## MAJOR ARTICLE

# A systematic review of nirmatrelvir/ritonavir and molnupiravir for the treatment of COVID-19

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**Background:** To address the need for treatments for patients with COVID-19, three therapies have been given either full approval or Emergency Use Authorization. These were based on randomized data showing a reduction in deaths/hospitalization, but since then, circulating viral strains and population immunity has changed.

**Methods:** We identified all trials testing nirmatrelvir/ritonavir and molnupiravir in patients with COVID-19 and assessed the pooled efficacy in a meta-analysis. We searched PubMed, Web of Science, Embase, and clinicaltrials.gov for clinical trials testing nirmatrelvir/ritonavir and molnupiravir for COVID-19. We calculated pooled estimates of hospitalization and death in patients with COVID-19 and the number of studies with published/reported data.

**Results:** Of the 23 studies found, 11 tested nirmatrelvir/ritonavir, 10 tested molnupiravir, and two tested both agents. The pooled estimate in reducing deaths and hospitalization for molnupiravir was 0.62 (95% CI: 0.15 to 2.53), and the pooled estimate for nirmatrelvir/ritonavir was 0.33 (95% CI: 0.03 to 3.35). The one nirmatrelvir/ritonavir trial that reported significant improvements tested people who were predominantly infected with earlier COVID-19 variants, whereas the two null trials were tested in people infected with more recent variants. The two positive molnupiravir

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trials included participants primarily with the delta variant, whereas the null trials were tested later, against more recent variants.

**Conclusions:** While early trial data show effectiveness of these therapies, the overall pooled effects are non-significant, suggesting that recommendations and use of approved oral COVID-19 treatment therapies need to be re-evaluated in the context of current viral strains and population immunity.

## INTRODUCTION

The emergence of the SARS-CoV-2 virus created an urgent need for treatments for individuals who have a high risk of serious outcomes from COVID-19. Three drugs have been approved by the US Food and Drug Administration (FDA) to reduce the risk of hospitalization and/or death for patients with mild to moderate COVID-19 - nirmatrelvir/ritonavir, molnupiravir, and remdesivir. Nirmatrelvir/ritonavir and molnupiravir are oral formulations and may be more likely to be used in the outpatient setting, compared to remdesivir that is administered intravenously, due to their ease of administration.

Based on randomized data showing reduced hospitalization/death, nirmatrelvir/ritonavir was given emergency Use Authorization (EUA) on December 22, 2021 (fully approved on May 25, 2023),[1,2] and molnupiravir was given EUA on December 23, 2021.[3] The early approvals were based on trials that excluded participants who were vaccinated (EPIC-HR), had not been previously infected with the SARS-CoV-2 virus (EPIC-HR), and/or were tested during earlier strains of the SARS-CoV-2 virus (e.g., delta) that are no longer circulating (EPIC-HR and EPIC-SR).[4,5] Since then, other trials have been planned and initiated (e.g., RECOVERY).[6] These trials have been tested against more contemporary strains of the virus and have included patients who have been vaccinated and/or acquired immunity through virus exposure.

Lingering symptoms from the SARS-CoV-2 virus have been reported by some, which has prompted additional studies to examine these therapies in the context of long COVID-19.

The evolving strains of the SARS-CoV-2 virus and increasing population immunity, either through vaccination or infection, results in changing effectiveness of the approved drugs. We have seen this in other COVID-19 therapies, such as bamlanivimab, which had its EUA revoked due to decreased effectiveness.[7] Yet, these oral drugs continued to be approved and recommended.[8] We therefore sought to systematically review all trials testing nirmatrelvir/ritonavir or molnupiravir in the treatment of COVID-19 and to characterize the available evidence for these therapies.

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## METHODS

We sought to systematically and comprehensively search all randomized trial data on FDA-approved oral drug therapies in treating mild to moderate COVID-19, including nirmatrelvir/ritonavir and molnupiravir. We searched PubMed using the search terms (nirmatrelvir and ritonavir) OR paxlovid AND covid. We searched Embase using the terms, (('nirmatrelvir'/exp OR nirmatrelvir) AND ('ritonavir'/exp OR ritonavir) OR 'paxlovid'/exp OR paxlovid) AND ('covid'/exp OR covid). We searched Web of Science using the search terms (NIRMATRELVIR and RITONAVIR) OR paxlovid AND covid AND randomized). For the molnupiravir search, we searched PubMed using molnupiravir AND covid. We searched Embase using ('molnupiravir'/exp OR molnupiravir) AND ('covid'/exp OR covid). We searched Web of Science using molnupiravir AND covid AND randomized. We included all interventional studies testing nirmatrelvir/ritonavir or molnupiravir for COVID-19, including long COVID-19, and the study population could include either hospitalized or non-hospitalized patients.

We further searched clinicaltrials.gov to find additional studies with unpublished data on this topic. The search criteria include COVID-19 in the "condition/disease" search box and either Paxlovid, nirmatrelvir/ritonavir, or molnupiravir in the "other" search box, restricted to interventional studies. Once trials were identified, we searched PubMed, Google, and Google scholar, using trial identification number and/or trial name to find published (peer-reviewed or not) result data.

All searches were made December 12, 2023. Embase and PubMed searches were restricted to randomized controlled trials. However, we later included a preprint publication on the RECOVERY trial, which was published after our initial search date.[6] We included studies reporting on the primary analysis of a randomized trial testing the efficacy of either the combination of nirmatrelvir and ritonavir or molnupiravir monotherapy. Studies needed to be in humans, and they needed to test one of the therapies against a standard of care at the time of the trial (i.e., we excluded studies that were head-to-head, such as nirmatrelvir/ritonavir vs molnupiravir). Finally, studies needed to test the intervention in the general population (i.e., we excluded studies in pregnant women or patients with kidney failure). We excluded non-randomized studies (including reviews and commentaries), secondary analyses of randomized data, bioavailability studies, simulation studies, and cellular/in-vitro studies. We also excluded studies that tested these therapies in preventing the incidence or transmission of COVID-19.

We abstracted trial data on dates of trial start and ending, phase, blinding status, number of patients (overall and in each treatment arm), primary outcome, study population, the number of people in each group with the outcome of hospitalization or death, predominant variant, vaccination status of participants, and trial registry number and name. From the trials on clinicaltrials.gov, we noted whether the trials were terminated, the primary outcome, and the study start and estimated end date.

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## Statistical analysis

We calculated descriptive statistics for studies evaluating these therapies. All analyses were done using R statistical software, version 4.2.1. We used the 'meta' package to calculate pooled relative risk of hospitalization and/or death for studies reporting the number of patients in each treatment arm with the outcome. We used a random-effects model to account for any between-study heterogeneity, and used the Mantel-Haenszel method to calculate the study weights. We used Knapp-Hartung adjustments in calculating confidence intervals around the pooled effects. We used a restricted maximum likelihood estimator for $\tau^2$.

In accordance with 45 CFR §46.102(f), this study was not submitted for University of California, San Francisco institutional review board approval because it involved publicly available data and did not involve individual patient data. We adhered to PRISMA reporting guidelines.

## RESULTS

For nirmatrelvir/ritonavir, we found 517 results in Web of Science, 34 in Embase, and 9 in PubMed. For molnupiravir, we found 59 results in Web of Science, 34 in Embase, and 16 in PubMed. We found 93 relevant studies on clinicaltrials.gov. After removing 85 duplicates from the search of publication databases and 31 duplicates from the clincaltrials.gov search, we searched 584 records from the published literature and 62 records on clinicaltrials.gov (Supplemental figure).

We found 23 studies that tested these therapies in patients with COVID-19 – 18 tested COVID-19 treatments and 5 tested long-COVID-19 treatments Characteristics of these trials are shown in the table, stratified by publication status and in the supplemental table. Eleven tested nirmatrelvir/ritonavir, 10 tested molnupiravir, and two tested both agents. Most were phase 2 or 2/3 (n=11; 47.8%) or phase 3 or 4 studies (n=9; 39.1%), 1 (5.6%) was a phase 1 trial, and two did not indicate the phase. Ten (43.5%) were open label, 12 (52.2%) were blinded, and 1 did not indicate. The most common primary outcome was change in symptoms (n=8; 34.8%), followed by hospitalization/death (n=6; 26.1%), followed by viral clearance (n=5; 21.7%), death (n=2; 8.7%), hospitalization (n=1; 4.3%), and quality of life (n=1; 4.3%). Omicron was the most common predominant variant (n=8; 34.8%), followed by delta (n=4; 17.4%), alpha (n=2; 8.7%), and delta/omicron (n=1; 4.3%), but the variant was not able to be determined in 8 studies (all without published trial data). Three trials were eventually terminated, and six trials were completed, according to clinicaltrials.gov.

The studies examining these therapies, a timeline of the study's enrollment history and their results are presented in Figure 1.

We were able to find reported results for 14 trials (Table). Of the trials with published results, 8 (57.1%) tested molnupiravir, 4 (28.6%) tested nirmatrelvir/ritonavir, and 2 (14.3%) tested both

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therapies. Five (35.7%) trials had a primary outcome of viral clearance, four (28.6%) trials had a primary outcome of hospitalization and death, 2 (14.3%) assessed COVID-19 symptoms, 2 (14.3%) assessed death, and 1 (7.1%) assessed hospitalization. All three terminated trials had published outcome data, indicating null results.

There were 4 trials that tested nirmatrelvir/ritonavir in long COVID-19. All used symptoms as a primary outcome for determining efficacy, and none had published results.

Three of the four trials that tested nirmatrelvir/ritonavir and reported death/hospitalization data, failed to find a difference (Figure 2). The one trial that reported significant improvements tested people who were predominantly with earlier COVID-19 variants (e.g., delta), whereas the three null trials were tested in people with more recent variants. The two nirmatrelvir/ritonavir trials that used a primary outcome of symptoms that had reported results were negative. Two of the five trials that tested molnupiravir and reported death/hospitalization data, found an improvement with molnupiravir. These two trials included participants primarily with the delta variant, whereas the null trials were tested later, against more recent variants. The one trial with symptoms as a primary outcome that also had published results was negative.

Figure 3 shows the pooled risk of hospitalization and/or death in studies testing nirmatrelvir/ritonavir and molnupiravir, sorted by the date the study stopped accrual. There were 8 studies (one that published data on both nirmatrelvir/ritonavir and molnupiravir) that had relevant information for the pooled estimate. 27,982 participants were included in the molnupiravir trials, and 2,320 participants were included in the nirmatrelvir/ritonavir trials. The pooled estimate for molnupiravir was 0.72 (95% CI: 0.31 to 1.63), and the pooled estimate for nirmatrelvir/ritonavir was 0.46 (95%CI: 0.10 to 2.08).

## DISCUSSION

We found 23 studies assessing nirmatrelvir/ritonavir and/or molnupiravir. Fourteen of these studies had published results, and two of these trials reported favorable results for nirmatrelvir/ritonavir and six trials reported favorable results for molnupiravir (4 based on viral clearance). Many of the primary outcomes were based on viral clearance, rather than patient-centered outcomes, such as hospitalization or death, and most positive trials were tested against unvaccinated populations and/or earlier strains of SARS-CoV-2.

A notable finding from our study is the lack of benefit for hospitalization and death in the pooled analysis. The only study that reported improvements in these outcomes was the EPIC-HR study, which is unique in that it included unvaccinated and non-hospitalized individuals. Similarly, the MOVE-OUT trial reported improvements in hospitalizations and deaths in unvaccinated, non-hospitalized patients. Positive trials were also the only trials in the pooled analysis to be tested when the Delta variant was the most common variant. Other trials that included vaccinated

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individuals and tested against other strains did not find significant improvements with these therapies.

A number of studies (39%) evaluating these therapies have yet to report results, and considering the resources spent on testing and implementation of these therapies, it is important to be able to have all results when considering effectiveness. Results for the EPIC-SR study, a study that failed to find benefit with nirmatrelvir/ritonavir, are only available as press-release data. Furthermore, the Panoramic study tested both nirmatrelvir/ritonavir and molnupiravir but has only published data on molnupiravir. According to clinicaltrials.gov, six studies of the 23 (26%) are complete, and of the six completed studies, we found published data for only three. These findings suggest that a full understanding of these drug's efficacy is incomplete. Moreover, because of publication bias, it is likely that many of the unpublished trials are or will be negative, and our results likely represent a better-case scenario than if all trials had reported data.

The efficacy of these anti-viral therapies has been primarily demonstrated in trials tested when earlier strains, such as the delta variant, were common. The lack of efficacy in more recent trials has not been discussed in the literature. It may be that there is little incentive to re-evaluate effectiveness since these drugs already have approval. Regardless, as with all medical interventions, it is important to regularly assess the effectiveness of therapies to ensure that treatment is evidence-based.

Several large, observational studies have been conducted, assessing the association between receipt of nirmatrelvir or molnupiravir and COVID-19 during the omicron wave. Their findings indicate a striking reduction in deaths and hospitalization, suggesting possible efficacy. However, because of the observational nature of these studies, there is likely unaccounted confounding, which is most evident by the almost immediate separation of the survival curves between those who received nirmatrelvir or molnupiravir and those who did not.[9,10] Indeed, other researchers have documented bias in these types of studies.[11–13] The randomized studies done during the omicron wave have failed to corroborate any hospitalization or mortality benefit.[6,14,15]

It is worth considering that these treatments may be beneficial to patients who are immunocompromised or significant risk factors for progression to severe disease. This should be further tested in high-quality randomized controlled studies. Although, it should be noted that two of the trials in this analysis included hospitalized patients, and both studies reported null findings.[6,14]

Despite declining effectiveness of these therapies, in terms of hospitalization and death, sales for nirmatrelvir/ritonavir and molnupiravir have continued to remain strong. The sales of nirmatrelvir/ritonavir are estimated to be $8 billion in 2023 and about $19 billion in 2022.[16] For molnupiravir, sales are estimated to be about $4.7 billion in 2023 and $5.7 billion in 2022.[17] Few cost-effectiveness analyses using randomized data have been done, but a recent analysis indicates that the use of molnupiravir is unlikely to be cost-effective in the general population, especially

when vaccination rates are high.[18] To date, there have not been any analyses on nirmatrelvir/ritonavir. Considering increasing vaccination/seroprevalence rates and the results of cost effectiveness studies, there may be better use of limited healthcare dollars.

Outcomes for determining effectiveness varied from serious outcomes, such as hospitalization and death, to ones less important for patients, such as viral clearance. Only one trial testing nirmatrelvir/ritonavir and two trials testing molnupiravir reported positive results for hospitalization and death, and no trial reported positive results when using the primary outcome of symptoms. Many of the positive trials used viral clearance as the primary outcome. And yet, there is low correlation between viral clearance and more serious outcomes, such as hospitalization, and likely any small correlation is limited to those who are unvaccinated and/or without prior infection.[19]

## Limitations

Our analysis is limited by several factors. It is possible that we did not find all randomized studies evaluating the effectiveness of these therapies. To capture as many studies as possible, we not only used three databases, but we also searched clincialtrials.gov to find additional studies. Second, we focused on hospitalization and death outcomes, rather than virus clearance, so our results may not reflect the findings at-large. While we do include these studies in our analysis, we wanted to focus on outcomes most important to the health of patients and the population. Third, the incompleteness of the study publications may affect the generalizability of our findings.

## CONCLUSION

In conclusion, the early data of nirmatrelvir/ritonavir and molnupiravir for the treatment of COVID-19 was positive, but trials during later strains of the SARS-CoV-2 virus have failed to show clinical benefit, in terms of hospitalization and death. Against the backdrop of an evolving strain of virus and increasing population immunity, approval data for currently available treatments for COVID-19 need to be re-evaluated, based on current strains and immunity.

*Data availability:* We used publicly available data. Data for these analyses can be obtained upon request to the primary author.

*Author contributions:* AH and VP conceptualized study design; AH abstracted data and VP reviewed data; AH conducted data analysis and wrote first draft; VP reviewed and finalized draft.

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**Table:** Characteristics of randomized studies evaluating the efficacy of nirmatrelvir/ritonavir or molnupiravir in patients with COVID and long COVID.

|  | No published data* | Published data |
|---|---|---|
| Number of trials | 9 | 14 |
| Drug (%) |  |  |
| Both | 0 (0.0) | 2 (14.3) |
| Molnupiravir | 2 (22.2) | 8 (57.1) |
| Nirmatrelvir/ritonavir | 7 (77.8) | 4 (28.6) |
| Phase (%) |  |  |
| 1 | 0 (0.0) | 1 (7.1) |
| 2 | 4 (44.4) | 3 (21.4) |
| 2/3 | 0 (0.0) | 4 (28.6) |
| 3 | 5 (55.6) | 3 (21.4) |

| | | |
|---|---|---|
| 4 | 0 (0.0) | 1 (7.1) |
| NI | 0 (0.0) | 2 (14.3) |
| Blind (%) | | |
| Blind | 6 (66.7) | 6 (42.9) |
| NI | 0 (0.0) | 1 (7.1) |
| Open | 3 (33.3) | 7 (50.0) |
| Number of participants (median (IQR)) | | 278 (152, 1130) |
| Predominant variant (%) | | |
| Alpha | 0 (0.0) | 2 (14.3) |
| Delta | 0 (0.0) | 4 (28.6) |
| Delta/omicron | 0 (0.0) | 1 (7.1) |
| NI | 8 (88.9) | 0 (0.0) |
| Omicron | 1 (11.1) | 7 (50.0) |
| Country (%) | | |
| Belgium | 0 (0.0) | 1 (7.1) |
| Canada | 1 (11.1) | 0 (0.0) |
| China | 0 (0.0) | 3 (21.4) |
| India | 0 (0.0) | 1 (7.1) |
| Multiple | 0 (0.0) | 5 (35.7) |
| Norway | 1 (11.1) | 0 (0.0) |
| Russia | 2 (22.2) | 0 (0.0) |
| South Africa | 1 (11.1) | 0 (0.0) |
| Sweden | 1 (11.1) | 0 (0.0) |
| Thailand | 0 (0.0) | 1 (7.1) |
| UK | 0 (0.0) | 2 (14.3) |
| US | 3 (33.3) | 1 (7.1) |
| Percent vaccinated (median (IQR)) | | 67.0 (0, 92) |
| Primary outcome (%) | | |
| Death | 0 (0.0) | 2 (14.3) |
| Hospitalization | 0 (0.0) | 1 (7.1) |
| Hospitalization/death | 2 (22.2) | 4 (28.6) |
| Quality of life | 1 (11.1) | 0 (0.0) |
| Symptoms | 6 (66.7) | 2 (14.3) |
| Viral clearance | 0 (0.0) | 5 (35.7) |
| Status on clincialtrials.gov (%) | | |
| Completed | 3 (33.3) | 3 (21.4) |
| Ongoing | 6 (66.7) | 8 (57.1) |
| Terminated | 0 (0.0) | 3 (21.4) |

*Data were considered unpublished if we were unable to find any peer-reviewed publications, preprints, conference abstracts reporting trial results, or if there were no results published on clinicaltrials.gov.

**Figure 1.** Timeline of trials testing nirmatrelvir/ritonavir and/or molnupiravir in patients with COVID-19.
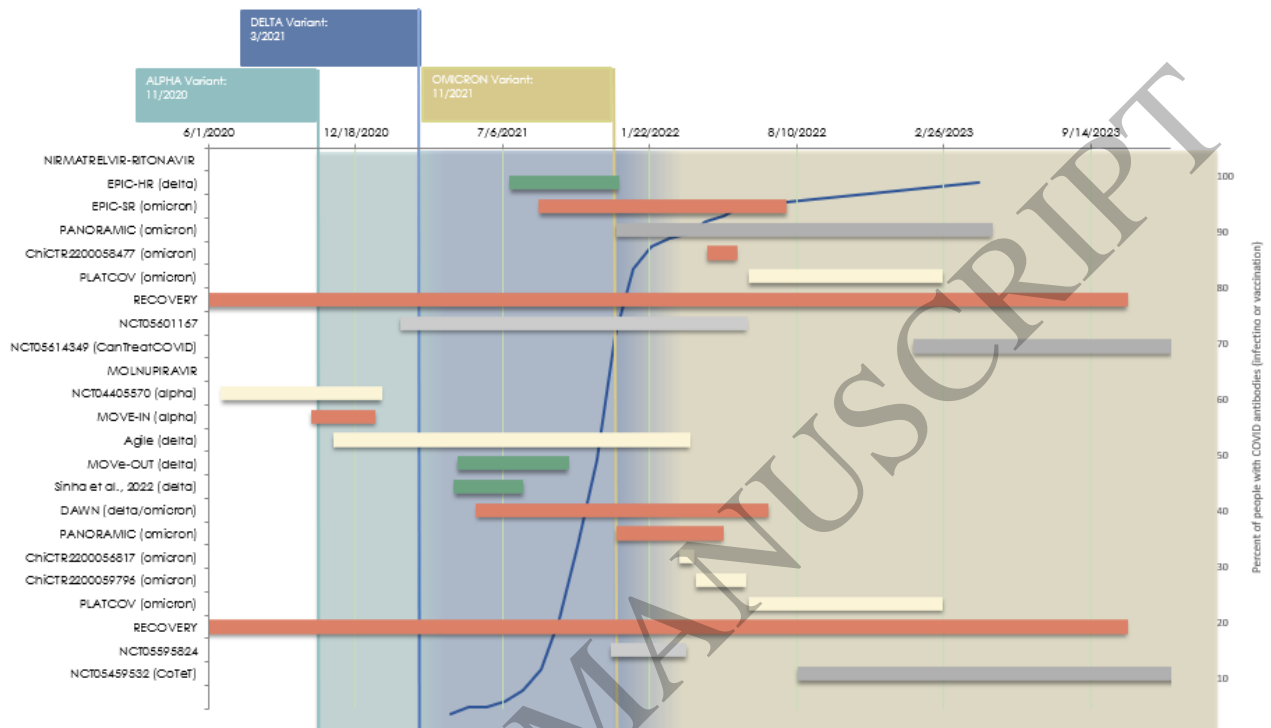


Red indicates negative results for hospitalization and death; green indicates positive results for hospitalization and death; yellow indicates softer outcomes (e.g., viral clearance) and gray indicates no published results. The width of the bar represents the time between the start and end of enrollment. The blue line in the background indicates the percentage of the population with COVID antibodies (https://covid.cdc.gov/covid-data-tracker/#nationwide-blood-donor-seroprevalence).

**Figure 2.** Percentages of patients with mortality and hospitalization outcomes in trials testing nirmatrelvir/ritonavir or molnupiravir against COVID-19.
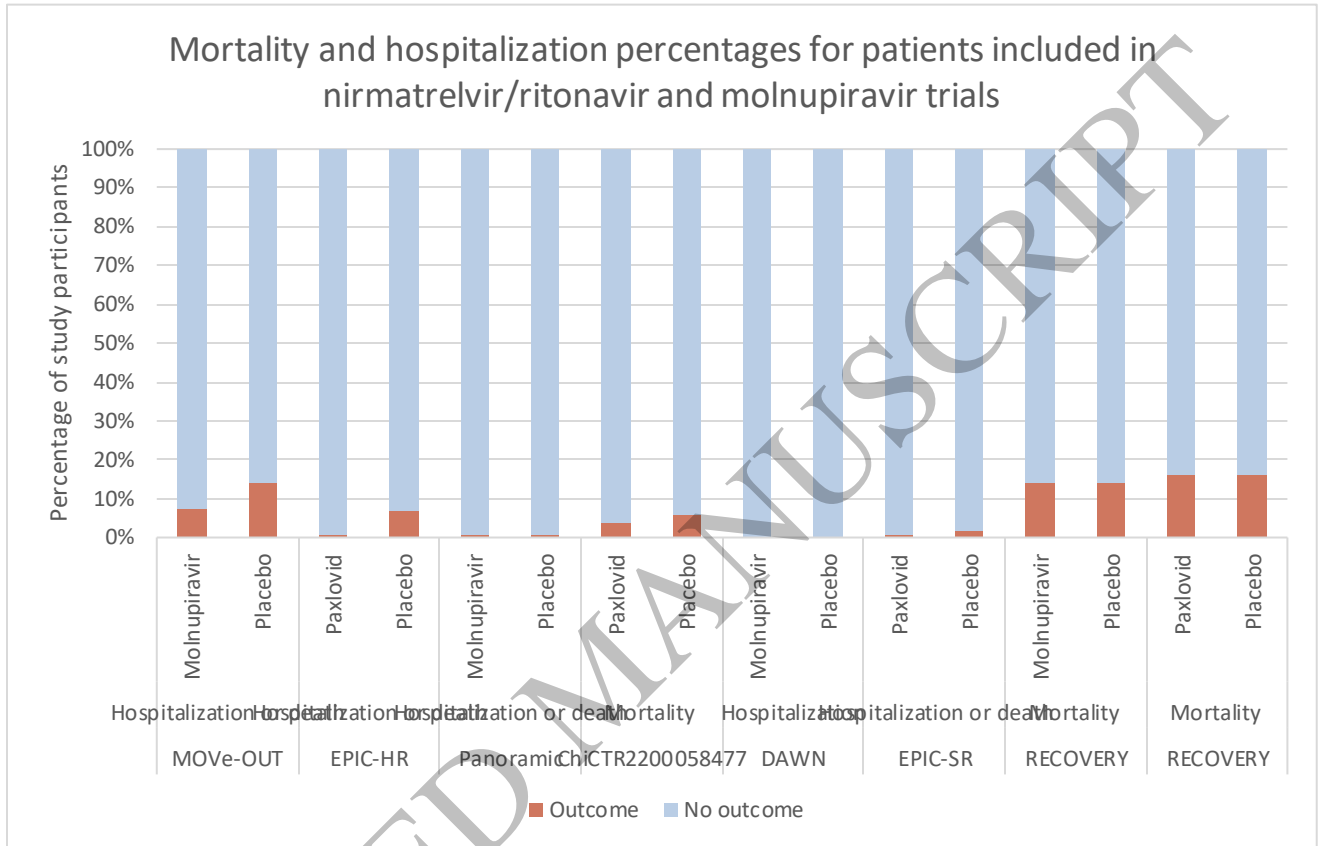
**Figure 3.** Forest plot of risk of hospitalization and/or death in trials testing nirmatrelvir/ritonavir or molnupiravir against COVID-19.