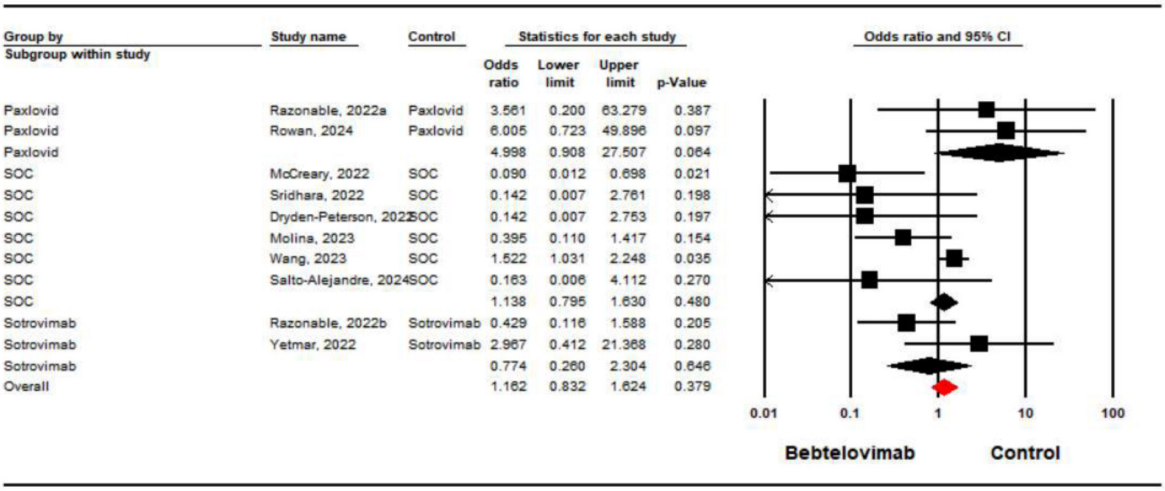


Figure S1. Forest plot of mortality rate for bebtelovimab subgroup compared to other treatment groups.

Bebtelovimab versus Paxlovid (OR=1.08; 95% CI: 0.83-1.41, p-value=0.534, I‧=²) (Figure S2). The forest plot (Figure S2) indicates point estimates near 1 in retrospective studies, suggesting no effect of Bebtelovimab on hospitalization, with high heterogeneity (I^2=72-82%) reflecting study variability and the wide RCT confidence interval (0.14-7.38) indicating low precision, necessitating cautious interpretation of the lack of benefit.

Death or hospitalization rate

Meta-analyses (14,21-23,30) stratified by study design showed no significant differences between Bebtelovimab and control groups in retrospective studies (OR=0.93; 95% CI: 0.58-1.48, p-value=0.775, I^2=54%) or RCTs (OR=1.02; 95% CI: 0.14-7.38, p-value=0.981, I^2=0) (Figure 4). The forest plot (Figure 4) shows point estimates close to 1 across studies, indicating no effect of Bebtelovimab on the composite outcome of death or hospitalization, with moderate heterogeneity in retrospective studies (I^2= 54%) and a wide RCT confidence interval (0.14-7.38) suggesting limited precision and consistent lack of clinical benefit.

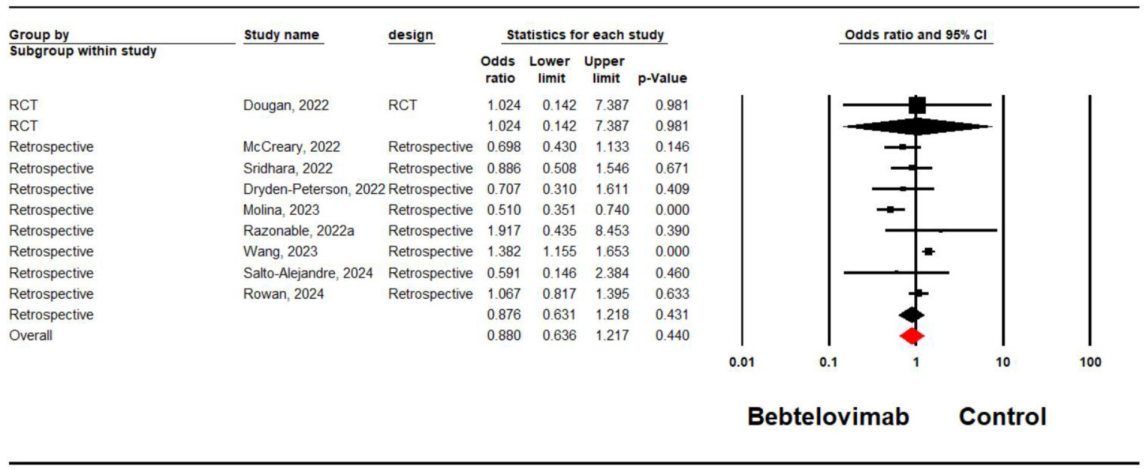


Figure 3. Forest plot of hospitalization rate between the Bebtelovimab and control groups.

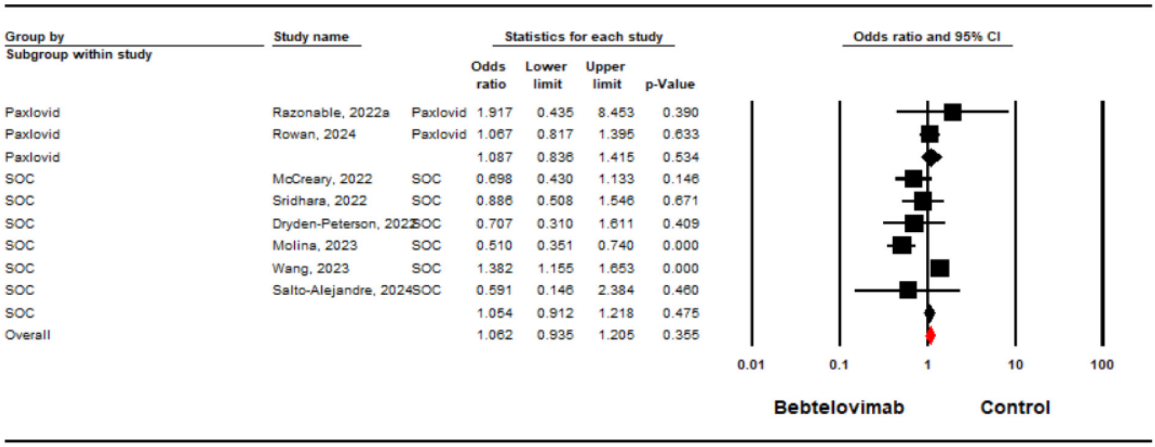


Figure S2. Forest plot of hospitalization rate for bebtelovimab subgroup compared to other treatment groups.

ICU admission

A meta-analysis of four studies (24-26,31) found no significant difference in ICU admission rates between the Bebtelovimab and control groups (OR=0.61; 95%CI: 0.36-1.03, p=0.068, I^2=25%). The forest plot (Figure 5) shows point estimates favoring Bebtelovimab in most studies, but the near-significant p-value and wide confidence interval indicate insufficient evidence for a clinical benefit, with low heterogeneity (I^2=25%) suggesting consistent findings across studies.

Publication bias

No evidence of publication bias was observed in this systematic review and meta-analysis (1-tailed p=0.07, 2 tailed p=0.14). No publication bias was detected for a pooled estimate of mortality rate (Beeg test = 1-tailed: 0.48, 2-tialed: 0.96; Eggar test = 1-tailed: 0.08, 2-tiled: 0.17) and hospitalization rate (Beeg test = 1 tailed: 0.29, 2-tialed: 0.58; Eggar test = 1 tailed: 0.12, 2-tiled: 0.24). However, tests for outcomes with fewer studies (*e.g.*, ICU admission) may lack power.

Discussion

This meta-analysis of 12 studies (1 RCT, 11 observational) evaluated the effectiveness of Bebtelovimab in patients with mild-to-moderate COVID-19 and found no significant benefit in reducing mortality, hospitalization, ICU admission, or the composite outcome of hospitalization or death. This meta-analysis evaluated Bebtelovimab's effectiveness in reducing COVID-19 mortality and found no statistically significant effect compared to control groups without Bebtelovimab. Subgroup analyses showed no significant advantage over treatments like Paxlovid, Sotrovimab, or standard of care. These findings are consistent with Liew *et al* (16), which reported no clinical benefit of

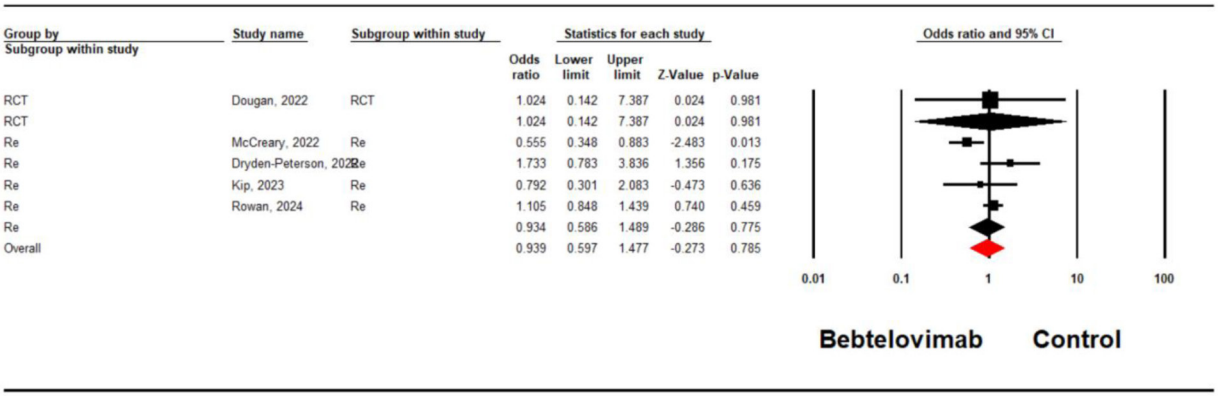


Figure 4. Forest plot of death or hospitalization rate between the Bebtelovimab and control groups.

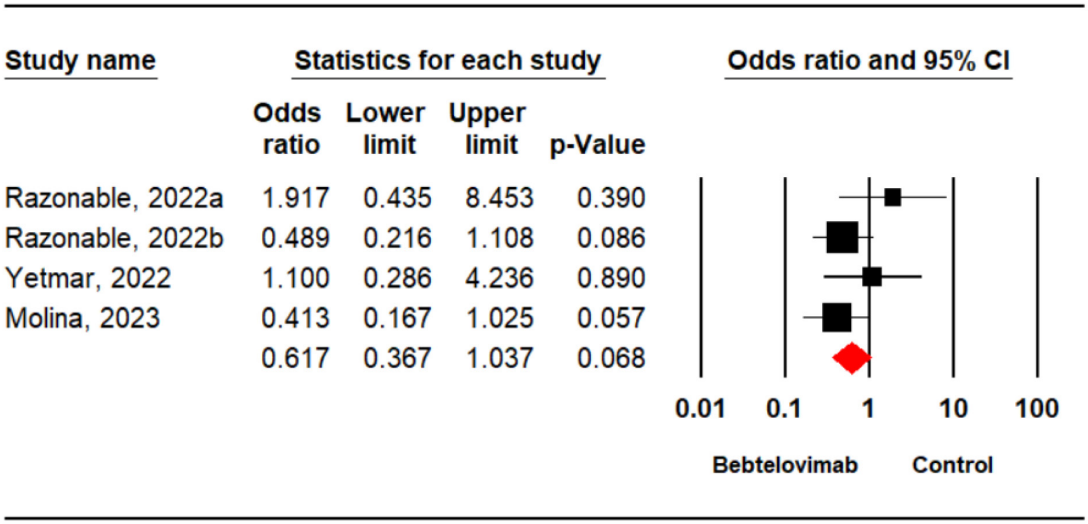


Figure 5. Forest plot of ICU Admission between the Bebtelovimab and control groups.

Bebtelovimab in reducing mortality in COVID-19 patients. In contrast, a meta-analysis by Luo *et al* (17) found Bebtelovimab significantly reduced mortality compared to standard of care. This discrepancy may stem from methodological differences, as Luo *et al* included only three studies, while our analysis incorporated 12 studies, covering a broader range of patient populations. The larger number of studies in this meta-analysis likely provides a more robust estimate of Bebtelovimab's effectiveness across diverse clinical scenarios. Additionally, Luo *et al*'s studies were conducted earlier in the pandemic, when *SARS-CoV-2* variants may have been more susceptible to monoclonal antibodies, influencing treatment outcomes. The present analysis, with 59,203 patients and more recent studies, suggests limited effectiveness in current settings dominated by resistant variants. The lack of superiority over Paxlovid, which reduced mortality and hospitalization by 89% in high-risk patients (32), or Sotrovimab, effective against COVID-19-related death (33), further indicates Bebtelovimab's limited utility in severe disease or against resistant variants. FDA restrictions on some monoclonal antibodies due to reduced efficacy against Omicron subvariants (34) contextualize these findings.

This meta-analysis of 12 studies found no significant reduction in hospitalization, composite outcome of hospitalization or death, or ICU admission with Bebtelovimab in COVID-19 patients compared to controls, aligning with Liew *et al* (16) and Luo *et al* (17). Subgroup analyses showed no advantage over Paxlovid or standard of care in preventing hospitalization (14,22,23,35). The diminished neutralizing capacity of Bebtelovimab against Omicron variants likely contributes to its limited efficacy (35). Variable treatment timing, as monoclonal antibodies are most effective early to halt

viral progression (36), may further explain the lack of benefit. Patient factors, such as age, comorbidities, or vaccination status, may influence outcomes, though data limitations prevented stratification. The single RCT's high risk of bias in randomization and blinding (Table S2) limits its reliability (14,22,23). Observational studies, comprising 11 of 12 studies, showed low to moderate bias but potential confounding (*e.g.*, vaccination status; Table S3). Some real-world studies suggested potential benefits for the composite outcome, but these were not statistically significant (14,22,23). These findings indicate limited clinical utility of Bebtelovimab in current settings. Paxlovid's superior performance in preventing hospitalization in high-risk patients (35) suggests alternative therapies may be more effective. The predominance of observational studies and their biases necessitate cautious interpretation. Further studies are needed to explore Bebtelovimab's role against evolving variants.

Several factors may explain Bebtelovimab's lack of effectiveness in reducing COVID-19 outcomes. Variable treatment timing, as monoclonal antibodies are most effective early to halt viral progression (37), likely diminished benefits. The rapid evolution of *SARS-CoV-2* variants, particularly Omicron, reduced Bebtelovimab's neutralizing capacity (38). Patient factors, such as age, comorbidities, or immune status, may influence outcomes, though data limitations prevented stratification (39). The single RCT's high bias risk, and observational studies' potential confounding necessitate cautious interpretation. These findings highlight challenges in using Bebtelovimab against evolving variants, underscoring the need for further research.

Limitations

This study has several limitations that warrant cautious interpretation. The inclusion of only one RCT, with high bias risk, limits evidence strength, while the predominance of observational studies introduces potential confounding. Variability in study designs, populations, and variant prevalence may affect pooled estimates. The small number of studies for ICU admission (four) reduces statistical power, particularly for publication bias tests. The focus on Omicron variants may not generalize to other strains, limiting applicability to future pandemics.

Conclusion

This meta-analysis of 12 studies (1 RCT, 11 observational) found that Bebtelovimab has no statistically significant effect on mortality, hospitalization, ICU admission, or the composite outcome of hospitalization or death in patients with mild-to-moderate COVID-19. Limitations include reliance on a single RCT with high bias risk (*e.g.*, randomization and blinding issues), predominance of observational studies with potential confounding (*e.g.*, variable vaccination status), moderate to high heterogeneity, and focus on Omicron variants, limiting generalizability. These findings suggest clinicians should prioritize alternative therapies (*e.g.*, Paxlovid) with proven efficacy for high-risk outpatients and policymakers should focus resources on developing variant-resistant treatments. Future research should prioritize large, well-designed RCTs targeting specific high-risk groups (*e.g.*, immunocompromised patients) and evaluate Bebtelovimab's efficacy against emerging *SARS-CoV-2* variants to guide its clinical role.

Conflict of Interest

There is no conflict of interest.

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