Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Antimicrobial Agents 62 (2023) 106870

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

Efficacy and Safety of Molnupiravir Treatment for COVID-19: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Fangyuan Tian[a,b,*], Qiyi Feng[c], Zhaoyan Chen[a,*]

[a] Department of Pharmacy, West China Hospital, Sichuan University, Chengdu, China
[b] Department of Epidemiology and Health Statistics, West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu, China
[c] Precision Medicine Research Center, Sichuan Provincial Key Laboratory of Precision Medicine, West China Hospital, Sichuan University, Chengdu, China

ARTICLE INFO

Article history:
Received 16 January 2023
Accepted 21 May 2023

Editor: Dr Y-W Lin

Keywords:
COVID-19
Molnupiravir
Randomized controlled trials
SARS-CoV-2

ABSTRACT

Introduction: There are currently some differences in the research results of molnupiravir. This study aimed to evaluate the efficacy and safety of molnupiravir in the treatment of COVID-19.
Methods: PubMed, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), ClinicalTrials.gov, ICTRP (International Clinical Trials Registry Platform) and medRxiv were searched to identify relevant randomised controlled trials (RCTs) from inception to 1 January 2023. The Cochrane risk of bias tool for randomised trials was used to assess the bias risk of the included studies. Revman 5.4 software was used for meta-analysis.
Results: Nine RCTs were included, including 31 573 COVID-19 patients, of whom 15 846 received molnupiravir. The meta-analysis results showed that the molnupiravir group had a higher proportion in terms of clinical improvement (Day 5 RR 2.41, 95% CI 1.18–4.92; Day 10 RR 1.45, 95% CI 1.04–2.01) and real-time polymerase chain reaction negativity (Day 5 RR 2.78, 95% CI 1.38–5.62; Day 10 RR 1.18, 95% CI 1.07–1.31). However, no significant difference was observed between the two groups in terms of mortality, hospitalisation, adverse events and serious adverse events.
Conclusions: Molnupiravir can accelerate the rehabilitation of COVID-19 patients, but it does not significantly reduce mortality and hospitalisation.

1. Introduction

The COVID-19 (coronavirus disease 2019) pandemic is the largest public health event that mankind has faced in the past century and a serious threat to the safety and health of human life worldwide [1,2]. According to the statistics of the World Health Organization, as of 11 January 2023, there have been 660.3 million confirmed cases of COVID-19 worldwide and 6.6 million deaths since the outbreak in December 2019 [3]. A study from the UK on > 2000 COVID-19 inpatients showed that 29% of the patients fully recovered 1 year after COVID-19 infection, and 71% of the patients had sequelae. The most common sequelae are fatigue, muscle pain, body slowing, poor sleep and dyspnoea [4]. A study on Chinese patients showed that 55% of inpatients still had sequelae, including fatigue, muscle weakness, dyspnoea and sleep difficulties 2 years after COVID-19 infection. Two years later, the health status of COVID-19 patients was significantly lower than that of the general population [5]. Therefore, it is very important to determine an effective treatment plan for patients with COVID-19 [6] and to use antiviral drugs early to alleviate COVID-19-related symptoms, which can improve patients' COVID-19 sequelae and reduce the risk of death and hospitalisation [7].

At the initial stage of the outbreak, some broad-spectrum antiviral drugs and drugs targeting other specific viruses—such as remdesivir, chloroquine phosphate and favipiravir—played an important role in the fight against the epidemic [8]. With the deepening understanding of the COVID-19 epidemic and SARS-CoV-2, great progress has been made in the research and development of oral small molecule drugs for SARS-CoV-2, which has made important contributions to the prevention and control of the epidemic [9]. At present, the research and development of oral small molecule drugs for COVID-19 are mainly 3CLpro (3C-like protease) and RdRp (RNA-dependent RNA polymerase) [10]. Molnupiravir (MK-4482, EIDD-2801), developed by Merck, is a prodrug and oral antiviral drug of β-D-N4 hydroxycytidine [11]. It is an RdRp inhibitor that was initially used to treat Venezuelan equine

* Corresponding authors: Department of Pharmacy, West China Hospital, Sichuan University, Chengdu, China.
E-mail addresses: tianfangyuan0608@163.com (F. Tian), chenzhaoyan1993@163.com (Z. Chen).

https://doi.org/10.1016/j.ijantimicag.2023.106870
0924-8579/

encephalitis virus. It was later found to be effective against coronaviruses that induce severe acute respiratory syndrome, Middle East respiratory syndrome, etc., and converted into anti-SARS-CoV-2 drugs [12]. Molnupiravir was first listed in the UK on 4 November 2021, and obtained the Food and Drug Administration (FDA) Emergency Use Authorization (EUA) on 23 December 2021 for the treatment of COVID-19 [13].

Some randomised controlled trials (RCTs) [14,15] and real-world studies [7,16] have reported the efficacy and safety of molnupiravir treatment for COVID-19. However, there are certain differences in the reported results. In addition, some studies have systematically reviewed molnupiravir treatment for COVID-19 [17–19]. Some studies have previously been published, but with some RCTs that differ from previous research results, the latest research evidence is unclear [17]. Limited by the relatively small number of included studies, some studies only carried out meta-analyses on safety [18], and some studies only carried out meta-analyses on clinical trials in a certain country [19]. Therefore, to provide more relevant evidence for further clinical application this study aimed to summarise and analyse the efficacy and safety of molnupiravir treatment for COVID-19.

2. Methods

2.1. Eligibility criteria

The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) checklist was followed in this study [20]. The following screening criteria were used: P, patients with confirmed COVID-19 by PCR test; I, molnupiravir as intervention; C, placebo or usual care as control; O, efficacy and safety for COVID-19 patients; and S, RCTs.

2.2. Search strategy and literature screening

The literature was retrieved from PubMed, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), ClinicalTrials.gov, ICTRP (International Clinical Trials Registry Platform) and medRxiv from inception up to 1 January 2023. The following search terms were used: “COVID-19”, “SARS-CoV-2”, “molnupiravir” and “randomized controlled trial”. All search strategies were developed and implemented independently by two investigators and then cross-checked. A sample of the search strategy based on PubMed is listed in Appendix 1. The RCTs included in this study were divided into two categories: RCTs that have been published or have not been published but have research results; and RCTs that are currently in progress. Reference lists of identified studies were also searched to avoid missing potentially relevant studies. After using EndNote X7 to screen duplicates, the two researchers read the title and abstract of these articles back-to-back for preliminary screening and further read the full text that initially met the inclusion criteria to determine whether they were finally included. When the two researchers disagreed, the third researcher made the final decision. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO Code No: CRD42023388502).

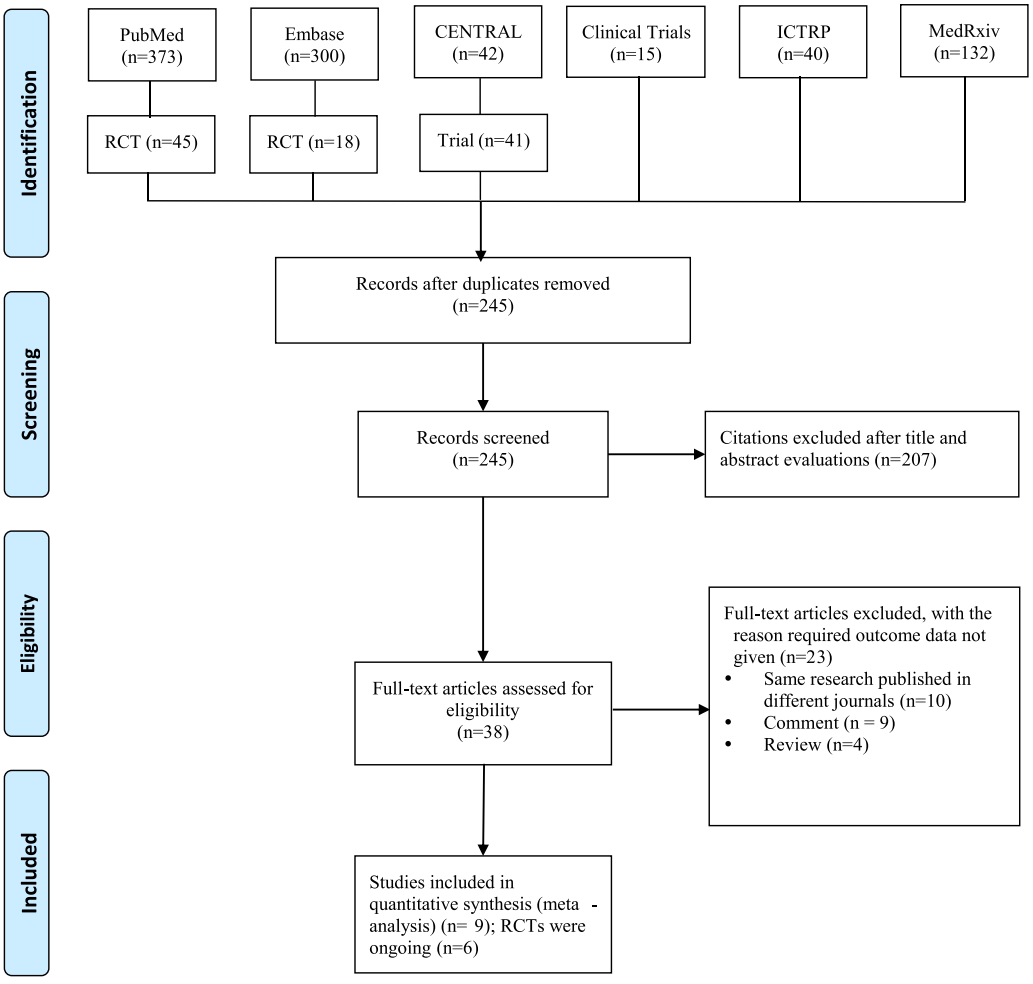

Fig. 1. Flow chart of study selection.

2.3. Data extraction

The following data were extracted from each included study and consisted of three parts: (1) the basic characteristics of the included studies, including the first author, publication year, clinical trial registration number, phase of clinical trials, centre, study population, group information, age range and sample size; (2) outcome to assess the efficacy and safety of molnupiravir, such as mortality, hospitalisation, clinical improvement, real-time polymerase chain reaction (RT-PCR) negativity, adverse events and serious adverse events; and (3) quality of the included studies assessed by the Cochrane Collaboration's tool for assessing risk of bias [21].

2.4. Statistical analysis

Meta-analysis was performed based on Review Manager 5.4 software (PROSPERO Code No: CRD42023388502). Outcomes were calculated by risk ratio (RR) and 95% confidence intervals (CI). The Q statistic test and I^2 test were used to test the heterogeneity between studies. When there was statistical heterogeneity, owing to the anticipated heterogeneity of the included studies, a random-effects model was used to estimate effect sizes, which provided more conservative estimates of the 95% CIs [22,23]. If there was no statistical heterogeneity between studies, the fixed effects model was used. A sensitivity analysis of the study was performed to examine the robustness of the results.

3. Results

3.1. Study selection

Through searching relevant databases, a total of 291 studies were conducted, including 45 studies from PubMed, 18 studies from Embase, 41 studies from CENTRAL, 55 ongoing clinical studies from ClinicalTrials.gov and ICTRP, and 132 studies from medRxiv, a preprint system of articles. After 46 duplicate studies were excluded, 245 studies were screened by the titles and abstracts, and 212 studies were excluded. Furthermore, 23 studies were screened out after reading the full texts. Therefore, nine studies [24–32] were included in the meta-analysis (Fig. 1; Table 1). The data of six ongoing trials were also collected (Fig. 1; Table 2).

3.2. Study characteristics

Nine RCTs [24–32] with a total of 31 573 participants were included for analysis. Of these, 15 846 patients were allocated to receive molnupiravir treatment regimens. All studies have disclosed protocols on the clinical trial registration website, of which eight are multicentre studies [24–31] and one is a single-centre study [32]. The study population mainly focused on patients with mild or moderate COVID-19. Patients in two studies received 200 mg, 400 mg or 800 mg of molnupiravir or placebo [24,25], and patients in the other seven studies received 800 mg of molnupiravir or placebo [26–32] (Table 1). The quality of the included studies is shown in Fig. 2. The overall quality of the study was relatively high. There were nearly six ongoing RCTs with molnupiravir registered with ClinicalTrials.gov or ICTRP; details of these RCTs are shown in Table 2.

3.3. Meta-analysis of efficacy

Seven RCTs reported the incidence of mortality [24–28,30,31] and eight RCTs reported the incidence of hospitalisation [24–31]. The mortality of the subgroup receiving molnupiravir treatment at 800 mg (0.03%; four of 14 929) was lower than that of the control group (0.11%; 16 of 15 097). There was no significant difference between the administration of molnupiravir at doses of 200 mg (RR 0.54, 95% CI 0.06–5.08; $P = 0.59$), 400 mg (RR 0.33, 95% CI 0.03–3.10; $P = 0.33$) and 800 mg (RR 0.35, 95% CI 0.12–0.99; $P = 0.05$) compared with the control. The hospitalisation of COVID-19 patients in the intervention groups who received molnupiravir treatment was 1.02% (200 mg subgroup, one of 98), 3.60% (400 mg subgroup, five of 139) and 1.10% (800 mg subgroup, 171 of 15 532), which were lower than that in the control group. There was no significant difference between the two groups (200 mg subgroup, RR 0.37, 95% CI 0.06–2.21; $P = 0.28$; 400 mg subgroup, RR 0.95, 95% CI 0.27–3.32; $P = 0.28$; 800 mg subgroup, RR 0.69, 95% CI 0.47–1.01; $P = 0.06$) (Fig. 3). On sensitivity analysis, after removing the largest study by Butler et al. [28], there was a significant difference between the two groups of hospitalisation, suggesting that these results should be interpreted with caution.

Four RCTs reported clinical improvement [28–31] and five RCTs reported RT-PCR [24,29–32]. After receiving molnupiravir treatment for 5 or 10 days, the clinical improvement (Day 5, RR 2.41, 95% CI 1.18–4.92; $P = 0.02$; Day 10, RR 1.45, 95% CI 1.04–2.01; $P = 0.03$) and RT-PCR negativity rate (Day 5, RR 2.78, 95% CI 1.38–5.62; $P = 0.004$; Day 10, RR 1.18, 95% CI 1.07–1.31; $P = 0.001$) were significantly higher in the intervention group than in the control group. However, there was no significant difference between the two groups after receiving molnupiravir treatment for 14 (clinical improvement: RR 1.02, 95% CI 0.93–1.12; $P = 0.65$; RT-PCR negativity: RR 1.07, 95% CI 0.97–1.18; $P = 0.19$) or 28 days (clinical improvement: RR 1.03, 95% CI 0.77–1.37; $P = 0.85$) compared with the control (Fig. 3).

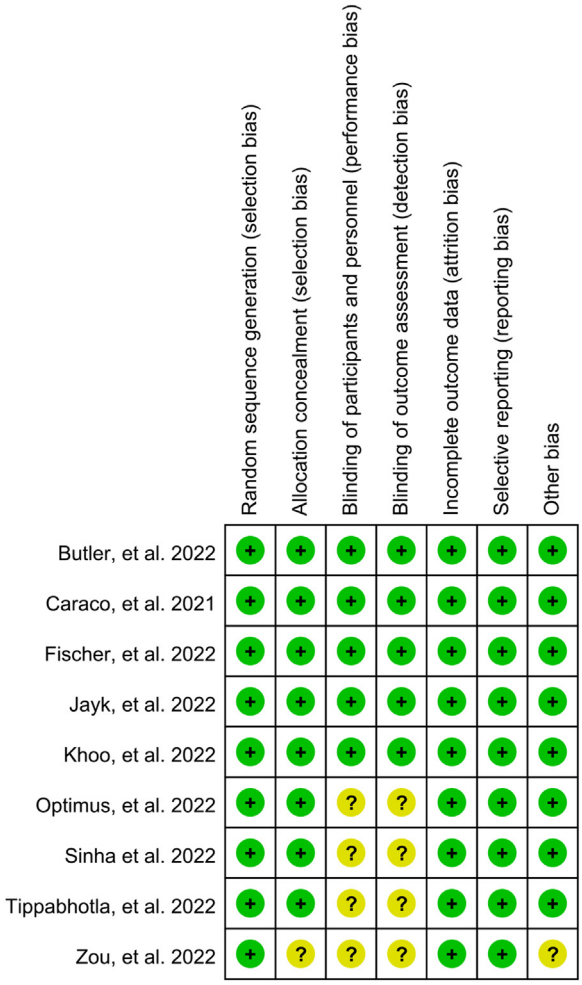

Fig. 2. Summary of risk of bias assessment in the meta-analysis.

Table 1
Characteristics of the included published studies.

Article	Clinical trials registration	Phase	Centre	Study population	Intervention group	Control group	Age range	Sample size	
								Intervention group	Control group
Fischer et al. 2022 [24]	NCT04405570	2a	Multicentre	Non-hospitalised with COVID-19	Molnupiravir 200/400/800 mg, twice daily for 5 days	Placebo	≥ 18 years	23/62/55	62
Caraco et al. 2021 [25]	NCT04575597	2/3	Multicentre	Non-hospitalised with COVID-19	Molnupiravir 200/400/800 mg, twice daily for 5 days	Placebo	≥ 18 years	75/77/76	74
Jayk et al. 2022 [26]	NCT04575597	3	Multicentre	Non-hospitalised adults with mild-to-moderate COVID-19	Molnupiravir 800 mg, twice daily for 5 days	Placebo	≥ 18 years	716	717
Khoo et al. 2022 [27]	NCT04746183	2	Multicentre	Non-hospitalised adults with mild-to-moderate COVID-19	Molnupiravir 800 mg, twice daily for 5 days	Placebo	≥ 18 years	90	90
Butler et al. 2022 [28]	ISRCTN30448031	NR	Multicentre	Patients with COVID-19	Molnupiravir 800 mg, twice daily for 5 days + usual care	Usual care	≥ 18 years	12 774	12 934
Optimus et al. 2022 [29]	CTRI/2021/06/033992	3	Multicentre	Patients with mild COVID-19	Molnupiravir 800 mg, twice daily for 5 days + usual care	Usual care	Aged 18–60 years	603	599
Tippabhotla et al. 2022 [30]	CTRI/2021/07/034588	3	Multicentre	Non-hospitalised with mild COVID-19	Molnupiravir 800 mg, twice daily for 5 days + usual care	Usual care	Aged 18–60 years	610	610
Sinha et al. 2022 [31]	CTRI/2021/05/033739	3	Multicentre	Patients with mild COVID-19	Molnupiravir 800 mg, twice daily for 5 days	Placebo	Aged 18–60 years	608	610
Zou et al. 2022 [32]	ChiCTR2200056817	NR	Single-centre	Patients with mild-to-moderate COVID-19	Molnupiravir 800 mg, twice daily for 5 days + usual care	Usual care	Aged 18–80 years	77	31

NR, not reported

Table 2
Characteristics of included ongoing studies.

Clinical trials registration	Status	Phase	Centre	Location	Intervention	Control	Age range	Sample size
NCT05459532	Recruiting	3	Multicentre	South Africa	Molnupiravir 800 mg every 12 hours for 5 days	Placebo	≥ 50 years	4000
IRCT20210901052358N1	Pending	3	Single centre	Iran	Molnupiravir 800 mg every 12 hours for 5 days	Placebo	≥ 18 years	60
CTRI/2021/08/035424	Not yet recruiting	3	Single centre	India	Molnupiravir 1600 mg every 12 hours for 5 days	Standard of care therapy	≥ 18 years	100
IRCT20210914052480N2	Recruiting	2/3	Single centre	Iran	Molnupiravir 200 mg every day for 5 days	Placebo	≥ 18 years	500
CTRI/2021/05/033736	Not yet recruiting	2/3	Single centre	India	Molnupiravir 800 mg every 12 hours for 5 days	Standard of care therapy	Aged 18–60 years	1282
PER-055-21	Not yet recruiting	3	Multicentre	International	Molnupiravir 800 mg every 12 hours for 5 days	Placebo	≥ 18 years	1332

3.4. Meta-analysis of safety

Eight RCTs reported adverse events [24–27,29–32] and serious adverse events [24–28,30–32]. The incidence of adverse events and serious adverse events in COVID-19 patients in the intervention groups who received molnupiravir 800 mg twice daily for 5 days of treatment was 16.51% (468 of 2835) and 0.70% (105 of 15 006), respectively, which was lower than that in the control group (17.19%, 480 of 2793; 0.79%, 120 of 15 128). There was no significant difference in terms of safety between the administration of molnupiravir at doses of 200 mg (adverse events: RR 1.17, 95% CI 0.63–2.16; $P = 0.62$; serious adverse events: RR 0.37, 95% CI 0.06–2.21; $P = 0.28$), 400 mg (adverse events: RR 0.84, 95% CI 0.50–1.42; $P = 0.52$; serious adverse events: RR 1.58, 95% CI 0.23–10.84; $P = 0.64$) and 800 mg (adverse events: RR 0.99, 95% CI 0.88–1.12; $P = 0.91$; serious adverse events: RR 0.88, 95% CI 0.68–1.13; $P = 0.32$) compared with the control (Fig. 3). On sensitivity analysis, there was a significant difference between the two groups in safety outcomes, suggesting that these results were robust.

4. Discussion

Molnupiravir showed antiviral activity against SARS-CoV-2 in vitro and in clinical trials [24,32]. Molnupiravir was approved

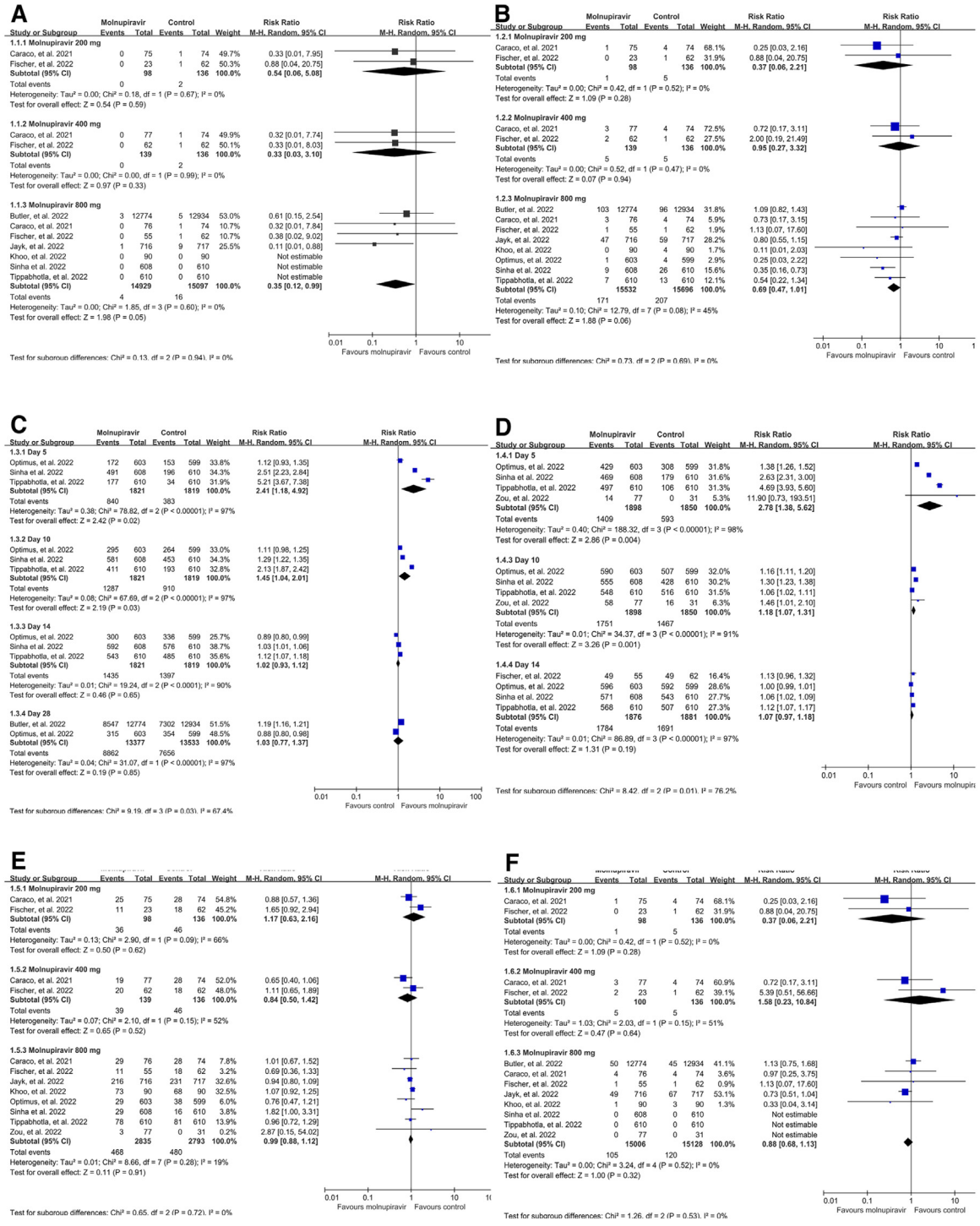

Fig. 3. Forest plot of the comparison of efficacy and safety between molnupiravir treatment and control. (A) Mortality. (B) Hospitalisation. (C) Clinical improvement. (D) RT-PCR negativity. (E) Adverse events. (F) Serious adverse event.

by the National Medical Products Administration of China for emergency review on 30 December 2022. Molnupiravir has been approved for import registration for the treatment of mild-to-moderate COVID-19 patients with advanced severe high-risk factors, such as advanced age, obesity or overweight, chronic kidney disease, diabetes, severe cardiovascular disease, chronic obstructive pulmonary disease, and severe high-risk factors such as active cancer. It was officially launched on 13 January 2022, becoming the third small molecule oral drug for COVID-19 in mainland China after nirmatrelvir-ritonavir (Paxlovid) and azvudine. The National Institutes of Health COVID-19 Treatment Guidelines Panel recommends using molnupiravir 800 mg orally twice daily for 5 days as an alternative therapy in non-hospitalised patients aged ≥ 18 years with mild-to-moderate COVID-19 who are at high risk of disease progression only when nirmatrelvir-ritonavir and remdesivir are unavailable, feasible to use or clinically appropriate [33]. The National Health Commission of the People's Republic of China released the Scheme for Diagnosis and Treatment of SARS-CoV-2 (10th Trial Edition) on 6 January 2023. Compared with the 9th Edition of the diagnosis and treatment plan previously released, in

addition to nirmatrelvir-ritonavir, monoclonal antibody, intravenous injection of human immunoglobulin and convalescent plasma, the antiviral treatment content added molnupiravir. It is mentioned in the plan that the applicable population of molnupiravir is adult patients with mild and moderate disease within 5 days of onset and high-risk factors for progression to severe disease by using molnupiravir 800 mg twice daily for 5 days [34].

Efficacy is an important indicator of molnupiravir treatment for COVID-19. It is noteworthy that the current study showed that three different doses of molnupiravir could not effectively improve the morality of patients with COVID-19 compared with the control group. Compared with the other two doses of molnupiravir, the use of molnupiravir 800 mg twice daily for 5 days was more effective in reducing mortality. The results of this study were similar to those of another meta-analysis [17]. Another meta-analysis showed that molnupiravir did not significantly reduce mortality in COVID-19 patients with high coverage of COVID-19 vaccine [35]. Moreover, molnupiravir demonstrated similar clinical outcomes to nirmatrelvir-ritonavir [36]. The hospitalisation rate of patients receiving molnupiravir treatment decreased; however, it still has no benefit in improving the hospitalisation of patients with COVID-19. The result of hospitalisation was different to another meta-analysis [17]. This was similar to the results of Butler et al. [28] but different from the results of Jayk et al. [26]. The study by Jayk et al. is a phase 3 clinical study with a small sample size. The study by Butler et al. is a real-world study with a larger sample size. Compared with the former, the latter often reflects the real clinical effect of drugs. In the Butler et al. study, 99% of patients with COVID-19 received at least one dose of the COVID-19 vaccine and 94% received three or more doses of the COVID-19 vaccine, which indicates that taking molnupiravir for people who received three doses of the COVID-19 vaccine cannot effectively reduce the hospitalisation rate related to COVID-19; however, it can effectively reduce the in-hospital disease progression and in-hospital death of patients after admission [7].

Molnupiravir can significantly increase the proportion of patients with improved clinical symptoms and achieve excellent clinical results in COVID-19 patients in the early stages. In terms of inhibiting COVID-19, it can inhibit the activity of COVID-19 and increase the proportion of RT-PCR negativity; therefore, it is better to use molnupiravir in the early stages of infection with SARS-CoV-2. This is mainly because molnupiravir acts through RdRp to induce the production of the SARS-COV-2 wrong mutation, thus inhibiting the replication of ARS-COV-2. In the initial stages of infection, the virus replicates a lot, so the application of molnupiravir has the best effect during this period. Therefore, the window period for most antiviral drugs is 5 days after the symptoms first appear, and it is ineffective to use such drugs as the disease progresses. A clinical study found that half of COVID-19 infections can be detected within 5 days after symptoms appear [37]. Such a short window has become a major defect in the use of such drugs. The current study found that patients who received molnupiravir within 10 days still had better clinical improvement and RT-PCR negativity. Further real-world studies are needed to confirm whether molnupiravir has better long-term clinical effects than other drugs.

In terms of safety, molnupiravir had no significant difference from the control group in adverse events or series of adverse events, which indicates that molnupiravir has good safety. The most common adverse effects of molnupiravir are diarrhoea, nausea and dizziness. However, some researchers have raised persistent concerns about the RNA mutation ability of molnupiravir, that is: it will cause mutations in the patient's own genetic material, which may lead to cancer or congenital defects [38]. This needs further exploration in follow-up research. Based on in vitro studies, neither molnupiravir nor its active metabolite NHC are inhibitors or inducers of major drug metabolising enzymes or inhibitors of major drug transporters. According to the EUA, no drug–drug interactions have been identified for molnupiravir.

It is believed that this study is the first meta-analysis on the efficacy of treatment in patients with COVID-19. Previous research only conducted related meta-analyses focused on the safety or population in a certain country. In addition, this study used high-quality papers published in reputable publications and conducted rigorous quality assessment procedures to reduce the occasional bias. Strict and practical inclusion criteria were also applied in this meta-analysis, and only randomised clinical studies were included for a full evaluation of the efficacy and safety of molnupiravir treatment for COVID-19. However, this study also had some limitations. There are still few real-world studies that could be included. Some data on the efficacy of molnupiravir on COVID-19 patients in clinical practice are still lacking, and there was a large gap in the sample size, outcome indicators and population of RCTs in this study. Due to the lack of quality, this study was unable to perform subgroup analysis based on risk factors such as older age and vaccination status, which may have affected the precision of the final results. Therefore, the efficacy and safety of molnupiravir treatment for COVID-19 still require large and high-quality studies for further confirmation.

5. Conclusion

Molnupiravir can accelerate the clinical improvement and RT-PCR negativity rate of COVID-19 patients, but it does not significantly reduce mortality and hospitalisation. The safety outcomes indicated that molnupiravir has good safety. Further large-scale studies are required to validate these findings.

Declarations

Funding: This work was supported by the Sichuan Science and Technology Program (Project number: 2022JDR0326, 2023JDR0246).
Competing Interests: The authors declare that they have no competing interests.
Ethical Approval: Not required.
Sequence Information: Not applicable.
Acknowledgments: This research was supported by National Key Clinical Specialties Construction Program.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106870.

References

[1] Schöley J, Aburto JM, Kashnitsky I, Kniffka MS, Zhang L, Jaadla H, et al. Life expectancy changes since COVID-19. Nat Hum Behav 2022;6(12):1649–59. doi:10.1038/s41562-022-01450-3.
[2] Tian F, Yang R, Chen Z. Safety and efficacy of COVID-19 vaccines in children and adolescents: A systematic review of randomized controlled trials. J Med Virol 2022;94(10):4644–53. doi:10.1002/jmv.27940.
[3] WHO. Coronavirus disease COVID-19. Geneva: World Health Organization. https://www.who.int/emergencies/diseases/novel-coronavirus-2019 [accessed 12 January 2023].
[4] PHOSP-COVID Collaborative GroupClinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. Lancet Respir Med 2022;10(8):761–75. doi:10.1016/S2213-2600(22)00127-8.
[5] Huang L, Li X, Gu X, Zhang H, Ren L, Guo L, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. Lancet Respir Med 2022;10(9):863–76. doi:10.1016/S2213-2600(22)00126-6.
[6] Hsu CK, Chen CY, Chen WC, Lai CC, Hung SH, Lin WT. Effect of sofosbuvir-based treatment on clinical outcomes of patients with COVID-19: a systematic review and meta-analysis of randomised controlled trials. Int J Antimicrob Agents 2022;59(3):106545. doi:10.1016/j.ijantimicag.2022.106545.

[7] Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. Lancet 2022;400(10359):1213–22. doi:10.1016/S0140-6736(22)01586-0.
[8] Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 2020;19(3):149–50. doi:10.1038/d41573-020-00016-0.
[9] Dejmek M, Konkoľová E, Eyer L, Straková P, Svoboda P, Šála M, et al. Non-Nucleotide RNA-Dependent RNA Polymerase Inhibitor That Blocks SARS-CoV-2 Replication. Viruses 2021;13(8):1585. doi:10.3390/v13081585.
[10] Yang H, Rao Z. Structural biology of SARS-CoV-2 and implications for therapeutic development. Nat Rev Microbiol 2021;19(11):685–700. doi:10.1038/s41579-021-00630-8.
[11] Lee CC, Hsieh CC, Ko WC. Molnupiravir-A Novel Oral Anti-SARS-CoV-2 Agent. Antibiotics (Basel) 2021;10(11):1294. doi:10.3390/antibiotics10111294.
[12] Hashemian SMR, Pourhanifeh MH, Hamblin MR, Shahrzad MK, Mirzaei H. RdRp inhibitors and COVID-19: Is molnupiravir a good option? Biomed Pharmacother 2022;146:112517. doi:10.1016/j.biopha.2021.112517.
[13] US Food & Drug Administration. Coronavirus (COVID-19) Update: FDA Authorizes Additional Oral Antiviral for Treatment of COVID-19 in Certain Adults; 2021 https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain.
[14] Mollan KR, Eron JJ, Krajewski TJ, Painter W, Duke ER, Morse CG, et al. Infectious Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Virus in Symptomatic Coronavirus Disease 2019 (COVID-19) Outpatients: Host, Disease, and Viral Correlates. Clin Infect Dis 2022;75(1):e1028–36. doi:10.1093/cid/ciab968.
[15] Johnson MG, Puenpatom A, Moncada PA, Burgess L, Duke ER, Ohmagari N, et al. Effect of Molnupiravir on Biomarkers, Respiratory Interventions, and Medical Services in COVID-19: A Randomized, Placebo-Controlled Trial. Ann Intern Med 2022;175(8):1126–34. doi:10.7326/M22-0729.
[16] Flisiak R, Zarębska-Michaluk D, Rogalska M, Kryńska JA, Kowalska J, Dutkiewicz E, et al. Real-world experience with molnupiravir during the period of SARS-CoV-2 Omicron variant dominance. Pharmacol Rep 2022;74(6):1279–85. doi:10.1007/s43440-022-00408-6.
[17] Fatima M, Azeem S, Saeed J, Shahid A, Cheema HA. COVID-19 Therapeutics Study Group. Efficacy and safety of molnupiravir for COVID-19 patients. Eur J Intern Med 2022;102:118–21. doi:10.1016/j.ejim.2022.05.024.
[18] Amani B, Zareei S, Amani B. Rapid review and meta-analysis of adverse events associated with molnupiravir in patients with COVID-19. Br J Clin Pharmacol 2022;88(10):4403–11. doi:10.1111/bcp.15449.
[19] Lawrence JM, Mirchandani M, Hill A. Evaluation of publication bias for 12 clinical trials of molnupiravir to treat SARS-CoV-2 infection in 13694 patients with meta-analysis. J Antimicrob Chemother 2023:dkac440. doi:10.1093/jac/dkac440.
[20] Moher D, Liberati A, Tetzlaff J, Altman DGPRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097.
[21] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al., Cochrane Statistical Methods Group The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. doi:10.1136/bmj.d5928.
[22] Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons; 2019. Available online at: https://training.cochrane.org/handbook/current .
[23] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1(2):97–111. doi:10.1002/jrsm.12.
[24] Fischer WA 2nd, Eron JJ Jr, Holman W, Cohen MS, Fang L, Szewczyk LJ, et al. A phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Sci Transl Med 2022;14(628):eabl7430. doi:10.1126/scitranslmed.abl7430.
[25] Caraco Y, Crofoot GE, Moncada PA. Phase /3 trial of molnupiravir for treatment of Covid-19 in Non-hospitalised adults. NEJM Evid 2022;1(2):EVIDoa2100043. doi:10.1056/EVIDoa2100043.
[26] Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for Oral Treatment of Covid-19 in Non-hospitalised Patients. N Engl J Med 2022;386(6):509–20. doi:10.1056/NEJMoa2116044.
[27] Khoo SH, FitzGerald R, Saunders G, Middleton C, Ahmad S, Edwards CJ, et al. Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Infect Dis 2022 S1473-3099(22)00644-2. doi:10.1016/S1473-3099(22)00644-2.
[28] Butler CC, Hobbs FDR, Gbinigie OA, Rahman NM, Hayward G, Richards DB, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. Lancet 2022 S0140-6736(22)02597-1. doi:10.1016/S0140-6736(22)02597-1.
[29] The Print (2021) Optimus announces interim clinical results from phase III clinical trials of molnupiravir conducted in India. https://theprint.in/ani-press-releases/optimus-announces-interim-clinical-results-from-phase-iii-clinical-trials-of-molnupiravir-conducted-in-india/699993/.
[30] Tippabhotla SK, Lahiri S, Raju R, Kandi C, Prasad N. Efficacy and Safety of Molnupiravir for the Treatment of Non-Hospitalized Adults With Mild COVID-19: A Randomized, Open-Label, Parallel-Group Phase 3 Trial. 2022. https://papers.ssrn.com/sol3/papers.cfmabstract_id=4042673.
[31] Sinha S NK, Suram VK, Chary SS, Naik S, Singh VB, Jain MK, et al. Efficacy and Safety of Molnupiravir in Mild COVID-19 Patients in India. Cureus 2022;14(11):e31508 PMID: 36532902; PMCID: PMC9751243. doi:10.7759/cureus.31508.
[32] Zou R, Peng L, Shu D, Zhao L, Lan J, Tan G, et al. Antiviral Efficacy and Safety of Molnupiravir Against Omicron Variant Infection: A Randomized Controlled Clinical Trial. Front Pharmacol 2022;13:939573. doi:10.3389/fphar.2022.939573.
[33] The COVID-19 Treatment Guidelines Panel (the Panel). Molnupiravir. https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/molnupiravir/ [accessed 12 January 2023].
[34] National Health Commission of the People's Republic of China. Scheme for Diagnosis and Treatment of SARS-CoV-2 (10th Trial Edition). http://www.nhc.gov.cn/ylyjs/pqt/202301/32de5b2ff9bf4eaa88e75bdf7223a65a.shtml [accessed 12 January 2023].
[35] Huang C, Lu TL, Lin L. Real-World Clinical Outcomes of Molnupiravir for the Treatment of Mild to Moderate COVID-19 in Adult Patients during the Dominance of the Omicron Variant: A Meta-Analysis. Antibiotics (Basel) 2023;12(2):393. doi:10.3390/antibiotics12020393.
[36] Tian F, Chen Z, Feng Q. Nirmatrelvir-ritonavir compared with other antiviral drugs for the treatment of COVID-19 patients: a systematic review and meta-analysis. J Med Virol 2023;95:e28732. doi:10.1002/jmv.28732.
[37] Ledford H, Maxmen A. African clinical trial denied access to key COVID drug Paxlovid. Nature 2022;604(7906):412–13. doi:10.1038/d41586-022-00919-5.
[38] Service RF. A prominent virologist warns COVID-19 pill could unleash dangerous mutants. Others see little cause for alarm. https://www.science.org/content/article/prominent-virologist-warns-covid-19-pill-could-unleash-dangerous-mutants-others-see-little-cause-alarm.