BJPS

Brazilian Journal of Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902024e231030

Review

Should molnupiravir be used for covid-19 outpatient management in individuals at high risk for disease severity? A systematic review and meta-analysis of randomized controlled trials

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There is currently no consensus on whether to initiate molnupiravir treatment for all outpatients at high risk of severe SARS-CoV-2 infection. PubMed, Embase and Cochrane databases were systematically searched for studies that allocated COVID-19 high-risk, non-hospitalized patients to molnupiravir or a control. We computed risk ratios (RR) for binary endpoints, with 95% confidence intervals (CI), random effects model was used and a p-value <0.05 was considered as statistically significant. We analyzed data into Review Manager 5.4. We included seven randomized studies, with total of 31,569 patients, of whom 15,706 (50.8%) underwent molnupiravir therapy. Molnupiravir therapy was associated with a significant reduction in all-cause mortality rate in this population compared with control (RR 0.31; 95% CI 0.12–0.80; P= 0.02; I^2: 0%) and in hospital admission (RR 0.79; 95% CI 0.66–0.94; P= 0.007; I^2: 47%). The use of molnupiravir was not associated with a significant reduction of all-cause mortality or hospital admission for subgroups including only patients with cardiovascular disease (RR 0.79; 95% CI 0.45–1.39; P= 0.41; I2: 0%) and diabetes (RR 0.85; 95% CI 0.51–1.42; P= 0.32; I2: 0%). Our results suggest that molnupiravir use might be considered in high-risk of severity disease, non-hospitalized patients.

Keywords: Molnupiravir. COVID-19. High-risk patients.

ABBREVIATIONS

CI – Confidence interval
COVID-19 – Coronavirus Disease 2019
CTRI–Clinical Trials Registry – India
DM–Diabetes Mellitus
GRADE – Grading of Recommendation, Assessment, Development, and Evaluations
HD – Heart Disease
NCT –National Clinical Trial
NR – Not Reported
P – P-value
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RevMan: Cochrane Review Manager software
RoB-2 – Revised Cochrane risk-of-bias tool for randomized trials
RSV– Respiratory Syncytial Virus
RCT – Randomized Controlled Trial(s)
RdRp – RNA-dependent RNA polymerase
RR- relative risks
SoC- Standard of care
VEEV – Venezuelan Equine Encephalitis Virus
WHO – World Health Organization

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INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic rapidly emerged as a serious threat to public health worldwide, with over 698 million confirmed cases and more than 6,9 million deaths reported to date (WHO, 2023). Despite the increasing number of vaccination and booster doses, numerous new COVID-19 cases continue to be reported (Butler *et al.*, 2023). While most patients with COVID-19 present with mild or moderate symptoms and experience a self-limiting disease, a subset of patients, particularly those with specific comorbidities classified as risk factors for critical illness, may progress to severe COVID-19 (Rufaida *et al.*, 2021).

Molnupiravir is an oral antiviral drug categorized as a ß-D-N4-hydroxycytidine prodrug. It has demonstrated efficacy against a range of viral pathogens, including influenza A and B viruses, Venezuelan equine encephalitis virus (VEEV), respiratory syncytial virus (RSV), norovirus, and human coronaviruses (Wen *et al.*, 2022). Specifically concerning its activity against COVID-19, molnupiravir targets the RNA-dependent RNA polymerase (RdRp), a vital protein required for virus replication (Jayk Bernal *et al.*, 2022).

Molnupiravir has recently attracted scientific attention due to its ability to decrease mortality in COVID-19 infected patients (Singh *et al.*, 2021). Although it appears to have the lowest efficacy compared to other drugs, only molnupiravir can be administered to patients with renal impairment, besides causing considerably less drug interactions (Pourkarim, Pourtaghi-Anvarian, Rezaee, 2022; Tian *et al.*, 2022).

Molnupiravir is safe and well tolerated in all doses prescribed (200, 400 and 800 mg twice daily). The most frequently observed adverse event was headache and diarrhea, there was no serious adverse events (Amani, Zareei, Amani, 2022).

Molnupiravir, being administered orally and effective against newer COVID-19 variants, is more practical and convenient for administration in outpatients fulfilling the unmet need for safe and effective oral drugs. Several studies have demonstrated the efficacy of molnupiravir in the context of COVID-19, showing both antiviral effectiveness and a reduction in mortality rates (Jayk Bernal *et al.*, 2022; Khoo *et al.*, 2023; Wong *et al.*, 2022). However, not all studies have reported such findings, and there has been considerable heterogeneity regarding the characteristics of the included patients, such as vaccination status, outpatient or hospitalized status, presence of risk factors for severe disease, and the timing of drug administration (Butler *et al.*, 2023).

In light of this controversy, we performed a meta-analysis evaluating the efficacy of molnupiravir 800mg twice a day for 5 days compared with standard of care or placebo in patients with COVID-19 and at least one risk factor for developing severe illness.

Several other meta-analyses have explored the efficacy of molnupiravir. However, our meta-analysis stands out as the only one exclusively focused on the population at high risk of severe infection. Malin *et al.* (2023) investigated the efficacy of molnupiravir in individuals with suspected or laboratory-confirmed SARS-CoV-2 infection, encompassing both outpatients and hospitalized patients, regardless of the presence of comorbidities. In contrast, our meta-analysis targeted a distinct population, specifically outpatients with laboratory-confirmed SARS-CoV-2 infection and comorbidities, including those that elevate the risk of severe SARS-CoV-2 infection, such as cardiopathy and diabetes mellitus.

In Gao *et al.*'s (2023) meta-analysis, they analyzed both healthy and unhealthy patients, including a subgroup at risk for severe disease comorbidities. However, they did not find significant results in the analyzed outcomes. Conversely, our meta-analysis focused solely on patients with high-risk comorbidities for severe disease, yielding significant improvements in the outcomes.

Tian *et al.* (2022), Sun *et al.* (2023), Beran *et al.* (2024), and Huang *et al.* (2023) did not specifically investigate patients with comorbidities, whereas our meta-analysis is specifically centered on this population. In their paper, Mali *et al.* (2023) did not conduct statistical analysis.

MATERIAL AND METHODS

Eligibility criteria and data extraction

Studies with the following characteristics were included: (1) published randomized controlled trials

(RCTs); (2) with at least 1 arm with molnupiravir; (3) with a control group (either placebo-controlled or standard of care-controlled); (4) any reported population at high risk for the development of severe illness from COVID-19, accordingly to World Health Organization (WHO, 2020) (age > 60 years; active cancer; chronic kidney disease; chronic obstructive pulmonary disease; obesity; cardiovascular disease; or diabetes mellitus); and (5) with acute mild-to-moderate RT-PCR-confirmed SARS-CoV-2 infection, symptoms onset occurring within a maximum of 7 days before randomization, mild or moderate illness was determined on the basis of definitions of WHO. There was no restriction concerning the date of publication, or language. We excluded studies with patients already hospitalized and unpublished studies.

Two authors (F.V.Z and A.C.F.F.S) independently reviewed the reports to determine their eligibility through consensus. All potentially relevant articles were reviewed by reading the full texts to identify eligible trial reports after excluding irrelevant studies. Data were manually extracted from eligible full-text articles.

Search strategy

MEDLINE (through PubMed), Embase, and Cochrane Library were systematically searched from inception to March 2024. References of eligible papers and systematic reviews were also searched for additional studies. We adopted a broad search strategy to maximize the identification of all studies that involved molnupiravir use, even if patients with a high risk of complications were not reported in the manuscript text.

The search strategy (title and abstract) was as follows (COVID-19 OR "coronavirus disease" OR "SARS-COV-2") AND (molnupiravir OR "RdRp inhibitor" OR "RNA-dependent RNA polymerase inhibitors" OR Lagevrio) AND (Non-Hospitalized OR Nonhospitalized OR outpatients). This systematic review and meta-analysis was registered in PROSPERO under the protocol CRD42023420400.

Endpoints and subgroup analysis

We extracted the following data from individual studies: (1) study characteristics: authors, study design, location, trial name, trial number of registration, sample size per group, study population, length of follow-up, percentage of patients at risk of severe disease, molnupiravir's dose, and SARS-CoV-2 variants; (2) patient characteristics: mean age and standard deviation, gender, comorbidities, the total number of molnupiravir-treated patients, total number of placebo-treated patients, and vaccination status; (3) outcomes: death and/ or hospital admission during the follow-up; and (4) subgroups: cardiovascular disease and diabetes.

To evaluate if an individual study had a stronger influence on the result, we conducted a leave-one-out sensitivity analyses of the all-cause mortality during COVID-19 treatment in high-risk patients.

Sensitivity analysis

We also evaluated the impact of individual studies on the combined results through successive leave-one-out analysis, ensuring the stability of the pooled analysis effect (Deeks *et al.*, 2023).

Quality assessment and quality of evidence

According to the recommendations from the Cochrane Handbook for Systematic Reviews of Interventions, we used the revised Cochrane risk-of-bias tool for randomized trials (RoB-2) to assess the risk of bias in RCTs (Sterne *et al.*, 2019). We selected mortality as the outcome for analyzing RoB-2, as this outcome exhibited the most statistically significant difference in our analysis. Disagreements were resolved through consensus after discussing reasons for discrepancy. The information was presented as a risk of bias graph and a risk of bias summary figure (Supplemental Figure 1).

The quality of evidence was evaluated following the Grading of Recommendation, Assessment, Development, and Evaluations (GRADE) guidelines (Balshem *et al.*, 2011) (Supplemental Figure 2).

Assessment of bias across studies: publication bias

No quantitative assessment of small studies or publication bias, such as funnel plot, was attempted

because the number of studies included in the meta-analysis was lower than ten.

Statistical Analysis

This meta-analysis was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocol (PRISMA) (Moher *et al.*, 2009). We analyzed data into the Cochrane Review Manager software (RevMan 5.4). Binary endpoints were summarized using the Mantel-Haenszel test with a random effects model, relative risks (RRs) with 95% confidence interval (CI) were calculated.

We assessed for heterogeneity using Cochrane's Q statistic and Higgins and Thompsons' I^2 statistics (Higgins *et al.*, 2023). The significance of the pooled ratios was determined by the Z test, and a p-value lower than 0.05 was considered statistically significant. A sensitivity analysis was conducted to assess the impact of each study on the overall pooled estimate R software environment, version 4.3.0 (R Foundation for Statistical Computing), was utilized for this analysis.

RESULTS

Figure 1 illustrates the overall protocol for the study and details the number of studies excluded. 370 studies were screened, and 47 studies were full text reviewed. We included 7 RCTs, comprising 31,569 patients: 15,548 (49.2%) in the molnupiravir group and 15,706 (50.8%) in the control group. The follow-up was between 28 and 30 days.

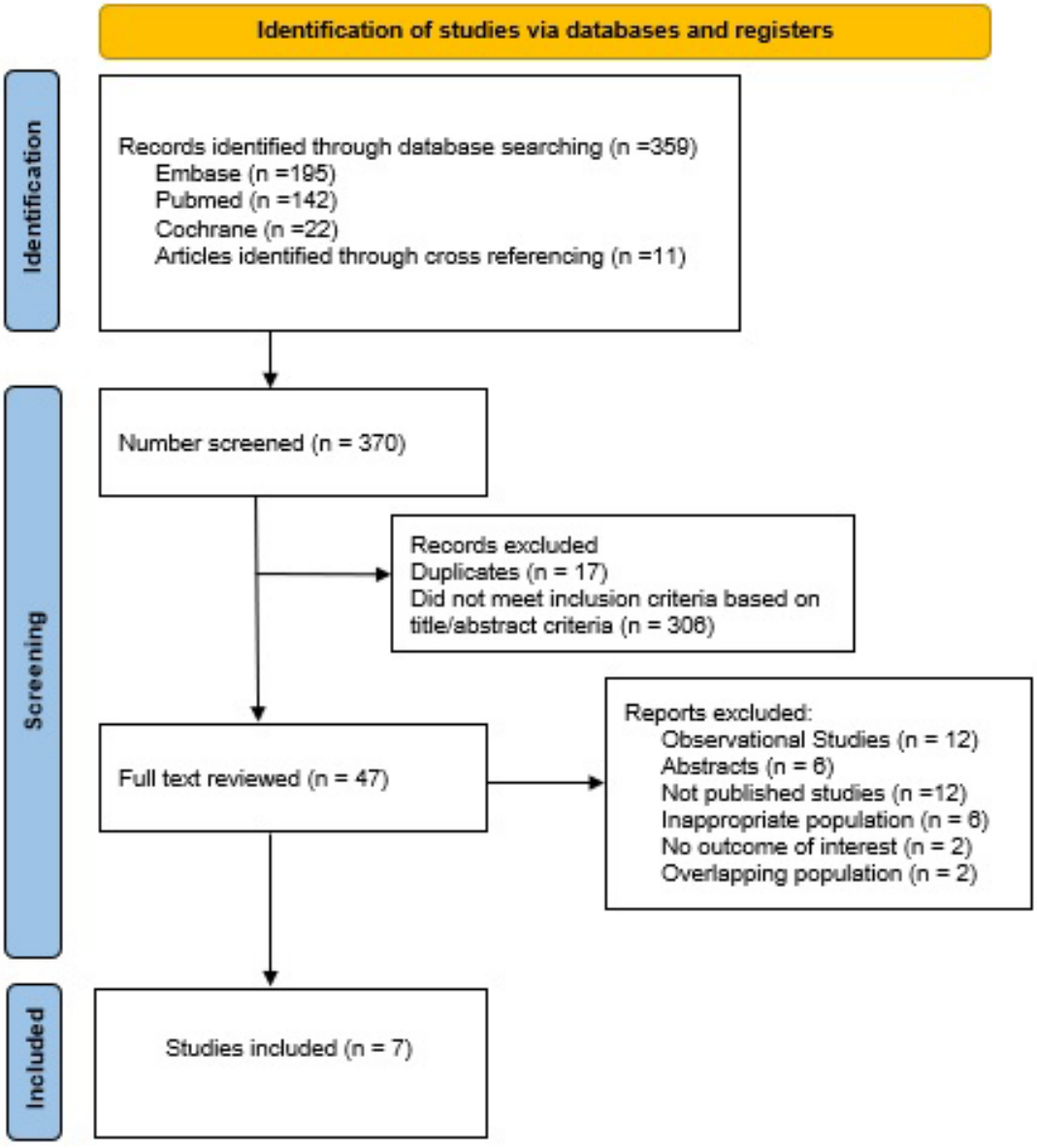

FIGURE 1 - PRISMA flow diagram of study screening and selection.

We excluded the AGILE-CST phase 1 and phase 2 studies because they did not report whether their populations included patients at high risk of disease severity (Khoo *et al.*, 2021; Khoo *et al.*, 2023). The mean age ranged from 35.0 to 72.2 years, with 17,649 (55.9%) female individuals. Over 29,113 (92,2%) had at least one factor of risk of severe disease, 2,345 (7.4%) patients had heart disease and 3,514 (11.1%) had diabetes mellitus, Tippabhotla *et al.*, 2022 did not provide data regarding the percentage or number of patients with cardiopathy or diabetes mellitus. The key characteristics of the included studies are summarized in Table I.

Molnupiravir therapy was associated with a significant reduction in all-cause mortality compared with control (RR 0.31; 95% CI 0.12–0.80; P= 0.02; I^2: 0%), as demonstrated in figure 2A.

TABLE I - Baseline characteristics included studies

Study	Location	Clinical trials registration number	Trial name	Drug Dose	Sample Size	Female %	Age, y., mean (SD)	Follow-up	Control	Patients at risk of severe disease %	DM§ N (%)	HD§ N (%)	Vaccination status	SARS-CoV-2 variants
Butler 2023	The United Kingdom	ISRCTN30448031	PANORAMIC	MP 800 mg twice daily for 5 d	25783	58.6	56.6 (12.6)	28 days	Standard of care	100	2988 (11.6)	1951 (7.5)	92.6%	Omicron
Caraco 2022	The United States, Brazil, Chile, Colombia, France, Germany, Israel, Russia, South Africa, Spain, and The United Kingdom.	NCT04575597	MOVe-OUT phase 2/3	MP 200 mg twice daily for 5 d; MP 400 mg twice daily for 5 d; and MP 800 mg twice daily for 5 d	302	47.4	49.2 (16.5)	29 days	Placebo	75.2	50 (16.6)	25 (8.3)	Unvaccinated	Nextstrain: 20A; 20B; 20C; and 20G
Fischer 2022	The United States	NCT04405570	NR	MP 200 mg twice daily for 5 d; MP 400 mg twice daily for 5 d; MP 800 mg twice daily for 5 d	202	51.5	40.1 (13.6)	28 days	Placebo	60.4	20 (10.0)	28 (14.0)	Unvaccinated	NR
Jayk Bernal 2022	The United States, Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Israel, Italy, Japan, Mexico, Russia, Philippines, Poland, South Africa, Spain, Sweden, Taiwan, Ukraine, and The United Kingdom	NCT04575597	MOVe-OUT phase 2	MP 800 mg twice daily for 5 d	1433	51.3	43.0 (11.8)	29 days	Placebo	100	228 (15.9)	167 (11.7)	Unvaccinated	Delta; Mu; Gamma
Johnson 2022	The United States, Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Israel, Italy, Japan, Mexico, Russia, Philippines, Poland, South Africa, Spain, Sweden, Taiwan, Ukraine, and The United Kingdom	NCT04575597	MOVe-OUT phase 3	MP 800 mg twice daily for 5 d	1411	51.4	43.5 (11.8)	29 days	Placebo	100	224	164	Unvaccinated	Delta; Mu; Gamma
Sinha 2022	India	CTRI/2021/05/033739	NR	MP 800 mg twice daily for 5 d	1218	31.6	35.0 (10.8)	28 days	Standard of care	4.1	4 (0.3)	10 (0.8)	NR	NR
Tippabhotla 2022	India	CTRI/2021/07/034588	NR	MP 800 mg twice daily for 5 d	1220	38.4	36.5 (11.0)	28 days	Standard of care	7.4	NR	NR	NR	NR

RCT: randomized controlled trial; MP: molnupiravir; d: days; †: Data are mean (SD), n (%), or median (IQR); y: years old; §: Data in total population; DM: Diabetes mellitus; HD: Heart disease.

Table 1. Baseline characteristics included studies.

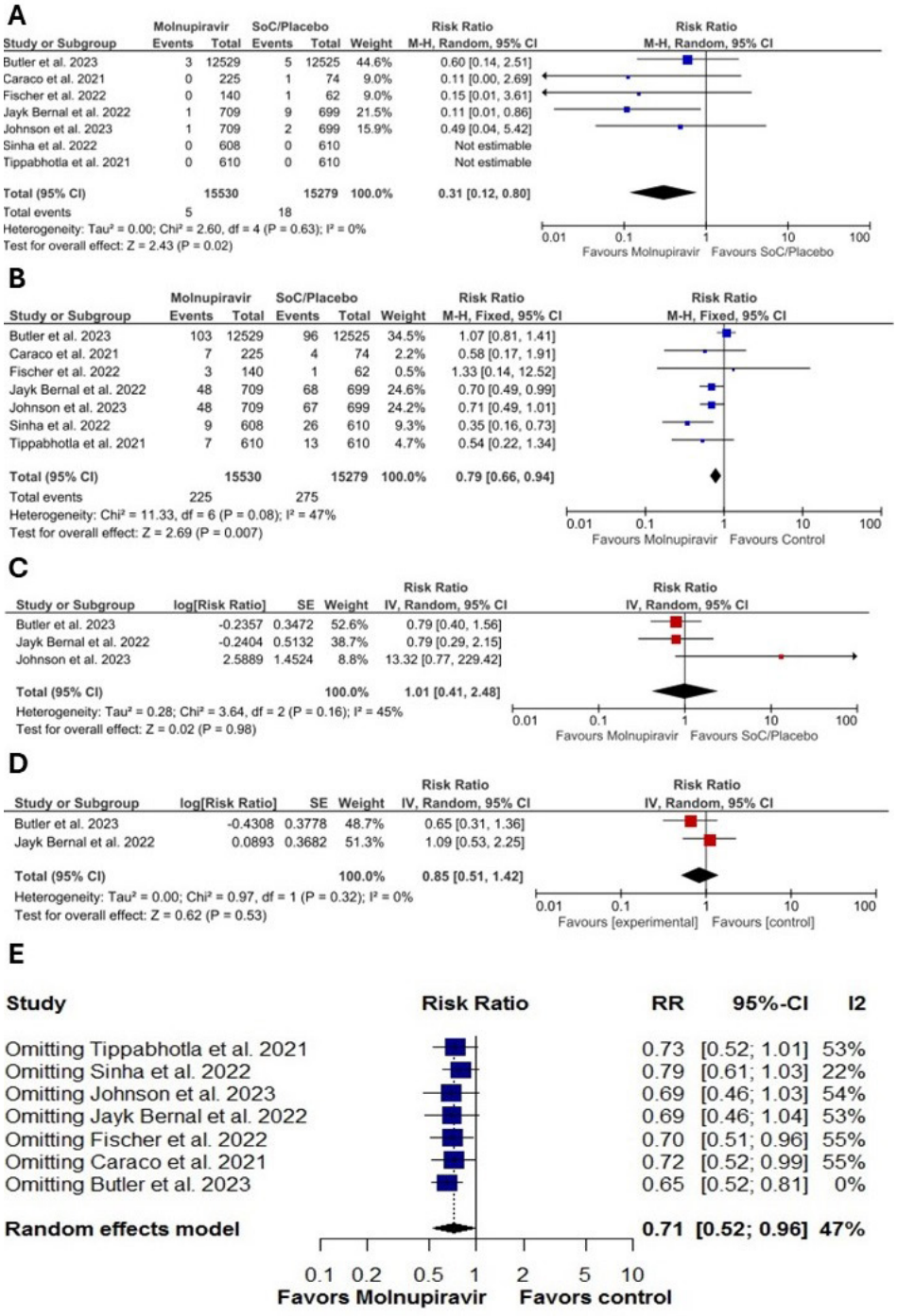

FIGURE 2 - A. Forest plot analysis for the outcome of all-cause mortality in high-risk patients during COVID-19 treatment. There is a significant reduction in mortality compared with the control group. B. Forest plot analysis for the outcome of hospital admission in high-risk patients during COVID-19 treatment. There is a significant reduction in hospitalization compared with the control group. C. Forest plot analysis for the outcome of all-cause mortality and/or hospital admission in cardiovascular disease patients during COVID-19 treatment. There is not a significant reduction in the composite outcome of all-cause mortality or hospitalization compared with the control group. D. Forest plot analysis for the outcomes of all-cause mortality and hospital admission in diabetes mellitus patients during COVID-19 treatment. There is not a significant reduction in the composite outcome of all-cause mortality or hospitalization compared with the control group. E. Forest plot analysis for sensitivity analysis of the outcome all-cause mortality during COVID-19 treatment. Favors molnupiravir group.

As illustrated by figure 2B, molnupiravir therapy was associated with a reduction in hospital admission compared with control (RR 0.79; 95% CI 0.66–0.94; P= 0.007; I2: 47%). As demonstrated below in Figure 2C, there was a reduction, not statistically significant, in all-cause mortality and hospital admission in patients with cardiovascular diseases infected with COVID-19 treated with molnupiravir 800mg twice a day for 5 days (RR 0.79; 95% CI 0.45–1.39; P= 0.41; I2: 0%). There was a no significant reduction in all-cause mortality and hospital admission in patients with diabetes mellitus infected with COVID-19 during molnupiravir treatment (RR 0.85; 95% CI 0.51–1.42; P= 0.32; I2: 0%) (Figure 2D).

We performed a leave-one-out sensitivity analysis, using random effect model, for both mortality and hospital admission endpoints. Overall, there was no change in the statistical significance of outcome in each of the leave-one-out tests, for the mortality endpoint. Changes in heterogeneity were observed when omitting the Butler *et al.* (2023), which resulted in decrease from I^2 = 47% to I^2 = 0%. The reduction in heterogeneity may be attributed to differences in Sars-Cov-2 variants between Butler *et al.* (2023) studied the Omicron variant, while the other investigations focused on the Delta, Mu, and Gamma variants. The sensitivity analyses for the primary endpoints are presented in Figure 2E.

RoB-2 evaluation of all-cause mortality outcome demonstrated low risk of bias in all domains, however, Fischer *et al.* (2022) was evaluated as some concerns in bias in selection of the reported results. Sinha *et al.* (2022) and Tippabhotla *et al.* (2022) demonstrated some concerns in bias due deviations from intended interventions. GRADE evaluation demonstrated high-quality evidence in all outcomes.

DISCUSSION

This systematic review and meta-analysis included seven RCTs, encompassed a total of 31,569 patients. The objective of this meta-analysis was to evaluate the efficacy of molnupiravir 800mg twice a day for five days in outpatients at high risk for severe COVID-19. The findings of this study revealed the following associations: 1) reduction in all-cause mortality compared with control group, 2) statistically significant decrease in hospital admission. Besides that, 3) in a subgroup analysis specifically focusing on patients with cardiovascular disease or diabetes, molnupiravir was associated with a reduction, without statistical significance, in the composite outcome of hospital admission and all-cause mortality.

The reduction in all-cause mortality in Sars-Cov-2 infected patients treated with molnupiravir without a serious adverse effect is a paradigm shift in COVID-19 infected patients, mainly in high-risk outpatients. Our study demonstrated a similar result of a reduction in mortality when compared with Wen *et al.* (2022), Jayk Bernal (2022), Cegolon *et al.* (2023), Lui *et al.* (2023), Wai *et al.* (2023), Yip *et al.* (2023) and Xie *et al.* (2023), and showed a different result when compared with Butler *et al.* (2023) (Adjusted odds ratio 1.06; 95% CI 0.81–1.41), which did not find a significative result due to different COVID-19 variants. Cegolon *et al.* (2023) analyzed 386 high-risk COVID-19 patients, and observed that patients receiving nirmatrelvir/ritonavir, sotrovimab or molnupiravir also had fewer complications and hospitalizations compared with standard of care (Cegolon *et al.*, 2023).

Overall, evidence supporting the effectiveness of molnupiravir when analyzing confounding and groups with different baseline characteristics such as vaccination status, SARS-CoV-2 variants, reinfections, and others specific groups, is limited. Vaccination remains the most important medical intervention available to lower the risks of hospitalization and death from COVID-19 (Pourkarim, Pourtaghi-Anvarian, Rezaee, 2022), but early treatment soon after the onset of symptoms with drugs such as molnupiravir has also been shown to be effective (Cegolon *et al.*, 2023). Furthermore, vaccination may not fully protect immunocompromised patients (Tian *et al.*, 2022). The mechanism of action of molnupiravir is independent of mutations in the spike protein, a protein which can affect the efficacy of vaccination and other drugs (Singh *et al.*, 2021).

The major strength of the present meta-analysis compared with other similar studies is that it focused on the analysis of patients with a high risk of complications and analyzed the efficacy of molnupiravir in the

subgroups of cardiovascular disease, and diabetes mellitus. Patients with at least one risk factor might have more benefits from the drug than healthier patients. Previous systematic reviews, such as Gao *et al.* (2023), Mali *et al.* (2023) and Weng *et al.* (2022) did not focused on high-risk infected patients.

Two other trials (NCT05595824 and NCT05459532) have been conducted in outpatients with COVID-19 and at least one risk factor for the development of severe illness. In some years, we might have new data on the effectiveness of molnupiravir in these patients. Some studies conducted in India have not yet reported their results, hence they were not included in our meta-analysis. These studies are identified as follows: CTRI/2021/08/035424, CTRI/2021/06/033938, CTRI/2021/05/033904, CTRI/2021/05/033693, CTRI/2021/06/033992, CTRI/2021/06/034130, CTRI/2021/06/034015, CTRI/2021/06/034220, CTRI/2021/05/033736, and CTRI/2021/05/033864.

This study had several limitations that should be acknowledge. First, the potential confounding effects of COVID-19 vaccination could not be assessed due to the absence of studies that specifically analyzed this variable in the high-risk group. Further research is required to elucidate these effects, considering factors such as vaccination specificities. Second, eligible studies included diverse variants of COVID-19. The PANORAMIC trial (Butler *et al*., 2023), Cegolon *et al.* (2023) and Lui *et al.* (2023) analyzed patients infected with omicron variant, but Jayk Bernal *et al.* (2022) mainly included patients infected with delta, gamma, and mu variants. Third, we struggled with the inability to investigate more high-risk subgroups of patients due to the utilization of study-level data instead of individual patient data.

CONCLUSIONS

Our study supports, with high-quality evidence, the use of molnupiravir for COVID-19 outpatients who have at least one risk factor for the development of severe illness, even in fully vaccinated population, molnupiravir might be recommended for the prevention of disease severity.

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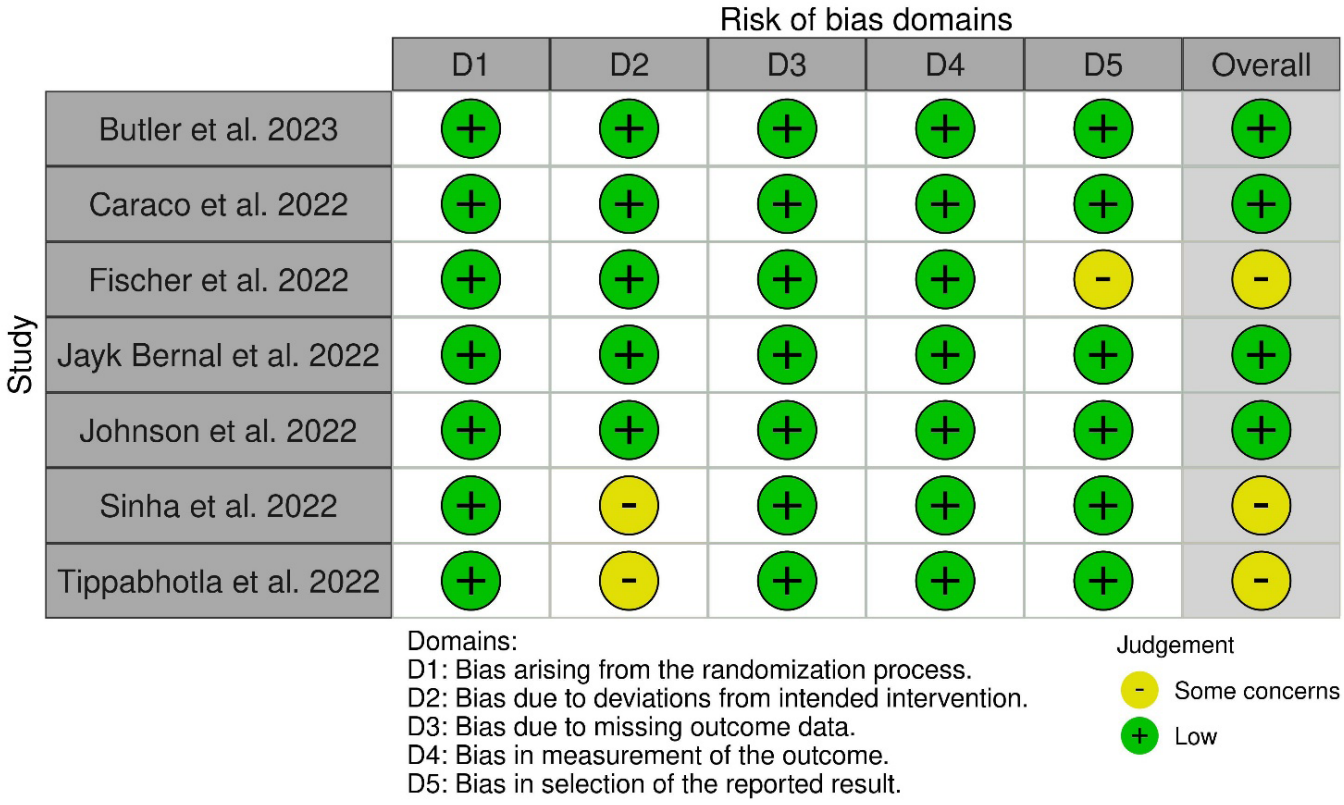
Received for publication on 23rd January 2024
Accepted for publication on 21st March 2024

SUPPLEMENTARY MATERIALS



SUPPLEMENTAL FIGURE 1 - RoB-2 – Revised Cochrane risk-of-bias tool for randomized trials.

Author(s): Fernanda Valeriano Zamora, Ana Clara Felix de Farias Santos, Andres Villca Zamora
Question: Molnupiravir compared to SoC or Placebo for high-risk COVID-19 patients
Setting: P: Individuals from populations identified as having a heightened susceptibility to severe COVID-19 illness, as delineated by the World Health Organization (WHO, 2020), including those aged 60 years and above, individuals with active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, cardiovascular disease, or diabetes mellitus, who present with acute mild-to-moderate symptoms and have tested positive for SARS-CoV-2 via RT-PCR within seven days of symptom onset. I: Molnupiravir 800 mg twice daily for 5 days C: Placebo or Standard of care O: All-cause mortality, hospital admission, all-cause mortality and/or hospital admission in subgroups (heart disease and diabetes mellitus) T: RCTs studies T: No time restriction
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Molnupiravir	SoC or Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: mean 29 days)												
7	randomised trials	not serious	not serious	not serious	not serious	none	5/15530 (0.0%)	18/15279 (0.1%)	**RR 0.31** (0.12 to 0.80)	**1 fewer per 1.000** (from 1 fewer to 0 fewer)	⨁⨁⨁⨁ High	CRITICAL
Hospital admission (follow-up: mean 29 days)												
7	randomised trials	not serious	not serious	not serious	not serious	none	225/15530 (1.4%)	275/15279 (1.8%)	**RR 0.79** (0.66 to 0.94)	**4 fewer per 1.000** (from 6 fewer to 1 fewer)	⨁⨁⨁⨁ High	CRITICAL
All-cause mortality and hospital admission in cardiovascular disease patients (follow-up: mean 29 days)												
2	randomised trials	not serious	not serious	not serious	not serious	none			**RR 0.79** (0.45 to 1.39)	**1 fewer per 1.000** (from 1 fewer to 0 fewer)	⨁⨁⨁⨁ High	IMPORTANT
All-cause mortality and hospital admission in diabetes mellitus patients (follow-up: mean 29 days)												
2	randomised trials	not serious	not serious	not serious	not serious	none			**RR 0.85** (0.51 to 1.42)	**1 fewer per 1.000** (from 1 fewer to 1 fewer)	⨁⨁⨁⨁ High	IMPORTANT

CI: confidence interval; **RR:** risk ratio

SUPPLEMENTAL FIGURE 2 - GRADE – Grading of Recommendation, Assessment, Development, and Evaluations.