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 tools 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 better efficacy than arbidol for the same outcomes (P<0.05). Lopinavir/ritonavir plus arbidol was effective compared to arbidol 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 used herein 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 worldwide (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, Cochrane 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 Clinical trial 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. There was no restriction on the language. 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 were 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 editorialials were excluded from the analysis.

Data Extraction and Quality Assessment
Cochrane risk of bias tool (RoB 2) and Newcastle-Ottawa Scale (NOS) were used for assessing the quality of randomized controlled and observational studies (22). 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 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 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 RR for adverse events (RR: 2.11; 95% CI: 0.76 to 5.83; P=0.15)(Figure 4).

**Lopinavir/ritonavir vs. chloroquine**

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),
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 MgMg twice daily 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=18), Antiviral drugs (N=18) | 5 |
| Xudan Chen et al. 2020, (23) | China | Retrospective; cohort; single center | 48 | 284 (131/153) | Lopinavir/ritonavir (N=78) | Arbidol (N=69) No *(N=84) | 9 |
| Deng et al. 2020, (24) | China | Retrospective; cohort; single center | 44.6 | 33 (17/16) | Lopinavir/ritonavir 400/100 MgMg twice daily (N=17) | Lopinavir/ritonavir 400/100 MgMg twice daily plus Arbidol 200 Mg three times daily (N=16) | 6 |
| Fan et al. 2021, (48) | China | Retrospective; observational, single center | 46.3 | 53 (30/25) | Lopinavir/ritonavir (N=9) | Arbidol (N=18), Arbidol plus Lopinavir/ritonavir (N=20), Other treatments (N=6) | 5 |
| Gao et al. 2020, (25) | China | Retrospective; single center | 33 | 129 (70/59) | Lopinavir/ritonavir 200/50 MgMg twice daily (N=51) | Chloroquine 500 Mg twice daily (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 MgMg twice daily 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 MgMg twice daily (N=6) | Chloroquine 500 Mg twice daily (N=10), Arbidol 200 Mg three times daily (N=11) | 7 |
| Karolyi et al. 2020, (28) | Austria | Cohort | 72 | 156 (92/64) | Lopinavir/ritonavir 400/100 MgMg twice daily (N=47) | Hydroxychloroquine 200 Mg twice daily (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 MgMg twice daily (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 MgMg twice daily (N=34) | Lopinavir/ritonavir 400/100 MgMg twice daily plus Arbidol 200 mg three times daily (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 MgMg twice daily (N=34) | Arbidol 200 Mg three times daily (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 MgMg 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 MgMg twice daily (N=50) | Arbidol 200 Mg three times daily (N=50) | RoB |

Table 1 continues....
Wen et al. 2020, (33) China Retrospective; cohort; single center 49.9 178 (81/97) Lopinavir/ritonavir 200/50 MgMg twice daily (N=59) Arbidol 200 Mg three times daily (N=36), Lopinavir/Ritonavir plus Arbidol (N=25), Conventional treatment group without any antiviral drugs (N=58) 7

Yan et al. 2020, (34) China Retrospective; cohort; single center 52 120 (54/66) Lopinavir/ritonavir 200/50 MgMg twice daily (N=59) No antiviral (N=42) 5

Yuan et al. 2020, (50) China Retrospective; cohort; single center 40 94 (42/52) Lopinavir/ritonavir 200/50 MgMg twice daily (N=46) IFN-α + LPV/RTV plus Ribavirin (N=41) 6

Zhu et al. 2020, (35) China Retrospective; cohort; multicenter 39.8 50 (26/24) Lopinavir/ritonavir 200/50 MgMg twice daily (N=34) Arbidol 200 Mg three times daily (N=16) 7

1Newcastle Ottawa Scale; 2Standard care included, as necessary, supplemental oxygen, non-invasive and invasive ventilation, antibiotic agents, vasopressor support, renal replacement therapy, and extracorporeal membrane oxygenation (ECMO); 3ICU care, Oxygen therapy, Antibiotics, Mechanical ventilation; 4Risk of bias tool

The results showed that there was no significant difference 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. hydroxychloroquine

Lopinavir/ritonavir showed significant efficacy compared to arbidol in terms of negative rate 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 RR for 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: -2.47 to 8.01; P=0.55), and disease progression (RR: 0.93; 95% CI: 0.11 to 7.98; P=0.94) (Table 2).

Lopinavir/ritonavir vs. arbidol

Lopinavir/ritonavir plus arbidol demonstrated a significant difference compared to arbidol 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=0.06), 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

| Study or Subgroup | LPV/r Events | Non-antiviral Events | Total | Weight | M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|-------------------|--------------|----------------------|-------|--------|---------------------|-------------------------------|
| C Y Wun 2020      | 6            | 56                   | 17    | 50     | 0.4%                | 0.95 [0.16, 5.82]             |
| Guiu Gao 2020     | 45           | 51                   | 69    | 59     | 46.9%               | 0.06 [0.07, 0.99]             |
| Jun Chen 2020     | 20           | 39                   | 27    | 35     | 33.9%               | 0.93 [0.71, 1.22]             |
| Yueling Li 2020   | 12           | 34                   | 7     | 17     | 10.9%               | 0.85 [0.41, 1.78]             |
| **Total (95% CI)** | **133**      | **169**              | **169** | **100.0%** | **0.03 [0.63, 1.09]** |
| **Total events**   | **291**      | **410**              |       |        |                     |                               |
| Heterogeneity: Tau² = 0.04; Ch² = 7.41; df = 3 (P = 0.06); I² = 59% |
| Test for overall effect: Z = 1.36 (P = 0.17) |

B. Negative rate of PCR on day 14

| Study or Subgroup | LPV/r Events | Non-antiviral Events | Total | Weight | M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|--------------|----------------------|-------|--------|---------------------|-------------------------------|
| Bin Cao 2020      | 32           | 50                   | 40    | 71     | 23.1%               | 0.96 [0.71, 1.31]             |
| C Y Wun 2020      | 45           | 50                   | 45    | 60     | 26.9%               | 0.90 [0.81, 1.02]             |
| Xudan Chen 2020   | 26           | 60                   | 40    | 121    | 37.1%               | 0.96 [0.63, 1.55]             |
| Yueling Li 2020   | 29           | 34                   | 17    | 17     | 11.0%               | 1.12 [0.65, 1.90]             |
| **Total (95% CI)** | **212**      | **267**              | **267** | **100.0%** | **0.83 [0.81, 1.05]** |
| **Total events**   | **141**      | **180**              |       |        |                     |                               |
| Heterogeneity: Tau² = 0.20; Ch² = 3 (P = 0.36); I² = 0% |
| Test for overall effect: Z = 1.18 (P = 0.25) |

C. PCR negative conversion time

| Study or Subgroup | LPV/r Mean | Non-antiviral Mean | Total | Weight | Mean Difference IV, Random, 95% CI |
|-------------------|------------|--------------------|-------|--------|----------------------------------|
| C Y Wun 2020      | 10.2       | 3.49               | 50    | 58     | 26.8%                            |
| Guiu Gao 2020     | 23.5       | 0.31               | 78    | 29.7   | 14.2                            |
| Xudan Chen 2020   | 12.5       | 2.62               | 60    | 11.3   | 121                             |
| Yueling Li 2020   | 9.5        | 0.34               | 34    | 9.3    | 5.2                             |
| **Total (95% CI)** | **282**    | **297**            | **297** | **100.0%** | **1.09 [-0.10, 2.29]**          |
| Heterogeneity: Tau² = 0.08; Ch² = 10.70; df = 4 (P = 0.03); I² = 65% |
| Test for overall effect: Z = 1.79 (P = 0.07) |

**Figure 3.** Risk ratio (RR) of lopinavir/ritonavir vs. no antiviral for outcomes of negative rate of PCR on day 7 (A) and day 14 (B), and mean difference (MD) for negative conversion time (C).

A. Rate of improvement on chest CT on day 7

| Study or Subgroup | LPV/r Events | Non-antiviral Events | Total | Weight | M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|-------------------|--------------|----------------------|-------|--------|---------------------|-------------------------------|
| C Y Wun 2020      | 21           | 59                   | 4     | 25     | 44.7%               | 2.22 [0.85, 5.82]             |
| Yueling Li 2020   | 11           | 28                   | 6     | 14     | 55.3%               | 0.82 [0.43, 1.60]             |
| **Total (95% CI)** | **32**       | **39**               | **39** | **100.0%** | **1.36 [0.56, 3.34]** |
| **Total events**   | **32**       | **10**               |       |        |                     |                               |
| Heterogeneity: Tau² = 0.23; Ch² = 2.17; df = 1 (P = 0.14); I² = 54% |
| Test for overall effect: Z = 0.67 (P = 0.50) |

**Figure 4.** continues...
B. Rate of improvement on chest CT on day 14

| Study or Subgroup | LPV/r Events Total | Non-antiviral Events Total | Weight | M. H. Random, 95% CI | Risk Ratio M. H. Random, 95% CI |
|-------------------|--------------------|---------------------------|--------|----------------------|---------------------------------|
| C Y Wen 2020      | 38                 | 59                        | 14     | 20                   | 43.1%                           |
|                   |                    |                           |        |                      | 1.15 [0.77, 1.71]               |
| Yuqing Li 2020    | 21                 | 28                        | 13     | 14                   | 56.9%                           |
|                   |                    |                           |        |                      | 0.81 [0.62, 1.05]               |
| Total (95% CI)    | 59                 | 77                        | 100.0% |                      | 0.84 [0.63, 1.10]               |
| Total events      | 27                |                           |        |                      |                                |
| Heterogeneity:    |                   |                           |        |                      |                                 |
| Tau² = 0.08, Ch² = 2.93, df = 1 (P = 0.29), P = 56% |
| Test for overall effect: Z = 0.20 (P = 0.77) |

C. Rate of cough alleviation on day 7

| Study or Subgroup | LPV/r Events Total | Non-antiviral Events Total | Weight | M. H. Random, 95% CI | Risk Ratio M. H. Random, 95% CI |
|-------------------|--------------------|---------------------------|--------|----------------------|---------------------------------|
| C Y Wen 2020      | 2                  | 59                        | 8      | 58                   | 47.2%                           |
|                   |                    |                           |        |                      | 0.33 [0.07, 1.58]               |
| Yuqing Li 2020    | 9                  | 21                        | 2      | 9                    | 52.8%                           |
|                   |                    |                           |        |                      | 1.93 [0.52, 7.21]               |
| Total (95% CI)    | 11                 | 67                        | 100.0% |                      | 0.84 [0.15, 4.70]               |
| Total events      | 27                |                           |        |                      |                                |
| Heterogeneity:    |                   |                           |        |                      |                                 |
| Tau² = 1.05, Ch² = 2.53, df = 1 (P = 0.49), P = 69% |
| Test for overall effect: Z = 0.20 (P = 0.84) |

D. Rate of cough alleviation on day 14

| Study or Subgroup | LPV/r Events Total | Non-antiviral Events Total | Weight | M. H. Random, 95% CI | Risk Ratio M. H. Random, 95% CI |
|-------------------|--------------------|---------------------------|--------|----------------------|---------------------------------|
| C Y Wen 2020      | 24                 | 55                        | 19     | 26                   | 76.4%                           |
|                   |                    |                           |        |                      | 1.12 [0.90, 1.41]               |
| Yuqing Li 2020    | 16                 | 21                        | 4      | 9                    | 93.8%                           |
|                   |                    |                           |        |                      | 1.91 [0.78, 3.30]               |
| Total (95% CI)    | 40                 | 66                        | 100.0% |                      | 1.41 [0.93, 2.13]               |
| Total events      | 48                |                           |        |                      |                                |
| Heterogeneity:    |                   |                           |        |                      |                                 |
| Tau² = 0.33, Ch² = 1.54, df = 1 (P = 0.56), P = 0% |
| Test for overall effect: Z = 0.91 (P = 0.84) |

E. Disease progress

| Study or Subgroup | LPV/r Events Total | Non-antiviral Events Total | Weight | M. H. Random, 95% CI | Risk Ratio M. H. Random, 95% CI |
|-------------------|--------------------|---------------------------|--------|----------------------|---------------------------------|
| C Y Wen 2020      | 3                  | 59                        | 3      | 56                   | 55.2%                           |
|                   |                    |                           |        |                      | 0.93 [0.21, 4.67]               |
| Yuqing Li 2020    | 8                  | 34                        | 2      | 17                   | 46.8%                           |
|                   |                    |                           |        |                      | 2.03 [0.49, 8.41]               |
| Total (95% CI)    | 11                 | 75                        | 100.0% |                      | 1.46 [0.52, 4.13]               |
| Total events      | 56                |                           |        |                      |                                |
| Heterogeneity:    |                   |                           |        |                      |                                 |
| Tau² = 0.43, Ch² = 1.03, df = 1 (P = 0.64), P = 0% |
| Test for overall effect: Z = 0.71 (P = 0.48) |

F. Hospital stay

| Study or Subgroup | LPV/r Events Mean | Non-antiviral Events Mean | Weight | M. H. Random, 95% CI | Mean Difference M. H. Random, 95% CI |
|-------------------|-------------------|---------------------------|--------|----------------------|--------------------------------------|
| Bin Cao 2020      | 14 0.83           | 93 0.83                   | 16     | 16 0.83              | 196 32.6%                            |
|                   |                   |                           |        |                      | -2.00 [-2.23, -1.77]                |
| Dong Yan 2020     | 23 1.34           | 75 1.54                   | 16.5   | 2.37              | 42 33.2%                             |
|                   |                   |                           |        |                      | 4.50 [3.72, 5.28]                   |
| Xuan Chen 2020    | 19 2.56           | 60 17.0                   | 17     | 2                   | 121 33.2%                           |
|                   |                   |                           |        |                      | 2.90 [2.07, 3.73]                   |
| Total (95% CI)    | 237               | 253                      | 100.0% |                      | 1.49 [2.69, 5.67]                   |
| Total events      | 250               |                           |        |                      |                                |
| Heterogeneity:    |                   |                           |        |                      |                                 |
| Tau² = 13.65, Ch² = 328.06, df = 2 (P = 0.00001), P = 90% |
| Test for overall effect: Z = 0.70 (P = 0.49) |

G. Adverse events

| Study or Subgroup | LPV/r Events Total | Non-antiviral Events Total | Weight | M. H. Random, 95% CI | Risk Ratio M. H. Random, 95% CI |
|-------------------|--------------------|---------------------------|--------|----------------------|---------------------------------|
| Bin Cao 2020      | 46                 | 95                        | 40     | 99                   | 95.3%                           |
|                   |                    |                           |        |                      | 0.59 [0.79, 1.30]               |
| C Y Wen 2020      | 24                 | 59                        | 6      | 69                   | 29.4%                           |
|                   |                    |                           |        |                      | 3.89 [1.74, 9.91]               |
| Jun Chen 2020     | 9                  | 52                        | 4      | 34                   | 25.5%                           |
|                   |                    |                           |        |                      | 1.47 [0.49, 4.40]               |
| Yuqing Li 2020    | 12                 | 34                        | 0      | 17                   | 9.9%                             |
|                   |                    |                           |        |                      | 12.96 [0.81, 204.97]            |
| Total (95% CI)    | 240               | 208                      | 100.0% |                      | 2.41 [0.76, 8.33]               |
| Total events      | 56                |                           |        |                      |                                |
| Heterogeneity:    |                   |                           |        |                      |                                 |
| Tau² = 0.74, Ch² = 15.30, df = 3 (P = 0.0020), P = 68% |
| Test for overall effect: Z = 1.43 (P = 0.15) |

Figure 4. Risk ratio (RR) of lopinavir/ritonavir vs. no 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**

We evaluate the current evidence on the efficacy and safety of lopinavir/ritonavir in treating COVID-19.

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

| Analysis                                      | No. of studies | Sample size | Pooled estimate (%95CI) | P   | Heterogeneity |
|-----------------------------------------------|----------------|-------------|-------------------------|-----|---------------|
| **Lopinavir/ritonavir vs. Chloroquine**       |                |             |                         |     |               |
| Negative rate of PCR on day 14                | 3              | 163         | 0.91 [0.64, 1.31]       | 0.62| 4.21          |
| PCR negative conversion time                  | 3              | 163         | 3.84 [-2.45, 10.12]     | 0.23| 37.99 < 0.0001|
| Hospital stay                                 | 2              | 92          | 6.24 [-1.49, 13.97]     | 0.11| 16.45 < 0.0001|
| **Lopinavir/ritonavir vs. hydroxychloroquine**|                |             |                         |     |               |
| Negative rate of PCR                          | 2              | 108         | 1.31 [1.00, 1.71]       | 0.05| 0.61          |
| Mortality rate                                | 2              | 132         | 0.67 [0.19, 2.30]       | 0.52| 0.18          |
| **Lopinavir/ritonavir vs. Arbidol**           |                |             |                         |     |               |
| Negative rate of PCR on day 7                 | 4              | 276         | 0.74 [0.57, 0.97]       | 0.03| 4.18          |
| Negative rate of PCR on day 14                | 5              | 328         | 0.68 [0.49, 0.95]       | 0.02| 24.07 < 0.0001|
| 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 < 0.0001|
| Rate of improvement on chest CT on day 7      | 2              | 156         | 0.87 [0.59, 1.29]       | 0.50| 0.29          |
| Rate of improvement on chest CT on day 14     | 2              | 156         | 1.01 [0.81, 1.26]       | 0.92| 0.24          |
| Disease progress                              | 2              | 164         | 0.93 [0.11, 7.98]       | 0.94| 5.64          |
| Rate of cough alleviation on day 7            | 2              | 141         | 0.62 [0.08, 4.71]       | 0.64| 5.48          |
| Rate of cough alleviation on day 14           | 2              | 141         | 1.23 [0.87, 1.74]       | 0.24| 0.32          |
| Adverse events                                | 5              | 367         | 2.28 [1.47, 3.52]       | 0.0002| 2.70 0.61 0% |

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. Tobaqy et al. (38) found 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 significant efficacy in terms of the negative rate of PCR on day 14 and PCR negative conversion time. However, no significant difference was observed between these drugs regarding the negative rate of PCR on day 7, rate of improvement on the chest CT, hospital stay, and disease progression. A meta-analysis done by Tobaqy 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 day 14. However, these differences were not significant in terms of the negative rate of PCR on day 7, PCR negative conversion time, rate of improvement on the chest CT, and hospital stay. Tobaqy and colleagues found a similar result for adding arbidol to lopinavir/ritonavir regarding PCR negative conversion time. Similar to the findings of Tobaqy et al. (38), our meta-analysis found higher adverse events in the lopinavir/ritonavir group compared with the control 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 control groups for adverse events in the studies Tobaqy 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 was observed (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, low-quality studies, and.

**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, it was associated with significant improvement in the negative rate of PCR on day 14 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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