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Coronavirus Pandemic

Paxlovid for the treatment of COVID-19: a systematic review and meta-analysis

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Abstract

Introduction: Paxlovid (nirmatrelvir/ritonavir) is a new oral antiviral drug that is used for coronavirus disease 2019 (COVID-19) and is administered to patients with mild to moderate disease for five consecutive days. This meta-analysis aimed to evaluate the efficacy of Paxlovid in COVID-19 patients.

Methodology: PubMed, Embase, Cochrane Library, and Web of Science databases were searched to identify relevant publications up to 9 March 2023. Three randomized controlled trial (RCT) studies, one prospective cohort study, and 25 retrospective cohort studies were identified for the meta-analysis.

Results: There was a significant difference between the Paxlovid and control groups in terms of hospitalization (RR = 0.53; 95% CI: 0.24–0.69, $p < 0.001$), all-cause mortality (RR = 0.36; 95% CI: 0.27–0.50, $p < 0.001$), hospitalization or death (RR = 0.50; 95% CI: 0.37–0.67, $p < 0.001$), intensive care unit admission (RR = 0.45; 95% CI: 0.27–0.73, $p = 0.001$), and emergency department visits (RR = 0.67; 95% CI: 0.54–0.83, $p < 0.001$). However, no significant difference was found between the two groups in terms of COVID‐19 rebound (OR = 1.18; 95% CI: 0.82–1.68, $p = 0.37$). In addition, the Paxlovid group had a significantly shorter hospital length of stay (weighted mean difference WMD = -1.11; 95% CI, -1.81, -0.41; $I^2 > 50\%$, $p < 0.05$), and polymerase chain reaction negative conversion time (WMD = -2.75; 95% CI, -3.60, -1.89, $I^2 > 50\%$, $p < 0.05$) than that of the control group.

Conclusions: Paxlovid can be considered an effective therapeutic agent for treating patients with COVID-19.

Key words: COVID-19; nirmatrelvir/ritonavir; Paxlovid; SARS-CoV-2; hospitalization.

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Introduction

The 2019 coronavirus disease (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus type 2 (SARS CoV-2) is one of the greatest threats to public health in the 21st century. Multiple antiviral drugs, monoclonal antibodies, and immunomodulatory drugs have been proposed as treatment methods for SARS-CoV-2 infection [1,2], but most of these measures have not effectively reduced the risk of progression to severe disease or are too expensive or difficult to treat widely. Paxlovid (nirmatrelvir/ritonavir) is a new oral antiviral drug produced by Pfizer (Ascoli Piceno, Italy) that is used to treat COVID-19 and is given to patients with mild to moderate disease for five consecutive days. A previous study reported that Paxlovid can reduce hospitalization or death by 89% [3], and early Paxlovid therapy can quickly clear the viral load of SARS-CoV-2 and shorten the virus clearance time in immunocompromised patients [4].

Previous studies have explored the impact of Paxlovid on the outcomes of hospitalization, death, negative conversion, and positive recovery in patients with COVID-19. However, research results are inconsistent [3,5–8]. Factors such as research type, reference drug, and sample selection may affect the results. Therefore, to obtain more comprehensive and objective results, this meta-analysis evaluated the efficiency of Paxlovid in the treatment of COVID-19.

Methodology

Search strategy

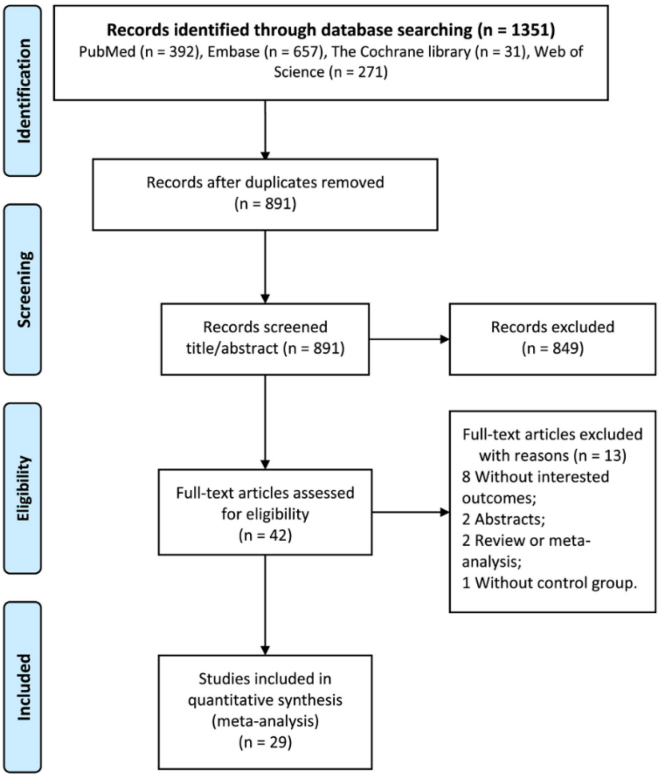
This research followed a predetermined retrieval strategy and conducted literature retrieval through the PubMed, Embase, Cochrane Library, and Web of Science databases. The search keywords included “Paxlovid”, “nirmatrelvir/ritonavir”, “COVID-19”,

"SARS-CoV-2", "Coronavirus Disease 2019", and "2019 novel coronavirus infection". Keywords of the same category were combined with "OR", and keywords of different categories are combined with "AND". While combining theme words with free words for retrieval, the retrieval formula was adjusted according to the characteristics of the database (specific retrieval steps are provided in Supplementary Table S1). The search included publications available as of 9 March 2023, and without language restrictions. In addition, this study also screened relevant reviews and included references to include more research data that could be used for meta-analysis.

Study selection

The inclusion criteria were as follows: (1) the subjects were patients diagnosed with COVID-19; (2) the treatment group was administered Paxlovid, while the control group had an unlimited treatment plan, including either placebo, no treatment, or other drug treatments; (3) the type of study was randomized controlled trial (RCT), prospective, or retrospective cohort study; and (4) the literature reported one or more of the following outcomes: hospitalization, all cause mortality, hospitalization or death, COVID-19 rebound, intensive care unit (ICU), emergency department visit (ED), hospital length of stay, and polymerase chain reaction (PCR) negative conversion time.

Figure 1. Flow diagram of the systematic literature search and articles selection process.



The exclusion criteria were as follows: (1) duplicate publications, reviews, conference abstracts, and comments; (2) studies with a sample size of less than 10 in the Paxlovid group (to reduce sample bias); (3) in the case of repeated publications or when the same data was used in multiple articles, only the one with the most complete research information was included, and the rest were excluded.

Data extraction and quality evaluation

Two investigators (Yu Wang and Yuya Yang) independently completed the literature screening work according to the above inclusion and exclusion criteria. The following data were collected: lead author, year of publication, research area, basic characteristics of the research object (sample size, age, gender composition), treatment plan, treatment time, follow-up time, and research outcomes. The reviewers resolved the extraction table, and, if there were any inconsistencies, they discussed and resolved them.

The Cochrane Bias Risk Assessment Tool (The Cochrane Collaboration tool for assessment risk [9]) was applied to evaluate the quality of randomized controlled studies. The methodological quality evaluation of non-randomized clinical studies was conducted using the risk of bias in non-randomized studies of interventions (ROBINS-I) [9].

Statistical analysis

We calculated the risk ratio (RR) with a 95% confidence interval (CI) for categorical variables and the weighted mean difference (WMD) with a 95% CI for continuous variables. The clinical heterogeneity and methodological heterogeneity included in the study were obvious, and a random effects model was used for meta-analysis.

Cochran's Q test and I^2 test were used for the heterogeneity test [10]; $p < 0.05$ and $I^2 > 50\%$ were considered high heterogeneity, and $p \geq 0.05$ and $I^2 \leq 50\%$ were considered not significant. The effects of factors such as region, study type, sample size, probability score matching (PSM), control protocol, hospitalization status, and bias size on heterogeneity and merger outcomes were evaluated through subgroup analysis. The one-by-one exclusion test was used to evaluate whether the impact of a single inclusion study on the meta-analysis results was significant [11]. Egger's test was used to evaluate whether there was a significant publication bias between studies [12]. The

statistical analysis was performed using Stata 12.0 software [13].

Results

Literature search

The literature search results and literature selection process are shown in Figure 1. A total of 1351 articles were obtained from the databases. After removing 460 duplicate articles, 891 studies were assessed for eligibility. Then, 849 articles that did not meet the inclusion criteria were removed. Finally, after reading the full texts of 42 articles, 13 studies were excluded. The manual search failed to identify studies that could be included in the analysis, and ultimately, 29 articles [3,5,6-8,14-37] were included in the meta-analysis.

Characteristics of studies and quality evaluation

A total of 29 articles were included in this meta-analysis, and the studies were conducted in the United States, China, Wales, Italy, and Canada. Among them, there were three RCT studies [3,7,14], one prospective cohort study [23], and 25 retrospective cohort studies [5,6,8,15-22,24-37]. The sample size ranged from 36 to 699,848, with a total of 1,189,778 cases. Among them, there were 559,124 patients in the Paxlovid group and 630,654 patients in the control group. The main characteristics are presented in Table 1.

The quality evaluation results are listed in Supplementary Tables S2 and S3, and the risk of bias of the three RCT studies was low. The risk of bias of the cohort study was low to moderate. Overall, the methodological quality included in the study was acceptable.

Meta-analysis results

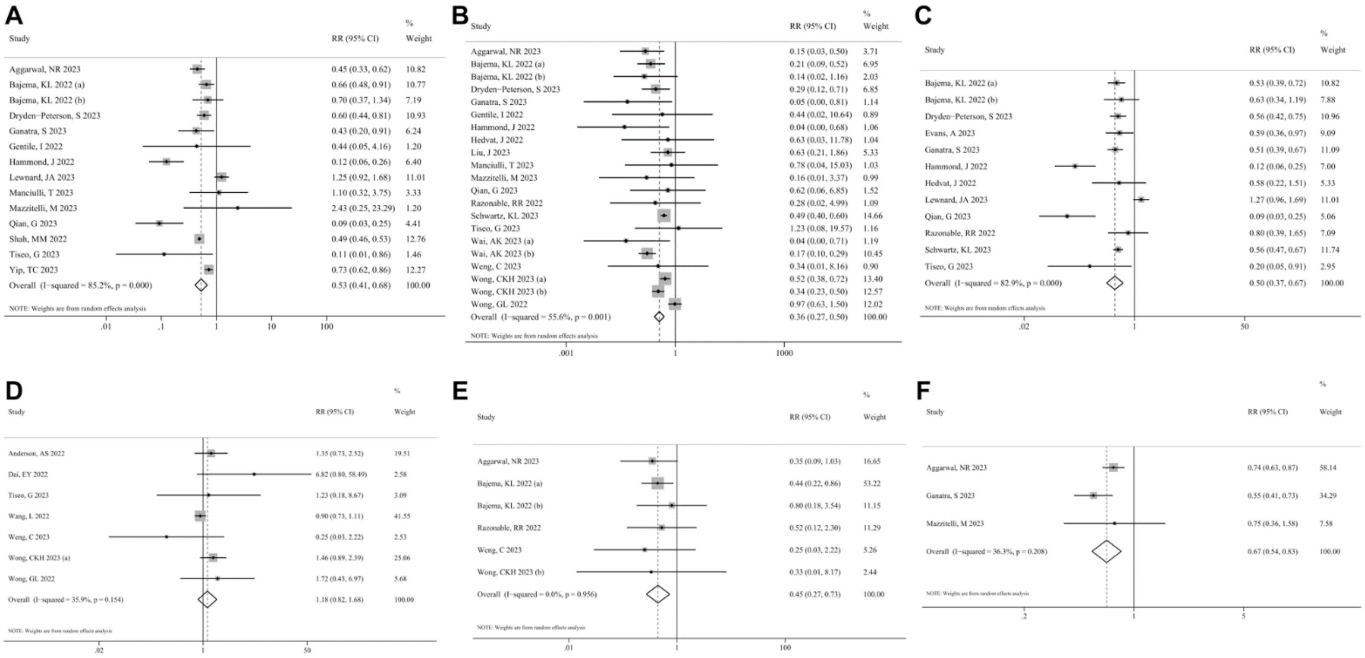
Figures 2A-F present the results of meta- analysis of hospitalization, all-cause mortality, hospitalization or death, COVID-19 rebound, ICU, and ED, respectively. The RRs and 95% CIs were 0.53 (0.41, 0.68, $p < 0.001$) for hospitalization, 0.36 (0.27, 0.50, $p < 0.001$) for all-cause mortality, 0.50 (0.37, 0.67, $p < 0.001$) for hospitalization or death, 1.18 (0.82, 1.68, $p = 0.37$) for COVID-19 rebound, 0.45 (0.27, 0.73, $p = 0.001$) for ICU, and 0.67 (0.54, 0.83, $p < 0.001$) for ED. The included literature on hospitalization, all-cause mortality, and hospitalization or death showed significant statistical heterogeneity ($I^2 > 50\%$, $p < 0.05$);

Table 1. Characteristics of 29 studies included in this meta-analysis.

Study	Location	Type	Timing of treatment	Age, years	Follow-up, months	Control	n, M/F	Patients
Aggarwal *et al.* [5]	USA	RCS	within 5 days	≥ 18	1	Untreated	16529, 6865/9664	Non-hospitalized
Anderson *et al.* [13]	USA	RCT	within 5 days	46 (18–88)	1	Placebo	1980, NR	Non-hospitalized
Bajema *et al.* [14]	USA	RCS	within 7 days	≥ 18	1	Untreated	3174, 2828/346	Non-hospitalized
						Molnupiravir	1538, 1383/145	Non-hospitalized
Dai *et al.* [15]	USA	RCS	NR	5-66	1	Untreated	36, 15/21	Non-hospitalized
Dryden-Peterson *et al.* [16]	USA	RCS	After 2 days	≥ 50	1	Not Paxlovid	44551, 17805/26746	Non-hospitalized
Evans *et al.* [17]	Wales	RCS	within 7 days	56.6 ± 17.7	1	Untreated	5575, NR	Non-hospitalized
Ganatra *et al.* [6]	USA	RCS	within 5 days	57.6 ± 16.3	1	Not Paxlovid	2260, 824/1436	Non-hospitalized
Gentile *et al.* [18]	Italy	RCS	within 5 days	64 (52, 75)	0.5	Molnupiravir	257, 124/133	Non-hospitalized
Hammond *et al.* [3]	USA	RCT	within 5 days	46 (18–88)	1	Placebo	2246, 1148/1098	Non-hospitalized
Hedvat *et al.* [19]	USA	RCS	within 5 days	≥ 18	1	Not Paxlovid	154, 64/90	Non-hospitalized
Lewnard *et al.* [20]	USA	RCS	within 5 days	≥ 12	1	Not Paxlovid	133426, 59437/73989	Non-hospitalized
Li *et al.* [21]	China	RCS	Any	56 (45, 66)	1	Untreated	482, 282/200	Hospitalized
Liu *et al.* [7]	China	RCT	within 5 days	70.4 ± 13.1	1	Not Paxlovid	264, 142/122	Hospitalized
Manciulli *et al.* [22]	Italy	RCS	NR	66.9 (52.4, 77.9)	1	Not Paxlovid	781, 394/387	Non-hospitalized
Mazzitelli *et al.* [23]	Italy	RCS	within 5 days	73 (62, 82)	1	Molnupiravir	909, 439/470	Non-hospitalized
Qian *et al.* [24]	USA	RCS	NR	58.3 ± 15.6	1	Not Paxlovid	704, 168/536	Non-hospitalized
Razonable *et al.* [25]	USA	RCS	within 7 days	66.2 (52.5, 74.7)	1	Not Paxlovid	3607, 1501/2106	Non-hospitalized
Schwartz *et al.* [26]	Canada	RCS	NR	50 (35, 67)	1	Untreated	177545, 65346/112199	Non-hospitalized
Shah *et al.* [27]	USA	RCS	within 5 days	≥ 18	1	Not Paxlovid	699848, NR	Non-hospitalized
Tiseo *et al.* [28]	Italy	PCS	within 5 days	69 (55, 78.25)	1	Not Paxlovid	562, 302/260	Non-hospitalized
Wai *et al.* [8]	China	RCS	within 5 days	almost ≥ 60	1	Not Paxlovid	33217, 15592/17625	Non-hospitalized
						Not Paxlovid	21138, 11708/9430	Hospitalized
Wang *et al.* [29]	USA	RCS	within 5 days	61.4 ± 15.6	1	Molnupiravir	4452, 1930/2522	Non-hospitalized
Wang *et al.* [30]	China	RCS	NR	76.4 ± 12.5	1	Not Paxlovid	760, 332/428	Hospitalized
Weng *et al.* [31]	China	RCS	within 5 days	82 (71, 89)	3	Untreated	163, 70/93	Hospitalized
Wong *et al.* [32]	China	RCS	within 5 days	78.9 ± 14.7	1	Not Paxlovid	4592, 2594/1998	Hospitalized
Wong *et al.* [33]	China	RCS	within 5 days	≥ 18	1	Not Paxlovid	1780, NR	Hospitalized
Wong *et al.* [34]	China	RCS	NR	65.4 ± 20.9	1	Not Paxlovid	12629, 6624/6005	Hospitalized
Yip *et al.* [35]	China	RCS	within 5 days	70.8 ± 12.0	1	Not Paxlovid	14477, 6671/7806	Non-hospitalized
Zhong *et al.* [36]	China	RCS	NR	76.37 ± 9.70	1	Not Paxlovid	142, 58/84	Hospitalized

NR: not reported; F: female; M: male; PCS: prospective cohort study; RCS: retrospective cohort study; RCT: randomized controlled trial.

Figure 2. Forest plot of Paxlovid versus control for hospitalization (A), mortality (B), hospitalization or death rate (C), COVID-19 rebound (D), ICU admission (E) and ED admission (F).



COVID-19: 2019 coronavirus disease; ICU: Intensive care unit; ED: emergency department; RR: risk ratio; CI: confidence interval.

while no statistical heterogeneity was observed in the other three outcome indicators ($I^2 < 50\%$, $p > 0.05$).

The meta-analysis showed that the Paxlovid group had a significantly shorter hospital length of stay (WMD = -1.11; 95% CI -1.81, -0.41; $I^2 > 50\%$, $p < 0.05$) (Figure 3A) and PCR negative conversion time (WMD = -2.75; 95% CI -3.60, -1.89; $I^2 > 50\%$, $p < 0.05$) (Figure 3B) than the control group.

Subgroup analysis

Since only three articles for ED were included, subgroup analysis was not suitable. The subgroup analysis results of other outcome indicators are presented in Table 2.

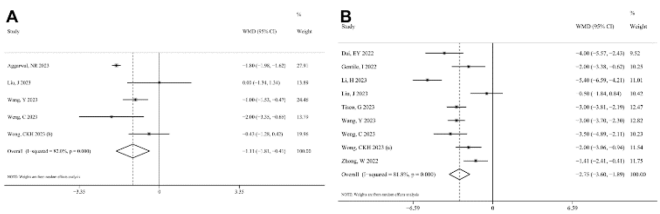
Paxlovid did not reduce hospitalization for the Italy subgroup (WMD = 0.64; 95% CI 0.19, 2.14; $p = 0.468$, p for heterogeneity = 0.171, I^2 = 40.1%), or molnupiravir subgroup (WMD = 0.74; 95% CI 0.41, 1.34; $p = 0.32$, p for heterogeneity = 0.521, $I^2 = 0$), while the results of the other subgroups did not suggest apparent subgroup effects.

Paxlovid did not have an apparent effect on all-cause mortality in Italy (WMD = 0.54; 95% CI 0.12, 2.37; $p = 0.412$, p for heterogeneity = 0.795, $I^2 = 0\%$); prospective cohort study PCS (WMD = 1.23, 95% CI 0.08, 19.61; $p = 0.884$); and RCT (WMD = 0.22, 95% CI 0.02, 3.03; $p = 0.26$; p for heterogeneity = 0.083, I^2 = 66.7%) subgroup; while the results of the other subgroups did not suggest apparent subgroup effects.

Sample Size > 10,000 (WMD = 0.73, 95% CI 0.44, 1.21; $p = 0.227$, p for heterogeneity < 0.001, $I^2 = 92\%$) and molnupiravir (WMD = 0.63; 95% CI 0.34, 1.18; $p = 0.148$) subgroup showed no apparent effect for hospitalization or death; while the results of the other subgroups did not suggest apparent subgroup effects. For COVID-19 rebound, the results of all subgroups were consistent with the results of all included studies.

Paxlovid did not have an apparent effect on ICUs in China (WMD = 0.28; 95% CI 0.05, 1.66; $p = 0.159$; p for heterogeneity = 0.889; I^2 = 0%), sample size >

Figure 3. Forest plot of Paxlovid versus control for hospital length of stay (A) and PCR negative conversion time (B).



PCR: polymerase chain reaction; WMD: weighted mean difference; CI: confidence interval.

10000 (WMD = 0.35, 95% CI 0.1, 1.18; p = 0.091), non-PSM (WMD = 0.42; 95% CI 0.12, 1.42; p = 0.159; p for heterogeneity = 0.588; I^2 = 0%), moderate risk (WMD = 0.42; 95% CI 0.12, 1.42; p = 0.159; p for heterogeneity = 0.588; I^2 = 0%); molnupiravir (WMD = 0.8; 95% CI 0.18, 3.55; p = 0.769); no Paxlovid (WMD = 0.48; 95% CI 0.13, 1.85; p = 0.287, p for heterogeneity = 0.801; I^2 = 0%); and hospitalized patient subgroup (WMD = 0.28; 95% CI 0.05, 1.66; p = 0.159; p for heterogeneity = 0.889; I^2 = 0%), while the results of the other subgroups were consistent with the results of all included studies.

Paxlovid did not have an apparent effect on hospital length of stay or PCR-negative conversion time in the RCT, PSM, and low-risk subgroups; and the results of the other subgroups were consistent with the results of all included studies.

Sensitivity analysis and publication bias

The sensitivity analysis results of each outcome indicator are shown in Figures 2A–F and Figures 3A–B. Application of the leave-one-out sensitivity analysis did not significantly alter the results of all included studies, indicating that no individual study significantly influenced the results. The results of the meta-analysis were stable. The results of the Egger test showed that all the p values were greater than 0.05, indicating no significant publication bias (data not shown).

Table 2. Subgroup analyses of the outcomes.

Outcomes	No. of study	RR/WMD (95% CI)	p value	Heterogeneity test	
				I^2 (%)	p_H
Hospitalization					
Overall	14	0.53 (0.41, 0.68)	< 0.001	85.2	< 0.001
Country					
USA	9	0.48 (0.35, 0.66)	< 0.001	88.0	< 0.001
Italy	4	0.64 (0.19, 2.14)	0.468	40.1	0.171
China	1	0.73 (0.62, 0.86)	< 0.001	NA	NA
Design					
RCS	12	0.60 (0.47, 0.77)	< 0.001	84.2	< 0.001
PCS	1	0.11 (0.01, 0.85)	0.034	NA	NA
RCT	1	0.12 (0.06, 0.26)	< 0.001	NA	NA
Sample Size					
> 10000	5	0.65 (0.48, 0.89)	0.006	92.4	< 0.001
< 10000	9	0.38 (0.21, 0.72)	0.003	76.9	< 0.001
PSM					
Yes	6	0.49 (0.34, 0.71)	< 0.001	82.0	< 0.001
No	8	0.55 (0.34, 0.90)	0.016	86.9	< 0.001
Quality					
Low risk	6	0.40 (0.25, 0.65)	< 0.001	75.8	0.001
Moderate risk	8	0.63 (0.44, 0.90)	0.011	89.4	< 0.001
Control group					
Untreated	3	0.36 (0.18, 0.73)	0.004	88.4	< 0.001
Molnupiravir	3	0.74 (0.41, 1.34)	0.320	0.0	0.521
Not Paxlovid	8	0.57 (0.41, 0.80)	0.001	89.6	< 0.001
All-cause mortality					
Overall	21	0.36 (0.27, 0.50)	< 0.001	55.6	0.001
Country					
USA	9	0.22 (0.13, 0.36)	< 0.001	0.0	0.805
Italy	4	0.54 (0.12, 2.37)	0.412	0.0	0.795
China	7	0.41 (0.24, 0.70)	0.001	80.3	< 0.001
Canada	1	0.49 (0.40, 0.60)	< 0.001	NA	NA
Design					
RCS	18	0.36 (0.26, 0.49)	< 0.001	59.1	0.001
PCS	1	1.23 (0.08, 19.61)	0.884	NA	NA
RCT	2	0.22 (0.02, 3.03)	0.260	66.7	0.083
Sample Size					
> 10000	6	0.33 (0.18, 0.62)	0.001	83.9	< 0.001
< 10000	15	0.41 (0.33, 0.51)	< 0.001	0.0	0.517
PSM					
Yes	8	0.32 (0.21, 0.49)	< 0.001	50.8	0.047
No	13	0.40 (0.24, 0.69)	0.001	59.9	0.003
Quality					
Low risk	9	0.33 (0.22, 0.50)	< 0.001	45.9	0.063
Moderate risk	12	0.39 (0.22, 0.67)	0.001	62.7	0.002
Control group					
Untreated	5	0.27 (0.13, 0.56)	0.001	53.5	0.072
Molnupiravir	3	0.19 (0.04, 0.83)	0.027	0.0	0.835

Outcomes	No. of study	RR/WMD (95% CI)	*p* value	Heterogeneity test	
				I^2 (%)	p_H
Not Paxlovid	13	0.40 (0.25, 0.62)	< 0.001	65.5	0.001
Patients					
Non-hospitalized	15	0.31 (0.20, 0.46)	< 0.001	18.4	0.248
Hospitalized	6	0.44 (0.26, 0.75)	0.003	81.9	< 0.001
Hospitalisation or death					
Overall	12	0.50 (0.37, 0.67)	< 0.001	82.9	0.001
Country					
USA	9	0.48 (0.32, 0.73)	< 0.001	87.1	< 0.001
Wales	1	0.59 (0.36, 0.97)	0.037	NA	NA
Canada	1	0.56 (0.47, 0.67)	< 0.001	NA	NA
Italy	1	0.21 (0.05, 0.91)	0.037	NA	NA
Design					
RCS	10	0.58 (0.45, 0.76)	< 0.001	79.6	< 0.001
PCS	1	0.21 (0.05, 0.91)	0.037	NA	NA
RCT	1	0.12 (0.06, 0.25)	< 0.001	NA	NA
Sample Size					
> 10000	3	0.73 (0.44, 1.21)	0.227	92.0	< 0.001
< 10000	9	0.41 (0.28, 0.59)	< 0.001	72.8	< 0.001
PSM					
Yes	5	0.46 (0.34, 0.63)	< 0.001	75.5	0.003
No	7	0.52 (0.31, 0.89)	0.016	84.3	< 0.001
Quality					
Low risk	6	0.45 (0.33, 0.61)	0.003	71.9	0.003
Moderate risk	6	0.57 (0.33, 0.97)	< 0.001	85.9	< 0.001
Control group					
Untreated	4	0.43 (0.28, 0.66)	< 0.001	81.4	0.001
Molnupiravir	1	0.63 (0.34, 1.18)	0.148	NA	NA
Not Paxlovid	7	0.52 (0.32, 0.85)	0.009	86.1	< 0.001
COVID-19 Rebound					
Overall	7	1.18 (0.82, 1.68)	0.370	35.9	0.154
Country					
USA	3	1.19 (0.67, 2.12)	0.556	57.7	0.094
China	3	1.29 (0.66, 2.53)	0.460	20.0	0.287
Italy	1	1.23 (0.17, 8.66)	0.835	NA	NA
Design					
RCS	5	1.18 (0.71, 1.95)	0.524	52.4	0.078
PCS	1	1.23 (0.17, 8.66)	0.835	NA	NA
RCT	1	1.35 (0.73, 2.52)	0.340	NA	NA
Sample Size					
> 10000	1	1.72 (0.43, 6.97)	0.445	NA	NA
< 10000	6	1.16 (0.79, 1.70)	0.456	43.2	0.117
PSM					
Yes	2	0.99 (0.71, 1.39)	0.951	32.7	0.223
No	5	1.46 (0.82, 2.59)	0.199	12.5	0.334
Quality					
Low risk	2	1.34 (0.74, 2.42)	0.331	0.0	0.927
Moderate risk	5	1.18 (0.71, 1.95)	0.524	52.4	0.078
Control group					
Untreated	3	1.34 (0.34, 5.28)	0.676	55.3	0.107
Molnupiravir	1	0.90 (0.73, 1.11)	0.324	NA	NA
Not Paxlovid	3	1.47 (0.94, 2.31)	0.094	0.0	0.960
Patients					
Non-hospitalized	4	1.14 (0.71, 1.81)	0.596	18.4	0.248
Hospitalized	3	1.29 (0.66, 2.53)	0.460	81.9	< 0.001
ICU					
Overall	6	0.45 (0.27, 0.73)	0.001	0.0	0.956
Country					
USA	4	0.46 (0.28, 0.78)	0.004	0.0	0.857
China	2	0.28 (0.05, 1.66)	0.159	0.0	0.889
Sample Size					
> 10000	1	0.35 (0.10, 1.18)	0.091	NA	NA
< 10000	5	0.47 (0.27, 0.81)	0.006	0.0	0.924
PSM					
Yes	4	0.45 (0.26, 0.78)	0.004	0.0	0.855
No	2	0.42 (0.12, 1.42)	0.159	0.0	0.588
Quality					
Low risk	4	0.45 (0.26, 0.78)	0.004	0.0	0.855
Moderate risk	2	0.42 (0.12, 1.42)	0.159	0.0	0.588
Control group					

Outcomes	No. of study	RR/WMD (95% CI)	*p* value	Heterogeneity test	
				I^2 (%)	p_H
Untreated	3	0.40 (0.23, 0.71)	0.002	0.0	0.864
Molnupiravir	1	0.80 (0.18, 3.55)	0.769	NA	NA
No Paxlovid	2	0.48 (0.13, 1.85)	0.287	0.0	0.801
Patients					
Non-hospitalized	4	0.46 (0.28, 0.78)	0.004	0.0	0.857
Hospitalized	2	0.28 (0.05, 1.66)	0.159	0.0	0.889
Hospital length of stay					
Overall	5	-1.11 (-1.81, -0.41)	0.002	82.0	< 0.001
Country					
USA	1	-1.80 (-1.98, -1.62)	< 0.001	NA	NA
China	4	-0.84 (-1.48, -0.20)	0.010	46.0	0.136
Design					
RCS	4	-1.29 (-1.98, -0.60)	< 0.001	81.7	0.001
RCT	1	0.00 (-1.34, 1.34)	1.000	NA	NA
Sample Size					
> 10000	1	-1.80 (-1.98, -1.62)	< 0.001	NA	NA
< 10000	4	-0.84 (-1.48, -0.20)	0.010	46.0	0.136
PSM					
Yes	3	-0.86 (-2.08, 0.37)	0.171	87.3	< 0.001
No	2	-1.30 (-2.20, -0.40)	0.005	45.2	0.177
Quality					
Low risk	3	-0.86 (-2.08, 0.37)	0.171	87.3	< 0.001
Moderate risk	2	-1.30 (-2.20, -0.40)	0.005	45.2	0.177
Control group					
Untreated	2	-1.80 (-1.99, -1.62)	< 0.001	0.0	0.774
Not Paxlovid	3	-0.69 (-1.22, -0.16)	< 0.001	22.9	0.273
Patients					
Non-hospitalized	1	-1.80 (-1.98, -1.62)	< 0.001	NA	NA
Hospitalized	4	-0.84 (-1.48, -0.20)	0.010	46.0	0.136
PCR negative conversion time					
Overall	9	-2.75 (-3.60, -1.89)	< 0.001	81.8	< 0.001
Country					
USA	1	-4.00 (-5.57, -2.43)	< 0.001	NA	NA
Italy	2	-2.66 (-3.59, -1.74)	< 0.001	33.2	0.221
China	6	-2.64 (-3.87, -1.40)	< 0.001	87.5	< 0.001
Design					
RCS	7	-3.01 (-4.00, -2.02)	< 0.001	81.5	< 0.001
RCT	1	-0.50 (-1.84, 0.84)	0.465	NA	NA
PCS	1	-3.00 (-3.81, -2.19)	< 0.001	NA	NA
PSM					
Yes	1	-0.50 (-1.84, 0.84)	0.465	NA	NA
No	8	-3.00 (-3.81, -2.19)	< 0.001	75.4	< 0.001
Quality					
Low risk	2	-1.81 (-4.26, 0.64)	0.147	89.8	0.002
Moderate risk	7	-3.01 (-4.00, -2.02)	< 0.001	81.5	< 0.001
Control group					
Untreated	3	-4.36 (-5.56, -3.16)	< 0.001	56.1	0.103
Molnupiravir	1	-2.00 (-3.38, -0.62)	0.005	NA	NA
Not Paxlovid	5	-2.08 (-2.95, -1.22)	< 0.001	76.3	0.002
Patients					
Non-hospitalized	3	-2.96 (-3.89, -2.03)	< 0.001	43.6	0.170
Hospitalized	5	-2.64 (-3.87, -1.40)	< 0.001	87.5	<0.001

ICU: intensive care unit; NA: not available; PCS: prospective cohort study; PSM: probability score matching; RCS: retrospective cohort study; RCT: randomized controlled trial; RR: risk ratio; WMD: weighted mean difference.

Discussion

A total of 29 research publications were included in this study. This study is, to our knowledge, the largest and most extensive systematic review and meta-analysis to date, comprehensively summarizing current evidence of the effect of Paxlovid on COVID-19. There was no significant publication bias between the studies, and the results were highly reliable. Sensitivity analysis also indicated that the results were highly reliable. Our results found that Paxlovid treatment not only reduced the risk of mortality and hospitalization rate, but also greatly reduced the length of hospital stay and PCR-negative conversion time. These findings are in line with previous meta‑analyses [38,39].

Previously published meta-analyses suggested that Paxlovid was not associated with reducing ED visits and ICU admissions [38,40], and we observed that Paxlovid effectively decreased ED visits and ICU admissions. This inconsistency could be explained by

differences in the number of included studies. Overall, we found that Paxlovid can reduce the relative risk of clinical deterioration.

Case reports have documented recurrence of COVID-19 symptoms or COVID‐19 rebound among patients treated with Paxlovid [40,41]. Our results showed that Paxlovid had no obvious effect on COVID‐19 rebound, which is similar to results reported by Pandit *et al.* [42]. Relatively few studies have reported COVID‐19 rebound, which can affect the effect size.

The present study has some limitations. First, most of the included studies were retrospective cohort studies, although some studies used PSM to reduce the occurrence of selection bias and confounding variables; however, due to the limitations of the research design, they were prone to bias and confounding. Second, there is substantial heterogeneity for some outcome indicators. Although we performed analyses to explore sources of heterogeneity, we found that sample size and control plan were the only heterogeneity influencing factors of the hospital length of stay. Finally, although there are relatively few studies on Paxlovid vs. molnupiravir, the differences in other outcome indicators between the Paxlovid and molnupiravir were not significant, except for all-cause mortality.

Conclusions

The present meta‐analysis showed that Paxlovid treatment reduced the risk of mortality and hospitalization. In addition, our meta‐analysis also indicated that Paxlovid treatment reduced the risk of ICU admission and ED visits; moreover, Paxlovid also greatly reduced the length of hospital stay and PCR-negative conversion time. Therefore, Paxlovid can be considered an effective therapeutic agent for treating patients with COVID‐19. However, more high-quality large-scale RCTs are needed for validation.

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Authorship statement

All authors meet the International Committee of Medical Journal Editors (ICMJE) authorship criteria and have made substantial contributions to one or more the following: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted.

Authors' contributions

YW and LF, study design, acquisition of data, and preparation of the manuscript; YB and LF, literature search, data acquisition, paper appraisals, and manuscript preparation; RS, analysis and the preparation of the manuscript; YW and YY, data interpretation and preparation of the manuscript; LZ, original information classification and the preparation of the manuscript. All authors have read and approved the final version of the manuscript.

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Annex – Supplementary Items

Supplementary Table 1. Database search strategies. Retrieval date: 3 September 2023.

Database	Search no.	Query	Items found
PubMed	1	"nirmatrelvir and ritonavir drug combination"[Supplementary Concept] OR "nirmatrelvir and ritonavir drug combination"[All Fields] OR "paxlovid"[All Fields] OR "nirmatrelvir ritonavir"[All Fields]	432
	2	"covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "sars2"[All Fields] OR "sars coronavirus 2"[All Fields] OR "coronavirus disease 2019"[All Fields] OR "2019 novel coronavirus"[All Fields]	339,085
	3	#1 AND #2	392
Embase	1	('paxlovid'/exp OR paxlovid OR (('nirmatrelvir'/exp OR nirmatrelvir) AND ('ritonavir'/exp OR ritonavir)))	690
	2	('covid 19'/exp OR 'covid 19' OR 'sars cov 2'/exp OR 'sars cov 2' OR sars2 OR 'sars coronavirus 2'/exp OR 'sars coronavirus 2' OR 'coronavirus disease 2019'/exp OR 'coronavirus disease 2019' OR '2019-ncov'/exp OR '2019-ncov' OR '2019 novel coronavirus'/exp OR '2019 novel coronavirus')	318,709
	3	#1 AND #2	657
Web of Science	1	Paxlovid OR (nirmatrelvir AND ritonavir) (All Fields)	314
	2	COVID-19 OR SARS-CoV-2 OR SARS2 OR SARS Coronavirus 2 OR Coronavirus Disease 2019 OR 2019-nCoV OR 2019 Novel Coronavirus (All Fields)	325,233
	3	#1 AND #2	271
The Cochrane library	1	(paxlovid):ti,ab,kw (Word variations were searched)	17
	2	(nirmatrelvir AND ritonavir):ti,ab,kw (Word variations were searched)	27
	3	#1 OR #2	38
	4	MeSH descriptor: [COVID-19] explode all trees	3,974
	5	MeSH descriptor: [COVID-19 Vaccines] explode all trees	378
	6	MeSH descriptor: [SARS-CoV-2] explode all trees	2,174
	7	(COVID-19 OR SARS-CoV-2 OR SARS2 OR "SARS Coronavirus 2" OR "Coronavirus Disease 2019" OR "2019-nCoV" OR "2019 Novel Coronavirus"):ti,ab,kw (Word variations were searched)	15,080
	8	#4 OR #5 OR #6 OR #7	15,080
	9	#3 AND #8	33
	10	#9 in Trials	31

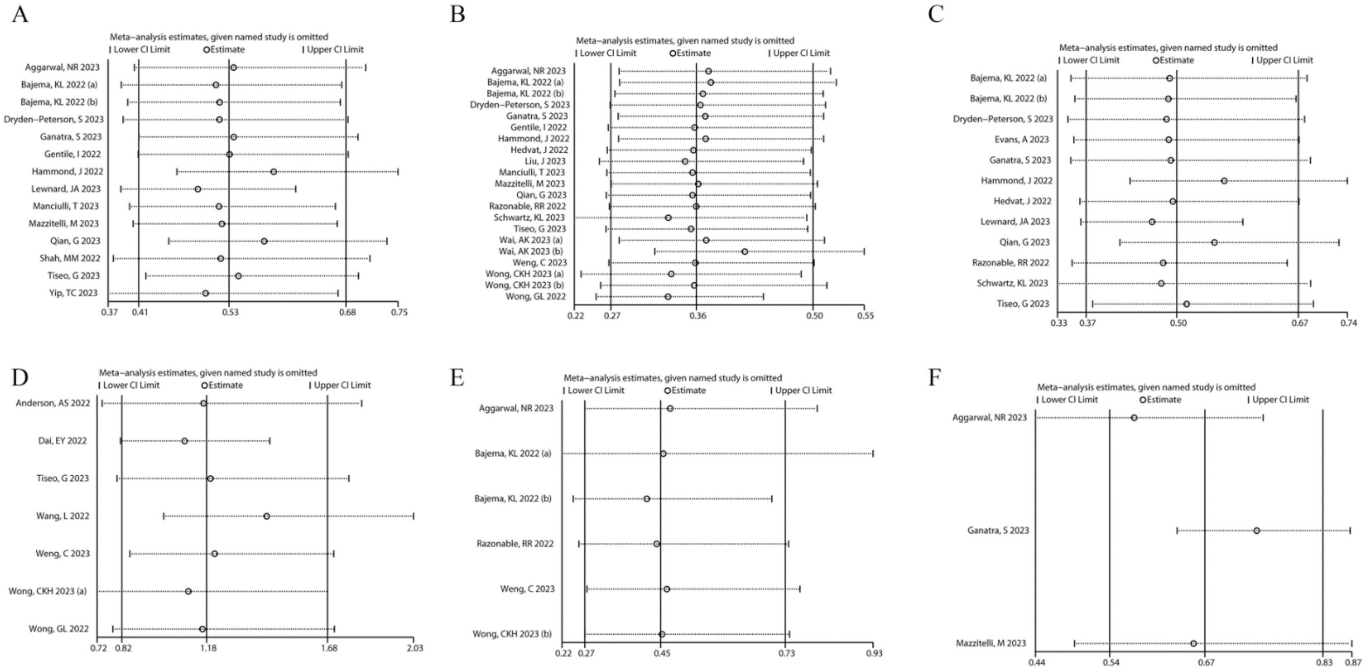
Supplementary Table 2. Quality assessment of the randomized controlled trial.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall
Anderson *et al*. [13]	Low	Low	Low	Low	Low	Low	Low	Low
Hammond *et al*. [3]	Low	Low	Low	Low	Low	Low	Low	Low
Liu *et al*. [7]	Low	Low	Unclear	Low	Low	Low	Low	Low

Supplementary Table 3. Quality assessment of the non-randomized controlled studies.

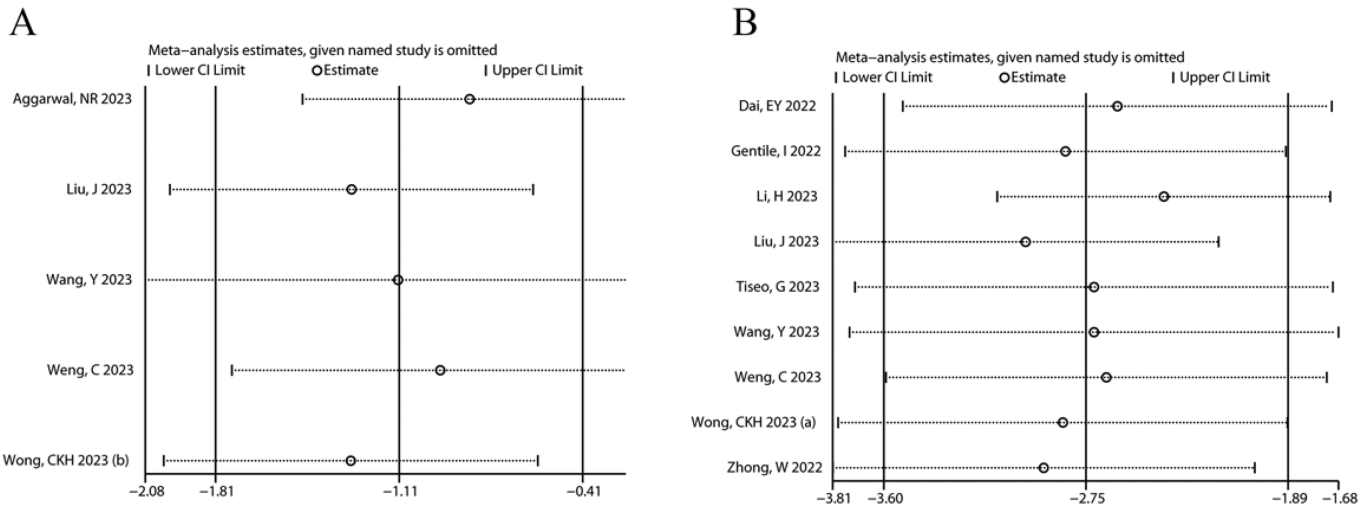
Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Aggarwal *et al*. [5]	Low	Low	Low	Low	Low	Low	Low	Low
Bajema *et al*. [14]	Low	Low	Low	Low	Low	Low	Low	Low
Dai *et al*. [15]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Dryden-Peterson *et al*. [16]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Evans *et al*. [17]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Ganatra *et al*. [6]	Low	Low	Low	Low	Low	Low	Low	Low
Gentile *et al*. [18]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Hedvat *et al*. [19]	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Lewnard *et al*. [20]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Li *et al*. [21]	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Manciulli *et al*. [22]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Mazzitelli *et al*. [23]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Qian *et al*. [24]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Razonable *et al*. [25]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Schwartz *et al*. [26]	Low	Low	Low	Low	Low	Low	Low	Low
Shah *et al*. [27]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Tiseo *et al*. [28]	Moderate	Low	Low	Low	Low	Low	Low	Low
Wai *et al*. [8]	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Wang *et al*. [29]	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Wang *et al*. [30]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Weng *et al*. [31]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Wong *et al*. [32]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Wong *et al*. [33]	Low	Low	Low	Low	Low	Low	Low	Low
Wong *et al*. [34]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Yip *et al*. [35]	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Zhong *et al*. [36]	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate

Supplementary Figure 1. Sensitivity analyses of efficacy outcome: hospitalization (A), mortality (B), hospitalization or death rate (C), COVID-19 rebound (D), ICU admission (E) and ED admission (F).



COVID-19: 2019 coronavirus disease; CI: confidence interval; ED: emergency department; ICU: intensive care unit.

Supplementary Figure 2. Sensitivity analyses of efficacy outcome: hospital length of stay (A) and PCR negative conversion time (B).



CI: confidence interval; PCR: polymerase chain reaction.