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Review Article

Safety of RNA-Dependent RNA Polymerase Inhibitors, Molnupiravir and VV116, for Oral Treatment of COVID-19: A Meta-Analysis

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Abstract

Background: The RNA-dependent RNA polymerase (RdRp) inhibitors, molnupiravir and VV116, have the potential to maximize clinical benefits in the oral treatment of COVID-19. Subjects who consume these drugs may experience an increased incidence of adverse events. This study aimed to evaluate the safety profile of molnupiravir and VV116.

Methods: A comprehensive search of scientific and medical databases, such as PubMed Central/Medline, Embase, Web of Science, and Cochrane Library, was conducted to find relevant articles in English from January 2020 to June 2023. Any kind of adverse events reported in the study were pooled and analyzed in the drug group versus the control group. Estimates of risk effects were summarized through the random effects model using Review Manager version 5.2, and sensitivity analysis was performed by Stata 17.0 software.

Results: Fifteen studies involving 32,796 subjects were included. Eleven studies were placebo-controlled, and four were Paxlovid-controlled. Twelve studies reported adverse events for molnupiravir, and three studies described adverse events for VV116. The total odds ratio (OR) for adverse events in the RdRp inhibitor versus the placebo-controlled group was 1.01 (95% CI=0.84-1.22; I^2=26%), P=0.88. The total OR for adverse events in the RdRp inhibitor versus the Paxlovid-controlled group was 0.32 (95% CI=0.16-0.65; I^2=87%), P=0.002. Individual drug subgroup analysis in the placebo-controlled study showed that compared with the placebo group, a total OR for adverse events was 0.97 (95% CI, 0.85-1.10; I^2=0%) in the molnupiravir group and 3.77 (95% CI=0.08-175.77; I^2=85%) in the VV116 group.

Conclusion: The RdRp inhibitors molnupiravir and VV116 are safe for oral treatment of COVID-19. Further evidence is necessary that RdRp inhibitors have a higher safety profile than Paxlovid.

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Keywords ● COVID-19 ● RNA-dependent RNA polymerase ● Nirmatrelvir and ritonavir drug combination ● GS-621763 ● Molnupiravir

What's Known

- Molnupiravir and VV116, novel RNA-dependent RNA polymerase inhibitors, have shown promise in COVID-19 clinical trials.
- Prior studies have reported various adverse events such as gastrointestinal symptoms, headaches, fatigue, and abnormal liver function tests, but a comprehensive and systematic assessment remains an area for further exploration.

What's New

- This is a comprehensive meta-analysis of the safety of the RNA-dependent RNA polymerase inhibitors, molnupiravir and VV116, for the oral treatment of COVID-19 based on available clinical trials.
- This study showed no increased adverse event risk compared to placebo and potentially lower risk than Paxlovid, another COVID-19 antiviral agent.

Introduction

Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), several variants of the virus have

been identified, including alpha, beta, gamma, delta, and omicron.[1] Vaccination may be the best solution to control the epidemic, but new novel coronavirus variants present a challenge to this measure. Individuals with weakened immune systems may not attain complete protection from vaccination, and there is growing apprehension about the effectiveness of existing vaccines against emerging COVID-19 variants.[2] Consequently, it becomes crucial to prioritize the investigation and creation of alternative treatments, specifically emphasizing the development of orally administered drugs to combat COVID-19. The exploration of oral medications assumes a pivotal role in managing the pandemic, particularly in situations where vaccines may not provide optimal protection or face accessibility challenges.[3, 4]

RNA-dependent RNA polymerase (RdRp) is an essential enzyme in RNA viruses that participates in RNA synthesis by forming phosphodiester bonds.[5] RdRp has been acknowledged as a valuable target for antiviral drugs in RNA virus infections such as SARS-CoV-2.[6] Apart from the best-known RdRp inhibitors, such as remdesivir and favipiravir, the US Food and Drug Administration (FDA) has issued an emergency license for molnupiravir.[4, 7] Molnupiravir is an orally active RdRp inhibitor.[4] It is a nucleoside analogue prodrug that is rapidly converted to nucleoside triphosphate (NTP) by an intracellular metabolic process. NTP inhibits viral polymerase by acting as an alternative substrate.[8] Molnupiravir has been evaluated in phase I, II, and III trials where it has shown promising efficacy and safety in patients with COVID-19. Bernal and others reported clinical benefit and adverse event rates comparable to the placebo group for molnupiravir in unvaccinated adults with COVID-19 in a phase III trial.[9]

VV116 (GS-621763) is a next-generation RdRp inhibitor. Unlike intravenously administered remdesivir, VV116 is an oral GS-441524 derivative (the active metabolite of remdesivir).[10, 11] VV116 has shown effectiveness against SARS-CoV-2 infection in preclinical studies.[12, 13] With no serious adverse events reported in clinical studies, VV116 demonstrated a satisfactory safety and tolerability profile.[14, 15] Recent trials have reported a lower incidence of adverse events in the VV116 group than in the nirmatrelvir-ritonavir (Paxlovid) group (67.4% vs. 77.3%).[16] Nevertheless, comprehensive and timely updated assessments remain an area for further exploration.

Given that the clinical administration of the RdRp inhibitors, molnupiravir and VV116, increased during the COVID-19 pandemic, a meta-analysis of the safety of these drugs is important. This study pools the currently available data from clinical trials of molnupiravir and VV116 in COVID-19 to assess their adverse events.

Materials and Methods

This meta-analysis was written to comply with the PRISMA statement.[17]

Inclusion and Exclusion Criteria

The inclusion criteria were based on the PICO framework as follows:

Population: Adult patients with confirmed or suspected COVID-19 infection who received oral treatment with RdRp inhibitors (molnupiravir or VV116) or control (placebo or Paxlovid) from January 2020 to June 2023.

Intervention: Oral administration of RdRp inhibitors (molnupiravir or VV116) at any dose, frequency, or duration.

Comparison: Oral administration of control (placebo or Paxlovid) at any dose, frequency, or duration.

Outcomes: Adverse events of any type, severity, or duration reported by the studies, such as gastrointestinal symptoms, headache, fatigue, and liver function test abnormalities.

The exclusion criteria were as follows: (1) unrelated research directions; (2) no relevant data; (3) review papers; (4) repeated articles; (5) studies on animal models, case reports, comments, and letters to the editor; (6) included articles must be in the English language.

Search Strategy

An extensive literature search was conducted in PubMed Central/Medline, Web of Science, Embase, and Cochrane Library. We also searched the clinical trials database ClinicalTrials.gov to explore further records. The following keywords were used in the search: molnupiravir (Lagevrio, EIDD-2801, MK-4482), GS-621763 (GS-441524 derivative, JT001, VV116), and COVID-19 (SARS-CoV-2, SARS2, SARS Coronavirus 2, Coronavirus Disease 2019, 2019-nCoV, 2019 Novel Coronavirus). The search strategy in PubMed Central/Medline was as follows: (molnupiravir[mh] OR molnupiravir OR Lagevrio or EIDD-2801 or MK-4482 OR GS-621763[mh] OR GS-621763 OR GS621763 OR GS 621763 OR "GS-441524 prodrug" OR JT001 OR JT-001 OR VV116 OR VV-116 OR "GS-441524 derivatives" OR "GS-441524 derivative") AND (COVID-19[mh] OR COVID-19 OR "COVID 19" OR "SARS-CoV-2" OR SARS2

OR "SARS Coronavirus 2" OR "Coronavirus Disease 2019" OR "2019-nCoV" OR "2019 Novel Coronavirus" OR "Severe Acute Respiratory Syndrome Coronavirus 2"). The rest of the detailed search strategy was as follows: Embase ('molnupiravir' OR 'lageviro' OR 'eidd-2801' OR 'mk-4482' OR 'gs-621763' OR 'gs621763' OR 'gs 621763' OR 'gs-441524 prodrug' OR 'jt001' OR 'jt-001' OR 'vv116' OR 'vv-116' OR 'GS-441524 derivatives' OR 'GS-441524 derivative') AND ('covid-19' OR 'covid 19' OR 'sars-cov-2' OR 'sars2' OR 'sars coronavirus 2' OR '2019-ncov' OR '2019 novel coronavirus' OR 'severe acute respiratory syndrome coronavirus 2' OR 'coronavirus disease 2019'); Web of science ALL=(molnupiravir OR Lagevrio or EIDD-2801 or MK-4482 OR GS-621763 OR GS621763 OR GS 621763 OR "GS-441524 prodrug" OR JT001 OR JT-001 OR VV116 OR VV-116 OR "GS-441524 derivatives" OR "GS-441524 derivative") AND ALL=(COVID-19 OR "COVID 19" OR "SARS-CoV-2" OR SARS2 OR "SARS Coronavirus 2" OR "Coronavirus Disease 2019" OR "2019-nCoV" OR "2019 Novel Coronavirus" OR "Severe Acute Respiratory Syndrome Coronavirus 2"); Cochrance Library (molnupiravir OR Lagevrio or EIDD-2801 or MK-4482 OR GS-621763 OR GS621763 OR GS 621763 OR "GS-441524 prodrug" OR JT001 OR JT-001 OR VV116 OR VV-116 OR "GS-441524 derivatives" OR "GS-441524 derivative") AND (COVID-19 OR "COVID 19" OR "SARS-CoV-2" OR SARS2 OR "SARS Coronavirus 2" OR "Coronavirus Disease 2019" OR "2019-nCoV" OR "2019 Novel Coronavirus" OR "Severe Acute Respiratory Syndrome Coronavirus 2") in Title Abstract Keyword;

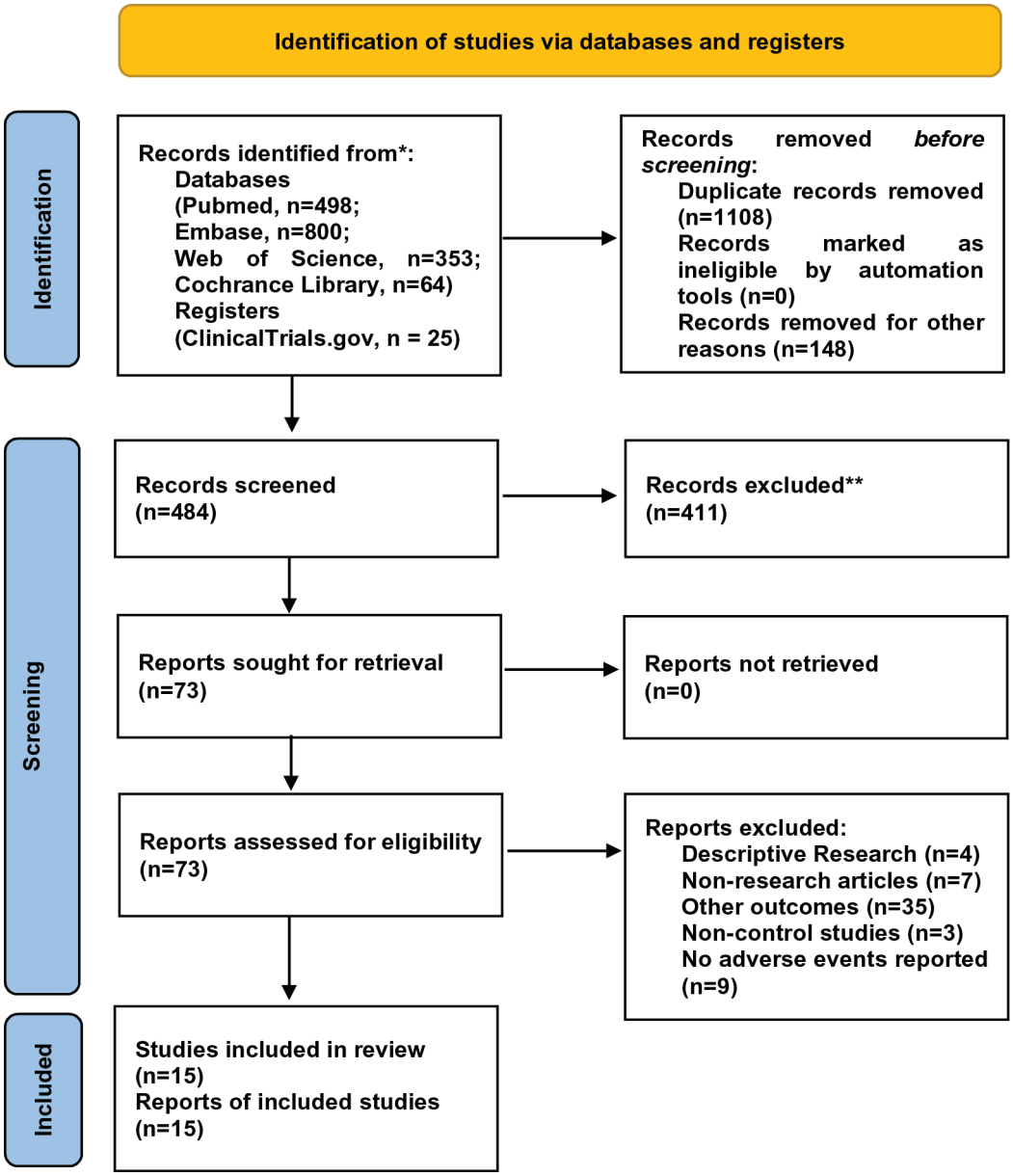

Figure 1: The PRISMA flowchart presenting the process of research screening.

ClinicalTrials.gov (molnupiravir OR Lagevrio or EIDD-2801 or MK-4482 OR GS-621763 OR GS621763 OR GS 621763 OR "GS-441524 prodrug" OR JT001 OR JT-001 OR VV116 OR VV-116 OR "GS-441524 derivatives" OR "GS-441524 derivative" OR COVID-19).

Data Extraction

Two reviewers (ZZ and JZ) extracted information including (1) study characteristics (name and country of first author, year of publication, intervention, and control, total number of subjects); (2) interventions and control (sample size); and (3) safety outcomes.

Risk of Bias within Individual Studies

The risk of publication bias was determined based on each study for different analysis purposes using funnel plots and Begg and Peters tests. In addition, the Cochrane risk of bias tool (ROB) determined the risk of bias for each included study for quality assessment. The leave-one-out method is used to confirm the robustness of the findings.

Statistical Analysis

A meta-analysis of adverse events for the drugs versus the control was conducted using Review Manager version 5.2 (Cochrane Collaboration, London, UK) and Stata 17.0 software (Stata Corporation, Texas, USA). The pooled effects of studies were calculated using the random effects model with the Mantel-Haenszel method. The odds ratio (OR) and 95% confidence interval (CI) were used to measure the effect. I^2 and P values were used to quantify the heterogeneity of the effects among the included studies. Publication bias was addressed through funnel plot analysis and statistical tests (Begg and Peters), with significance considered at P<0.1. Additionally, a leave-one-out analysis systematically excluded each study, allowing for a re-examination of the data to assess the stability and consistency of pooled effects. Levels of evidence and review findings were assessed following Cochrane Collaboration and Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) guidelines.[18]

Results

Characteristics of Studies

As of 4 June 2023, a total of 1,740 references were searched; 1,108 duplicate references were excluded and then screened according to inclusion and exclusion criteria. Finally, a total of 15 studies were included. Figure 1 illustrates the overall program of the study and details the number of studies excluded. In addition, the main information on the included randomized controlled trials is shown in table 1.

Safety Outcomes

A total of 32,796 subjects were involved in the 15 included studies.[9, 14-16, 19-29] 11 studies were placebo-controlled[9, 14, 15, 19-26] and four were Paxlovid-controlled.[16, 27-29] Twelve studies reported adverse events with molnupiravir,[9, 19-29] and three studies described adverse events with VV116.[14-16]

A separate pooled analysis of the adverse events of RdRp inhibitors in two different control groups was performed. The overall OR of adverse events for the RdRp inhibitor versus placebo-controlled group was 1.01 (95% CI=0.84-1.22; I^2=26%), P=0.88 (figure 2A). No significant difference was observed in the incidence of

Table 1: Basic information about the included studies

Author, year, country	Intervention	Control	Subjects (n)	Intervention group		Control group	
				Adverse events (n)	Total (n)	Adverse events (n)	Total (n)
Bernal, 2022, Russia[9]	Molnupiravir	Placebo	1433	216	716	231	717
Fischer, 2022, USA[19]	Molnupiravir	Placebo	202	42	140	18	62
Johnson, 2023, USA[20]	Molnupiravir	Placebo	1411	216	710	231	701
Khoo, 2021, UK[21]	Molnupiravir	Placebo	18	9	12	5	6
Khoo, 2023, UK[22]	Molnupiravir	Placebo	180	73	90	68	90
Sinha, 2022, India[23]	Molnupiravir	Placebo	1218	29	608	16	610
Zou, 2022, China[24]	Molnupiravir	Placebo	108	3	77	0	31
Butler, 2023, UK[25]	Molnupiravir	Placebo	25708	50	12774	45	12934
Arribas, 2022, Spain[26]	Molnupiravir	Placebo	293	121	218	46	75
Bruno,2022, Italy[27]	Molnupiravir	Paxlovid	719	55	554	65	165
Bruno, 2022, Italy[28]	Molnupiravir	Paxlovid	168	12	147	4	21
Tiseo, 2023, Italy[29]	Molnupiravir	Paxlovid	562	23	109	116	236
Qian, 2022, China[14]	VV116	Placebo	86	31	67	10	19
Shen, 2022, China[15]	VV116	Placebo	136	9	60	0	76
Cao, 2023, China[16]	VV116	Paxlovid	771	259	384	299	387

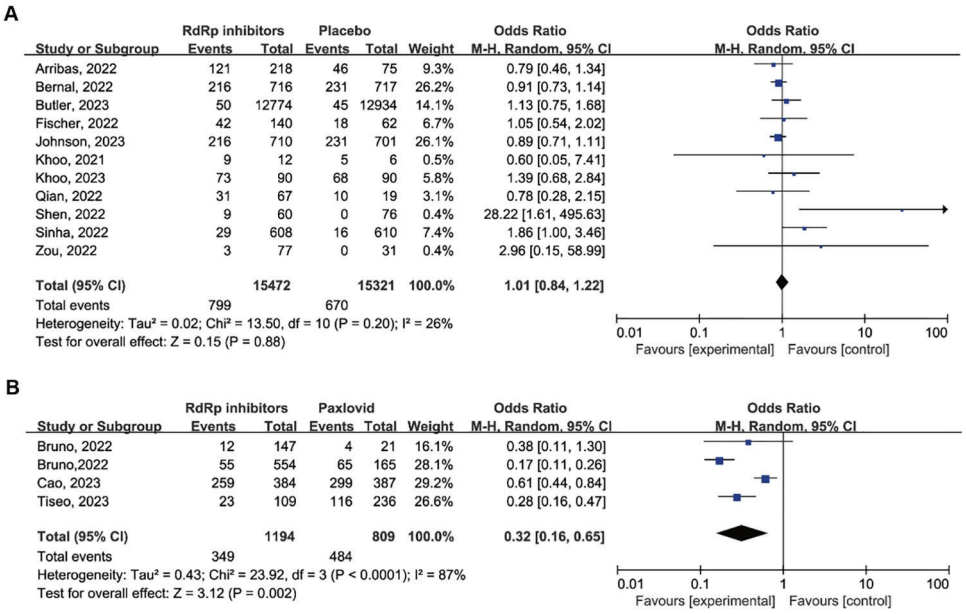

Figure 2: Adverse event rates in the RNA-dependent RNA polymerase (RdRp) inhibitor group are compared with those in the placebo group (A) or the Paxlovid group (B).

adverse events between the drug and placebo groups, and leave-one-out analysis further confirmed the reliability of this result (table 2). In the RdRp inhibitor versus the Paxlovid-controlled group, the total number of adverse events was 349 and 484, respectively. The overall OR for adverse events among COVID-19 patients in the RdRp inhibitors vs. Paxlovid group was 0.32 (95% CI=0.16-0.65; I^2=87%), P=0.002 (figure 2B). None of the included studies resulted in significant differences due to their larger effect sizes (table 3). Funnel plots and quality assessment tools (ROB) determined the risk of bias for each included study (figure 3), and Begg and Peters tests suggested the absence of a significant small sample effect (publication bias) (RdRp inhibitors versus placebo group: Begg, P=0.16, Peters, P=0.94; RdRp inhibitors versus Paxlovid group: Begg, P>0.999, Peters, P=0.40) (table 4). Additionally, our analysis showed that adverse events occurred more frequently in the Paxlovid group (60.0%). Although the small-sample effect was not significant, the quality of evidence for the safety evaluation outcome of RdRp inhibitors versus Paxlovid was rated as low, given the unclear/high risk of bias in some of the studies and the small number of studies included. The low evidence grading suggests that further studies are likely to have an important impact on our confidence in the effect estimates and are likely to change the estimates (table 5).

A subgroup analysis of individual drugs in placebo-controlled studies was conducted. Compared to the placebo group, the total OR of adverse events was 0.97 (95% CI=0.85-1.10; I^2=0%) in the molnupiravir group and 3.77 (95% CI=0.08-175.77; I^2=85%) in the VV116 group. There is no significant difference in adverse event occurrence between the medication group and the placebo group (figure 4).

Table 2: Leave one out analysis in the RNA-dependent RNA polymerase (RdRp) inhibitor versus placebo group

Omitted study	OR [95%CI]	I^2	P value
None	1.01 [0.84, 1.22]	26%	0.88
Arribas, 2022	1.05 [0.86, 1.29]	30%	0.64
Bernal, 2022	1.08 [0.84, 1.38]	31%	0.56
Butler, 2023	1.01 [0.81, 1.25]	30%	0.95
Fischer, 2022	1.02 [0.83, 1.26]	33%	0.84
Johnson, 2023	1.08 [0.85, 1.37]	29%	0.53
Khoo, 2021	1.02 [0.84, 1.25]	33%	0.81
Khoo, 2023	1.00 [0.82, 1.21]	28%	0.97
Qian, 2022	1.03 [0.85, 1.26]	32%	0.76
Shen, 2022	0.96 [0.84, 1.10]	0%	0.57
Sinha, 2022	0.94 [0.82, 1.08]	1%	0.38
Zou, 2022	1.01 [0.84, 1.23]	31%	0.89

Table 3: Leave one out analysis in the RNA-dependent RNA polymerase (RdRp) inhibitor versus Paxlovid group

Omitted study	OR [95%CI]	I^2	P value
None	0.32 [0.16, 0.65]	87%	0.002
Bruno, 2022	0.31 [0.14, 0.71]	92%	0.005
Bruno,2022	0.42 [0.23, 0.77]	69%	0.005
Cao, 2023	0.22 [0.15, 0.34]	32%	<0.001
Tiseo, 2023	0.34 [0.12, 0.92]	91%	0.03

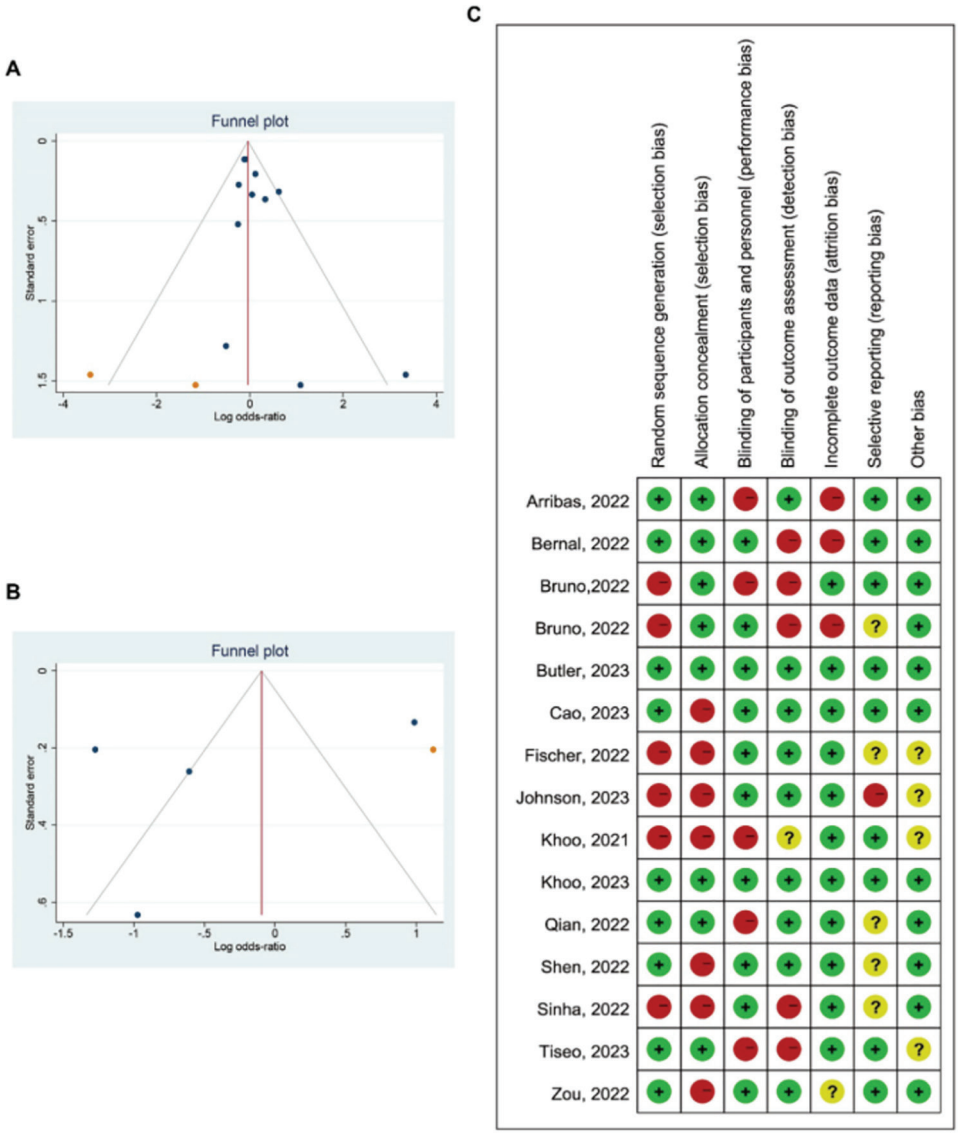

Figure 3: Publication bias and quality assessments performed for the included studies. Funnel plots assess study publication bias in the RNA-dependent RNA polymerase (RdRp) inhibitor versus placebo group (A) or Paxlovid group (B). The quality assessment tool (ROB) determines the risk of bias for each included study (C).

Table 4: Meta bias based on Begg and Peters test

RdRp inhibitors versus placebo group				RdRp inhibitors versus Paxlovid group			
Begg test		Peters test		Begg test		Peters test	
z	P value	z	P value	z	P value	z	P value
1.40	0.16	-0.07	0.94	-0.34	>0.999	-0.84	0.40

Discussion

This meta-analysis found that RdRp inhibitors were not associated with an increased risk of adverse events compared to placebo in COVID-19 patients. The analysis produced a total odds ratio (OR) for adverse events of 1.01 (95% CI, 0.84-1.22) in the drug and placebo groups,

Table 5: Summary of the evidence and quality of the findings (GRADE)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk [Control]	Corresponding risk [Experimental]			
RdRp inhibitors vs. Placebo	Study population		OR 1.01 (0.84 to 1.22)	30793 (11 RCTs)	⊕⊕⊕⊕ high
	44 per 1000	52 per 1000 (4 to 811)			
	Medium risk population				
	31 per 1000	33 per 1000 (15 to 46)			
RdRp inhibitors vs. Paxlovid	Study population		OR 0.32 (0.16 to 0.65)	2003 (4 RCTs)	⊕⊕⊖⊖ low
	292 per 1000	598 per 1000 (190 to 772)			
	Medium risk population				
	19 per 1000	229 per 1000 (190 to 492)			

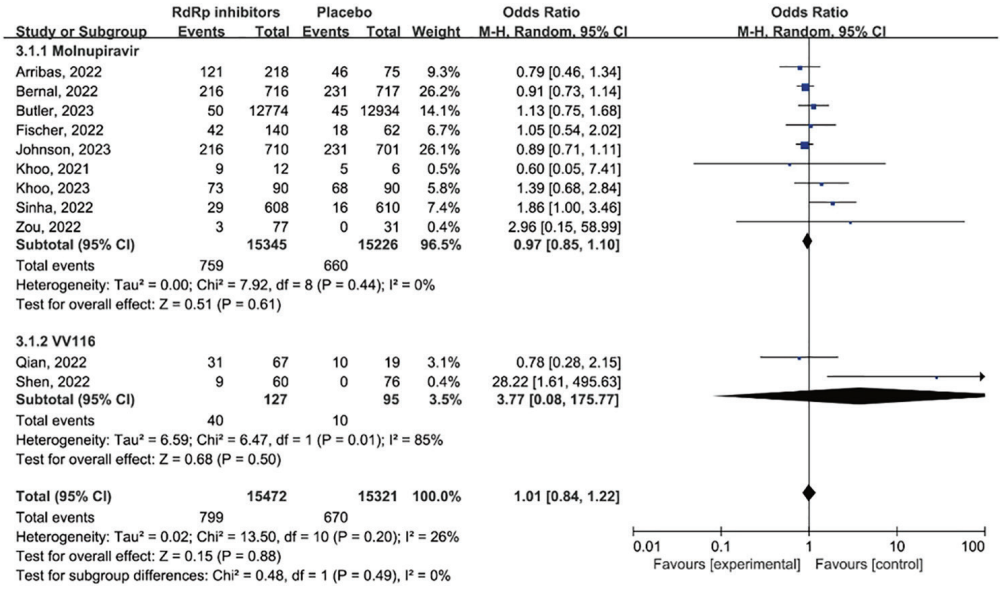

Figure 4: Forest plot presenting a subgroup analysis for the incidence of adverse events for individual RdRp inhibitor drugs versus placebo.

indicating no significant difference in adverse event incidence between these two groups. However, another antiviral drug, Paxlovid, appeared to have a higher incidence of adverse events than RdRp inhibitors. These findings suggest that RdRp inhibitors are well tolerated for the treatment of COVID-19 and may have an advantage over Paxlovid in terms of safety.

RdRp inhibitors are a class of antiviral drugs that target the RdRp enzyme, which is essential for the replication of RNA viruses, such as SARS-CoV-2.[8] Molnupiravir is a mutagenic nucleotide analogue that induces lethal mutations in the viral genome.[5] VV116 (GS-621763) is a 1'-CN-substituted adenine C-nucleoside analog that inhibits the RdRp activity by competing with natural nucleotides.[10] Both drugs have shown promising efficacy against COVID-19 in preclinical and clinical studies.[6, 10, 16] Notably, most adverse events related to molnupiravir and VV116 in the included studies were mild, with few reports of serious adverse events. Common adverse events associated with RdRP inhibitors encompassed rash, nausea, diarrhea, and headache. Consistent with our findings, previous meta-analyses conducted by Wen and others[30] and Amani and others[31] also reported no significant differences in the occurrence of adverse events between the molnupiravir group and the control group. Amani and others[31] also performed a subgroup analysis based on intervention type and dose and found no significant difference in adverse events between the molnupiravir and placebo groups. Although clinical trials for VV116 are limited, these findings collectively emphasize the favorable safety profile of RdRp inhibitors.

A pooled analysis of four studies that compared adverse events between RdRp inhibitors and Paxlovid in COVID-19 patients

was also conducted in our study. Paxlovid is a combination protease inhibitor that blocks the cleavage of viral polyproteins and thus prevents the maturation of SARS-CoV-2.[7] Paxlovid has been shown to reduce the risk of hospitalization and death in high-risk COVID-19 patients.[32] However, Paxlovid was found to be associated with a higher incidence of adverse events than RdRp inhibitors in our study, with an OR of 0.32 (95% CI, 0.16-0.65). This suggests that RdRp inhibitors may have a better safety profile than Paxlovid. The most common adverse events reported with Paxlovid were nausea, vomiting, diarrhea, and abdominal pain. These adverse events were also mostly mild and transient, but some serious adverse events were reported, such as liver injury and allergic reactions.[33-35] Currently, to our knowledge, no pooled analyses comparing the incidence of adverse events between the RdRp inhibitors, either molnupiravir or VV116 and Paxlovid, have been reported. More evidence is needed to confirm our findings and to explore the potential mechanisms underlying the difference in safety between these two classes of antiviral drugs.

The present study highlights the risk of adverse events that may be imposed by RdRp inhibitors. This meta-analysis has several strengths. First, the most recent and relevant studies on the safety of RdRp inhibitors in COVID-19 patients were included here. Second, a comprehensive search of multiple databases and preprint servers was performed to identify eligible studies. Third, the risk of bias for each included study was assessed using a standardized tool; and sensitivity analyses were performed to test the robustness of the obtained results. Nevertheless, caution is warranted in interpreting our primary findings. First, the restricted number of studies examining the safety of the comparison group with Paxlovid, coupled with a small sample size, raises concerns about a potential bias and results in overestimation. Notably, although small sample effects did not show significance, a mild to moderate asymmetry can be observed within the funnel plots, which may be attributed to the low sensitivity and specificity of these evaluation methods and may be confounded by other factors since the Cochrane Risk of Bias tool found that the risk of bias was unclear or high in some studies. Therefore, we could not completely exclude the possibility of publication bias, especially for the safety of the VV116 with only three studies. Second, we could not perform subgroup analyses based on other variables, such as severity of disease, duration of treatment, dose of drug, age, sex, comorbidities, and concomitant medications, due to insufficient data and heterogeneity among studies. These variables may have influenced the occurrence and severity of adverse events in different groups of patients. Third, we could not assess the long-term safety of RdRp inhibitors or Paxlovid, as most studies had a short follow-up period (less than 30 days). Long-term follow-up studies are needed to monitor the potential delayed or chronic adverse effects of these drugs. Fourth, the impact of adverse events on the quality of life or the cost-effectiveness of RdRp inhibitors or Paxlovid could not be evaluated, as these outcomes were not reported in the included studies. These outcomes are important to consider when choosing the optimal antiviral treatment for COVID-19 patients.

Conclusion

This study shows that the RdRp inhibitors molnupiravir and VV116 are safe for oral treatment of COVID-19 with no significant difference in the incidence of adverse events compared to the placebo. More evidence is needed to support the conclusion that RdRp inhibitors have a higher safety profile than Paxlovid.

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Authors' Contribution

Z.Z: Conceptualization; Data interpretation; Formal analysis; Writing, original draft preparation; Software; Resources. Y.S: Conceptualization; Writing-review & editing; Supervision; Funding acquisition; Project administration. J.Z: Investigation; Methodology; Supervision; Writing-review & editing. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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