**Peer Review File**

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**Reviewer A**

1. In 2023, a meta-analysis with a similar theme has already been published (PMID: 37146726). Please highlight, in the discussion section, the distinctions and advantages of the current study compared to this research.

**Response:** We have thoroughly read the recommended article (PMID: 37146726). Compared to it, our article has distinct advantages. Firstly, in terms of the study population, our article covers confirmed COVID-19 patients, close contacts, and healthy individuals, while the recommended article focused only on confirmed COVID-19 patients, with a relatively narrow population scope. Secondly, our study includes a broader range of outcome indicators, such as viral load, mortality and mechanical ventilation rates, all-cause mortality, infection rates, discharge rates, and specific outcomes (such as hospitalization, emergency room visits, and mortality rates following treatment with casirivimab and imdevimab). In contrast, the mentioned article only studied mortality and hospitalization rates. Therefore, our study has a wider population coverage, more comprehensive research indicators, and is more valuable for research and publication.

In the discussion section of our text, specifically on page 16 and 17, line 341 to 347, we have added relevant content to clarify the differences between the two articles and highlight the advantages of our study.

2. Analysis based on age and the dosage of Casirivimab and Imdevimab is needed.

**Response:** Thank you for your suggestions. We have carefully considered the issues you raised and made our best efforts to analyze them. Here are the details:

Regarding medication dosages: Among the 12 studies we included, two articles (Huang and McCreary) did not provide clear medication dosages, and one article (T. Norton, S. Ali) did not specify the medication administration method. Although the remaining nine articles (as detailed in the chart below) provide medication dosages and methods, there were significant differences in both the specific administration methods and dosages used. Among these studies, five articles (Somersan Karakaya, Herman, Hooper, Horby, Weinreich) used intravenous injection, three articles (Isa, O'Brien 2021, O'Brien 2022) used subcutaneous injection, and one study employed both intravenous and subcutaneous injection methods (Portal Celhay). The dosages used varied widely, including 0.3g, 0.6g, 1.2g, 2.4g, and 8.0g. After a careful review of the included studies, we found that although some studies, such as Somersan-Karakaya, designed two groups with different dosages (2.4g and 8.0g), they did not conduct statistical analysis on certain outcome indicators according to different dosages, such as death and mechanical ventilation rates, all-cause mortality, or discharge rates. Statistical analysis was conducted on some outcome indicators based on medication dosages, but only one article reported such analysis. Therefore, it is necessary to discard these outcome

indicators such as death and mechanical ventilation rates in subgroup analysis based on medication dosages. The subcutaneous injection group only involved two dosages: 0.6g and 1.2g. However, there was a lack of data on these dosages for certain outcome indicators in the included studies. Consequently, only three outcome indicators (viral load, all-cause mortality, and adverse events) were suitable for subgroup analysis based on medication dosages. We have included the results of the subgroup analysis in the "Efficacy Outcomes" and "Discussion" sections of the manuscript and attached the corresponding forest plots. The forest plots have been renumbered for clarity. Please refer to page 10 on line 207-209, and page 11 on line 222-224, page 13 on line 258-259 and line 267-268, page 17 on line 357-363, page 22 on line 525, 528, and page 23 on line 535, 539 of the manuscript for detailed information.

*Statistical chart of different medication doses:*

| | Iv | | | | Sc | | | |
|---|---|---|---|---|---|---|---|---|
| 0.3g | Portal-Celhay[1] | | | | | | | |
| 0.6g | Portal-Celhay[1] | | | | Portal-Celhay[1] | | | |
| 1.2g | Herman[2] | Portal-Celhay[1] | Weinreich[3] | | Isa[4] | O'BrieN[5] | O'BrieN[6] | Portal-Celhay[1] |
| 2.4g | Somersan-Karakaya[7] | Hooper[8] | Portal-Celhay[1] | Weinreich[3] | | | | |
| 8.0g | Somersan-Karakaya[7] | Hooper[8] | Horby[9] | | | | | |

Regarding age, the 12 studies included in our analysis adopted different grouping methods, lacking a standardized approach for age classification. Additionally, none of the 12 studies reported the relationship between age and outcome indicators, which precluded further analysis in age. Nevertheless, we are grateful for your valuable suggestions, which have provided us with insights into future research.

3. The discussion section should include content related to clinical guidance, specifically addressing what specific guidance the current study provides for identifying the most beneficial population and scenarios in clinical practice.

**Response:** Thank you for your valuable suggestions. We have included the clinical advantages and the most beneficial population in the Discussion section, specifically on page 15, lines 301-307.

**Reviewer B**

This study assessed the efficacy and safety of casirivimab and imdevimab for treating COVID-19 and found its promising effect. Although the study provided useful information, I have several suggestions.

Major comment

1. Please divided the study subjects into two groups - patients with COVID-19 and without COVID-19 and do the meta-analysis accordingly.

**Response:** Thank you for your excellent suggestion. Dividing the study subjects into COVID-19 group and non-COVID-19 group and conducting a meta-analysis would indeed provide a clearer understanding of the effectiveness and safety of casirivimab and imdevimab in these two different populations. We have grouped the 12 included RCTs as follows: three articles analyzed the non-COVID-19 group (Herman, Isa, O'Brien(2021)) and 9 articles analyzed the COVID-19 group (Somersan-Karakaya, Hooper, Horby, Huang, McCreary, O'Brien (2022), Portal-Celhay, T. Norton, S. Ali, Weinreich). Outcome indicators involved viral load, all-cause mortality, and adverse events. After subgroup analyses, we concluded that in terms of viral load, the drug was not associated with whether the study population was COVID-19 patients or non-COVID-19 patients and whether they were hospitalized or not. While for all-cause mortality, there was a statistically significant improvement in COVID-19 patients, independent of whether they were hospitalized or not. In terms of adverse effects, the drug reduced the rate of arbitrary adverse events in non-hospitalized COVID-19 patients and reduced the rate of serious adverse events ≥ grade 3 in hospitalized COVID-19 patients. We have added relevant content to the Conclusions and Discussion section and attached the renumbered forest plot. Please refer to page 10 on line 205-207, page 11 on line 222-224, page 13 on line 256-258 and line 265-267, page 22 on line 524,527, and page 23 on line 533, 537 of the manuscript for detailed information.

2. I think you assessed the preventing effect. Please correct title after removing "treating".

**Response:** Thank you for your careful consideration of the title. The include study populations covered both uninfected individuals and close contacts. Therefore, we believe that the revised title is indeed better. We have already changed the title to "preventing and treating COVID-19."

3. For patients with COVID-19, please did the subgroup analysis according the need of hospitalization.

**Response:** Thank you very much for your professional suggestions. Among our 12 studies, the study population included both hospitalized patients and outpatients. Specifically, three studies (Somersan-Karakaya, Hooper, and Horby) focused on hospitalized patients and six studies (Huang, McCreary, O'Brien (2022), Portal-Celhay, T. Norton, S. Ali, and Weinreich) on outpatients.
The involved outcome indicators in our study were viral load, all-cause mortality, and adverse events. We have already addressed the effectiveness and safety of the drug in hospitalized and non-hospitalized patients in Question 1. The relevant content has been added to the corresponding sections of the manuscript. Specifically, you can refer to page 10 on line 205-207, page 11 on line 222-224, page 13 on line 256-258 and line 264-266, page 22 on line 524-525 and line 527-528, page 23 on line 533-534 and line 537-538 for further details.

Minor comment

1. Please define "clinical outcomes of special interest" in the method section.

**Response:** Thanks for your valuable comments. We have defined "clinical outcomes of special interest" on page 12, line 242 of the manuscript.

2. English editing is needed to improve the reading.

**Response:** Thanks the reviewers for pointing out our English language problems. We have revised the manuscript carefully to improve the expression and correct grammatical errors.

3. The quality of figures is poor.

**Response:** We are sorry for the poor quality of figures. We have improved the quality of figures in the revised manuscript.

4. Please revise the result part of abstract section. The present writing about outcomes is unclear.

**Response:** Thank you very much for your valuable feedback. We have revised the result part of the abstract section to make it clearer and understandable. The specific changes are presented on page 2 to 3, lines 39-48 of the manuscript. We appreciate your suggestions and hope that the revised version meets your expectations.

**Reviewer C**

Dear authors
Thank you for your valuable work
My comments include:
1) There are some grammar and language errors in manuscript.
For example, in abstract
- "Compared with placebo" should be "Compared to placebo"
- "the incidence of Grade 3 or severer adverse events" should be "the incidence of Grade 3 or more severe adverse events".
So, you should perform editing for your manuscript to make it more understandable to

the readers.

**Response:** Thank you very much for pointing out the grammatical and linguistic errors in our manuscript. We have revised the grammar and language errors on line 40 and line 44 of page 2. In addition, we have carefully checked the whole manuscript and made further corrections to improve the language, making it more accessible and understandable. We appreciate your feedback and hope that the revised version meets your expectations.

2) In the abstract section (results subsection)

1- The P- value of zero is not accurate in (WMD=-0.73, 95%CI [-1.09~-0.38], P=0.00). In such case, you should write the P- value to be < 0.01 and not = zero.

You should also modify this value in your result, discussion, and conclusion sections

**Response:** Thank you for pointing out the mistake in P-value. We have corrected the results of the abstract, conclusion, and discussion sections in line 43 on page 2, line 201 on page 10, line 204 on page 10, line 212 on page 11, line 226 on page 11, line 230 on page 11, line 233 on page 11, line 235 on page 12, and line 252 on page 12. We appreciate your careful review and hope that the revised version is more accurate and clearer.

2- In this part

"as well as the mortality and incidence of mechanical ventilation among patients who were seronegative at baseline (OR=0.64, 95%CI [0.42~1.00], P=0.05). Moreover, this therapy increased the discharge rates among patients who were seronegative at baseline (OR=1.54, 95%CI [1.00–2.35], P=0.05)."

As two P- values are = 0.05, and confidence intervals of OR pass by 1

So, we can say that there are no statistically significant differences between the groups compared, and this is in contrast to your inference that antibodies cas/ imde reduce mortality and incidence of mechanical ventilation and increase discharge rates.

So, you should revise your statistical tests you used and ensure the values of both P-values and CIs of OD in these outcomes.

If these values are correct, you should write that there are no statistically significant differences between groups in these outcomes and cas/ imde combination not reduce mortality and incidence of mechanical ventilation and not improve discharge rates in seronegative patients at baseline.

You should also modify this value in your result, discussion, conclusion sections, and in your key findings.

**Response:** Thank you for pointing out our statistical errors. After carefully reviewing the manuscript and data, we found that there was no statistical difference in the outcome indicators of mortality, mechanical ventilation rate, and discharge rate among patients who were seronegative at baseline. We have corrected the conclusions in the result, discussion, and conclusion sections, as well as the key findings. Additionally, we have checked other data to ensure accuracy. The specific changes are presented on line 214 to 216 of page 11, line 234 to 240 of page 12, and line 293 to 295 of page 14.

3- regarding this word "N= 27,179", you should state that this is number of participants as some readers may not understand it

**Response:** Thank you for making such a good suggestion. We have amended the

description on line 36 on page 2 to make it more understandable.

3) In the introduction section, you should write a short paragraph on a lack of efficacy of cas/ imde in treatment of COVID-19 triggered by the Omicron variant with an appropriate reference as FDA recommendations.
**Response:** Thank you for such an expert opinion. We have added the lack of efficacy of cas/imde in treatment of COVID-19 triggered by the Omicron variant to the discussion section on page 17 to 18, lines 364-373 to provide a fuller picture of the advantages and disadvantages of this antibody. .

4) in materials and methods
Line 115 (exclusion criteria,), the word review is repeated twice. You should remove one.
**Response:** We apologize for this error. We have removed the duplicate and reviewed the full manuscript again to avoid similar issues. See page 7, line 136 for details.

5) In the results section
- lines 183, and 235
as I said P- value can't be zero you should write it as <0.01
**Response:** We thank the reviewer for the issue about P-value again. We have corrected all similar issues in the manuscript.
See page 10, line 201 and page 11, line 226 and page 11, line 233 for details.

6) In the discussion section
1- Some verbs should be replaced with easier and familiar verbs. For example, unveiled, curtailed, and duo should be replaced with indicated, prevented, and combination
**Response:** Many thanks to the reviewer for the questions. We have revised the discussion section to replace some verbs with easier and familiar verbs as you suggested.

2- The main reason of disparity between some findings of your meta-analysis and the previous one is lack of variant identification. It's known that cas/imde lack antiviral activity against Omicron variant as labelled by FDA.
So, this reason should be added to the reasons you have provided.
**Response:** We have included Omicron-related content in the Discussion section and explained the mechanism by which the antibody is ineffective in in treatment of COVID-19 triggered by the Omicron variant. See page 17 to 18, lines 364-373 for details.

3- you have listed the strengths of your study, but you should mention the word "strengths" in the text of your discussion. So, readers can reach them easily by search in manuscript.
**Response:** Thank you for this friendly suggestion. We have added "strengths" to the discussion section on page 15 line 302 to help readers reach them easily by search in manuscript.

7) In conclusion section
The reduction in discharge rates should be revised as I said previously. By ensuring P-

value of this outcome.
If P- value equal to 0.05 and CI passes by 1. So, you should remove your conclusion of reduction of discharge rates by antibodies combination.
**Response:** Thank you for pointing out this issue. We have removed all conclusions of reduction of discharge rates by antibodies combination from the manuscript.

8) In references section
The citations in text (number) should be spaced from last word by one space as you adhere them to the last words.
**Response:** Thank you for the valuable comments. We have modified the citation format in the text by adding one space in the appropriate places.

9) It's better to supply a PRISMA checklist to your study as supplementary material.
**Response:** We thank the reviewer for the suggestion. We have provided a PRISMA checklist as the supplemental materials.

10) It's better to strengthen your results by citing these papers in your discussion as these papers concluded the same findings you have obtained.
1- Paper 1 that support the reduction in mortality and lacking of serious adverse effects of antibodies combination compared to other antiviral agents.
https://doi.org/10.1016/j.jcvp.2023.100151
2- paper 2 supplies the improvement in multi organ functions and WHO scale that you don't measure in your meta-analysis.
https://doi.org/10.1515/med-2023-0768
3- paper 3 that supplies the reduction in need for IMV and the decrease in the duration of this need.
https://dx.doi.org/10.12998/wjcc.v11.i26.6105
**Response:** Thank you for such a good suggestion. We have cited these papers in our discussion on page 15 line 313 to 319 to strengthen our results and enrich the manuscript .

**References**


1. Portal-Celhay C, F.-N. 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 Network Open* **2022,** *5* (8), e2225411. doi:10.1001/jamanetworkopen.2022.25411.
2. Herman GA, O. B. M., 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. *The Lancet. Infectious diseases* **2022,** *22* (10), 1444-1454.
3. Weinreich DM, S. S., Norton T, et al. , REGEN-COV antibody combination and outcomes in outpatients with covid-19. *New England Journal of Medicine* **2021,** *385*. doi:10.1056/NEJMoa2108163.
4. Isa F, F.-N. E., Meyer J, et al. , Repeat subcutaneous administration of casirivimab and imdevimab in adults is well-tolerated and prevents the occurrence of COVID-19. *International journal of infectious diseases* **2022,** *122*, 585-592.
5. O'Brien MP, F.-N. E., Musser BJ, et al. , Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. *New England journal of medicine* **2021,** *385* (13), 1184-1195.
6. O'Brien MP, F.-N. 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 - Journal of the American Medical Association* **2022,** *327* (5), 432-441.
7. Somersan-Karakaya S, M. E., Menon VP, et al. , Casirivimab and Imdevimab for the Treatment of Hospitalized Patients With COVID-19. *The Journal of infectious diseases* **2022,** *227* (1), 23-34.
8. Hooper AT, S.-K. S., McCarthy SE, et al., Casirivimab and Imdevimab Treatment in Seropositive, Hospitalized COVID-19 Patients With Non-neutralizing or Borderline Neutralizing Antibodies. 2022. doi.org/10.1101/2022.06.14.22276389.
9. Horby, P. W., Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* **2022,** *399* (10325), 665-676.