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Original Article

Molnupiravir for the treatment of COVID-19 outpatients: An updated meta-analysis

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Abstract *Background:* The majority of available data on molnupiravir come from an unvaccinated COVID-19 population. Therefore, we conducted this meta-analysis to integrate evidence from recent randomized controlled trials (RCTs) as well as observational studies stratified by vaccination status to determine the clinical efficacy and safety of molnupiravir in COVID-19 outpatients.
Methods: We searched PubMed, Embase, the Cochrane Library, medRxiv, and ClinicalTrials.gov from inception to November 2023. We conducted our meta-analysis using RevMan 5.4 with risk ratio (RR) as the effect measure.
Results: We included 8 RCTs and 5 observational studies in our meta-analysis. Molnupiravir reduced the risk of all-cause mortality (RR 0.28; 95% CI: 0.20–0.79, $I^2 = 0\%$) but did not decrease the hospitalization rate (RR 0.67; 95% CI: 0.45–1.00, $I^2 = 53\%$) in the overall population; in the immunized population, no benefits were observed. Molnupiravir lowered the rate of no recovery (RR 0.78; 95% CI: 0.76–0.81, $I^2 = 0\%$) and increased virological clearance at day 5 (RR 2.68; 95% CI: 1.94–4.22, $I^2 = 85\%$). There was no increase in the incidence of adverse events.

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Conclusions: Molnupiravir does not decrease mortality and hospitalization rates in immunized patients with COVID-19. However, it does shorten the disease course and increases the recovery rate. The use of molnupiravir will need to be considered on a case-by-case basis in the context of the prevailing social circumstances, the resource setting, drug costs, and the healthcare burden.

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Introduction

COVID-19 is an acute, infectious respiratory illness caused by the virus SARS-CoV-2. Having originated in Wuhan, China, in December 2019, SARS-CoV-2 spread rapidly across the globe and was classified by the World Health Organization (WHO) as a pandemic by March 2020. Since then, COVID-19 vaccine development has been underway, with several successful vaccines being introduced through worldwide vaccine campaigns.[1] To date, about 71% of the global population is estimated to have received at least one dose of the COVID-19 vaccine.[2] Many novel therapeutic agents, such as nirmatrelvir/ritonavir and remdesivir,[3,4] as well as repurposed medications, such as famotidine and fluvoxamine,[5,6] are also under investigation, with several already in use as part of effective treatment regimens for COVID-19.

Molnupiravir, an oral antiviral that works by producing lethal mutagenesis in SARS-CoV-2, has been licensed for the treatment of patients who have mild to moderate COVID-19 with a high risk of progression to severe disease.[7] While clinical trials on molnupiravir continue, the majority of available data come from an unvaccinated population, which shows that molnupiravir is effective in reducing the risk of mortality and hospital admission in COVID-19 outpatients but not in hospitalized patients.[8] However, a recent large trial of molnupiravir conducted in immunized outpatients demonstrated that molnupiravir does not decrease COVID-19-related hospitalization or mortality,[9] indicating the need to reevaluate existing evidence for it to be applicable in the current pandemic era in which the majority of the world population is immunized to COVID-19.[10] Therefore, in this meta-analysis, we integrate evidence from recent randomized controlled trials (RCTs) as well as observational studies stratified by vaccination status, to determine the clinical efficacy and safety of molnupiravir in COVID-19 outpatients.

Methods

This systematic review and meta-analysis, registered with PROSPERO (CRD42023390092), was conducted according to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary Table 1).[11]

Search strategy and study selection

A comprehensive search of the PubMed, Embase, Cochrane Library, medRxiv, and ClinicalTrials.gov databases was conducted to identify studies evaluating the safety and efficacy of treatment with molnupiravir in COVID-19 outpatients. The search strategy included the use of MeSH terms related to COVID-19 and molnupiravir from a period covering the inception of the databases up until January 2023 (updated November 2023). In addition, the review included a search of grey literature and the examination of reference lists from relevant articles.

All articles were at first imported into Mendeley Desktop 1.19.8 where duplicates and irrelevant articles were removed through a rigorous screening process by two independent authors. For our primary analysis, we included data from only RCTs. For our subgroup analysis based on previous immunity versus no immunity to SARS-CoV-2, we also included data from observational studies due to the paucity of data in the COVID-19-immunized population.

Data extraction and quality assessment

Data extraction was carried out using a pre-piloted extractions sheet. The primary outcomes were all-cause mortality and risk of hospitalization. The secondary outcomes consisted of the rate of no recovery (the proportion of patients with no symptomatic recovery at follow-up), the proportion of patients with virological clearance at day 5 and days 14—15, and the incidence of adverse events (AEs) and serious adverse events (SAEs). The quality of the included studies was assessed using the revised Cochrane Risk of Bias Tool (RoB 2.0) for RCTs and the Newcastle Ottawa Scale (NOS) for observational studies.

Data analysis

Data were synthesized using a random-effects model with risk ratio (RR) as the effect measure in RevMan 5.4. The Chi^2 test and the I^2 statistic were used to evaluate heterogeneity. The values of the I^2 statistic were interpreted according to the guidance present in the Cochrane Handbook for Systematic Reviews of Intervention.[12] We conducted a subgroup analysis based on previous immunity versus no immunity to SARS-CoV-2. We defined previous immunity to SARS-CoV-2 as being vaccinated, having a history of proven infection or both. We were not able to assess publication bias as the number of included studies in each of our outcomes was less than 10.

Results

Search results and risk of bias assessment

A total of 8 RCTs and 5 observational studies were included in the analysis.[9,13—22] The detailed results of the selection process are depicted in Fig. 1. The summary of the included

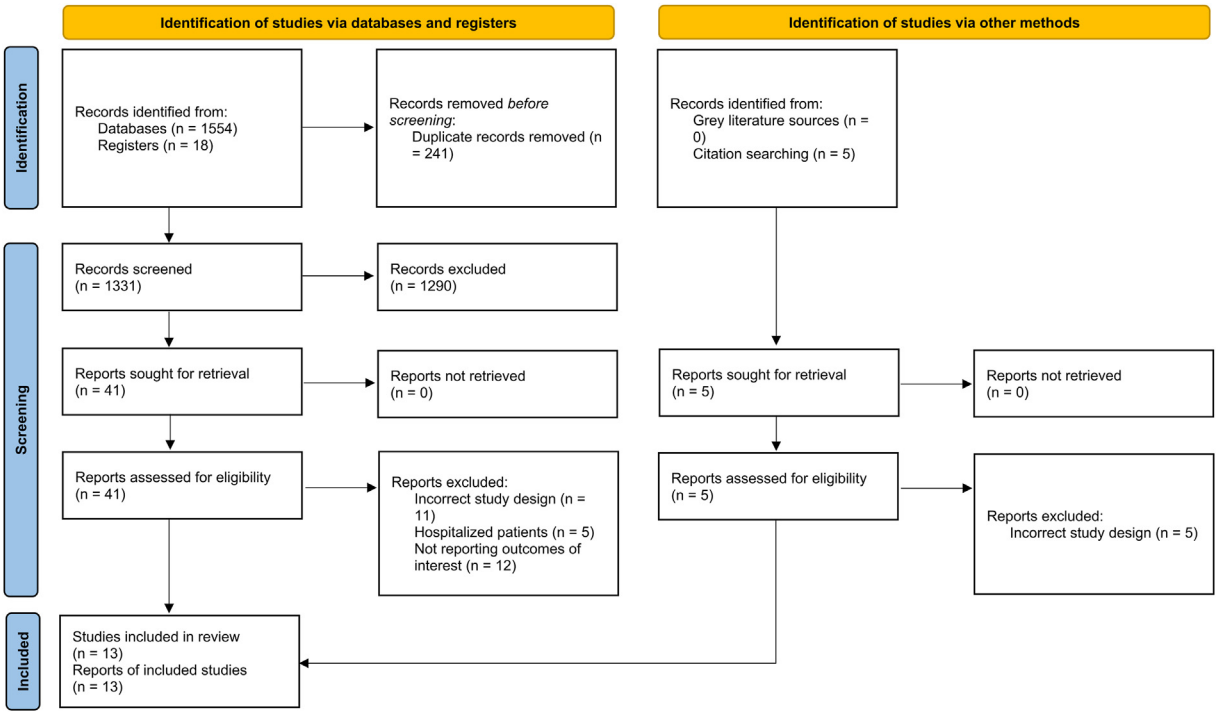

Figure 1. PRISMA 2020 flowchart.

studies can be found in Table 1. All studies were of high quality (Supplementary Table 2 and Supplementary Fig. 1).

Results of the meta-analysis

Primary outcomes

The pooled results from 7 RCTs demonstrated a significant reduction in all-cause mortality in patients receiving molnupiravir as compared to the control group (RR 0.28; 95% CI: 0.20—0.79, I^2 = 0%; Fig. 2A). When stratified according to immunity to SARS-CoV-2 and with the addition of data from observational studies, this benefit was not observed in the immunized population (RR 0.65; 95% CI: 0.25—1.69, I^2 = 0%; Supplementary Fig. 2). Molnupiravir caused a borderline non-significant reduction in the risk of hospitalization (RR 0.67; 95% CI: 0.45—1.00, I^2 = 53%; Fig. 2B). In the subgroup analysis with the incorporation of observational data, there was no benefit observed in either immunized (RR 0.93; 95% CI: 0.78—1.11, I^2 = 28%) or non-immunized groups (RR 0.92; 95% CI: 0.60—1.39, I^2 = 77%; Supplementary Fig. 3).

Secondary outcomes

There was a significantly lower rate of no recovery (RR 0.78; 95% CI: 0.76—0.81, I^2 = 0%; Supplementary Fig. 4) in patients receiving molnupiravir. Although there was a higher proportion of patients achieving virological clearance at 5 days in the molnupiravir group (RR 2.68; 95% CI: 1.94—4.22, I^2 = 85%; Supplementary Fig. 5), there was no significant difference in virological clearance at 14—15 days (RR 1.05; 95% CI: 0.99—1.12, I^2 = 63%; Supplementary Fig. 5). Molnupiravir did not increase the risk of either AEs (RR 0.99; 95% CI: 0.90—1.10, I^2 = 11%; Supplementary Fig. 6) or SAEs (RR 0.85; 95% CI: 0.61—1.19, I^2 = 18%; Supplementary Fig. 6).

Discussion

To the best of our knowledge, this is the largest meta-analysis to date that evaluated the effectiveness of molnupiravir in COVID-19 patients and also stratified according to the status of immunity in the patients. The findings of our review demonstrate that molnupiravir can reduce the risk of mortality in non-immunized patients but there is no benefit in immunized (largely vaccinated) patients. There was little evidence of the benefit of molnupiravir in either immunized or non-immunized populations. However, molnupiravir did improve recovery rates with greater virological clearance in 5 days and did not increase the incidence of adverse events.

In the PANORAMIC trial conducted by Butler et al. on 25,708 patients—of which 94% had received at least three doses of the COVID-19 vaccine—it was identified that molnupiravir does not decrease COVID-19-related hospitalization or mortality in a vaccinated population.[9] We extend their findings by stratifying all the existing evidence on the basis of the immunization status of the patients. The lack of benefit may be attributed to the newer milder strains of the SARS-CoV-2 which coupled with the fact that there is an already low event rate of mortality and hospitalization in vaccinated patients means that the baseline risk of this population for these outcomes is very low. Therefore, the use of molnupiravir in the current world scenario where most patients are already immunized to SARS-CoV-2 is likely to bring little advantage with regards to mortality or hospitalization.[23] These findings contrast directly with the

Table 1 Summary of characteristics of included studies.

Sr No	Author, year	Type of study	Population	Intervention	Comparator	Follow-up duration
Randomized Controlled Trials						
1	Caraco et al., 2021	Phase II/III double-blind RCT	• 302 adults with COVID positivity 7 days before randomization • Unvaccinated for COVID-19	• Molnupiravir 200 mg, 400 mg, 800 mg (1:1:1) • BD for 5 days	Placebo	29 days
2	Tippabholta et al., 2022	Phase III RCT	• 1220 adults with COVID-19 infection • ≥18 and ≤ 60 years	• Molnupiravir 800 mg (four 200 mg capsules) • BD for 5 days	SOC	28 days
3	Fischer et al., 2021	Phase IIa RCT	• 204 adults • ≥18 years • Unvaccinated for COVID-19	• Molnupiravir 800 mg (four 200 mg capsules) • BD for 5 days • Other intervention groups included: 200 mg molnupiravir (n = 23) and 400 mg molnupiravir (n = 62)	Placebo	28 days
4	Bernal et al., 2022	Phase III double-blind RCT	• 1433 adults with COVID positivity within 5 days before randomization • Unvaccinated for COVID-19	• Molnupiravir 800 mg (four 200 mg capsules) • BD for 5 days	SOC	29 days
5	Khoo et al., 2021(a)	Phase Ib IIa RCT	• 18 participants with COVID positivity within 5 days of symptom onset	• Molnupiravir 300 mg, 600 mg, 800 mg • BD for 5 days	Placebo or SOC	29 days
6	Khoo et al., 2022 (b)	Phase II double-blind RCT	• 180 participants with COVID positivity within 5 days of symptom onset • Both vaccinated and unvaccinated	• Molnupiravir 800 mg • BD for 5 days	Placebo or SOC	29 days
7	Butler 2022	Open-label RCT	• 26411 Non-hospitalized participants with COVID positivity within 5 days of symptom onset • >40 years • Vaccinated for COVID-19	• Molnupiravir 800 mg • BD daily for 5 days.	SOC	28 says
8	Sinha 2022	Phase IIa RCT	• 1218 patients with COVID positivity within 5 days of symptom onset • ≥18 to ≤60 years	• Molnupiravir 800 mg (four 200 mg capsules) • BD for 5 days	SOC	28 days
Observational Studies						
1.	Arbel et al., 2022	Retrospective Cohort	• 19,868 patients with confirmed SARS-COV2 • >40 years • Both vaccinated and unvaccinated	• At least one dose of molnupiravir during the study period	SOC	35 days
2.	Wong et al., 2022	Retrospective Cohort	• 60,214 patients with confirmed SARS-CoV-2 infection from Feb 26 to June 26, 2022 • ≥18 years • Both vaccinated and unvaccinated	• Molnupiravir 800 mg • BD for 5 days	SOC	41 days

(*continued on next page*)

Table 1 (*continued*)

Sr No	Author, year	Type of study	Population	Intervention	Comparator	Follow-up duration
3.	Inaba et al., 2023	Retrospective Cohort	• 294 patients with confirmed SARS-CoV-2 from May 1 2022 to Oct 2022 • ≥20 years • Vaccinated for COVID-19	• Molnupiravir	SOC	28 days
4.	Butt et al., 2023	Retrospective cohort	• 65,010 patients with confirm SARS-CoV-2 infection between 1 Jan 2022 and 31st august 2022 • >18 years • Both vaccinated and unvaccinated	• Molnupiravir 800 mg BD	SOC	30 days
5.	Bajema et al., 2023	Retrospective target trial emulation study	• 168,570 patients • Aged ≥18 years at the time of positive SARSCoV-2 test performed January 1, 2022-July 31, 2022 • Both vaccinated and unvaccinated	• Molnupiravir for 5 days	SOC	30 and 180 days

BD = Twice a day, PO = Oral administration, SOC = Standard of Care, RCT = Randomized Controlled Trial.

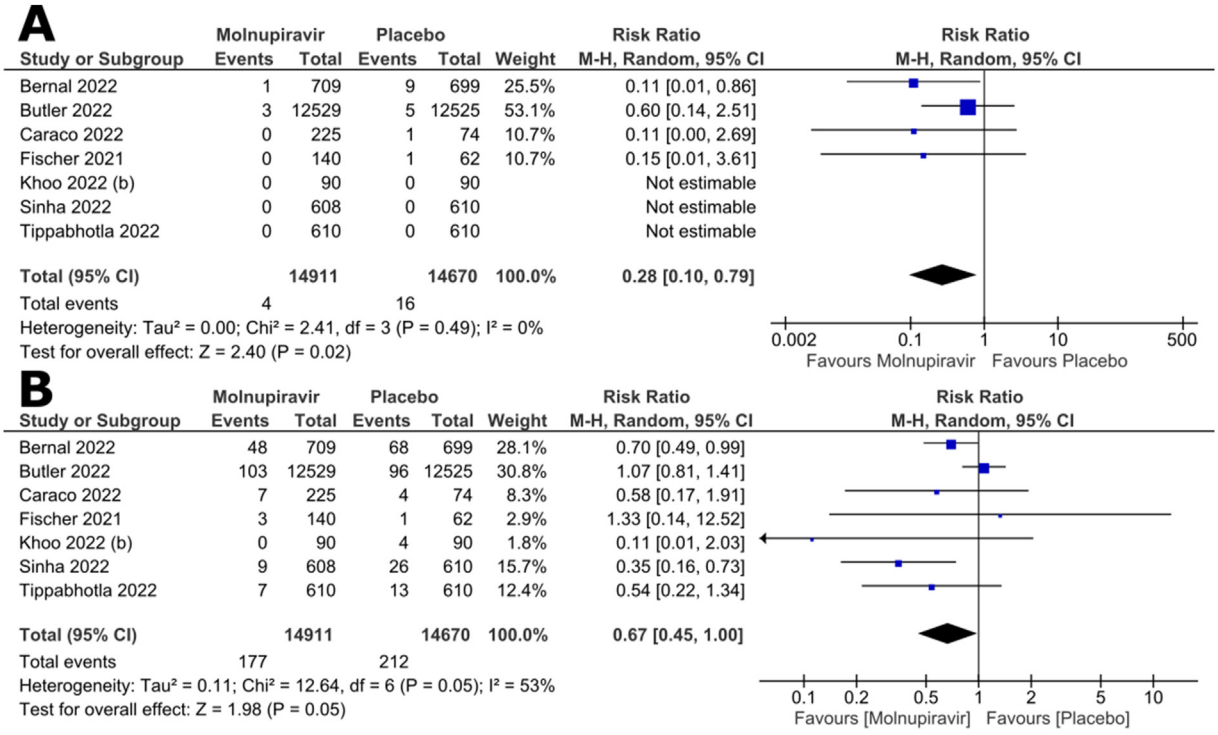

Figure 2. Effect of molnupiravir on: A) all-cause mortality; and B) risk of hospitalization in COVID-19 patients.

results of earlier molnupiravir trials which showed promise in non-immunized patients but these findings have little applicability in the current pandemic era.[8]

On the other hand, our meta-analysis did divulge that molnupiravir hastens virological clearance, and accordingly improves recovery rates in COVID-19 patients. This benefit is also consistent even in immunized patients as corroborated by the results of the PANORAMIC trial.[9] Rapid viral clearance may also contribute to a decreased risk of transmission. Additional advantages include that it is administered for only a short duration of time (5 days), and can be given on an outpatient basis, therefore, ensuring

greater compliance. However, despite its convenience, it is important to consider that molnupiravir is a costly antiviral.[24] Thus, there is a need to balance the cost of the drug with its clinical advantage of easing the disease burden on healthcare services in the long run by hastening recovery and reducing the need for follow-up. Moreover, some concerns have been raised about viral rebound after discontinuation of molnupiravir therapy which can limit long-term virological clearance[25,26]; nevertheless, some sources have shown this rebound phenomenon to be rare.[27] Furthermore, while we found that molnupiravir did not increase the incidence of adverse events, there have been potential concerns about molnupiravir generating new SARS-CoV-2 variants and causing mutations in humans due to its mechanism of action.[28] Further studies on the short-term and long-term cost-benefit analysis of molnupiravir, and virological analyses to monitor for mutagenesis are required to clarify the current role of molnupiravir.

While several prior meta-analyses have evaluated the role of molnupiravir in the treatment of COVID-19 patients,[29—32] they have also included hospitalized patients for whom molnupiravir is not approved due to a lack of benefit. Furthermore, none of these meta-analyses has investigated the efficacy of molnupiravir in the immunized population; this is an important knowledge gap to address as most of the world population already has immunity to COVID-19 either through vaccination or prior infections.[2] Therefore, our meta-analysis focused on the re-appraisal of the evidence base to answer this research question.

There are several limitations of our meta-analysis. The inclusion of real-world data possibly introduced confounding bias in our subgroup analyses; however, due to the lack of randomized controlled data in immunized patients, this was necessary and appropriate as recommended by the Cochrane guidelines.[33] Additionally, the dosing of molnupiravir given in the observational studies did not match that of the RCTs, contributing to heterogeneity in our results. Moreover, since the PANORAMIC trial had a low representation of the highest-risk patients who are the most clinically vulnerable,[9] and our analysis of the immunized subgroup of patients was greatly influenced by its results, our findings may not be applicable in this patient population.

In conclusion, treatment with molnupiravir does not decrease mortality and hospitalization rates in immunized patients with COVID-19. However, it does shorten the disease course and increases the recovery rate. The use of molnupiravir will need to be considered on a case-by-case basis in the context of the prevailing social circumstances, the resource setting, drug costs and the healthcare burden. Further large-scale RCTs, especially in patients at the highest risk from COVID-19 complications, are required to strengthen the findings of this meta-analysis, and to determine longer-term outcomes of molnupiravir.

Authors' contributions

Conception and design of study: H.A. Cheema, A. Shahid, K.Y. Lee, S. Abdul Rab; **acquisition of data**: M. Butt, U. Malik, H.A. Cheema; **data analysis and/or interpretation**: A.U. Rehman, S. Sahra, R. Sah, U. Malik, S. Abdul Rab; **drafting or writing of the manuscript**: S. Abdul Rab, U. Malik, S. Sahra, M. Butt, A. Shahid; **substantial revision or critical review of the manuscript**: H.A. Cheema, A.U. Rehman, R. Sah, K.Y. Lee.

All authors have approved the final version of the manuscript.

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Availability of data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2024.03.002.