Efficacy and safety of lopinavir/ritonavir in the treatment of COVID-19: A systematic review

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ABSTRACT

Introduction

Lopinavir/ritonavir (LPV/r) displays antiviral activity against Middle Eastern respiratory syndrome (MERS) and severe acute respiratory syndrome coronaviruses (SARS-CoV). The effects of LPV/r to treat patients with coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus are poorly understood. Here, we systematically reviewed clinical literature reporting the use of LPV/r for the treatment of patients with COVID-19 to assess the effectiveness of LPV/r for the treatment of COVID-19.

Areas covered

We systematically searched the PubMed and MedRxiv databases for studies that described treatment of COVID-19 patients with LPV/r compared with other therapies. Of the 858 resultant studies, 16 studies were included in our qualitative review and consisted of 3 randomized control trials, 3 open-label trials, and 10 observational studies.

Expert opinion

Our systematic review revealed that currently there appears to be no evidence of effectiveness and clinical benefit of LPV/r in the treatment of patients with COVID-19. Specifically, LPV/r does not appear to improve clinical outcome, mortality, time to RT-PCR negativity, or chest computed tomography (CT) clearance in patients with COVID-19.

Keywords: coronavirus; SARS virus; severe acute respiratory syndrome; pneumonia; antiviral agents; lopinavir/ritonavir

Article highlights

- Lopinavir/ritonavir (LPV/r) has shown antiviral activity against Middle Eastern respiratory syndrome (MERS) and severe acute respiratory syndrome coronaviruses (SARS-CoV) as demonstrated by both in vitro and clinical studies.
- LPV/r has been reported in the treatment of patients with COVID-19; however, its effectiveness is not clear.
- We systematically reviewed existing clinical literature that reported the use of LPV/r in the treatment of patients with COVID-19 to assess the effectiveness of LPV/r for the treatment of COVID-19.
- Based on our review, LPV/r does not appear to improve clinical outcome, mortality, time to RT-PCR negativity, or chest computed tomography clearance in patients with COVID-19.

1.0 INTRODUCTION

In December 2019, a cluster of pneumonia cases of unknown origins occurred in Wuhan City of Hubei Province, China and was later attributed to the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) responsible for causing coronavirus disease 2019 (COVID-19) pandemic [1,2]. Current evidence suggests that the majority of the transmission occurs via close contact from person to person, specifically when an infected person coughs or sneezes, the SARS-CoV-2 virus is released in the surrounding air via respiratory droplets [3]. The disease severity ranges from asymptomatic to mild infections or to a severe pneumonia-like condition with multi-organ dysfunction [4-8].

Lopinavir/ritonavir (LPV/r), a combined protease inhibitor, is an United States-Food and Drug Administration-approved treatment for HIV/AIDS; however, it was also shown to display an *in vitro* antiviral activity against a previous SARS-CoV during the 2003 SARS outbreak[9-11] and also against Middle East respiratory syndrome coronavirus (MERS-CoV) [12-14]. Additionally, clinical studies have also reported the use of LPV/r for the treatment of patients with SARS and MERS. In a retrospective, multicenter study, LPV/r was associated with a significant reduction in the overall mortality and intubation rate in patients with SARS compared with a matched cohort who received standard treatment ($P<0.05$)[15]. Furthermore, in a study involving healthcare workers exposed to patients with severe MERS, lower rates of infection were reported in those who received post-exposure 14-day prophylaxis with LPV/r and oral ribavirin[16]. However, the effectiveness of LPV/r in the treatment of COVID-19 is not clear. Here, we systematically reviewed the clinical literature that described the use of LPV/r for the treatment of patients with COVID-19 to evaluate the effectiveness of LPV/r for the COVID-19 treatment.

2.0 Methods

2.1 Literature Search

We systematically searched PubMed, medRXiv, Web of Science, and Scopus databases from May 2020-July 2020 using the following search string: "(lopinavir/ritonavir) AND (randomized OR trial OR observational OR comparative OR mortality OR PCR OR adverse) AND(COVID-19)". For medRXiv database, we used "lopinavir/ritonavir COVID-19" as a search string. Additionally, we reviewed bibliographies of the included studies to retrieve relevant studies not found during our initial electronic database search and contacted experts in the field for relevant articles. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17].

2.2 Study search, selection, and quality assessment

All original research studies published in the English language that reported the use of LPV/r for the treatment of patients with COVID-19 were included in this review. We excluded i*n vitro* and *in vivo* studies, reviews, case reports, abstract-only research articles, and single-armed studies (with no comparison group). Retrieved studies were independently screened by at least two authors for inclusion-exclusion.

2.3 Data Extraction and Study Outcomes

Data were extracted by two authors (Blinded for Review) and checked for accuracy independently by two authors (Blinded for Review). When available, we collected background characteristics, including age, sex, body mass index (BMI), race, and comorbidities, such as hypertension, smoking, alcoholism, coronary artery disease [CAD], chronic obstructive pulmonary disease [COPD] and hyperlipidemia. Additionally, intervention-related information, such as dose and regimen, the period of follow-up, concomitant medications were collected. The

included outcomes were viral clearance measured by reverse-transcription polymerase chain reaction (RT-PCR) negativity and/or improvement on chest computed tomography (CT), mortality, and adverse events (AEs) (further categorized into cardiac, gastrointestinal, or respiratory).

3.0 RESULTS

3.1 Search Results

Our systematic search returned a total of 858 studies, of which 16 were included in our review for qualitative analysis (**Figure 1**). Among these 16 studies, 3 were randomized controlled trials (RCTs)[18-20], 3 non-randomized trials[21-23], and 10 retrospective cohort studies [24-33] (listed in **Table 1**).

3.2 Other treatment arms

Other (control) therapies included arbidol (umifenovir), favipiravir, interferon-α, ribavirin, tocilizumab (TCZ), steroids, hydroxychloroquine (HCQ), chloroquine (CQ), danoprevir, and azithromycin. Because of the wide variation in control therapies across studies, we could not perform sub-analyses based on a specific control therapy used.

3.3 Open-label RCTs

Cao et al conducted Lopinavir Trial for Suppression of SARS-Cov-2 in China) (LOTUS China) trial to determine the efficacy and safety of LPV/r in hospitalized adult patients with severe COVID-19 compared with standard of care (SOC) alone that included supplemental oxygen as necessary, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal replacement therapy, and extracorporeal membrane oxygenation [ECMO][18]. The time to clinical improvement (an improvement of two points on a seven-category ordinal scale or

discharge from the hospital) was equal in both LPV/r+SOC group and SOC group (16 days vs. 16 days; Hazard Ratio [HR]=1.31; 95% confidence interval (CI), 0.95 – 1.80). Lower 28-day mortality, though not statistically significant, was reported in the LPV/r+SOC group (19/99, 19%) as compared to the SOC (25/100, 25%). Patients in the LPV/r+SOC group had a shorter stay in the intensive care unit (ICU) than those in the SOC group (median, 6 days vs. 11 days, respectively, 95% CI,-9 to 0) and on day 14, there was a higher number of patients with clinical improvement in the LPV/r group as compared to SOC group (45% vs 30%). No significant difference between the two groups with respect to duration of oxygen therapy, duration of hospital stay, invasive mechanical ventilation, and time from randomization to death. The RT-PCR negativity rates were similar between the two groups at 28 days (59.3% [35/59] in the LPV/r group vs. 57.7% [41/71] in the SOC group)[18].

In a single center study, Li et al compared the efficacy of LPV/r and arbidol in 86 patients with COVID-19[20]. Patients were randomized into 3 groups 1) LPV/r (200mg/50 mg two tablets, twice daily for 7-14 days; n=34); 2) arbidol (100 mg, two tablets three times a day for 7-14 days; n=35); and 3) SOC including HCQ (n=17). The primary outcome of time to RT-PCR negativity was similar among the three groups (9.0 days in the LPV/r group, 9.1 days in the arbidol group, and 9.3 days in the SOC group). The rates of RT-PCR negativity on day 7 of treatment were 35.3 % (12/34) in the LPV/r group, 37.1% (13/35) in the arbidol group, and 41.2% (7/17) in the SOC group, and on day 14, the rates were 85.3% (29/34) in the LPV/r, 91.4% (32/35) in the arbidol group and 76.5% (13/17) in the SOC group (p=0.352). At 7 days, 23.5% (8/34) of the patients in the LPV/r group, 8.6% (3/35) in the arbidol group, and 11.8% (2/17) in the SOC group deteriorated to severe/critical status (p=0.206). Among 13 patients with deteriorated condition, 2 patients who progressed to critical clinical status belonged to the LPV/r group. Mechanical

ventilation due to respiratory failure was needed in 2 (15.4%) patients. Improvement in chest CT findings were reported in 46.2% (6/13) and 76.9% (10/13) on day 7 and day 14, respectively. No significant difference was noted regarding the rate of antipyresis, resolution of cough or change in chest CT findings. The rate of improvement in chest CT was similar among the groups (39.3% [11/28] LPV/r group, 39.4% [13/33] arbidol group, and 42.9% [6/14] SOC group). Neither groups required cessation of therapy due to AEs. In the LPV/r group, 35.3% (12/34) experienced AEs, such as diarrhea (26.5% [9/34]), loss of appetite (14.7%, [5/34]) and a 2.5-fold elevation of alanine aminotransferase (ALT) above the upper limit of the normal range (2.9% [1/34]). In the arbidol group, 14.3% (5/35) had AEs, including diarrhea (8.6%, 3/35) and nausea (5.9%, 2/34). One patient in the SOC group developed severe diarrhea at 3 days[20].

In a multicenter trial, Hung et al examined the use of LPV/r in reducing the days to viral shedding and clinical improvement in patients with mild to moderate COVID-19[19]. Forty-one patients received LPV/r alone and 86 patients received LPv/r+Ribavirin+IFN-β1b (combination group). Median time from onset of symptoms to the start of treatment was 4 days (3-8) for the LPV/r group and 5 days (4-7) for the combination group. The time to negative RT-PCR was significantly shorter in the combination group than the LPV/r alone group (7 days [5–11]) vs 12 days [8–15], respectively; HR 4·37; 95% CI 1·86–10·24], p=0·0010). The clinical improvement was significantly shorter in the combination group, as defined by NEWS2 score of o (4 days [3–8] in the combination group vs 8 days [7–9] in the LPV/r; HR 3·92; 95% CI 1·66–9·23, p<0.0001) and SOFA score of 0 (3·0 days [1·0–8·0] vs 8·0 days [6·5–9·0]; HR 1·89 95%CI 1·03–3·49, p=0·041). In multivariate analysis, combination treatment (HR 4·27; 95% CI 1·82–10·02, p=0·0010) and a normal baseline chest X-ray (HR 1.97; 95%CI 1.11-3.50, p= 0.021) were independently associated with RT-PCR negativity on day 7. AEs were reported in 49% (20/41)

of patients in the LPV/r group and 48% (41/86) in the combination group. The most commonly reported AEs included diarrhea (41% [52/127]), fever (38% [48/127]) nausea (34% [43/127]) and raised ALT (14% [18/127]). Sinus bradycardia was reported in 4 patients, and one serious AE in the LPV/r group, the elevation of liver enzymes, necessitated discontinuation of the treatment[19].

3.4 Open-labelled non-randomized clinical trials

Cai et al examined the efficacy of LPV/r and favipiravir in patients with moderate COVID-19[21]. The median time to viral clearance was 11 days in the LPV/r group and 4 days in the favipiravir group. In a multivariate Cox regression model, T lymphocyte count (HR 1.002; 95% CI 1-1.005) and antiviral therapy (HR 3.434; 95% CI 1.162-10.148) were independent factors that affected the viral clearance; favipiravir was better at influencing viral clearance than LPV/r. At 14 days, the favipiravir group (91.4% [32/35]) showed significantly higher improvement rated on the chest CT findings compared to the LPV/r group (62.2% [28/45]) (p=0.004). In the favipiravir group, 2 patients had diarrhea and 1 patient had a liver injury. In the LPV/r group, 5 patients had diarrhea, 5 had vomiting, 6 had nausea, 4 had a rash, 3 had liver injury, and 2 patients had chest tightness and palpitations[21].

Ye e t al compared the efficacy of LPV/r treatment with arbidol and interferon aerosol inhalation treatment in COVID-19 patients; adjuvant drugs like methoxyphenamine capsules, eucalyptol limonene and pinene enteric soft capsules, and moxifloxacin were administered to both the groups[23]. The median time to viral clearance was shorter in the LPV/r group (7.8±3.09 days) than that in the arbidol+interferon group (12.0±0.82 days; p=0.0219). The body temperature of the patients in the LPV/r group returned to normal body temperature in a shorter time (4.8±1.94 days vs 7.3±1.53 days in the arbidol+IFN group; p=0.0364). The safety of the

treatments was reported by analyzing the levels of ALT and aspartate aminotransferase (AST). No significant side effects were reported in the LPV/r group[23].

Huang et al compared the efficacy of LPV/r (n=12) with CQ (n=10) in COVID-19 patients[22]. At day 13, all 10 patients in the CQ group were reported RT-PCR negativity while 11/12 patients in the LPV/r group were RT-PCR negative. The RT-PCR tests on day 7,10, and 14 were higher in the CQ group (7/10 [70%],9/10 [90%], and 10/10 [100%], respectively) than that in the LPV/r group (7/12 [58.33%], 9/12 [75%], and 11/12 [91.67%]). On day 14, an improvement on chest CT imaging was reported in 75% (9/12) patients in the LPV/r group and in 100% patients in the CQ group. Neither group reported serious AEs[22].

3.5 Retrospective Observational studies

A pilot study by Lan et al compared the clinical outcomes of LPV/r alone (n=34) treatment with a combination of LPV/r and arbidol (n=39) in a total of 73 patients with moderate to severe COVID-19[27]. Patients were classified as ordinary or heavy cases based on the diagnosis and treatment protocol issued by the General Office of National Health Commission[34]. LPV/r group had 61.8%, (21/34) ordinary cases and 38.2%,(13/34) with severe disease, whereas LPV/r +arbidol group had 71.8%, (28/39) ordinary cases and 29.2%(11/39) with severe disease. Mortality was similar between both the groups (LPV/r :2.9% [1/34] and LPV/r +arbidol: 2.6% [1/39]). In the LPV/r +arbidol group, two patients worsened clinically, requiring the ICU admission. Viral clearance was reported in 97.1% (33/34) and 92.3% (36/39) in the LPV/r and LPV/r +arbidol group, respectively. Time to RT-PCR negativity was 9.9 (±7.5) days in the LPV/r group and 11.5 (±9) days in the LPV/r + arbidol group. Improvement in chest CT findings was reported in 91.2% (31/34) of the patients in the LPV/r group and in 84.6% (33/39) in the LPV/r /arbidol group[27].

Capra et al examined TCZ and SOC therapies in 85 patients with COVID-19-related pneumonia (TCZ+SOC: n=62; SOC: n=23)[24]. SOC consisted of LPV/r, HCQ, and oxygen therapy. Patients received TCZ within 4 days of hospital admission. Patients that received TCZ+SOC had a greater survival rate, adjusted for age, comorbidities, and baseline PCR levels, compared to those that received SOC (HR 0.35; 95% CI 0.004-0.347, p=0.004). Among patients with a concluded outcome (discharge or death), 92% (23/25) of the patients in the TCZ+SOC group were discharged (mean 12.5 days) and 8% (2/25) had died, while 42% (8/19) of the patients in the SOC group were discharged and 58% (11/19) had died. Among patients with no concluded outcome, 65% (24/37) of TCZ+SOC patients improved clinically and 27% (10/27) worsened. All patients in the SOC group (100%, 4/4) without a concluded outcome worsened clinically[24].

In a single-center cohort study, Kim et al compared viral clearance and clinical improvement in patients with mild to moderate COVID-19 treated with LPV/r or HCQ[26]. Clinical outcome was assessed using the seven-category ordinal scale recommended by the WHO R&D blueprint group[35]. At 6 weeks, 87.1% (27/31) and 61.8% (21/34) of patients had RT-PCR negativity in the LPV/r group and HCQ group, respectively. The median time to RT-PCR negativity was 21 days in the LPV/r group and 28 days in the HCQ group (p=0.029). Based on a Cox proportional hazards model adjusted for demographics and laboratory parameters, patients ≤ 65 years old (adjusted HR, 2.64; 95% CI 1.43 to 4.87, p=0.002) and treatment with LPV/r (adjusted HR, 2.28; 95% CI 1.24 to 4.21, p=0.008) were independently associated with RT-PCR negativity. At 6 weeks, mortality in the LPV/r group was 2.9% (1/31) and 3.2% (1/34) in the HCQ group. Clinical improvement at 6 weeks was reported in 96.8% (30/31) patients in the LPV/r group and in 90.6% (29/34) patients in the HCQ group. The time to clinical improvement was similar in

both the groups (median, LPV/r, 18 days vs 21 days, HCQ, p=0.216). The number of AEs reported in the LPV/r group was 29 (93.5%) and 26 (76.5%) in the HCQ[26].

Zhu et al studied 50 hospitalized patients with COVID-19; 34 patients received LPV/r and 16 patients received arbidol, in addition to oxygen therapy, and atomized inhalation of recombinant human interferon-α2b injection[33]. At day 7, 8 patients (50%) in the arbidol group and 8 patients (23.5%) in the LPV/r group were RT-PCR negative. At 14 days, all patients in the arbidol group had undetectable viral RNA compared to 19 patients in the LPV/r group. The time to RT-PCR negativity was shorter in the arbidol group (9.5 days [5.3-11]) than in the LPV/r group (11.5 days [8.8-17]) [33].

In a single-center study, Deng et al studied viral clearance and chest CT improvement in 33 patients with laboratory-confirmed COVID-19, when treated with LPV/r alone (n=17) or with a combination of LPV/r +arbidol (n=16), in addition to supportive therapy that included oxygen therapy, immunoglobulin, corticosteroids, antibacterial agents, and vasopressor agents, when necessary[25]. At 7 days, 75% (12/16) of the patients in the LPV/r +arbidol group and 35% (6/17) in the LPV/r group had RT-PCR negativity ($p < 0{\cdot}05$). At 14 days, 94% (15/16) of the patients in the LPV/r +arbidol group and 53% (9/17) in the LPV/r group showed viral clearance by RT-PCR ($p < 0{\cdot}05$). Additionally, chest CT scans improved in 29.4% (5/17) patients in the LPV/r group and 68.7% (11/16) patients in the LPV/r +arbidol group[25].

Yan et al examined factors leading to prolonged viral shedding and the efficacy of LPV/r compared with corticosteroids in 120 non-critically ill COVID-19 patients (median age 52 years; 45% (54/120) males), and the severity of the clinical illness was assessed using the sixth version of the Chinese guidelines[30]. LPV/r was administered in 65% (78/120) of the patients, while

45% (54/120) received corticosteroids. The median duration of initiation of LPV/r from symptom onset was 10 days (9-10). The baseline characteristics were similar between both the groups; however, patients in the LPV/r group had severe COVID-19. The median duration of viral shedding was 23 days, with 50.8% patients (61/120) requiring ≤23 days and 49.2% (59/120) patients requiring >23 days to RT-PCR negativity. In a multivariate logistic regression model, no LPV/r treatment (Odds Ratio [OR] 2.42; 95% CI 1.10–5.36, p=0.029) and age >50 years (OR 1.03, 95% CI 1.00–1.05, p=0.03) were independently associated with prolonged viral shedding[30].

Zhang et al compared time to RT-PCR negativity and duration of hospital stay in 33 patients with COVID-19 who were treated with LPV/r or danoprevir[32]. All patients in both the groups achieved 100% negative RT-PCR. However, in the danoprevir group, all patients reported RT-PCR negativity by day 13 (median time 7 days, average time 8 days), whereas in the LPV/r group, all patients had a negative RT-PCR within 21 days (median time 12 days, average time 12.5 days). The average time to RT-PCR negativity was significantly different between the danoprevir group and the LPV/r group (p=0.0388) [32].

In a matched-cohort study, Yu et al analyzed the efficacy of LPV/r in 128 hospitalized patients with COVID-19 pneumonia, of which 64 patients were coinfected with influenza (54 had influenza A and 10 had influenza B) [31]. A total of 37 patients received LPV/r, of which 27 were coinfected with influenza A/B, and 91 patients received SOC. The median duration of viral shedding was longer in patients coinfected with influenza than those without co-infection (17.0 days vs 12.0 days; p < .001). At 28 days, 91.9% (34/37) of patients in the LPV/r group had a negative viral conversion of SARS-CoV-2, compared to the 81.3% (74/91) in the SOC arm. Among patients with influenza coinfection on LPV/r, 85.2% (23/27) had a negative viral

conversion of SARS CoV-2 compared to 70.3% (26/37) in SOC arm. The median time to negative conversion of SARS-CoV-2 was significantly lower in the LPV/r group than in the SOC group (13.0 days [10.0- 16.0] vs 16.5 days [12.25- 23.75], p=0.003). In the LPV/r group, 94.1% (32/34) of patients showed radiological improvement at 4 weeks compared to 81.7% (67/82) in the SOC arm. Based on a Cox proportional hazard model, the improvement on chest CT at 4 weeks indicated that treatment with LPV/r potentially improved outcome in COVID-19 patients coinfected with influenza (HR=1.878; 95%CI=1.103-3.196, p=0.020) [31].

Panagopoulos et al examined the efficacy of LPV/r as a third agent among 16 patients, of which 8 patients received LPV/r in addition to HCQ and azithromycin and 8 received HCQ and azithromycin (control group)[29]. The patients in the LPV/r group had more severe radiological findings as compared to the control group (100% [8/8] vs 37.5% [3/8]), along with persistent fever and lymphocytopenia. The days to RT-PCR negativity was lower in the LPV/r group (8.86 (±1.68) vs 13.8 (±2.68) days in control group, p=0.003)[29].

4.0 EXPERT OPINION

We systematically reviewed 16 studies that reported the use of LPV/r for the treatment of a total of 774 patients with COVID-19 and found no correlation to decreased mortality, RT-PCR negativity, or chest CT clearance with LPV/r treatment. However, our findings are limited by the heterogeneity in the reported data. For example, the assessment of both clinical improvement and time to clinical improvement varied across the studies included in this review. In addition to assessing the clinical status, the studies by Cao et al[18] and Kim et al[26] used the seven-category ordinal scale recommended by the WHO R&D blueprint group[35]. Moreover, the duration of follow up differed among studies; 14 days was the most common follow up duration, although some studies followed up patients for up to 6 weeks.

In a randomized trial of severe COVID-19 patients, treatment with LPV/r (400/100 mg) twice daily for 14 days compared to SOC elicited a decrease in the number of days of the ICU stay among the survivors; however, the trial failed to show a decrease in the time to clinical improvement (HR for clinical improvement, 1.31; 95% CI, 0.95 to 1.80). Mortality at 28 days was similar in the LPV/r group and the SOC group (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI −17.3 to 5.7)[18]. Few studies showed a favorable outcome with LPV/r, either alone or in combination with other therapies, with respect to time to viral clearance and improvement in symptoms[19,23,25,26,30].

Capra et al reported lower mortality rates in severely ill COVID-19 patients who received LPV/r in combination with HCQ and TCZ; however, no meaningful benefit was noted in terms of mortality in COVID-19 patients when treated with LPV/r alone[24]. Preliminary results of the Randomised Evaluation of COVid-19 therapy (RECOVERY) trial showed no significant difference in the primary endpoint of 28-day mortality in patients treated with LPV/r versus those who received SOC (22.1% LPV/r vs. 21.3% SOC; relative risk 1.04; 95% CI 0.91-1.18; p=0.58); moreover, LPV/r treatment did not show any benefits with respect to progression to mechanical ventilation or length of hospital stay[36]. Similarly, the interim results of the Solidarity trial organized by World Health Organization (WHO) reported little to no benefits in terms of mortality in hospitalized COVID-19 patients treated with LPV/r when compared to those who received SOC[37].

As an antiretroviral agent, LPV/r is usually well tolerated despite the common gastrointestinal side effects of diarrhea, nausea, and vomiting. Though uncommon, drug-induced pancreatitis, elevated triglyceride levels, elevated transaminase levels, and adverse drug-drug interactions have been reported[38]. In the trial by Cao et al, nearly 14% of patients were unable to complete

the 14-day course of therapy due to gastrointestinal AEs, and two patients reported self-limited skin eruptions[18].

LPV/r was recognized as an antiviral agent during the 2003 SARS outbreak when it was shown to have *in vitro* activity against the causative agent SARS-CoV[10]. SARS-CoV-2 replicates through cleavage of polyproteins, and the enzymes responsible for this cleavage are two proteases, 3-chymotripsin-like protease (3CLpro) and papain-like protease (PLpro)[39]. LPV/r has been shown to inhibit SARS-Co-V 3CLpro *in vitro*[40,41]; however, it is thought to have a poor selectivity index, necessitating higher doses to achieve efficacy *in vivo*[42]. Baldelli et al analyzed the data related to therapeutic drug monitoring and reported higher concentrations of LPV/r in COVID-19 patients as compared to that in HIV patients, and the threshold concentration of lopinavir was more than 7000 ng/ml in almost all the COVID-19 patients[43]. Pharmacokinetic studies in HIV patients have reported poor drug tolerability at higher drug concentrations[44]. Together, these findings suggest against the use of higher doses of LPV/r in COVID-19 patients to achieve effectiveness in clinical setting.

Based on our systematic review of the available clinical literature, there appeared to be no significant benefit of LPV/r treatment in the clinical outcomes of COVID-10 patients with respect to mortality, chest CT clearance, or RT-PCR negativity. Due to the heterogeneous nature of the comparison groups, we were unable to perform a meta-analysis of the data to offer statistical conclusions regarding the clinical benefit of LPV/r. The limited clinical benefits prompted several groups including the WHO SOLIDARITY trial and the RECOVERY trial from the NHS to terminate the LPV/r arm, and the Infectious Diseases Society of America and the National Institutes of Health (NIH) recommends against the use of LPV/r in the treatment of COVID-19 outside of clinical trials[45,46].

The major limitation of this review is that the data reporting quality varied widely across studies, with lack of standard protocols to monitor the clinical outcomes; for example, some clinical outcomes was measured differently among the studies, and the duration of follow up also varied among the studies. Because of the heterogeneity in the available data, we could not perform a meta-analysis. Finally, most of the studies included in our review were non-randomized and retrospective in nature. Further larger studies are necessary to assess the effectiveness of LPV/r for the treatment of patients with COVID-19.

5.0 Conclusion

Our systematic review of the clinical literature describing the use of LPV/r for the treatment of patients with COVID-19 suggests no improvement in clinical outcomes or survival in COVID-19 patients treated with LPV/r.

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TABLES

Table 1. Studies using Lopinavir/Ritonavir for COVID-19 Treatment

Author	N	Age	Male sex n/N (%)	COVID-19 Severity	Arm	Dose & Regimen	Follow-Up Length (days)	Mortality	RT-PCR negativity	Days to RT-PCR negativity Mean (±SD); Median [IQR]	Chest CT improvement	Conclusions
Randomized Controlled Trials												
Li et al.(China) [20]	34	50.7 (±15.4)	17/34 (50.0%)	Mild / moderate	LPV/r	200/50 mg twice daily for 7-14 days	14	--- ---	29/34 (85.3%)	9 (±5)	21/28 (75.0%)	Neither LPV/r nor ARB improved outcomes compared to SOC
	35	50.5 (±14.6)	16/35 (45.7%)		ARB	200 mg three times daily for 7-14 days	14		32/35 (91.4%)	9.1 (±4.4)	23/33 (69.7%)	
	17	44.3	7/17 (41.2%)		SOC		14		13/17 (76.5%)	9.3 (±5.2)	13/14 (92.9%)	
Cao *et al.*(China) [18]	99	58 [50-68]	61/99 (61.6%)	Severe	LPV/r	400/100 mg twice daily for 14 days	28	19/99 (19.2%)	39/99 (39.4%)		--- ---	No difference in outcomes between

	100	58 [48-68]	59/100 (59.0%)		SOC		28	25/100 (25.0%)	41/100 (41.0%)			LPV/r and SOC
Hung *et al.*(China) [19]	86	51 [31-61.3]	45/86 (52.3%)	Mild/ moderate	LPV/r +RV+IFNβ1b	400/100 mg twice daily + 400 mg twice daily + 8 million U on alternate days for 14 days	30	N/A	N/A	7 [5-11]	N/A	Favors LPV/r +RV+IFNβ1b over LPV/r in time to viral clearance
	41	52 [33.5-62.5]	23/41 (56.1%)		LPV/r	400/100 mg twice daily for 14 days	30	N/A	N/A ---	12 [8-15]	N/A	
Non-randomized Clinical Trials												
Cai *et al.*(China) [21]	35	43 [35.5-59]	14/35 (40.0%)	Moderate	FPV+IFNα1b	Day 1: 1600 mg twice daily; Days 2-14: 600 mg twice daily; + 5 million U	14	--- ---	--- ---	4 [2.5-9]	32/35 (91.4%)	FPV was more effective than LPV/r in limiting disease progression and enhancing viral clearance

		49 [36-61]	21/45 (46.7%)			twice daily						
	45				LPV/r +IFNα1b	400/100 mg twice daily + 5 million U twice daily for 1-14 days	14			11 [8-13]	28/45 (62.2%)	
Ye *et al.*(China) [23]	42		21/42 (50.0%)	---	LPV/r	400/100 mg twice daily or 800/200 mg once daily	N/A	N/A	N/A	7.8 (±3.09)	N/A	Favors LPV/r over ARB for viral clearance
	5		1/5 (20%)		ARB+IFN	200 mg three times daily + 5 million U twice daily	N/A	N/A	N/A	12 (±0.82)	N/A	

Huang *et al.*(China) [22]	10	41.5 [33.8-50]	7/10 (70%)	Mild-severe	CQ	500 mg twice daily for 10 days	14	N/A	10/10 (100%)	N/A	10/10 (100%)	No difference in outcomes between CQ and LPV/r
	12	53 [41.8-63.5]	6/12 (50.0%)		LPV/r	400/100 mg twice daily for 10 days	14	N/A	11/12 (91.7)	N/A	9/12 (75.0%)	
Retrospective Observational Studies												
Zhu et al.(China) [33]	34	40.5 [34.8-52.3]	20/34 (58.8%)	---	LPV/r +IFNα2b	400/100 mg twice daily + 5 million U twice daily for 7 days	14	--- ---	19/34 (55.9%)	11.5 [8.8-17]	--- ---	ARB exhibited better viral clearance than LPV/r
	16	26.5 [23.3-52.5]	6/16 (37.5%)		ARB+IFNα2b	200 mg three times daily	14		16/16 (100%)	9.5 [5.3-11]		
Deng et al.(China)l [25]	16	41.8 (±14.08)	7/16 (43.8%)	Mild-severe	LPV/r +ARB	400/100 mg twice daily + 200 mg three times daily for 5-21 days	7	--- ---	12/16 (75.0%)		11/16 (68.8%)	Favors LPV/r alone over LPV/r +ARB for viral clearance and chest CT improvement
	17	47.25 (±17.25)	10/17 (58.8%)		LPV/r	400/100 mg twice daily for	7		6/17 (35%)		5/17 (29.4%)	

						5 -21 days			-		
Yan et al.(China) et al[30]	78 42	50 [34-61] 57 [36.5-66]		Moderate/ severe	LPV/r Corticosteroid			--- ---	--- ---		--- ---	Favors LPV/r over corticosteroid for viral clearance
Capra et al. (Italy)[24]	62 23	63 [54-73] 70 [55-80]	45/62 (72.6%) 19/23 (82.6%)	Severe	LPV/r +HCQ+TZ LPV/r		N/A N/A	2/62 (3.2%) 11/23 (47.8%)	N/A N/A	N/A N/A	N/A N/A	Survival and respiratory function better with LPV/r +HCQ+TZ compared to LPV/r alone
Lan *et al.*(China) [27]	39 34	52.3 (±15.8) 59.5 (±13.6)	26/39 (66.7%) 11/34 (32.4%)	Moderate/ severe	LPV/r +ARB LPV/r	400/100 mg twice daily + 200 mg three times daily 400/100 mg twice daily	N/A N/A	1/39 (2.6%) 1/34 (2.9%)	36/39 (92.3%) 33/34 (97.1%)	11.5 (±9) 9.9 (±7.5)	33/39 (84.6%) 31/34 (91.2%)	No difference in outcomes between LPV/r +ARB and LPV/r alone
Liu *et al.*(China) et al[28]	1 9	40 (±0)		Mild-severe	LPV/r			0/1 (0%) 0/6 (0%)	1/1 (100%)		--- ---	Sustained LPV/r use

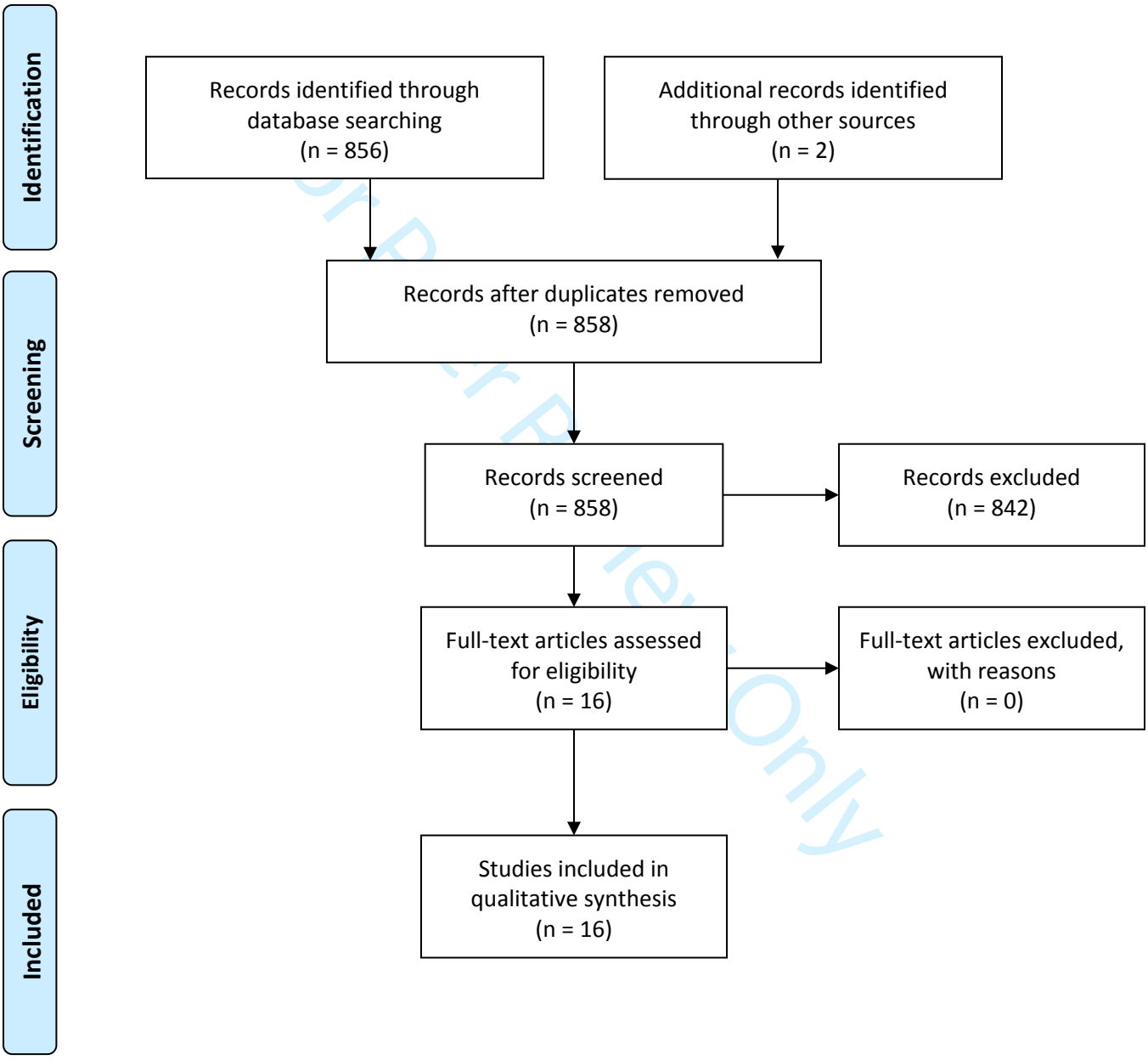
		43.3 (±10.3)			LPV/r +IFNα2b				6/6 (100%)			may provide benefit
Kim *et al.* (Korea) [26]	31	64.3 (±14.6)	11/31 (35.5%)	Mild/ moderate	LPV/r	400/100 mg twice daily	42	1/31 (3.2%)	27/31 (87.1%)	21	--- ---	Favors LPV/r over HCQ in time to viral clearance, no benefit for clinical responses
	34	64.3 (±16.3)	14/34 (41.2%)		HCQ	400 mg daily	42	1/34 (2.9%)	21/34 (61.8%)	28		
Panagopoulos et al. (Greece)[29]	8	55.75 (±19.71)	6/8 (75%)	---	HCQ+AZ+ LPV/r			--- ---	--- ---		--- ---	Favors HCQ+AZ+LPV/r over HCQ+AZ in time to viral clearance
	8	59.75 (±10.51)	4/8 (50%)		HCQ+AZ							
Zhang et al. (China) [32]	5	44 [N/A]	2/5 (40%)	Mild-severe	DP	100 mg twice daily	13	--- ---	5/5 (100%)	8 (N/A); 7 [N/A]	--- ---	Favors DP over LPV/r in time to viral clearance
	28	43 [N/A]	9/28 (32.1%)		LPV/r	400/100 mg twice daily or	21		28/28 (100%)	12.5 [N/A]; 12 [N/A]		

						800/200 mg daily						
Yu et al. (China) l[31]	37	56.0 [43.5-68.0]	15/37 (40.5%)	Severe	LPV/r	N/A	28	7/37 (19%)	34/37 (91.9%)	13.0 [10.0-16.0]	32/34 (94.1%)	Favors LPV/r over SOC for mortality, SAE, and resolution of COVID-19 pneumonia
	91	61.0 [50.0-68.0]	40/91 (44.0%)		SOC	N/A	28	23/91 (25%)	74/91 (81.3%	16.5 [12.25-23.75]	67/82 (81.7%)	

Data are presented as Mean(SD); median[IQR]; n/N (%).
LPV/r=lopinavir/ritonavir, ARB=arbidol, FPV=favipiravir, CQ=chloroquine, IFN=interferon, SOC=standard of care, RV=ribavirin, HCQ=hydroxychloroquine, TZ=tocilizumab, AZ=azithromycin, DP=danoprevir, SAE=serious adverse events; CT=computed tomography

Figures

Figure 1. PRISMA Diagram of search records and inclusions



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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