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.

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Letter to the Editor

Efficacy and safety of molnupiravir for COVID-19 patients

Dear Editor,

The Coronavirus Disease 2019 (COVID-19) continues to be a major source of morbidity and mortality across the globe. Current medical therapy against COVID-19 includes drugs that work by inhibiting viral entry into the cell, inhibiting SARS-CoV2 RNA, inhibiting viral proteases, inhibiting host factors crucial for infection, and immunomodulators [1]. However, most of these therapies are limited by their high cost and parenteral administration that needs to be performed in an in-hospital setting by trained medical staff to avoid adverse effects [1,2]. Thus, there is an urgent need for effective oral agents, especially in non-hospitalized patients. Molnupiravir, an oral RdRp inhibitor exhibiting advantageous pharmacokinetics, has recently attracted attention due to its ability to inhibit viral replication, reduce viral load rapidly and cause fast recovery [3]. Several trials of molnupiravir have been in COVID-19 patients but may have been underpowered to detect a decrease in mortality. Hence, we conducted this meta-analysis to increase the statistical power of the available evidence by combining it and evaluating the safety and efficacy of molnupiravir for the treatment of COVID-19 patients.

This meta-analysis was registered in PROSPERO (CRD42022320099) and conducted according to the guidance in the Cochrane Handbook for Systematic Reviews of Interventions [4]. A comprehensive search of PubMed, Embase and the Cochrane Library was carried out from inception to March 2022 using a search strategy consisting of the following terms: (“COVID-19″ or “coronavirus disease 2019″ or “novel coronavirus" or “SARS-CoV-2″) AND (“Molnupiravir" or “EIDD-2801″ or “MK-4482″). Additionally, ClinicalTrials.gov and grey literature sources (Open Access Theses and Dissertations [OATD] and OpenGrey) were searched to retrieve any additional studies. The reference lists of relevant articles were also screened. Only randomized controlled trials (RCTs) evaluating molnupiravir in COVID-19 patients were considered eligible for our meta-analysis. Out of a total of 170 articles that were obtained through our search, we finally included 6 randomized controlled trials (RCTs) consisting of 3481 patients. The summary of

Table 1
Summary of characteristics of included studies.

Sr No	Author, year	Registration	Types of study	Population	Intervention	Comparator
1	Arribas et al., 2021	NCT04575584	Phase II/III double-blind RCT	• 304 patients • ≥18 year • In-hospital treatment of COVID-19	• Molnupiravir 200 mg, 400 mg, 800 mg (1:1:1) • PO • BD for 5 days	Placebo
2	Caraco et al., 2021	NCT04575597	Phase II/III double-blind RCT	• 302 non-hospitalized adults with COVID positivity 7 days before randomization	• Molnupiravir 200 mg, 400 mg, 800 mg (1:1:1) • PO • BD for 5 days	Placebo
3	Tippabholta et al., 2022	CTRI/2021/07/034,588	Phase III RCT	• 1220 non-hospitalized adults with COVID-19 infection • ≥18 and ≤60 years	• Molnupiravir 800 mg (four 200 mgi capsules) • PO • BD for 5 days	SOC treatment
4	Fischer et al., 2021	NCT04405570	Phase IIa RCT	• 204 Non- hospitalized adults • ≥18 years	• Molnupiravir 800 mg (four 200 mg capsules) • BD for 5 days • Findings are presented for licensed dose only (800 mg) • Other intervention groups included: 200 mg molnupiravir (n = 23) 400 mg molnupiravir (n = 62)	Placebo
5	Bernal et al., 2022	NCT04575597	Phase III double-blind RCT	• 1433 non-hospitalized adults with COVID positivitywithin 5 days before randomization	• Molnupiravir 800 mg (four 200 mg capsules) • PO • BD daily for 5 days.	SOC
6	Khoo et al. 2021	NCT04746183	Phase Ib IIa RCT	• 18 Non-Hospitalized participants with COVID positivity within 5 days of symptom onset	• Monlupiravir 300 mg, 600 mg, 800 mg • PO • BD for 5 days	Placebo or SOC

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

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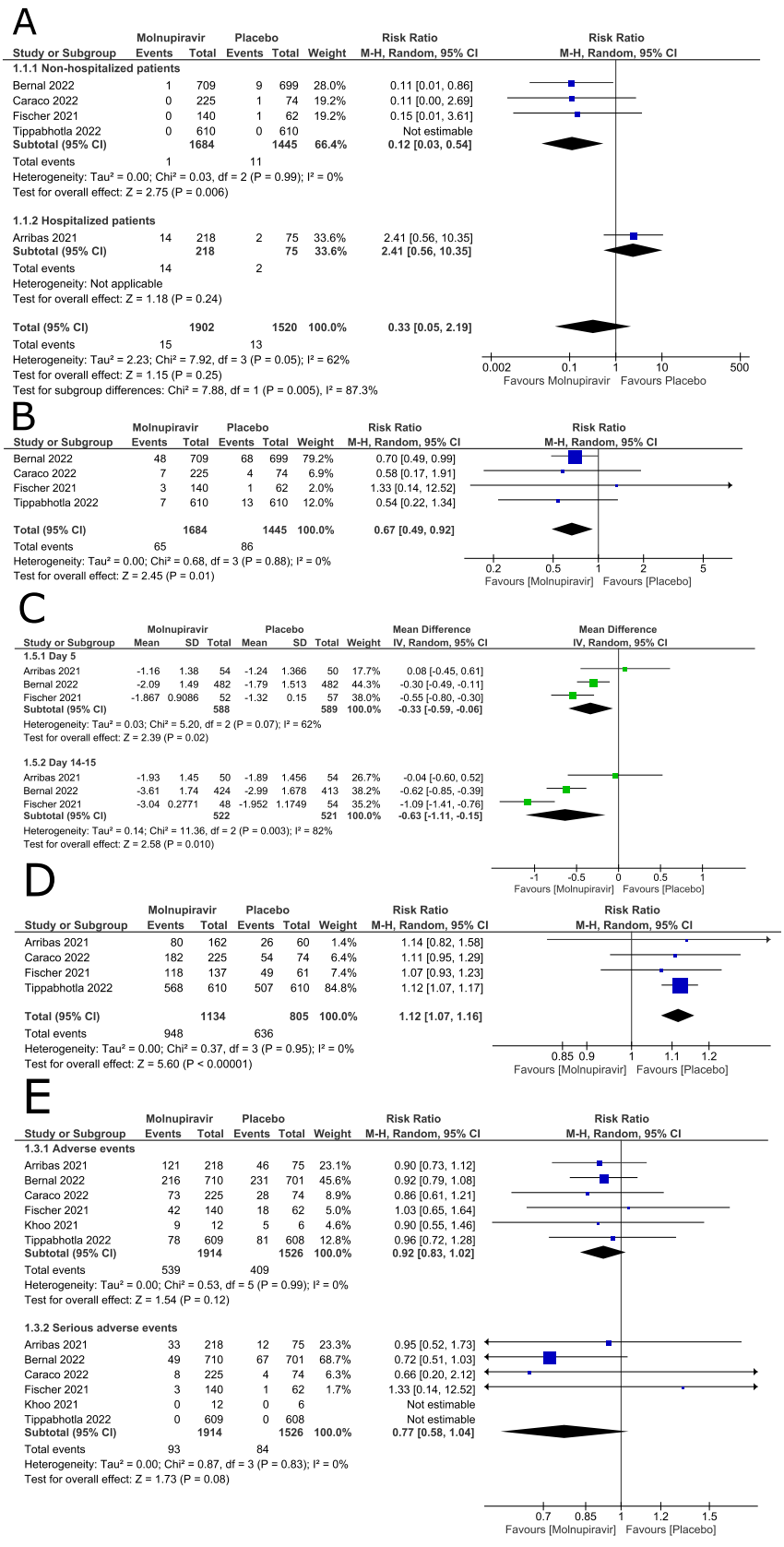

Fig. 1. Forest plot for the efficacy and safety of molnupiravir in randomized controlled trials. (A) 28–30 day mortality. (B) Hospitalization. (C) Mean reduction in viral load. (D) Virological clearance (negative PCR). (E) Adverse events. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

included trials is presented in Table 1. The revised Cochrane Risk of Bias Tool (RoB 2.0) was used to assess the quality of included trials; all trials were found to be at a low risk of bias. Our primary outcomes were 28–30 day mortality and hospitalization. RevMan 5.4 was used to pool data using a random-effects model with risk ratios (RRs) and mean differences (MDs) as effect measures.

The results from 5 RCTs showed that molnupiravir as compared to placebo reduced the risk of mortality only in non-hospitalized patients (RR 0.12; 95% CI: 0.03–0.54, I^2= 0%; Fig. 1A) with no benefit being observed in hospitalized patients. The risk of hospitalization was also less in patients receiving molnupiravir (RR 0.67; 95% CI: 0.49–0.92, I^2=0%; Fig. 1B). The decrease in viral RNA from baseline was greater for molnupiravir as compared to placebo at day 5 (MD −0.33; 95% CI: −0.59 to −0.06, I^2=62%; Fig. 1C) and day 14–15 (MD −0.63; 95% CI: −1.11 to −0.15, I^2=82%; Fig. 1C). The proportion of patients achieving virological clearance (negative PCR) at the end of the trial was higher in the treatment group (RR 1.12; 95% CI: 1.07–1.16, I^2=0%; Fig. 1D). Molnupiravir did not increase the risk of either adverse events (RR 0.92; 95% CI: 0.83–1.02, I^2=0%; Fig. 1E) or serious adverse events (RR 0.77; 95% CI: 0.58–1.04, I^2= 0%; Fig. 1E) in patients receiving the drug.

To the best of our knowledge, this is the first meta-analysis assessing the efficacy and safety of molnupiravir in COVID-19 patients. The primary findings of our study indicate that molnupiravir is effective in reducing the risk of mortality in non-hospitalized patients by 88%. It also decreases the risk of hospitalization and reduces viral RNA load with no increase in adverse events. However, similar to other non-immunomodulatory direct antiviral treatments, molnupiravir did not show any benefit in hospitalized patients in the only trial reported in this population to date [5]. Two other trials (CTRI/2021/05/033,864 and CTRI/2021/08/0,354,242) conducted in hospitalized patients were terminated early due to futility but the results have not been published yet. The presumed explanation for this lack of benefit of direct antivirals in hospitalized patients is the late initiation of treatment when the disease is already advanced. Therefore, the highest benefit of molnupiravir is likely to be seen with early initiation of treatment.

The therapeutic effect of molnupiravir can be described based on its 2-step mutagenesis mechanism. In the first step, RdRp uses positive-strand genomic RNA +gRNA to synthesize a negative-strand genomic RNA -gRNA. In step 2, the M-containing RNA is used to synthesize subgenomic RNA containing a mutation introduced by M-containing RNA in -gRNA that leads to mutagenesis proving deadly for the virus [6]. Concerns have been raised over this mutagenic mechanism possibly leading to the creation of deadlier viral variants or causing cancerous mutations in humans. However, in vivo studies in rodents have shown that molnupiravir does not cause mutagenesis in mammals at substantially greater doses than those used in clinical practice [7]. As with any new treatment, long-term clinical pharmacovigilance data will be needed to further allay these concerns.

The current treatment plan for non-hospitalized COVID-19 patients involves remdesivir and monoclonal antibodies like sotrovimab; however, these treatments require complex parenteral administration and are expensive [2]. Molnupiravir, being oral and also effective against newer COVID-19 variants [8], is more practical and convenient for administration in ambulatory patients fulfilling the unmet need for safe and effective oral drugs in this population [9]. The huge reduction in the risk of mortality observed in our meta-analysis is highly encouraging. Future trials should evaluate the efficacy of molnupiravir in breakthrough infections as well as in comparison with other approved treatments for COVID-19.

Limitations of our study include the inability to investigate more subgroups as we used study level data instead of individual patient data, and the unavailability of the results of two trials which may result in publication bias. It may be speculated that molnupiravir may only be effective in some subgroups of hospitalized patients; therefore, publication of the results of these trials might help in investigating this.

In conclusion, our study supports the use of molnupiravir in non-hospitalized patients with COVID-19. Further research should be focused on evaluating its comparative efficacy in relation to other available treatments.

Statements and declarations

Financial support

No financial support was received for this study.

Human and animal participants

Research involving human participants and/or animals: No animals or human subjects were used in the current study.

Informed consents

No informed consents were required for the purpose of the current study.

Availability of data

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

Conflicts of interest

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

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References

[1] Tian L, Pang Z, Li M, Lou F, An X, Zhu S, et al. Molnupiravir and its antiviral activity against COVID-19. Front Immunol 2022;13.
[2] Dal-Ré R, Becker SL, Bottieau E, Holm S. Availability of oral antivirals against SARS-CoV-2 infection and the requirement for an ethical prescribing approach. Lancet Infect Dis 2022. https://doi.org/10.1016/s1473-3099(22)00119-0.
[3] Imran M, Kumar Arora M, Asdaq SMB, Khan SA, Alaqel SI, Alshammari MK, et al. Discovery, development, and patent trends on molnupiravir: a prospective oral treatment for covid-19. Molecules 2021;26. https://doi.org/10.3390/molecules26195795.
[4] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane handbook for systematic reviews of interventions. 2nd ed. Hoboken, New Jersey: Wiley Blackwell; 2019. https://doi.org/10.1002/9781119536604.
[5] Arribas JR, Bhagani S, Lobo SM, Khaertynova I, Mateu L, Fishchuk R, et al. Randomized trial of molnupiravir or placebo in patients hospitalized with Covid-19. NEJM Evid 2022;1. https://doi.org/10.1056/EVIDoa2100044.
[6] Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: a systematic review of literature. Diabetes Metab Syndr 2021;15:102329. https://doi.org/10.1016/J.DSX.2021.102329.
[7] Troth S, Butterton J, Deanda CS, Escobar P, Grobler J, Hazuda D, et al. Letter to the editor in response to Zhou et al. J Infect Dis 2021;224:1442–3. https://doi.org/10.1093/infdis/jiab362.
[8] Rosenke K, Okumura A, Lewis MC, Feldmann F, Meade-White K, Bohler WF, et al. Molnupiravir (MK-4482) is efficacious against omicron and other SARS-CoV-2 variants in the syrian hamster COVID-19 model. BioRxiv 2022. https://doi.org/10.1101/2022.02.22.481491.
[9] Vitiello A, Troiano V, La Porta R. What will be the role of molnupiravir in the treatment of COVID-19 infection? Drugs Ther Perspect 2021;37:579–80. https://doi.org/10.1007/S40267-021-00879-2.

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