Taylor & Francis
Taylor & Francis Group

Expert Review of Anti-infective Therapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierz20

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

Betsy Ann Joseph , Mahmoud Dibas , Kirk W. Evanson , Geeta Paranjape , Charan Thej Reddy Vegivinti , Pragadeesh Thamarai Selvan , Kavitha Saravu , Nitin Gupta , Yashwitha Sai Pulakurthi , Praneeth Reddy Keesari , Sriram Varsha , Spandana Chittajallu , Adam A. Dmytriw , Natalie L. Reierson , Nick Mikoff , Shelby Kamrowski , Megan Schmidt , Amber R. Davis , John M. Pederson , Hemant K. Mishra , Jillienne C. Touchette & Kevin Kallmes

To cite this article: Betsy Ann Joseph , Mahmoud Dibas , Kirk W. Evanson , Geeta Paranjape , Charan Thej Reddy Vegivinti , Pragadeesh Thamarai Selvan , Kavitha Saravu , Nitin Gupta , Yashwitha Sai Pulakurthi , Praneeth Reddy Keesari , Sriram Varsha , Spandana Chittajallu , Adam A. Dmytriw , Natalie L. Reierson , Nick Mikoff , Shelby Kamrowski , Megan Schmidt , Amber R. Davis , John M. Pederson , Hemant K. Mishra , Jillienne C. Touchette & Kevin Kallmes (2020): Efficacy and safety of lopinavir/ritonavir in the treatment of COVID-19: A systematic review, Expert Review of Anti-infective Therapy, DOI: 10.1080/14787210.2021.1848545

To link to this article: https://doi.org/10.1080/14787210.2021.1848545

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
https://doi.org/10.1080/14787210.2021.1848545

Taylor & Francis
Taylor & Francis Group

REVIEW

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

Betsy Ann Joseph[a], Mahmoud Dibas [b], Kirk W. Evanson[c], Geeta Paranjape[c], Charan Thej Reddy Vegivinti[d], Pragadeesh Thamarai Selvan[d], Kavitha Saravu [e], Nitin Gupta[e], Yashwitha Sai Pulakurthi[f], Praneeth Reddy Keesari[f], Sriram Varsha[g], Spandana Chittajallu [h], Adam A. Dmytriw[i], Natalie L. Reierson[a], Nick Mikoff[a], Shelby Kamrowski[a], Megan Schmidt[a], Amber R. Davis[c], John M. Pederson [c], Hemant K. Mishra[j], Jillienne C. Touchette[c] and Kevin Kallmes[a]

[a]Department of Data Research, Nested Knowledge, St. Paul, MN, USA; [b]College of Medicine, Sulaiman Al Rajhi University, Qassim, Saudi Arabia; [c]Department of Medical Writing, Superior Medical Experts, St. Paul, MN, USA; [d]Department of General Medicine, Kasturba Medical College, Manipal Academy of Higher Education (MAHE), Manipal, India; [e]Department of Infectious Diseases, Kasturba Medical College, Manipal Academy of Higher Education (MAHE), Manipal, India; [f]Department of Internal Medicine, Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, India; [g]Department of Internal Medicine, Kasturba Medical College, Manipal Academy of Higher Education (MAHE), Manipal, India; [h]Department of Internal Medicine, Rangaraya Medical College, Kakinada, India; [i]Neuroradiology & Neurointervention Service, Brigham and Women's Hospital, Harvard Medical School, Boston, USA; [j]Department of Veterinary and Biomedical Sciences, University of Minnesota – Twin Cities, Minneapolis, MN, USA

ABSTRACT

Objectives: To systematically review the clinical literature reporting the use of Lopinavir/ritonavir (LPV/r) for the treatment of patients with Cornonavirus disease 19 (COVID-19) to assess the efficacy of LPV/r for the treatment of COVID-19.

Methods: The authors systematically searched PubMed and MedRxiv databases for studies describing treatment of COVID-19 patients using LPV/r compared to other therapies. Articles were excluded if they were case reports, opinion editorials, preclinical studies, single-armed studies, not written in English, not relevant to the topic, or published before May 2020. The included outcomes were viral clearance as measured by reverse-transcription polymerase chain reaction (RT-PCR) negativity and/or improvement on chest computed tomography (CT), mortality, and adverse events.

Results: Among 858 total studies, 16 studies met the inclusion criteria and were included in the qualitative review. These studies consisted of 3 randomized control trials, 3 open-label trials, and 10 observational studies. Most of these studies did not report positive clinical outcomes with LPV/r treatment.

Conclusion: The systematic review revealed insufficient evidence of effectiveness and clinical benefit of LPV/r in the treatment of COVID-19 patients. Specifically, LPV/r does not appear to improve clinical outcome, mortality, time to RT-PCR negativity, or chest CT clearance in patients with COVID-19.

ARTICLE HISTORY
Received 26 August 2020
Accepted 5 November 2020

KEYWORDS
Coronavirus; sars virus; severe acute respiratory syndrome; pneumonia; antiviral agents; lopinavir/ritonavir

1. 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 the coronavirus disease 2019 (COVID-19) pandemic [1,2]. Current evidence suggests transmission primarily 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]. Disease severity ranges from asymptomatic to mild infections or severe pneumonia-like condition with multi-organ dysfunction [4–8].

Lopinavir/ritonavir (LPV/r), a combined protease inhibitor, is the United States-Food and Drug Administration-approved treatment for HIV/AIDS; however, it is also known to have *in vitro* antiviral activity against a previous SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV) [9–14]. Clinical studies have also reported the use of LPV/r for the treatment of patients with SARS and MERS. For example, 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.

CONTACT Kevin Kallmes Kevinkallmes@supedit.com Kevin Kallmes Nested Knowledge, MN 55117, USA

Supplemental data for this article can be accessed here.

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.
- The authors 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 this 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.

2. 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 the bibliographies of 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 that reported the use of LPV/r for the treatment of patients with COVID-19 were included in this review. We excluded *in vitro* and animal studies, reviews, case reports, abstract-only research articles, single-armed studies (with no comparison group) and articles not written in English language. 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 (SK and MS) and checked for accuracy independently by two authors (JP and KW). When available, background characteristics were collected, 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, and 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. 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), 3 non-randomized trials, and 10 retrospective cohort studies (the baseline characteristics of all the included studies are summarized in Table 1) [18–33].

3.2. Other treatment arms

Other (control) therapies included umifenovir (UMF) (arbidol), favipiravir, interferon-α, ribavirin, tocilizumab (TCZ), steroids, hydroxychloroquine (HCQ), chloroquine (CQ), danoprevir, and azithromycin. There was a wide variation in control therapies and the standard of care (SOC) across studies; therefore, subanalyses based on specific control therapy used could not be performed.

3.3. Open-label RCTs

The outcomes of interests of open-label RCTs are summarized in Table 2.

Cao et al. conducted the Lopinavir Trial for Suppression of SARS-Cov-2 in China (LOTUS China) to determine the efficacy and safety of LPV/r in hospitalized adult patients with severe COVID-19 compared with the SOC [18]. The time to clinical improvement (an improvement of two points on a seven-category ordinal scale or discharge from the hospital) was equal between both the LPV/r+ SOC and SOC groups (16 days vs. 16 days; Hazard Ratio [HR] = 1.31; 95% confidence interval (CI), 0.95–1.80) [34]. 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%) (−5.8 percentage points; 95%CI [−17.3 to 5.7]). 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, a higher number of patients showed clinical improvement in the LPV/r group as compared to the SOC group (45% vs 30%). However, no significant difference was observed between the two groups with respect to duration of oxygen therapy, duration of hospital stay, invasive mechanical ventilation, and time from randomization to death [18].

In a single-center study, Li et al. compared the efficacy of LPV/r and umifenovir in 86 patients with COVID-19 [20]. 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 umifenovir group, and 9.3 days in the SOC group, [p = 0.981]). 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 umifenovir 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 umifenovir group, and 76.5% (13/17) in the SOC group (p = 0.352). During the course of the illness, a total of 13 patients, 23.5% (8/34) of the LPV/r group, 8.6% (3/35) of the umifenovir group, and 11.8% (2/17) of the

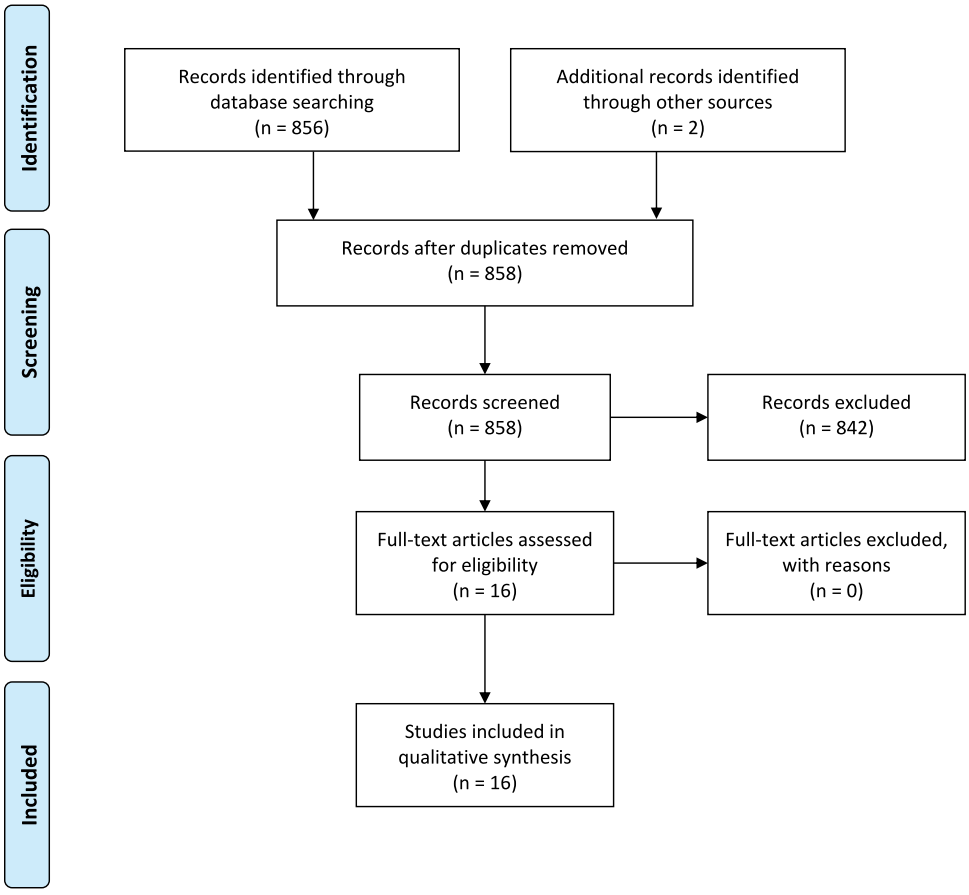

Figure 1. PRISMA Diagram of search records and inclusions (The template for the flow chart is adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097).

SOC group, deteriorated to a severe state, and no significant difference was found between the three groups with regards to deterioration to a severe state (p = 0.206). Of the 13 patients, 2 patients who progressed to critical clinical status belonged to the LPV/r group. Two patients (15.4%) needed mechanical ventilation due to respiratory failure. Improvement in chest CT findings in these 13 patients was 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. Neither group 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 umifenovir 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]. 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, based on the National Early Warning Score 2 (NEWS2) score of 0 (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 the Sequential Organ Failure Assessment (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 a 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 48.8% (20/41) of patients in the LPV/r group and 47.7% (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

The outcomes of interests of non-randomized clinical trials are summarized in Table 3.

Cai et al examined the efficacy of LPV/r and favipiravir in patients with moderate COVID-19 [21]. 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;

Table 1. Baseline characteristics of the 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)
Randomized Controlled Trials							
Li et al [20] (China)	34	50.7 (±15.4)	17/34 (50.0%)	Mild/moderate	LPV/r	200/50 mg twice daily for 7–14 days	14
	35	50.5 (±14.6)	16/35 (45.7%)		UMF	200 mg three times daily for 7–14 days	14
	17	44.3	7/17 (41.2%)		SOC		14
Cao et al [18] (China)	99	58 [50–68]	61/99 (61.6%)	Severe	LPV/r	400/100 mg twice daily for 14 days	28
	100	58 [48–68]	59/100 (59.0%)		SOC		28
Hung et al [19] (China)	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	30
	41	52 [33.5–62.5]	23/41 (56.1%)		LPV/r	U on alternate days for 14 days	30
						400/100 mg twice daily for 14 days	
Non-randomized Clinical Trials							
Cai et al [21](China)	35	43 [35.5–59]	14/35 (40.0%)	Moderate	FPV+IFNα1b	Day 1: 1600 mg twice daily; Days 2–14: 600 mg twice	14
	45	49 [36–61]	21/45 (46.7%)		LPV/r + IFNα1b	daily; + 5 million U twice daily	14
						400/100 mg twice daily + 5 million U twice daily for 1–14 days	
Ye et al [23](China)	42	N/A	21/42 (50.0%)	N/A	LPV/r	400/100 mg twice daily or 800/200 mg once daily	N/A
	5	N/A	1/5 (20%)		UMF+IFN	200 mg three times daily + 5 million U twice daily	N/A
Huang et al [22](China)	10	41.5 [33.8–50]	7/10 (70%)	Mild-severe	CQ	500 mg twice daily for 10 days	14
	12	53 [41.8–63.5]	6/12 (50.0%)		LPV/r	400/100 mg twice daily for 10 days	14
Retrospective Observational Studies							
Zhu et al [33](China)	34	40.5 [34.8–52.3]	20/34 (58.8%)	N/A	LPV/r + IFNα2b	400/100 mg twice daily + 5 million U twice daily for	14
	16	26.5 [23.3–52.5]	6/16 (37.5%)		UMF+IFNα2b	7 days	14
						200 mg three times daily	
Deng et al [25](China)	16	41.8 (±14.08)	7/16 (43.8%)	Mild-severe	LPV/r + UMF	400/100 mg twice daily + 200 mg three times daily for	7
	17	47.25 (±17.25)	10/17 (58.8%)		LPV/r	5–21 days	7
						400/100 mg twice daily for 5 − 21 days	
Yan et al [30](China)	78	50 [34–61]	35/78 (44.9%)	Moderate/severe	LPV/r	400/100 mg twice daily for 10+ days	40
	42	57 [36.5–66]	19/42 (45.2%)		Corticosteroid	25 mg daily during hospitalization	40
Capra et al [24] (Italy)	62	63 [54–73]	45/62 (72.6%)	Severe	LPV/r + HCQ+TZ	N/A	N/A
	23	70 [55–80]	19/23 (82.6%)		LPV/r		N/A
Lan et al [27](China)	39	52.3 (±15.8)	26/39 (66.7%)	Moderate/severe	LPV/r + UMF	400/100 mg twice daily + 200 mg three times daily	N/A
	34	59.5 (±13.6)	11/34 (32.4%)		LPV/r	400/100 mg twice daily	N/A
Liu et al [28](China)	1	40 (±0)	1/1 (100%)	Mild- severe	LPV/r	400 mg twice daily	9
	9	43.3 (±10.3)	3/9 (33.3%)		LPV/r + IFNα2b	400 mg twice daily + 5 million U twice daily	2–18
Kim et al [26] (Korea)	31	64.3 (±14.6)	11/31 (35.5%)	Mild/moderate	LPV/r	400/100 mg twice daily	42
	34	64.3 (±16.3)	14/34 (41.2%)		HCQ	400 mg daily	42
Panagopoulos et al [29] (Greece)	8	55.75 (±19.71)	6/8 (75%)	N/A	HCQ+AZ+ LPV/r	N/A	N/A
	8	59.75 (±10.51)	4/8 (50%)		HCQ+AZ	N/A	N/A
Zhang et al [32] (China)	5	44 [N/A]	2/5 (40%)	Mild- severe	DP	100 mg twice daily	13
	28	43 [N/A]	9/28 (32.1%)		LPV/r	400/100 mg twice daily or 800/200 mg daily	21
Yu et al [31] (China)	37	56.0 [43.5–68.0]	15/37 (40.5%)	Severe	LPV/r	N/A	28
	91	61.0 [50.0–68.0]	40/91 (44.0%)		SOC	N/A	28

Data are presented as Mean(SD); median[IQR]; n/N (%).
N/A = not available, LPV/r = lopinavir/ritonavir, ARB = umifenovir (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

Table 2. Outcomes from the randomized control trials.

Author	Follow-Up Length (days)	Mortality	RT-PCR negativity	Days to RT-PCR negativity Mean (±SD); Median [IQR]	Chest CT improvement	Conclusions
Li et al [20](China)	14	N/A	29/34 (85.3%)	9 (±5)	21/28 (75.0%)	Neither LPV/r nor UMF/ improved outcomes compared to SOC
	14	N/A	32/35 (91.4%)	9.1 (±4.4)	23/33 (69.7%)	
	14	N/A	13/17 (76.5%)	9.3 (±5.2)	13/14 (92.9%)	
Cao et al [18](China)	28	19/99 (19.2%)	39/99 (39.4%)	N/A	N/A	No difference in outcomes between LPV/r and SOC
	28	25/100 (25.0%)	41/100 (41.0%)	N/A	N/A	
Hung et al [19](China)	30	N/A	N/A	7 [5–11]	N/A	Favors LPV/r + RV+IFNβ1b over LPV/r in time to viral clearance
	30	N/A	N/A	12 [8–15]	N/A	

Data are presented as Mean(SD); median[IQR]; n/N (%).
N/A = not available, LPV/r = lopinavir/ritonavir, UMF = Umifenovir (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

Table 3. Outcomes from the non randomized clinical trials.

Author	Follow-Up Length (days)	Mortality	Mortality	RT-PCR negativity	Days to RT-PCR negativity Mean (±SD); Median [IQR]	Chest CT improvement	Conclusions
Cai et al [21](China)	14	N/A	N/A	N/A	4 [2.5–9]	32/35 (91.4%)	FPV was more effective than LPV/ r in limiting disease progression and enhancing viral clearance
	14	N/A	N/A	N/A	11 [8–13]	28/45 (62.2%)	
Ye et al [23](China)	N/A	N/A	N/A	N/A	7.8 (±3.09)	N/A	Favors LPV/r over UMF/for viral clearance
	N/A	N/A	N/A	N/A	12 (±0.82)	N/A	
Huang et al [22](China)	14	N/A	N/A	10/10 (100%)	N/A	10/10 (100%)	No difference in outcomes between CQ and LPV/r
	14	N/A	N/A	11/12 (91.7%)	N/A	9/12 (75.0%)	

Data are presented as Mean(SD); median[IQR]; n/N (%).
N/A = not available, LPV/r = lopinavir/ritonavir, UMF = umifenovir, 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

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 experienced 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 et al. compared the efficacy of LPV/r treatment with umifenovir and interferon aerosol inhalation treatment in COVID-19 patients [23]. The body temperature of the patients in the LPV/r group returned to normal body temperature in a shorter time period compared to that in the umifenovir +IFN group (4.8 ± 1.94 days vs 7.3 ± 1.53 days in the umifenovir +IFN group; p = 0.0364). The safety of these treatment protocols was reported by analyzing the levels of ALT and aspartate aminotransferase (AST). No significant side effects were reported in the LPV/r group [23].

3.5. Retrospective observational studies

The outcomes of interest reported in the retrospective observational studies are summarized in Table 4.

A pilot study by Lan et al. compared the clinical outcomes of LPV/r alone (n = 34) and treatment with a combination of LPV/r and umifenovir (n = 39) in a total of 73 patients with moderate to severe COVID-19 [27]. Patients were classified as ordinary or severe cases of COVID-19 infection based on the diagnosis and treatment protocol issued by the General Office of the National Health Commission [35]. Mortality was similar between both the groups (LPV/r:2.9% [1/34] and LPV/r + umifenovir: 2.6% [1/39], [p = >0.99]). In the LPV/r + umifenovir group, two patients worsened clinically, requiring ICU admission. Viral clearance was reported in 97.1% (33/34) and 92.3% (36/39) in the LPV/r and LPV/r + umifenovir group, respectively [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]. The SOC consisted of LPV/r, HCQ, and oxygen therapy. Patients received TCZ within 4 days of hospital admission. Patients who received TCZ+SOC had a greater survival rate 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), 92.0% (23/25) of the patients in the TCZ+SOC group were discharged (mean 12.5 days) and 8.0% (2/25) had died, while 42.1% (8/19) of the patients in the SOC group were discharged and 57.9% (11/19) had died. Among patients with no concluded outcome, 64.8% (24/37) of TCZ+SOC patients improved clinically and 37.0% (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

Table 4. Outcomes from the retrospective cohort studies.

Author	Follow-Up Length (days)	Mortality	RT-PCR negativity	Days to RT-PCR negativity Mean (±SD); Median [IQR]	Chest CT improvement	Conclusions
Zhu et al. [33] (China)	14 14	N/A N/A	19/34 (55.9%) 16/16 (100%)	11.5 [8.8–17] 9.5 [5.3–11]	N/A N/A	UMF/exhibited better viral clearance than LPV/r
Deng et al. [25] (China)	7 7	N/A N/A	12/16 (75.0%) 6/17 (35%)-	N/A N/A	11/16 (68.8%) 5/17 (29.4%)	Favors LPV/r alone over LPV/r + UMF/for viral clearance and chest CT improvement
Yan et al. [30] (China)	40 40	N/A N/A	N/A N/A	22 [18–29] 28.5 [19.5–38]	N/A N/A	Favors LPV/r over corticosteroid for viral clearance
Capra et al. [24] (Italy)	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. [27] (China)	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 + UMF/and LPV/r alone
Liu et al. [28] (China)		0/1 (0%) 0/6 (0%)	1/1 (100%) 6/6 (100%)	7 (±0) 12.5 (±2.9)	N/A N/A	Sustained LPV/r use may provide benefit
Kim et al. [26] (Korea)	42 42	1/31 (3.2%) 1/34 (2.9%)	27/31 (87.1%) 21/34 (61.8%)	21 28	N/A N/A	Favors LPV/r over HCQ in time to viral clearance, no benefit for clinical responses
Panagopoulos et al. [29] (Greece)	8 8	N/A N/A	N/A N/A-	8.86 (±1.68) 13.8 (±2.68)	N/A N/A	Favors HCQ+AZ+LPV/r over HCQ+AZ in time to viral clearance
Zhang et al. [32] (China)	13 21	N/A N/A	5/5 (100%) 28/28 (100%)	8 (N/A); 7 [N/A] 12.5 [N/A]; 12 [N/A]	N/A N/A	Favors DP over LPV/r in time to viral clearance
Yu et al. [31] (China)	28 28	7/37 (19%) 23/91 (25%)	34/37 (91.9%) 74/91 (81.3%	13.0 [10.0–16.0] 16.5 [12.25–23.75]	32/34 (94.1%) 67/82 (81.7%)	Favors LPV/r over SOC for mortality, SAE, and resolution of COVID-19 pneumonia

Data are presented as Mean(SD); median[IQR]; n/N (%).
N/A = not available, LPV/r = lopinavir/ritonavir, UMF = umifenovir (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

moderate COVID-19 treated with LPV/r or HCQ [26]. Clinical outcome was assessed using the seven-category ordinal scale recommended by the World Health Organization (WHO) R&D blueprint group [34]. 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. 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 (68.0%) patients received LPV/r and 16 (32.0%) patients received umifenovir, in addition to oxygen therapy, and atomized inhalation of recombinant human interferon-α2b injection [33]. Patients who received UMF exhibited better viral clearance than LPV/r [33].

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 [30,35]. The baseline characteristics were similar between both 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, not having received 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].

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 < 0.001). 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 81.3% (74/91) in the SOC group. 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 the SOC group. 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 group. 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].

4. Discussion

We systematically reviewed studies that reported the use of LPV/r for the treatment of patients with COVID-19. This systematic review of patients with COVID-19 found no correlation between LPV/r treatment and decreased mortality, RT-PCR negativity, or chest CT clearance. 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 included studies included. In addition to assessing the clinical status, the studies by Cao et al. and Kim et al. used the seven-category ordinal scale recommended by the WHO R&D blueprint group [18,26,34]. 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.

Few studies showed a favorable outcome with LPV/r, either alone or in combination with other therapies, with respect to time of viral clearance and improvement in symptoms [19,23,25,26,30]. The cohort of patients in these studies largely had mild to moderate disease, and while there was a favorable outcome with regards to viral clearance and improvement in symptoms, most of these studies did not report mortality rates. Additionally, these studies mostly looked at outcome variables (i.e., mortality, RT-PCR negativity, time to RT-PCR negativity, and chest CT clearance) individually [23,25,30]. These factors, in addition to the smaller sample size, may have contributed to the lack of strong evidence for the effectiveness of LPV/r as an antiviral agent in patients with COVID-19. Kim et al. reported favorable outcome with respect to viral clearance; however, this did not correlate with clinical improvement [26].

Moreover, in a randomized trial of severe COVID-19 patients, treatment with LPV/r (400/100 mg) twice daily for 14 days compared to the 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]. Panagopoulos et al. reported a favorable outcome with LPV/r when used in combination with HCQ and azithromycin in patients with severe symptoms and radiological findings, with no increase in AEs [29]. Yan et al. reported LPV/r was not an independent factor in prolonged viral shedding, while the use of corticosteroids did not change the outcome in this cohort of non critically ill hospitalized patients. Though the evidence from other studies does not support this conclusion, we suggest that LPV/r could be considered as a potential treatment option in an outpatient setting.

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 the 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*; however, it is thought to have a poor selectivity index, necessitating higher doses to achieve efficacy *in vivo* [40–42]. 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 a 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-19 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 a lack of standard protocols to monitor the clinical outcomes; for example, some clinical outcomes were measured differently among the studies, and the duration of follow-up also varied among the studies. The heterogeneity of the available data prevented

a meta-analysis from being conducted. Finally, most of the studies included in our review were non-randomized and retrospective. Further, clinical trials are necessary to assess the effectiveness of LPV/r for the treatment of patients with COVID-19.

5. Conclusion

The results of this systematic review indicate there is no survival or clinical benefit of LPV/r treatment of COVID-19 infection. Larger clinical trials are necessary to explore the potential effectiveness of LPV/r in reducing mortality and time to viral clearance.

Acknowledgments

We acknowledge Karl Holub, Stephen Mead, and Darian Lehmann-Plantenberg for their design and support of the Nested Knowledge meta-analytical software.

Declaration of interest

BA Joseph, NL Reierson, N Mikoff, S Kamrowski, and M Schmidt work for Nested Knowledge and Superior Medical Experts. JM Pederson is employed by Nested Knowledge, Superior Medical Experts, and Marblehead Medical. KM Kallmes works for and holds equity in Nested Knowledge, Superior Medical Experts, and Marblehead Medical. KW Evanson, G Paranjape, AR Davis, JM Pederson, JC Touchette are employed by Superior Medical Experts. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Mahmoud Dibas http://orcid.org/0000-0003-1690-1084
Kavitha Saravu http://orcid.org/0000-0001-6399-1129
Spandana Chittajallu http://orcid.org/0000-0002-3985-0809
John M. Pederson http://orcid.org/0000-0003-2551-4828

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Control ECfDPa. Rapid risk assessment: cluster of pneumonia cases caused by a novel coronavirus, Wuhan, China, 2020 2020 [updated 2020 11 Feb; cited 2020 Aug 18]. Available from: https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-cluster-pneumonia-cases-caused-novel-coronavirus-wuhan
2. WHO. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020 2020 [updated 11 Feb 2020; cited 2020; cited 2020 Feb 2020; cited 2020 Aug 11 Feb 2020; cited 2020 Aug 18. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020
3. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(13):1199–1207.
4. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–513.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
6. Liu K, Fang YY, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl). 2020;133(9):1025–1031.
7. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. Jama. 2020;323(11):1061–1069.
8. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–1720.
9. Chen F, Chan KH, Jiang Y, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol. 2004;31(1):69–75.
10. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004;59(3):252–256.
11. Wu CY, Jan JT, Ma SH, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci U S A. 2004;101(27):10012–10017.
12. Chan JF, Yao Y, Yeung ML, et al. Treatment with Lopinavir/Ritonavir or Interferon-β1b improves outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. J Infect Dis. 2015;212(12):1904–1913.
13. de Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother. 2014;58(8):4875–4884.
14. Pillaiyar T, Meenakshisundaram S, Manickam M. Recent discovery and development of inhibitors targeting coronaviruses. Drug Discov Today. 2020;25(4):668–688.
15. Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J. 2003;9(6):399–406.
16. Park SY, Lee JS, Kim J, et al. 2491. Post-exposure prophylaxis with ribavirin plus lopinavir/ritonavir for Middle East respiratory syndrome in healthcare workers. Open Forum Infect Dis. 2018;5(suppl_1):S747–S748.
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clin Res Ed). 2009;339(jul21 1):b2700.
18. Cao B, Wang Y, Wen D, et al. A trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020;382(19):1787–1799.

•• ***Cao et al reported the use of lopinavir-ritonavir in patients hospitalized with severe COVID-19 infection, which is a group that needs to be addressed given that those with mild to moderate illnesses have a better outcome. We also found it useful that the protocols used to measure clinical outcomes was standardized using the seven-category ordinal scale.***

19. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020;395(10238):1695–1704.
20. Li Y, Xie Z, Lin W, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. Medicine (Baltimore). 2020doi: 10.1016/j.medj.2020.04.001 [Epub ahead of print].
21. Cai Q, Yang M, Liu D, et al. Experimental Treatment with Favipiravir for COVID-19: an Open-Label Control Study. Engineering. 2020 Mar 18.doi: 10.1016/j.eng.2020.03.007 [Epub ahead of print].
22. Huang M, Tang T, Pang P, et al. Treating COVID-19 with Chloroquine. J Mol Cell Biol. 2020;12(4):322–325.

23. Ye XT, Luo YL, Xia SC, et al. Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019. Eur Rev Med Pharmacol Sci. 2020;24(6):3390–3396.
24. Capra R, De Rossi N, Mattioli F, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med. 2020;76:31–35.
•• ***In this study the investigators looked at three drugs of importance in COVID-19. Though this study was a retrospective study, the study looked at the effectiveness of Lopinavir -ritonavir in patients with severe disease.***
25. Deng L, Li C, Zeng Q, et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. J Infect. 2020;81(1):e1–e5.
26. Kim JW, Kim EJ, Kwon HH, et al. Lopinavir-ritonavir versus hydroxychloroquine for viral clearance and clinical improvement in patients with mild to moderate coronavirus disease 2019. Korean J Intern Med. 2020 Jun 16.doi: 10.3904/kjim.2020.224.Online ahead of print.
• ***In this study the patients were followed up for a longer duration than most other studies and the two most crucial outcomes of mortality and viral clearance were assessed.***
27. Lan X, Shao C, Zeng X, et al. Lopinavir-ritonavir alone or combined with arbidol in the treatment of 73 hospitalized patients with COVID-19: a pilot retrospective study. MedRxiv. 2020 Apr 25;20079079.
28. Liu F, Xu A, Zhang Y, et al. Patients of COVID-19 may benefit from sustained Lopinavir-combined regimen and the increase of Eosinophil may predict the outcome of COVID-19 progression. Int J Infect Dis. 2020;95:183–191.
29. Panagopoulos P, Petrakis V, Panopoulou M, et al. Lopinavir/ritonavir as a third agent in the antiviral regimen for SARS-CoV-2 infection. J Chemother. 2020;1-5. doi:10.1080/1120009X.2020.1775424.
30. Yan D, Liu XY, Zhu YN, et al. Factors associated with prolonged viral shedding and impact of lopinavir/ritonavir treatment in hospitalised non-critically ill patients with SARS-CoV-2 infection. Eur Respir J. 2020;56(1):2000799.
• ***The outcome of this study was contrary to what our major conclusion, however this being a retrospective study does not have strong evidence. However, we believe that larger clinical trials to study the effectiveness of lopinavir-ritonavir in decreasing viral clearance should be explored.***
31. Yu C, Zhang Z, Guo Y, et al. Lopinavir/ritonavir is associated with pneumonia resolution in COVID-19 patients with influenza coinfection: A retrospective matched-pair cohort study. J Med Virol. 2020. doi: 10.1002/jmv.26260.
32. Zhang Z, Wang S, Tu X, et al. A comparative study on the time to achieve negative nucleic acid testing and hospital stays between danoprevir and lopinavir/ritonavir in the treatment of patients with COVID-19. J Med Virol. 2020. doi: 10.1002/jmv.26141.Online ahead of print.
33. Zhu Z, Lu Z, Xu T, et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. J Infect. 2020;81(1):e21–e23.
34. WHO. R&D Blueprint and COVID-19 2020 [cited 2020 Oct 12]. Available from: https://www.who.int/teams/blueprint/covid-19
35. Commission CMH. Chinese management guideline for COVID-19 (version 6.0): Chinese municipal health commission; 2020 cited 2020 Feb 19, [in Chinese].
36. Health NDoP. No clinical benefit from use of lopinavir-ritonavir in hospitalised COVID-19 patients studied in RECOVERY 2020 [cited 2020 Aug 19]. Available from: https://www.recoverytrial.net/news/no-clinical-benefit-from-use-of-lopinavir-ritonavir-in-hospitalised-covid-19-patients-studied-in-recovery
37. WHO. WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19 2020 [cited 2020 Oct 12]. Available from: https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19
38. Chandwani A, Shuter J. Lopinavir/ritonavir in the treatment of HIV-1 infection: a review. Ther Clin Risk Manag. 2008;4(5):1023–1033.
39. Barretto N, Jukneliene D, Ratia K, et al. The papain-like protease of severe acute respiratory syndrome coronavirus has deubiquitinating activity. J Virol. 2005;79(24):15189–15198.
40. Groneberg DA, Hilgenfeld R, Zabel P. Molecular mechanisms of severe acute respiratory syndrome (SARS). Respir Res. 2005;6(1):8.
41. Liu C, Zhou Q, Li Y, et al. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. ACS Cent Sci. 2020;6(3):315–331.
42. Nitulescu GM, Paunescu H, Moschos SA, et al. Comprehensive analysis of drugs to treat SARS-CoV-2 infection: mechanistic insights into current COVID-19 therapies (Review). Int J Mol Med. 2020;46(2):467–488.
43. Baldelli S, Corbellino M, Clementi E, et al. Lopinavir/ritonavir in COVID-19 patients: maybe yes, but at what dose? J Antimicrob Chemother. 2020;75(9):2704–2706.
44. Solas C, Poizot-Martin I, Drogoul MP, et al. Therapeutic drug monitoring of lopinavir/ritonavir given alone or with a non-nucleoside reverse transcriptase inhibitor. Br J Clin Pharmacol. 2004;57(4):436–440.
45. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious diseases society of America guidelines on the treatment and management of patients with COVID-19. Clin Infect Dis. 2020. doi: 10.1093/cid/ciaa478. Online ahead of print.
46. NIH. Lopinavir/Ritonavir and Other HIV Protease Inhibitors 2020 [updated 2020 Jul 17; cited 2020 Oct 12]. Available from: https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/lopinavir-ritonavir-and-other-hiv-protease-inhibitors/