

## META-ANALYSIS

# Rapid review and meta-analysis of adverse events associated with molnupiravir in patients with COVID-19

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**Aims:** The aim of this study was to evaluate the safety profile of molnupiravir in COVID-19 patients.

**Methods:** PubMed, Cochrane Library, medRxiv and Google Scholar were searched for articles published up to April 25, 2022. Meta-analysis was performed using Comprehensive Meta-Analysis software.

**Results:** Four trials involving 2241 patients met the inclusion criteria. No significant difference was observed between molnupiravir at 200, 400 and 800 mg compared with placebo (200 mg: risk ratio [RR] = 0.97; 95% confidence interval [CI]: 0.78–1.20;  $P = .80$ ; 400 mg: RR = 0.81; 95% CI: 0.64–1.02;  $P = .07$ ; 800 mg: RR = 0.94; 95% CI: 0.83–1.06;  $P = .36$ ) for any adverse events (AEs); at 200, 400 and 800 mg compared with placebo (200 mg: RR = 0.81; 95% CI: 0.41–1.63;  $P = .57$ ; 400 mg: RR = 0.82; 95% CI: 0.41–1.61;  $P = .56$ ; 800 mg: RR = 0.80; 95% CI: 0.59–1.08;  $P = .15$ ) for serious adverse events; at 200, 400 and 800 mg compared with placebo (200 mg: RR = 1.74; 95% CI: 0.48–6.30;  $P = .39$ ; 400 mg: RR = 1.07; 95% CI: 0.28–4.09;  $P = .91$ ; 800 mg: RR = 0.47; 95% CI: 0.17–1.28;  $P = .14$ ) for AEs leading to death; and at 200, 400 and 800 mg compared with placebo (200 mg: RR = 1.50; 95% CI: 0.26–8.55;  $P = .64$ ; 400 mg: RR = 0.99; 95% CI: 0.17–5.68;  $P = .99$ ; 800 mg: RR = 0.61; 95% CI: 0.31–1.23;  $P = .17$ ) for treatment discontinuation due to AEs.

**Conclusion:** This meta-analysis showed that the use of three doses of molnupiravir (200, 400 and 800 mg) is safe for COVID-19 patients. Further research is needed to confirm the present findings.

### KEYWORDS

COVID-19, molnupiravir, safety, SARS-CoV-2

## 1 | INTRODUCTION

Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, several variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been identified, including alpha, beta, gamma, delta and omicron.<sup>1</sup> Although vaccination may be the best solution to control COVID-19 disease, it takes a long time for public immunity because vaccines have public acceptance problems,<sup>2</sup> complex transportation and storage issues. Therefore, the discovery and

development of alternative treatments, particularly effective anti-COVID-19 drugs, seem crucial.<sup>3,4</sup> Although no specific, safe and effective anti-SARS-CoV-2 drug has been approved,<sup>4,5</sup> remdesivir, an antiviral agent, initially developed against Ebola in 2015,<sup>6</sup> is approved for the treatment of COVID-19. However, it is used only in hospitalized patients, and its reducing effect on mortality rate has been controversial.<sup>7–10</sup> Therefore, repurposing drugs approved by the US Food and Drug Administration (FDA) may be of great assistance to keep a curb on the pandemic.<sup>4</sup> In this regard, the FDA has issued an

emergency license for paxlovid and molnupiravir manufactured by Pfizer and Merck, respectively, for patients with COVID-19.<sup>11</sup> Molnupiravir (also known as MK-4482, EIDD-2801 and MOV, proposed trade name: Lagevrio) is a  $\beta$ -D-N4-hydroxycytidine prodrug and oral antiviral drug which is demonstrated to be useful against influenza A and B viruses, Ebola, chikungunya, Venezuelan equine encephalitis virus (VEEV), respiratory syncytial virus (RSV), HCV, norovirus, and human coronaviruses.<sup>12-14</sup> Given the fact that the clinical administration of molnupiravir has increased during the COVID-19 pandemic while it is under phase III clinical trial against COVID-19<sup>15,16</sup> and there are some concerns about molnupiravir's potential for causing adverse events,<sup>17</sup> this study aimed to evaluate molnupiravir-related adverse events in COVID-19 patients.

## 2 | METHODS

The present study was prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Rapid Review (PRISMA-RR) guideline which is an evidence-based protocol for rapid reviews of primary studies.<sup>18</sup>

### 2.1 | Literature search

A literature search among full-texts or abstracts available on PubMed, Cochrane Library, medRxiv and Google Scholar was conducted to determine relevant evidence up to April 25, 2022. The reference lists of relevant studies were monitored for additional citations. Moreover, we searched clinical trial databases, including [ClinicalTrials.gov](https://clinicaltrials.gov) and the European Union Clinical Trials Register to explore further records. All these steps were conducted by two authors independently (Ba.A. and Be.A.). There was no limitation on language. The key search terms were SARS-CoV-2, COVID-19, molnupiravir and adverse events. The following search strategy was applied for searching PubMed: (((((((Coronavirus[Title/Abstract]) OR (Coronavirus[MeSH Terms])) OR (COVID-19[Title/Abstract])) OR (SARS-CoV-2[Title/Abstract])) OR (COVID-19[MeSH Terms]) OR (SARS-CoV-2[MeSH Terms])) OR (2019 novel coronavirus infection[Title/Abstract])) OR (2019-nCoV infection[Title/Abstract])) AND ((Molnupiravir[Title/Abstract])).

### 2.2 | Study selection

We included studies if they fulfilled the following criteria:

1. Population: patients with laboratory-confirmed positive COVID-19 test.
2. Intervention: molnupiravir.
3. Control: placebo.
4. Safety outcomes of interest: the incidence of adverse events (AEs), serious adverse events (SAEs), death caused by AEs, and discontinued due to AEs.

The studies conducted on animal models, case reports, case series and letters to the editor were excluded from our study.

### 2.3 | Data extraction and quality assessment

We used the Cochrane Collaboration tool to assess the risk of bias for randomized controlled trials (RCTs).<sup>19</sup> Data was retrieved by the same data extraction form. We extracted information including (1) study characteristics (author, year, place and phase); (2) patient characteristics (sample size, sex and mean age); (3) intervention and comparison (sample size and treatment dose); and (4) safety outcomes. All steps stated above were performed independently by two authors (Be.A. and S.Z.).

### 2.4 | Evidence synthesis

We performed a meta-analysis on the AEs of various doses of molnupiravir versus placebo using Comprehensive Meta-Analysis software, version 3.0. The risk ratio (RR) with a 95% confidence interval (CI) was used for dichotomous variables. The random-effects model was used for studies with  $I^2 > 50\%$  or  $P < .1$ . Otherwise, the fixed-effect model was applied.

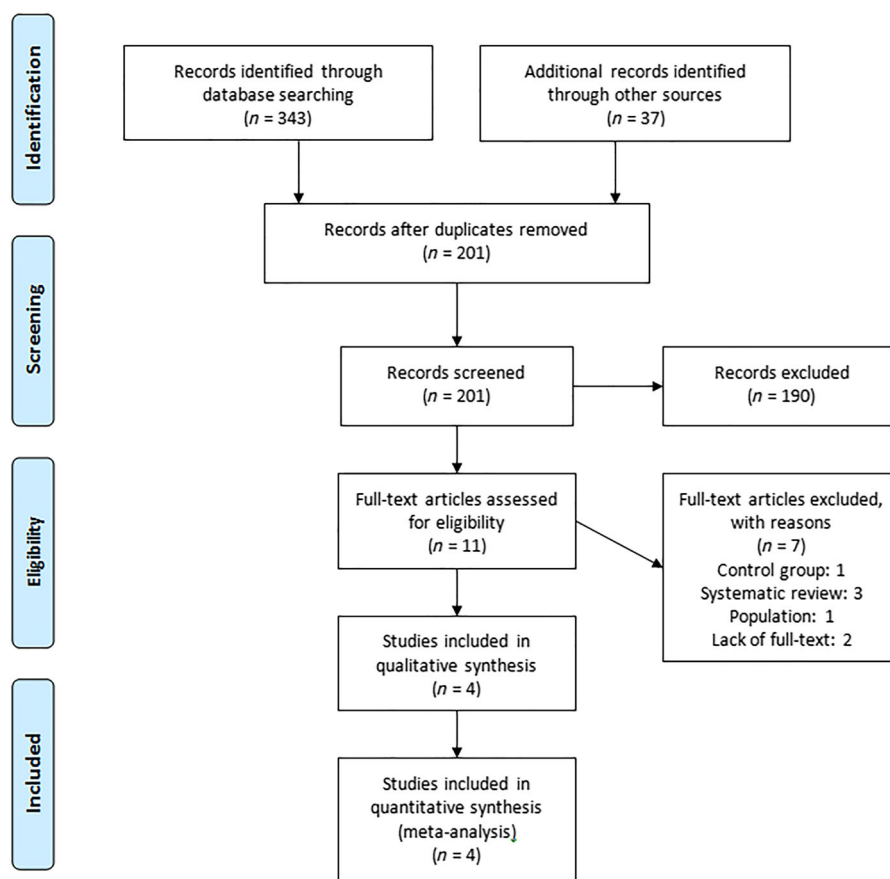
## 3 | RESULTS

### 3.1 | Characteristics of studies

Figure 1 illustrates the overall protocol for the study and details the number of studies excluded. Moreover, the main characteristics of included RCTs are presented in Table 1. A total of 201 records were entered into the screening process following the removal of duplicates from 11 records that had met the eligibility criteria. As a result, four RCTs<sup>20-23</sup> with a total of 2241 participants remained for analysis. The studies conducted by Painter et al.<sup>24</sup> and Khoo et al.<sup>25</sup> were excluded since molnupiravir was evaluated in healthy subjects and the control group was the standard of care. There were two studies<sup>21,23</sup> with the identical NCT number (NCT04575597) which seemed to be prepared according to an interim analysis. We decided to include both studies in our meta-analysis because they featured different population sizes and administered doses. In Caraco et al.'s study,<sup>21</sup> patients received 200, 400 or 800 mg of molnupiravir or placebo, while in Jayk Bernal et al.'s study,<sup>23</sup> patients were randomly assigned to receive 800 mg of molnupiravir or placebo. However, these studies were included in a sensitivity analysis.

### 3.2 | Risk of bias assessment

The assessment of the risk of bias using the Cochrane Collaboration tool is presented in Figure 2.

**FIGURE 1** PRISMA flow diagram of the included studies in the meta-analysis**TABLE 1** The main characteristics of studies included in the meta-analysis

Author, year	Place	Study design	Setting	Severity of COVID-19	Patients (n, male)	Mean age	Intervention (n)	Control (n)	Treatment dose (BID)	Treatment duration (days)
Arribas, 2022 <sup>20</sup>	International	RCT	Hospitalized	Mild to severe	304, 230	NR	Molnupiravir (218)	Placebo (n = 78)	200, 400, 800 mg	5
Jayk Bernal, 2022 <sup>23</sup>	International	RCT	Nonhospitalized	Mild or moderate	1433, 698	43	Molnupiravir (716)	Placebo (n = 717)	800 mg	5
Caraco, 2022 <sup>21</sup>	International	RCT	Nonhospitalized	Mild or moderate	302, 159	49.2	Molnupiravir (228)	Placebo (n = 72)	200, 400, 800 mg	5
Fischer, 2022 <sup>22</sup>	USA	RCT	Nonhospitalized	Mild or moderate	202, 98	NR	Molnupiravir (140)	Placebo (n = 62)	200, 400, 800 mg	5

BID, twice a day; NR, not reported; RCT, randomized controlled trial.

### 3.3 | Safety outcome

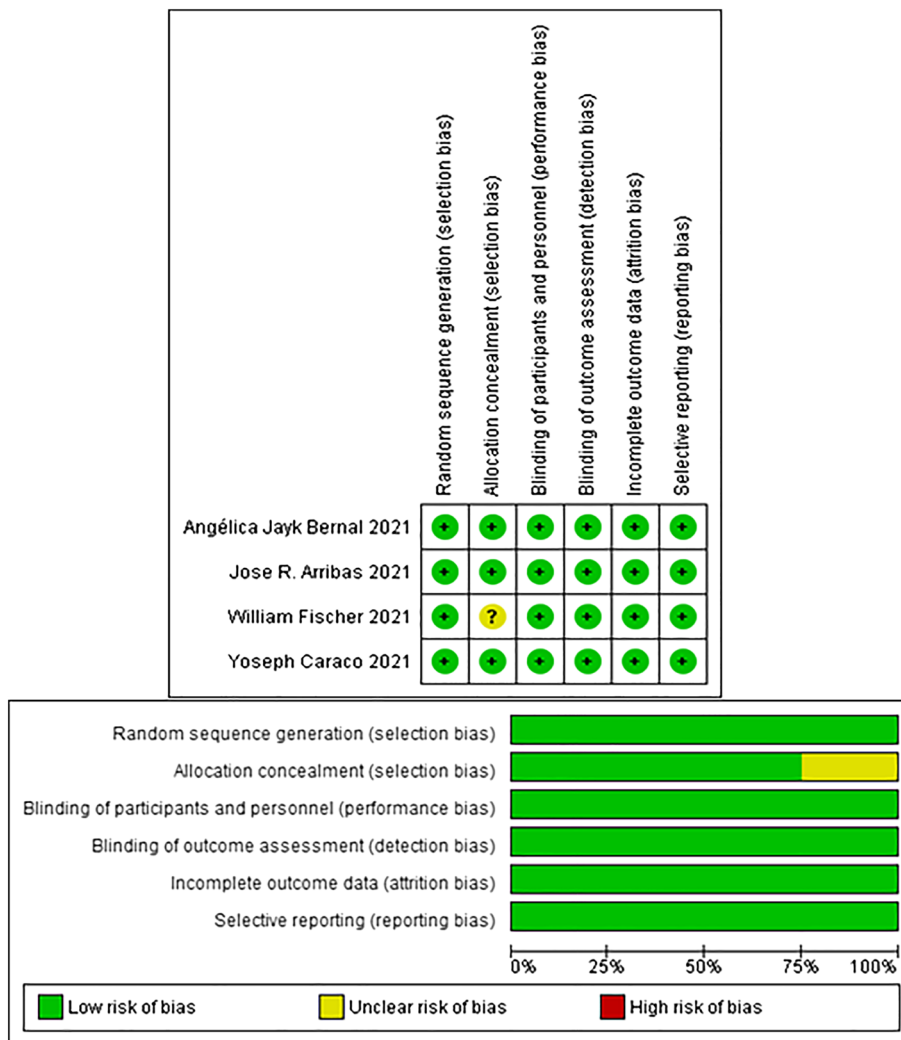
#### 3.3.1 | Meta-analysis of any adverse events

Four RCTs<sup>20-23</sup> including 1823 patients reported the incidence of any AEs. As the pooled risk ratio of four studies suggests, there was no significant difference between the administration of molnupiravir at doses of 200 mg, 400 mg and 800 mg compared with placebo (200 mg: RR = 0.97; 95% CI: 0.78–1.20;  $P = .80$ ; 400 mg: RR = 0.81;

95% CI: 0.64–1.02;  $P = .07$ ; 800 mg: RR = 0.94; 95% CI: 0.83–1.06;  $P = .36$ ) for any AEs (Figure 3).

#### 3.3.2 | Meta-analysis of serious adverse events

Serious adverse events were also reported in all included studies.<sup>20-23</sup> The results of the meta-analysis showed no significant differences between patients receiving molnupiravir at doses of 200 mg, 400 mg



**FIGURE 2** Risk of bias assessment in the selected studies; (+): low risk of bias, (?): unclear risk of bias

and 800 mg compared with placebo (200 mg: RR = 0.81; 95% CI: 0.41–1.63;  $P = .57$ ; 400 mg: RR = 0.82; 95% CI: 0.41–1.61;  $P = .56$ ; 800 mg: RR = 0.80; 95% CI: 0.59–1.08;  $P = .15$ ) for SAEs (Figure 4).

### 3.3.3 | Meta-analysis of adverse events leading to death

All studies<sup>20–23</sup> reported AEs leading to death among patients with COVID-19. No significant difference was observed between the molnupiravir groups at doses of 200 mg, 400 mg and 800 mg compared with placebo (200 mg: RR = 1.74; 95% CI: 0.48–6.30;  $P = .39$ ; 400 mg: RR = 1.07; 95% CI: 0.28–4.09;  $P = .91$ ; 800 mg: RR = 0.47; 95% CI: 0.17–1.28;  $P = .14$ ) for AEs leading to death (Figure 5).

### 3.3.4 | Meta-analysis of treatment discontinuation due to adverse events

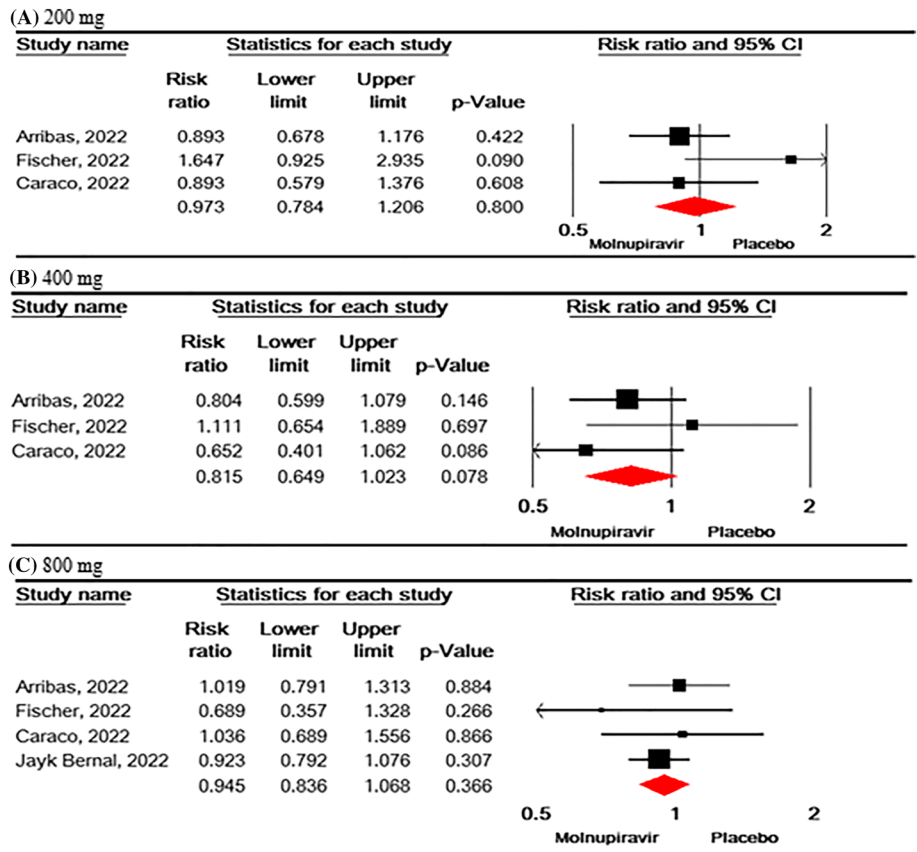
The result of the meta-analysis showed that there was no significant difference between molnupiravir at 200 mg, 400 mg and 800 mg

compared with placebo (200 mg: RR = 1.50; 95% CI: 0.26–8.55;  $P = .64$ ; 400 mg: RR = 0.99; 95% CI: 0.17–5.68;  $P = .99$ ; 800 mg: RR = 0.61; 95% CI: 0.31–1.23;  $P = .17$ ) for treatment discontinuation due to AEs (Figure 6).

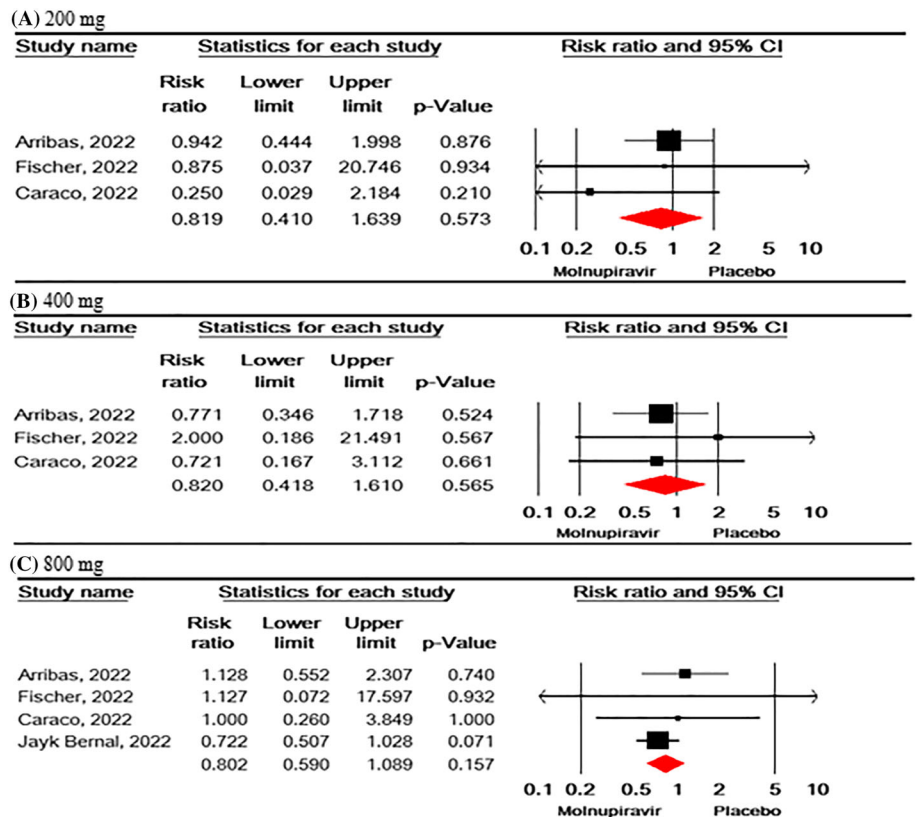
### 3.3.5 | Subgroup and sensitivity analyses

We performed a subgroup analysis based on hospitalized and non-hospitalized patients receiving molnupiravir or placebo (Table 2). The result showed no significant difference between the two groups in hospitalized and non-hospitalized patients. To perform a sensitivity analysis, we included a phase I, open-label, dose-escalating, randomized controlled study<sup>25</sup> in our analysis. No significant difference was observed between the molnupiravir and placebo/standard of care groups in terms of AEs (Table 2). In addition, since two of the included RCTs<sup>21,23</sup> in our meta-analysis have been published with an identical NCT number, we removed one of them,<sup>21</sup> which was a phase II trial with a small sample size, before analysing the data. No significant change was observed in the results for outcomes of interest including AEs, SAEs, AEs leading to death and discontinuation due to AEs (Table 2).

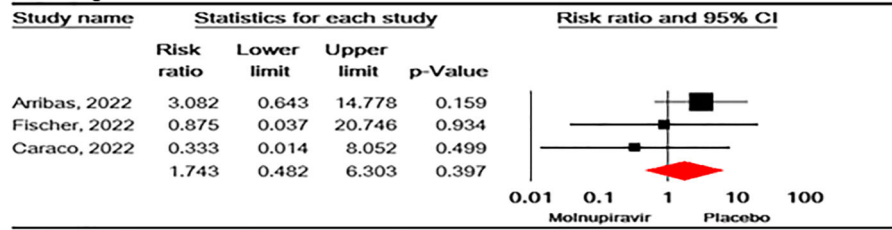
**FIGURE 3** Forest plot of molnupiravir at doses of 200 mg (A), 400 mg (B) and 800 mg (C) compared with placebo for the incidence of any adverse event



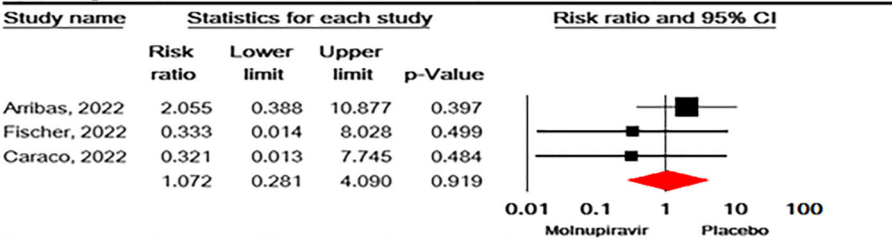
**FIGURE 4** Forest plot of molnupiravir at doses of 200 mg (A), 400 mg (B) and 800 mg (C) compared with placebo for serious adverse events



(A) 200 mg



(B) 400 mg



(C) 800 mg

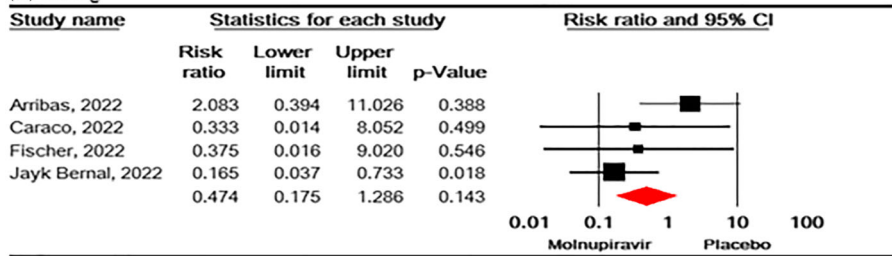
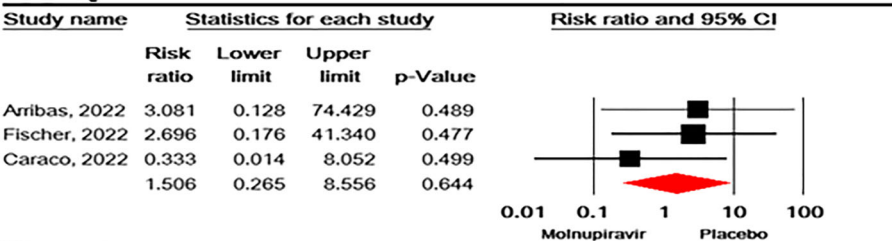
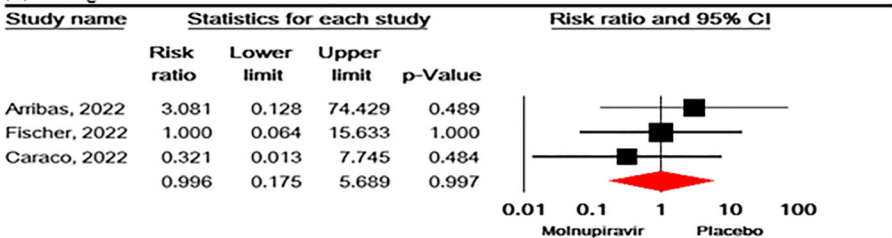


FIGURE 5 Forest plot of molnupiravir at doses of 200 mg (A), 400 mg (B) and 800 mg (C) compared with placebo for adverse events leading to death

(A) 200 mg



(B) 400 mg



(C) 800 mg

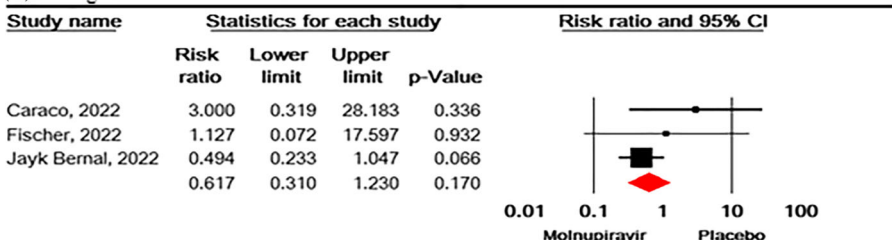


FIGURE 6 Forest plot of molnupiravir at doses of 200 mg (A), 400 mg (B) and 800 mg (C) compared with placebo for treatment discontinuation due to any adverse events



**TABLE 2** Subgroup and sensitivity analyses of safety outcome of molnupiravir for treatment of COVID-19

Analysis	No. of studies	N	Point estimate (95% CI)	P-value	Heterogeneity		
					Q-value	P-value	I-square
<b>Sensitive analysis</b>							
AEs-800 mg (PBO/SOC)	5	1833	0.94 [0.83, 1.06]	0.31	3.18	0.52	0.00
AEs- 800 mg	3	1675	0.93 [0.82, 1.06]	0.31	1.30	0.52	0.00
Serious AEs- 800 mg	3	1675	0.79 [0.57, 1.08]	0.14	1.26	0.53	0.00
Death- 800 mg	3	1675	0.51 [0.08, 3.10]	0.47	4.97	0.08	59.80
Discontinuation-800	2	1528	0.52 [0.25, 1.08]	0.08	0.32	0.57	0.00
<b>Subgroup analysis</b>							
<b>Any AEs</b>							
200 mg	3	381	0.97 [0.78, 1.20]	0.80	3.713	0.15	46.14
Nonhospitalized	2	233	1.11 [0.78, 1.57]	0.54	2.768	0.09	63.86
Hospitalized	1	148	0.89 [0.67, 1.17]	0.42	0.000	1.00	0.00
400 mg	3	423	0.81 [0.64, 1.02]	0.07	2.12	0.34	5.76
Nonhospitalized	2	275	0.83 [0.58, 1.19]	0.31	2.10	0.14	52.40
Hospitalized	1	148	0.80 [0.59, 1.07]	0.14	0.00	1.00	0.00
800 mg	4	1823	0.94 [0.83, 1.06]	0.36	1.51	0.67	0.00
Nonhospitalized	3	1676	0.92 [0.80, 1.06]	0.26	1.07	0.58	0.00
Hospitalized	1	147	1.01 [0.79, 1.31]	0.88	0.00	1.00	0.00
<b>Serious AEs</b>							
200 mg	3	381	0.81 [0.41, 1.63]	0.57	1.28	0.52	0.00
Nonhospitalized	2	233	0.37 [0.06, 2.23]	0.28	0.41	0.52	0.00
Hospitalized	1	148	0.94 [0.44, 1.99]	0.87	0.00	1.00	0.00
400 mg	3	423					
Nonhospitalized	2	275	0.95 [0.27, 3.31]	0.94	0.51	0.47	0.00
Hospitalized	1	148	0.77 [0.34, 1.71]	0.52	0.00	1.00	0.00
800 mg	4	1823					
Nonhospitalized	3	1676	0.74 [0.52, 1.04]	0.08	0.30	0.86	0.00
Hospitalized	1	147	1.12 [0.55, 2.30]	0.74	0.00	1.00	0.00
<b>AEs leading to death</b>							
200 mg	3	381					
Nonhospitalized	2	233	0.54 [0.05, 5.11]	0.59	0.17	0.67	0.00
Hospitalized	1	148	3.08 [0.64, 14.77]	0.15	0.00	1.00	0.00
400 mg	3	423					
Nonhospitalized	2	275	0.32 [0.03, 3.10]	0.33	0.00	0.98	0.00
Hospitalized	1	148	2.05 [0.38, 10.87]	0.39	0.00	1.00	0.00
800 mg	4	1823					
Nonhospitalized	3	1676	0.20 [0.06, 0.72]	0.01	0.31	0.85	0.00
Hospitalized	1	147	0.08 [0.39, 11.02]	0.38	0.00	1.00	0.00
<b>Discontinuation due to AEs</b>							
400 mg	3	423					
Nonhospitalized	2	275	0.61 [0.07, 4.93]	0.64	0.28	0.59	0.00
Hospitalized	1	148	3.08 [0.12, 74.42]	0.48	0.00	1.00	0.00

AE, adverse event; CI, confidence interval; PBO, placebo; RR, risk ratio; SOC, standard of care.

## 4 | DISCUSSION

The present study aimed to scrutinize the AEs associated with molnupiravir prescription in COVID-19 patients. Molnupiravir,  $\beta$ -d-N4-hydroxycytidine-5'-isopropyl ester (EIDD-2801), is classified as a mutagenic nucleotide analogue with high potential for the treatment of seasonal influenza viral infections.<sup>26</sup> Against COVID-19, it targets a vital protein for SARS-CoV-2 replication called RNA-dependent RNA polymerase (RdRp) as an inhibitor<sup>12</sup> which in turn has the virtue of COVID-19 management<sup>27</sup> because this enzyme is essential for COVID-19 proliferation<sup>28</sup> and it has been shown that drugs that target RdRp are beneficial against SARS-CoV-2 infection.<sup>27</sup> Currently, other RdRp inhibitors, such as remdesivir and favipiravir, are prescribed.<sup>29</sup>

The findings of the meta-analysis, which included four pieces of research, found no significant relationship between all doses of molnupiravir prescribed (200, 400 and 800 mg twice daily) and placebo for the incidence of AEs and SAEs. These findings are consistent with studies<sup>30-32</sup> showing that molnupiravir in COVID-19 patients is safe and well tolerated. In the meta-analysis conducted by Wen et al.,<sup>32</sup> in which three new antiviral treatments including molnupiravir, fluvoxamine and paxlovid for COVID-19 were examined, no significant difference was observed between these drugs and the control group regarding the incidence of adverse events which is consistent with our findings. However, their study considered all these drugs as a single intervention group and did not conduct a subgroup analysis based on the type of intervention and dosages.

Our meta-analysis also indicated that molnupiravir at 200, 400 and 800 mg twice daily was not significantly associated with AEs leading to death. Furthermore, no significant difference was observed between molnupiravir at all dosages and placebo groups regarding AEs leading to treatment discontinuation. A review of clinical and pre-clinical evidence<sup>33</sup> showed the safety and tolerability of molnupiravir in COVID-19 patients.

This rapid review highlights the risk of AEs and SAEs that molnupiravir may impose and explores its potential threat of death in COVID-19 patients. However, this study is not without limitations. First, only a small number of studies on the safety of molnupiravir were available. Second, most available studies with phase II and II/III clinical trials had a small sample size which might increase bias and overestimation of our findings.<sup>34,35</sup> Moreover, due to an insufficient number of studies, the subgroup analysis of other variables such as phases of clinical trials was practically impossible. Finally, since only one RCT was published regarding AEs of molnupiravir in patients hospitalized with COVID-19, further evidence on hospitalized patients with molnupiravir administration is required to evaluate the safety of molnupiravir.

## 5 | CONCLUSION

Meta-analysis of AEs reported in published RCTs showed that molnupiravir in all prescribed doses (200 mg, 400 mg and 800 mg twice daily) compared with placebo is a safe therapeutic intervention and

well tolerated in patients with COVID-19. However, except for one study, other studies included in our meta-analysis were phase II clinical trials; therefore, further phase III clinical trials are needed to confirm the safety profile of molnupiravir in COVID-19 patients.

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### COMPETING INTERESTS

The authors declare that there are no conflicts of interest.

### CONTRIBUTORS

Behnam Amani and Bahman Amani conceived, administered and supervised the project. Bahman Amani and Behnam Amani conducted the meta-analysis. Bahman Amani, Sara Zareei and Behnam Amani conducted investigations and were responsible for the methodology. Sara Zareei and Behnam Amani collected the data. Bahman Amani wrote the original draft. All of the authors were responsible for reviewing and editing the manuscript.

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None.

### DATA AVAILABILITY STATEMENT

Data are available online for the included studies.<sup>20-23</sup>

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