Lopinavir/Ritonavir for COVID-19: a Systematic Review and Meta-Analysis

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ABSTRACT -- Purpose: To provide the latest evidence on the efficacy and safety of lopinavir/ritonavir compared to other treatment options for COVID-19. **Methods:** We searched PubMed, Cochran Library, Embase, Scopus, and Web of Science for the relevant records up to April 2021. Moreover, we scanned medRxiv, Google Scholar, and clinical registry databases to identify additional records. We have used the Newcastle-Ottawa Scale and Cochrane risk of bias tool to assess the quality of studies. This Meta-analysis was conducted using RevMan software (version 5.3). **Results:** Fourteen studies were included. No significant difference was observed between lopinavir/ritonavir and non-antiviral treatment groups in terms of negative rate of PCR (polymerase chain reaction) on day 7 (risk ratio [RR]: 0.83; 95% CI: 0.63 to 1.09; P=0.17), and day 14 (RR: 0.93; 95% CI: 0.81 to 1.05; P=0.25), PCR negative conversion time (mean difference [MD]: 1.09; 95% CI: -0.10 to 2.29; P=0.07), secondary outcomes, and adverse events (P>0.05). There was no significant difference between lopinavir/ritonavir and chloroquine as well as lopinavir/ritonavir and hydroxychloroquine regarding the efficacy outcomes (P>0.05). However, lopinavir/ritonavir showed significantly lower efficacy than arbidol for primary outcomes (P<0.05). Lopinavir/ritonavir plus arbidol was effective compared to lopinavir/ritonavir alone in terms of the negative rate of PCR on day 7 (P=0.02). However, this difference was not significant regarding other efficacy outcomes (P>0.05). **Conclusion:** Lopinavir/ritonavir has no more treatment effects than other therapeutic agents in COVID-19 patients.

INTRODUCTION

It has been more than a year since the onset of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and its pandemic (1). Since the outbreak of coronavirus worldwide and its spread, the World Health Organization (WHO) has declared the disease an emergency public health problem (2). Furthermore, according to the WHO dashboard, 123 million people and more than 2.7 million people have died of COVID-19 disease as of March 22, 2021 (3). Currently, only a few drugs in specific areas and for use in conditional patients have been approved, and vaccine candidates have recently been approved or authorized for emergency use worldwide. Vaccination and the development of medical drugs are essential for the effective control of COVID-19. While several vaccines are being introduced to the market, they are inaccessible to many parts of the world (4). The first approved drug for COVID-19 was remdesivir, which was approved by the US Food and Drug Administration (FDA) on October 22, 2020, for hospitalized patients of 12 years and older (5). Several other treatment options are used to treat this disease, including lopinavir/ritonavir, nucleoside analogs, neuraminidase inhibitors, peptide (EK1), arbidol, RNA synthesis inhibitors (such as TDF, 3TC), anti-inflammatory drugs, and Shufengjiedu as well as lianhuaqingwen capsules, a Chinese traditional medicine (9).

Lopinavir is a protease inhibitor class that is used in fixed-dose combination with another protease inhibitor, ritonavir (lopinavir/ritonavir), for the treatment of human immunodeficiency virus (10), including off-label use for the treatments in COVID-19 (11). The combination is approved for AIDS treatment (12).

The results of several studies have shown that lopinavir/ritonavir combination as the initial treatment leads to a decrease in the death rate among

SARS patients (13, 14). Several studies found that COVID-19 patients treated with lopinavir/ritonavir show clinical improvement (15), and it was effective in treating acute respiratory illnesses (16, 17). On the other hand, several studies demonstrated that lopinavir/ritonavir was not effective in treating COVID-19 patients (18-20). This study aimed to evaluate the efficacy and safety of lopinavir/ritonavir compared to other treatment options for treating COVID-19 patients.

METHODS

The protocol for this systematic review and meta-analysis has been registered in PROSPERO with the number CRD42020207848. We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist when writing this report (21).

Literature search strategy

A systematic search was conducted in PubMed, Cochran Library, Embase, Scopus, and Web of Science for the relevant records up to April 2021. To identify other records, medRxiv, Google Scholar, and clinical registry databases, including ClinicalTrials.gov, The European Union Clinical Trials Register, and the Chinese Clinical Trial Registry were scanned. Finally, the references list of the final studies and review articles were reviewed for more citations. We limited our search to articles with English abstract or fulltext. The following is our search strategy used to search for relevant articles published in PubMed: ((((((((((Coronavirus[MeSH Terms]) OR (Novel coronavirus[MeSH Terms])) OR (2019 novel coronavirus infection[MeSH Terms])) OR (2019-nCoV infection[MeSH Terms])) OR (coronavirus pandemic[MeSH Terms])) OR (COVID-19[Title/Abstract])) OR (SARS-CoV-2[Title/Abstract])) OR (Coronavirus[Title/Abstract])) OR (2019-nCoV[Title/Abstract])) OR (Novel coronavirus[Title/Abstract])) AND (lopinavir/ritonavir [Title/Abstract]).We followed a similar logic while performing search in other databases.

Study selection

Two authors independently screened identified records based on inclusion and exclusion criteria. Disagreements were resolved by discussion among the authors. Discrepancies were resolved via conversation and by involving a third author. After removing duplicates, the remaining articles were independently reviewed based on title, abstract, and full text by two authors. The studies were selected based on the following criteria: 1). patients with confirmed COVID-19; 2). lopinavir/ritonavir as treatment intervention; 3). other interventions as a comparison (any treatment agents or conventional/control treatments); 4). clinical improvement and mortality rate as outcomes; 5). clinical trials or observational studies. Studies conducted on animal models, case reports, letters to editors, and editorials were excluded from the analysis.

Data Extraction and Quality Assessment

Cochrane risk of bias tool (RoB 2) and Newcastle-Ottawa Scale (NOS) (22) were used for assessing the quality of randomized controlled and observational studies. Data were extracted using a constructed data extraction form. The extracted data included the following: 1). study characteristics (year, country, design, and follow-up); 2). patient's characteristics (sample size, sex, and age); 3). Interventions (dosage); 4). and outcomes (viral clearance, mortality rate, and any adverse events). These steps were performed independently by two authors.

Evidence synthesis

A meta-analysis was performed to compare the efficacy and safety of lopinavir/ritonavir with other therapeutic agents, using RevMan software, version 5.3. The mean difference (MD) and risk ratio (RR) with a 95% confidence interval (CI) were used for continuous and dichotomous variables, respectively. Statistical heterogeneity was assessed using I-square > 50% and Chi-square with a significance level $p < 0.1$. The random-effects method was used for statistical heterogeneity. Otherwise, the fixed-effect method was used.

RESULTS

Figure 1 depicts the search process, exclusion of duplicates, and screening based on the title, abstract, and full text of the documents. Eighteen eligible studies were identified. Among these, four studies were lack of accessible data and necessary criteria for synthesis, and finally, fourteen studies (18, 23-35) were included for meta-analysis. These studies

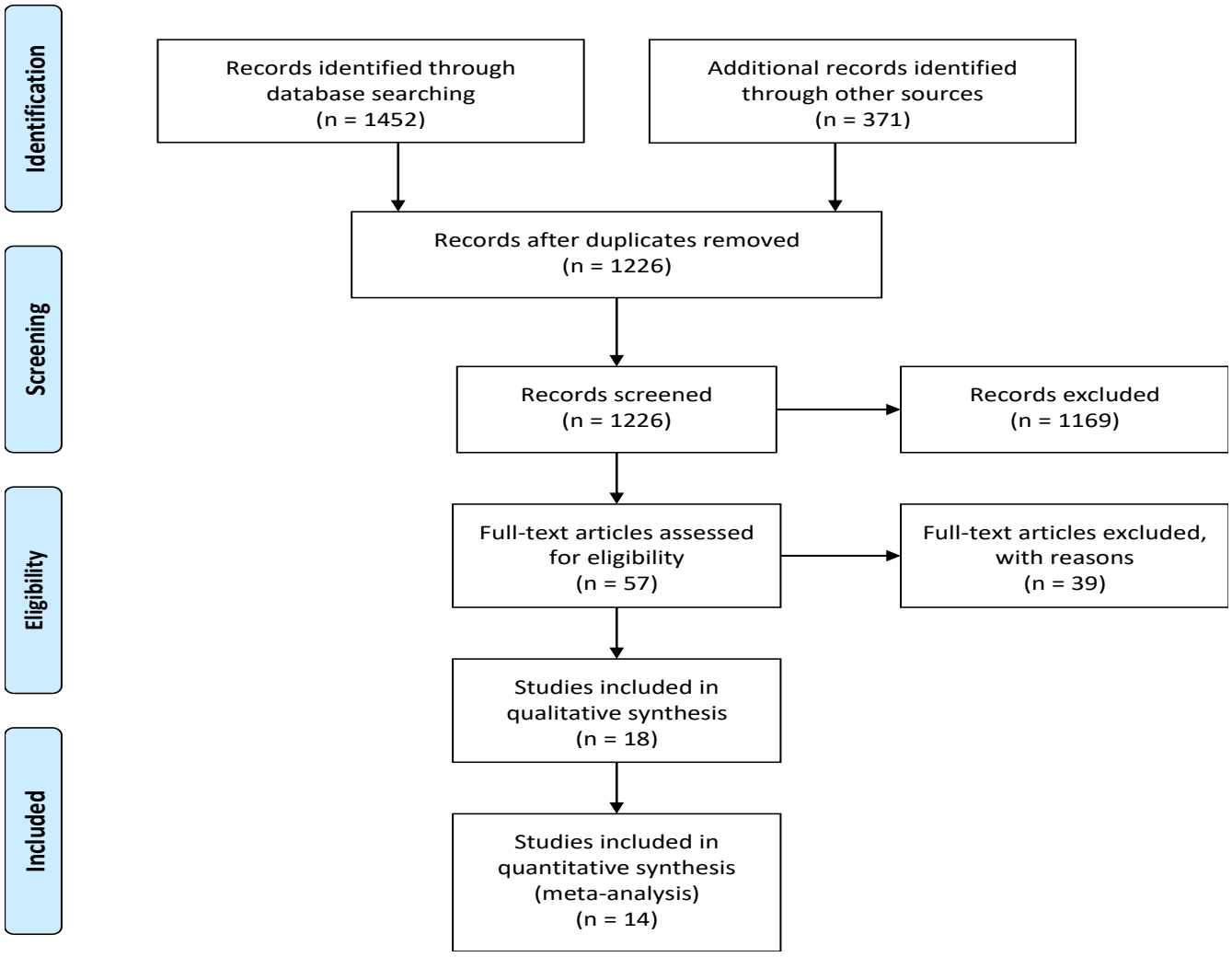


Figure 1. Flow diagram of the study selection process

included a total of 1634 patients. The characteristics of the studies and results from the quality assessment of the included studies are presented in Table 1. Assessment of the risk of bias using the Cochrane Collaboration tool is presented in Figure 2.

Efficacy

Lopinavir/ritonavir vs. non-antiviral

The result of meta-analysis showed that there was no significant difference between lopinavir/ritonavir and non-antiviral groups in terms of negative rate of PCR on day 7 (RR: 0.83; 95% CI: 0.63 to 1.09; P=0.17) and day 14 (RR: 0.93; 95% CI: 0.81 to 1.05; P=0.25), and PCR negative conversion time (MD: 1.09; 95% CI: -0.10 to 2.29; P=0.07) (Figure 3).

For the secondary outcomes, there was no significant difference between lopinavir/ritonavir and non-antiviral groups in terms of rate of improvement on the chest CT on day 7 (RR: 1.36; 95% CI: 0.56 to 3.34; P=0.50) and day 14 (RR: 0.94; 95% CI: 0.63 to 1.40; P=0.76), rate of cough alleviation on day 7 (RR: 0.84; 95% CI: 0.15 to 4.79; P=0.84) and day 14 (RR: 1.41; 95% CI: 0.93 to 2.13; P=0.11), disease progression (RR: 1.46; 95% CI: 0.52 to 4.13; P=0.48), hospital stay (MD: 1.49; 95% CI: -2.69 to 5.67; P=0.49), and adverse events (RR: 2.11; 95% CI: 0.76 to 5.83; P=0.15) (Figure 4).

Table 1. Characteristics of individual studies

First author, year	Country	Study design	Mean age	N (Male/Female)	Intervention (N)	Control (N)	NOS[1]
Cao et al. 2020, (18)	China	Randomized open-label controlled trial; single center	58	199 (120/79)	Lopinavir/ritonavir 400/100 mg/mg *bid* plus standard care (N=99)	Standard care* (N=100)	RoB**
Jun Chen et al. 2020, (27)	China	Retrospective; cohort; single center	48	134 (69/65)	Lopinavir/ritonavir (N=52)	Arbidol 200 mg three time daily (N=34), no antiviral drugs (N=48)	5
Xudan Chen et al. 2020, (23)	China	Retrospective; cohort; single center	48	284 (131/153)	Lopinavir/ritonavir (N=60)	Arbidol (N=69), no antiviral (N=121), other treatments (62)	9
Deng et al. 2020, (24)	China	Retrospective; cohort; single center	44.6	33 (17/16)	Lopinavir/ritonavir 400/100 mg/mg *bid* (N=17)	Lopinavir/ritonavir 400/100 mg/mg *bid* plus arbidol 200 mg *tid* (N=16)	6
Fan et al. 2021, (48)	China	Retrospective; observational, single center	46.3	55 (30/25)	Lopinavir/ritonavir (N=9)	Arbidol (N=18), arbidol plus lopinavir/ritonavir (N=20), Other treatments (N=8)	5
Gao et al. 2020, (25)	China	Retrospective; single center	33	129 (70/59)	Lopinavir/ritonavir 200/50 mg/mg *bid* (N=51)	Chloroquine 500 mg *bid* (N=19), standard care (N=59)	5
Horby et al. 2020, (19)	United Kingdom	Randomized, Open labeled Trial, multicenter	66.3	5040 (3077/1963)	Lopinavir/ritonavir 400/100 mg/mg *bid* plus standard care (N=1616)	Standard care (N=3424)	RoB
Huang et al. 2020, (26)	Hong Kong	Retrospective; cohort; single center	Not reported	27 (12/15)	Lopinavir/ritonavir 400/100 mg/mg *bid* (N=6)	Chloroquine 500 mg *bid* (N=10), arbidol 200 mg three times (N=11)	7
Karolyi et al. 2020, (28)	Austria	Cohort	72	156 (92/64)	Lopinavir/ritonavir 400/100 mg/mg *bid* (N=47)	Hydroxychloroquine 200 mg *bid* (N=20), No treatment (N=89)	6
Kim et al. 2021, (29)	South Korea	Retrospective; cohort; single center	64.3	65 (25/40)	Lopinavir/ritonavir 400/100 mg/mg *bid* (N=31)	Hydroxychloroquine 400 mg once daily (N=34)	6
Lan et al. 2020, (30)	China	Retrospective; cohort; multicenter	55.8	73 (37/36)	Lopinavir/ritonavir 400/100 mg/mg *bid* (N=34)	Lopinavir/ritonavir 400/100 mg/mg *bid* plus arbidol 200 mg *tid* (N=39)	7
Li et al 2020, (31)	China	Randomized open-label controlled trial; single center	49.4	86 (40/46)	Lopinavir/ritonavir 200/50 mg/mg *bid* (N=34)	Arbidol 200 mg *tid* (N=35), no antiviral medication (control) (N=17)	RoB
LU et al. 2021, (49)	China	Retrospective; cohort; multicenter	6	115 (65/50)	Lopinavir/ritonavir maximum dose 400/100 mg twice a day (N=23)	Untreated controls (N=92)	7
Nojomi et al. 2020, (32)	Iran	Randomized, Open labeled trial	56.4	100 (60/40)	Lopinavir/ritonavir 400/100 mg/mg *bid* (N=50)	Arbidol 200 mg *tid*(N=50)	RoB
Wen et al. 2020, (33)	China	Retrospective; cohort; single center	49.9	178 (81/97)	Lopinavir/ritonavir 200/50 mg/mg *bid* (N=59)	Arbidol 200 mg *tid* (N=36), lopinavir/Ritonavir plus Arbidol (N=25), conventional treatment group without any antiviral drugs (N=58)	7

Table 1 continues ...

Yan et al. 2020, (34)	China	Retrospective; cohort; single center	52	120 (54/66)	Lopinavir/ritonavir 200/50 mg/mg *bid* (N=78)	No antiviral (N=42)	5
Yuan et al. 2020, (50)	China	Retrospective; cohort; single center	40	94 (42/52)	Lopinavir/ritonavir plus IFN-α (N=46)	IFN-α plus LPV/RTV plus ribavirin (N=21)	6
Zhu et al. 2020, (35)	China	Retrospective; cohort; multicenter	39.8	50 (26/24)	Lopinavir/ritonavir 200/50 mg/mg *bid* (N=34)	Arbidol 200 mg *tid* (N=16)	7

[1]Newcastle Ottawa Scale; *Standard care included, as necessary, supplemental oxygen, non-invasive and invasive ventilation, antibiotic agents, vasopressor support, renal replacement therapy, and extracorporeal membrane oxygenation (ECMO); ** Risk of bias

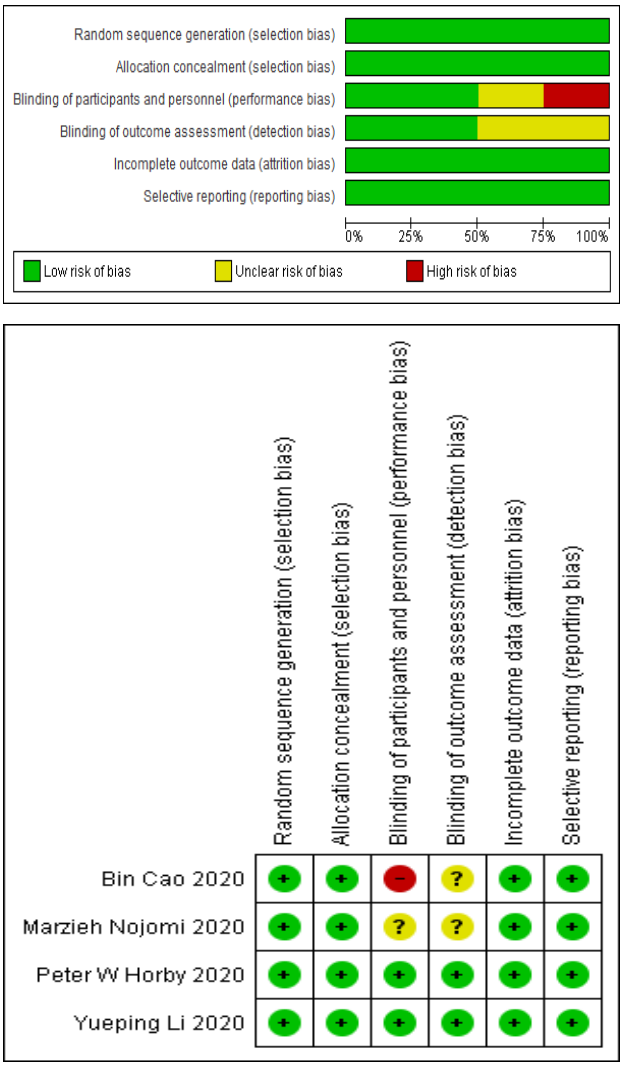


Figure 2. Risk of bias in the selected studies

Lopinavir/ritonavir vs. chloroquines

The result of the meta-analysis showed that there was no significant difference between lopinavir/ritonavir and chloroquine in terms of the negative rate of PCR on day 14 (RR: 0.91; 95% CI: 0.64 to 1.31; P=0.62), or between lopinavir/ritonavir and hydroxychloroquine in terms of the negative rate of PCR (RR: 1.31; 95% CI: 1.00 to 1.71; P=0.05), and mortality (RR: 0.67; 95% CI: 0.19 to 2.30; P=0.52) (Table 2).

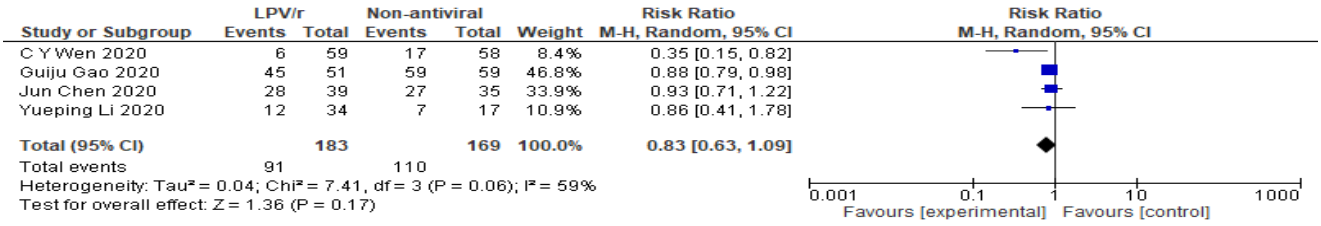
Lopinavir/ritonavir vs. arbidol

Lopinavir/ritonavir showed significantly lower efficacy compared to arbidol in terms of negative rate of PCR on day 7 (RR: 0.74; 95% CI: 0.57 to 0.97; P=0.03) and day 14 (RR: 0.68; 95% CI: 0.49 to 0.95; P=0.02), PCR negative conversion time (MD: 2.28; 95% CI: 0.72 to 3.83; P=0.004), and higher adverse events (RR: 2.28; 95% CI: 1.47 to 3.52; P=0.0002). While, not significant difference was observed between these drugs in terms of rate of improvement on the chest CT on day 7 (RR: 0.87; 95% CI: 0.59 to 1.29; P=0.50) and day 14 (RR: 1.01; 95% CI: 0.81 to 1.26; P=0.92), rate of cough alleviation on day 7 (RR: 0.62; 95% CI: 0.08 to 4.71; P=0.64) and day 14 (RR: 1.23; 95% CI: 0.87 to 1.74; P=0.24), hospital stay (MD: 1.87; 95% CI: -4.27 to 8.01; P=0.55), and disease progression (RR: 0.93; 95% CI: 0.11 to 7.98; P=0.94) (Table 2). There was neither significant differences in the hospital stay between the treatments (Table 2).

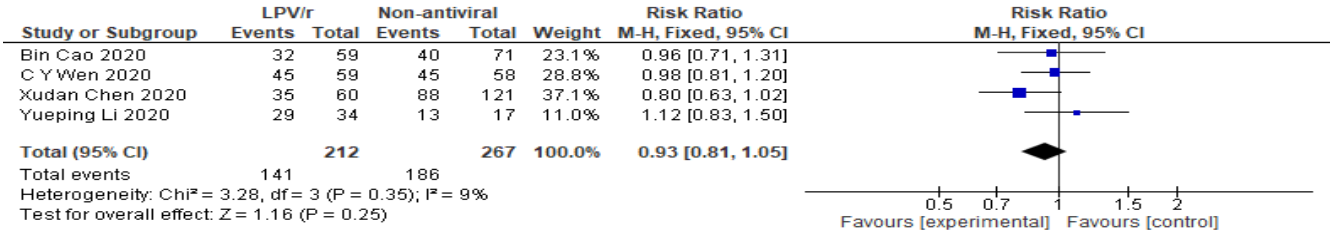
Lopinavir/ritonavir plus arbidol vs. lopinavir/ritonavir

Lopinavir/ritonavir plus arbidol demonstrated a significant difference compared to lopinavir/ritonavir alone in terms of negative rate of PCR on day 7 (RR: 2.06; 95% CI: 1.13 to 3.76; P=0.02), However, this difference was not significant in terms of negative rate of PCR on day 14 (RR: 0.99; 95% CI: 0.55 to 1.80; P=0.99), PCR negative conversion time (MD: 2.21; 95% CI: -0.13 to 4.54; P=0.06), rate of improvement on the chest CT on day 7 (RR: 1.05; 95% CI: 0.20 to 5.50; P=0.96), and hospital stay (MD: 1.51; 95% CI: -3.94 to 6.97; P=0.59) (Table 2).

A. Negative rate of PCR on day 7



B. Negative rate of PCR on day 14



C. PCR negative conversion time

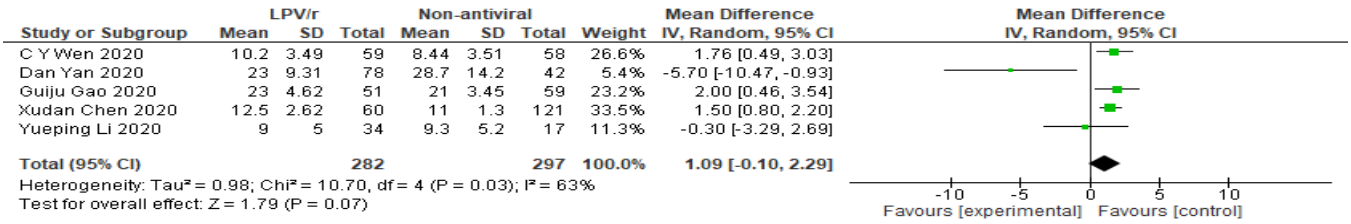
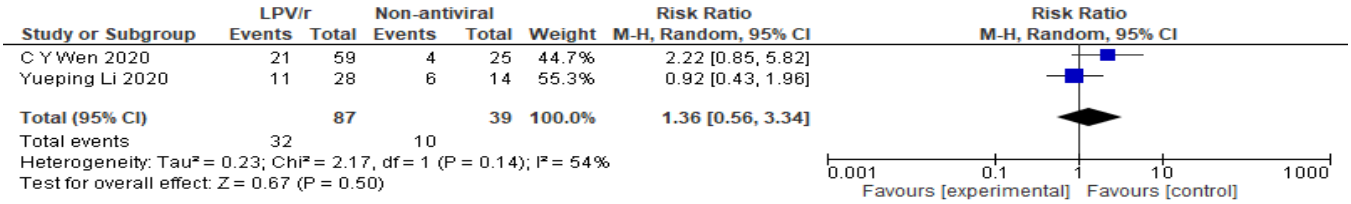


Figure 3. Risk ratio (RR) of lopinavir/ritonavir vs. non-antiviral for outcomes of negative rate of PCR on day 7 (A) and day 14 (B), and mean difference (MD) for PCR negative conversion time (C).

A. Rate of improvement on chest CT on day 7



B. Rate of improvement on chest CT on day 14

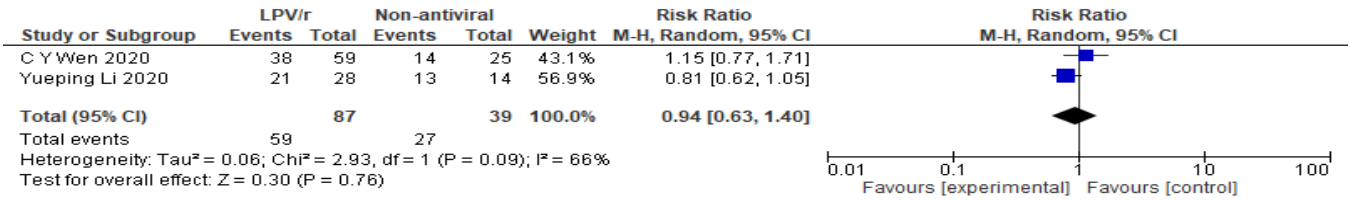
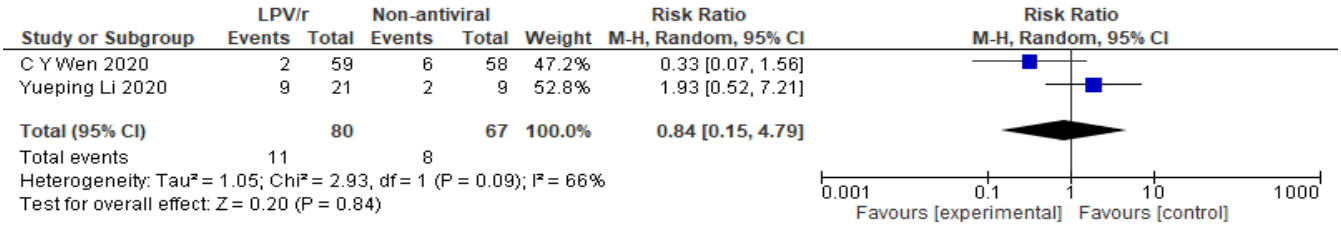
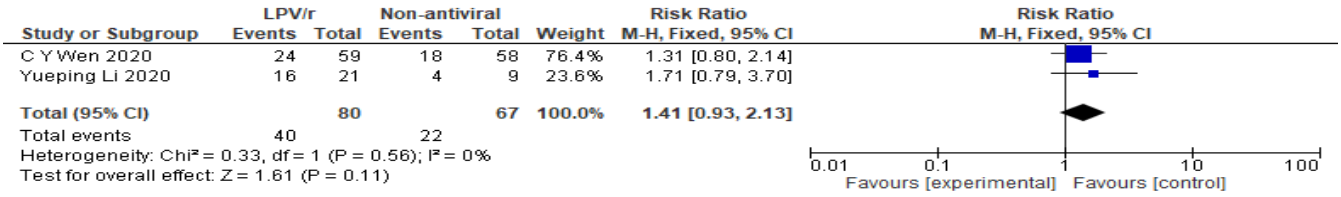


Figure 4. continues…

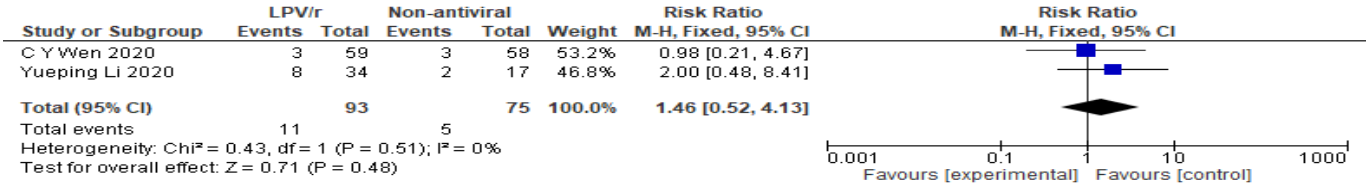
C. Rate of cough alleviation on day 7



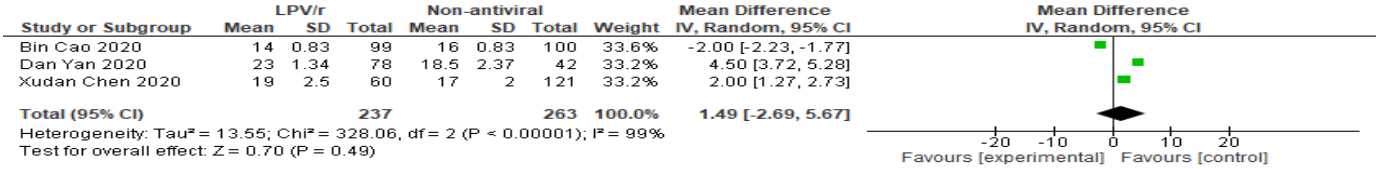
D. Rate of cough alleviation on day 14



E. Disease progress



F. Hospital stay



G. Adverse events

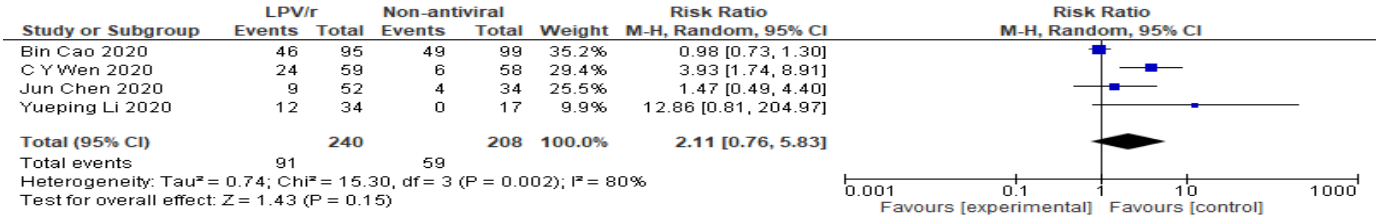


Figure 4. Risk ratio (RR) of lopinavir/ritonavir vs. non-antiviral for outcomes of rate of improvement on chest CT on day 7 (A) and day 14 (B), rate of cough alleviation on day 7 (C) and day 14 (D), disease progress (E), mean difference (MD) for hospital stay (F), and adverse events (G).

Adverse Events

No significant difference was observed between lopinavir/ritonavir and non-antiviral groups for adverse events (RR: 2.11; 95% CI: 0.76 to 5.83; P=0.15). However, patients taking lopinavir/ritonavir showed higher adverse events than patients taking arbidol (RR: 2.28; 95% CI: 1.47 to 3.52; P=0.0002) (Table 2).

DISCUSSION

The purpose of this study was to evaluate the current evidence on the efficacy and safety of

lopinavir/ritonavir in treating COVID-19. The result of our meta-analysis showed that, compared to no-antiviral as control group, lopinavir/ritonavir was not significantly more effective in any outcomes including negative rate of PCR, PCR negative conversion time, rate of improvement on the chest CT, rate of cough alleviation, disease progression, and hospital stay. The current diagnosis of COVID-19 infection is mainly made by the Real-Time Reverse Transcription-Polymerase Chain Reaction (rRT-PCR), which is a standard test for laboratory diagnosis of COVID-19 infection (36, 37). The type of molecular test is Viral RNA and is laboratory-based. The typical sampling site for PCR is through nasopharyngeal swab, sputum. This test provides a relatively fast result (average 3-4 hours), and the number of samples in each batch is up to 96 samples (37).

These findings are in line with prior systematic review and meta-analyses. Tobaiqy et al. (38) found

Table 2. Pooled meta-analysis results for Lopinavir/ritonavir vs. other treatment interventions

Analysis	No. of studies	Sample size	Pooled estimate (%95CI)	P	Heterogeneity		
					Chi^2	P	I^2
Lopinavir/ritonavir vs. chloroquine							
Negative rate of PCR on day 14	3	163	0.91 [0.64, 1.31]	0.62	4.21	0.12	52%
PCR negative conversion time	3	163	3.84 [-2.45, 10.12]	0.23	37.99	< 0.00001	95%
Hospital stay	2	92	6.24 [-1.49, 13.97]	0.11	16.45	< 0.0001	94%
Lopinavir/ritonavir vs. hydroxychloroquine							
Negative rate of PCR	2	108	1.31 [1.00, 1.71]	0.05	0.61	0.43	0%
Mortality rate	2	132	0.67 [0.19, 2.30]	0.52	0.18	0.67	0%
Lopinavir/ritonavir vs. arbidol							
Negative rate of PCR on day 7	4	276	0.74 [0.57, 0.97]	0.03	4.18	0.24	28%
Negative rate of PCR on day 14	5	328	0.68 [0.49, 0.95]	0.02	24.07	< 0.0001	83%
PCR negative conversion time	5	328	2.28 [0.72, 3.83]	0.004	21.91	0.0002	82%
Hospital stay	3	214	1.87 [-4.27, 8.01]	0.55	50.39	< 0.00001	96%
Rate of improvement on chest CT on day 7	2	156	0.87 [0.59, 1.29]	0.50	0.29	0.59	0%
Rate of improvement on chest CT on day 14	2	156	1.01 [0.81, 1.26]	0.92	0.24	0.62	0%
Disease progress	2	164	0.93 [0.11, 7.98]	0.94	5.64	0.02	82%
Rate of cough alleviation on day 7	2	141	0.62 [0.08, 4.71]	0.64	5.48	0.02	82%
Rate of cough alleviation on day 14	2	141	1.23 [0.87, 1.74]	0.24	0.32	0.57	0%
Adverse events	5	367	2.28 [1.47, 3.52]	0.0002	2.70	0.61	0%
Lopinavir/ritonavir plus arbidol vs. lopinavir/ritonavir							
Negative rate of PCR on day 7	2	117	2.06 [1.13, 3.76]	0.02	0.01	0.91	0%
Negative rate of PCR on day 14	3	193	0.99 [0.55, 1.80]	0.99	9.44	0.009	79%
PCR negative conversion time	3	229	2.21 [-0.13, 4.54]	0.06	6.61	0.04	70%
Hospital stay	2	145	1.51 [-3.94, 6.97]	0.59	6.46	0.01	85%
Rate of improvement on chest CT on day 7	2	117	1.05 [0.20, 5.50]	0.96	6.99	0.008	86%

no significant antiviral effect of lopinavir/ritonavir versus control. The finding of a meta-analysis by Verdugo-Paiva et al. (39) indicated that lopinavir/ritonavir has no significant effect on the length of hospital stay, consistent with our findings. Vargas et al. (40) showed that there was no sufficient evidence for whether lopinavir/ritonavir is beneficial in the treatment of patients with COVID-19.

Meta-analysis of lopinavir/ritonavir versus chloroquine showed no significant difference

between these interventions in terms of the negative rate of PCR, hospital stay, and PCR negative conversion time in patients with COVID-19. The present analysis includes additional data which has become available since the above publications.
The results showed that lopinavir/ritonavir had no clinical benefit compared to hydroxychloroquine in patients with COVID-19.

Compared with arbidol, lopinavir/ritonavir showed significantly lower efficacy in terms of the negative rate of PCR and PCR negative conversion time. However, no significant difference was observed between these drugs regarding rate of improvement on the chest CT, hospital stay, and disease progression. A meta-analysis done by Tobaiqy et al. showed no different treatment between lopinavir/ritonavir and arbidol in terms of PCR negative conversion time, rate of improvement on the chest CT, rate of cough alleviation, and time to body temperature recovery. It should be noted that our meta-analysis included more recent studies than these previously published systematic reviews.

We have also conducted a meta-analysis on adding arbidol to lopinavir/ritonavir as a combination therapy versus lopinavir/ritonavir alone. The result showed a significant improvement for the negative rate of PCR on day7. However, these differences were not significant in terms of the negative rate of PCR on day14, PCR negative conversion time, rate of improvement on the chest CT, and hospital stay. Tobaiqy and colleagues found a similar result for adding arbidol to lopinavir/ritonavir regarding PCR negative conversion time. Similar to the findings of Tobaiqy et al. (38), our meta-analysis found higher adverse events in the lopinavir/ritonavir group compared with the arbidol group. Also, in a study conducted by Patel et al. (41), there was no difference in patients treated with lopinavir-ritonavir than supportive care, consistent with our study. A significant difference was observed between lopinavir/ritonavir and arbidolgroups for adverse events in the studies by Tobaiqy et al. (38) and Patel et al. (41). Authors observed more adverse events in lopinavir/ritonavir versus arbidol.

The results of a systematic review (42) showed that there was a significant difference between lopinavir/ritonavir and standard care in time to clinical improvement. Evidence from this systematic review showed that there were no benefits for lopinavir/ritonavir compared with standard care in patients with COVID-19. The results of a review suggested that, at the current time, clinicians should not abandon the use of lopinavir/ritonavir for the treatment of COVID-19 (43).

Cheng et al. demonstrated that lopinavir/ritonavir did not reduce the duration of SARS-CoV-2. Therefore, it may not be recommended for COVID-19 patients with mild pneumonia (15). However, lopinavir/ritonavir plus IFN-α combination therapy may help shorten the duration of SARS-CoV-2 (44).

Patients taking lopinavir/ritonavir showed a higher rate of adverse events compared to patients taking arbidol. The results of a meta-analysis showed that lopinavir/ritonavir led to adverse events such as moderate or severe diarrhea in HIV-1-infected (45), and liver injury in COVID-19 patients (46). Another study showed that serious adverse events in lopinavir/ritonavir were less than the standard care (42). Common adverse events of lopinavir/ritonavir in patients with COVID-19 are gastrointestinal disturbances, in particular diarrhea, dyslipidaemia, diabetes mellitus, pancreatitis, and hepatic disorders (47). The major limitations of this study were the small number of included studies, small sample size, and low-quality studies.

CONCLUSION

The findings of our systematic review and meta-analysis failed to establish any beneficial effect of lopinavir/ritonavir compared with non-antiviral treatment, chloroquine, and hydroxychloroquine in treating patients with COVID-19. However, compared with arbidol, lopinavir/ritonavir was associated with significantly lower improvement in the negative rate of PCR and PCR negative conversion time in COVID-19 patients. High-quality studies with a large sample size are needed to establish the safety and efficacy of lopinavir/ritonavir.

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