CADTH COVID-19 PANDEMIC

COVID-19 CADTH HEALTH TECHNOLOGY REVIEW

Lopinavir–Ritonavir for the Treatment and Prevention of COVID-19: A Review of Clinical Effectiveness

On October 15, 2020, interim study results from the World Health Organization's Solidarity Trial were released in pre-print (ISRCTN83971151). The Solidarity Trial is a large, international, adaptive, open-label, randomized controlled trial launched by the World Health Organization and other partners to evaluate several treatments for COVID-19. The interim results report on the findings of four separate treatments compared with local standard of care in hospitalized patients with COVID-19: remdesivir, lopinavir and ritonavir, interferon beta-1a, and hydroxychloroquine. The primary outcome was in-hospital mortality. The intention-to-treat analyses included 11,255 patients enrolled from 405 hospitals in 30 countries, including Canada. No treatment had a statistically significant reduction in 28-day in-hospital mortality compared with its control. Caution should be exercised in interpreting any interim study results. In addition, pre-print reports have not been peer-reviewed. Publication of full study results in a peer-reviewed journal are pending.

The findings of the Solidarity Trial do not change the overall conclusions of CADTH's Health Technology Review on lopinavir and ritonavir in the treatment of COVID-19.

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Questions or requests for information about this report can be directed to **requests@cadth.ca**

Abbreviations

COVID-19	coronavirus disease
ELACOI	efficacy of lopinavir plus ritonavir and arbidol against novel coronavirus infection
LOTUS	lopinavir trial for suppression of SARS-Cov-2
LPVR	lopinavir/ritonavir
RECOVERY	randomized evaluation of COVID-19 therapy
RT-PCR	reverse-transcriptase-polymerase-chain-reaction
RCT	randomized controlled trial
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Context and Policy Issues

Coronavirus disease (COVID-19) is an infectious disease caused by a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was discovered in late 2019.[1,2] The symptoms of COVID-19 include cough, difficulty breathing, fever, loss of taste or smell, and gastrointestinal symptoms, and in severe cases COVID-19 can lead to death.[2] These symptoms can vary in severity and may take up to 14 days to appear after exposure. The virus spreads primarily through respiratory droplets, and some studies have suggested that viral transmission can also occur from pre-symptomatic and asymptomatic people.[1,2]

In March 2020, the WHO declared COVID-19 a global pandemic,[3] and in Canada 120,132 confirmed cases and 8,987 deaths have been reported, as of August 10, 2020.[4] At the time of writing this report, remdesivir had been authorized by Health Canada for the treatment of patients with severe COVID-19 symptoms,[5] and several other treatments are being used off-label or are being investigated as part of a clinical trial for COVID-19. One of the proposed treatments that is currently being investigated for COVID-19 is a combination of lopinavir and ritonavir.[6,7] Lopinavir/ritonavir (LPVR) is an oral antiretroviral protease inhibitor used for the treatment of HIV.[8] Ritonavir inhibits the metabolism of lopinavir, thus prolonging the bioavailability of the lopinavir.[9] The potential mechanism of action of LPVR is that it may inhibit the action of a key enzyme involved in the replication of viral RNA (i.e., 3-chymotrypsin-like protease), thus disrupting the replication of the SARS-CoV-2 virus and its release from host cells. Lopinavir has shown antiviral effects against SARS-CoV-2 in vitro,[10] however, there is uncertainty around the clinical effectiveness of LPVR in patients with COVID-19.[11]

The purpose of the current report is to review and summarize the evidence regarding the clinical effectiveness of lopinavir–ritonavir for the treatment and prevention of COVID-19.

Research Question

What is the clinical effectiveness of lopinavir–ritonavir for the treatment and prevention of coronavirus disease (COVID-19)?

Key Findings

Two relevant randomized controlled trials were identified that addressed the clinical effectiveness of lopinavir–ritonavir for the treatment of coronavirus disease (COVID-19). When compared to patients treated with standard care alone, or treated with standard care plus arbidol, no clinical benefit was observed in patients with treated with lopinavir–ritonavir plus standard care. The body of evidence in this report was small, heterogenous, and had high uncertainty, and additional evidence from larger, adequately powered studies is needed to confirm these findings.

No evidence regarding the clinical effectiveness of lopinavir–ritonavir for the prevention of COVID-19 was identified.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, Embase, PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were lopinavir, ritonavir and COVID-19. No filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2018 and July 21, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Individuals with confirmed or suspected coronavirus disease (COVID-19) or those at risk of infection
Intervention	Lopinavir–ritonavir (used as a treatment or as a prophylactic; alone or in combination with other therapies)
Comparator	No treatment; placebo; standard care; other active treatments (e.g., remdesivir)
Outcomes	Clinical effectiveness (e.g., mortality, length of hospital stay, severity of clinical symptoms, viral load, safety [e.g., rate of adverse events])
Study Designs	Randomized controlled trials

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2018. Due to the rapidly evolving situation with COVID-19, and the speed at which new evidence is being published,

systematic reviews were excluded from this report. Relevant systematic reviews identified in the literature search are listed in Appendix 5.

Critical Appraisal of Individual Studies

The included randomized controlled trials (RCTs) were critically appraised by one reviewer using the Downs and Black checklist[12] as a guide. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 287 citations were identified in the literature search. Following screening of titles and abstracts, 244 citations were excluded and 43 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full text review. Of these potentially relevant articles, 42 publications were excluded for various reasons, and two RCTs met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[13] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Two RCTs[14,15] were identified and included in this report, and are summarized below. Additional details regarding the characteristics of included publications are provided in Appendix 2, Table 2.

Study Design

Both RCTs[14,15] were published in 2020. One RCT,[14] the LOTUS trial (Lopinavir Trial for Suppression of SARS-CoV-2), was a two-arm, open-label, single-centre RCT. The other RCT,[15] the ELACOI trial (Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection), was a three-arm, single-centre RCT.

Country of Origin

Both RCTs[14,15] were conducted in China.

Patient Population

Both RCTs[14,15] included adults with COVID-19 confirmed by reverse-transcriptase–polymerase chain-reaction (RT-PCR) recruited from single hospitals in China. In the LOTUS trial[14] the patients also had pneumonia confirmed by chest imaging and oxygen saturation of 94% or below (N = 199), and the median time between symptom onset and treatment was 13 days. The patients in the ELACOI trial[15] had mild (e.g., mild clinical symptoms but no signs of pneumonia) or moderate (e.g., fever, respiratory symptoms and pneumonia on imaging) clinical status (N = 86), and the number of days between symptom onset and treatment ranged from two to eight (varied by treatment arm). Both RCTs[14,15] excluded people allergic to the intervention drugs, and the ELACOI trial[15] excluded patients with gastrointestinal issues that might affect absorption.

Interventions and Comparators

In the LOTUS trial[14] the intervention group received oral LPVR (400 mg lopinavir, 100 mg ritonavir) twice daily for 14 days in addition to standard care, whereas the control group received standard care alone. Standard care treatments included oxygen support, ventilation, antibiotics, medications for blood pressure support, and renal replacement therapy.[14] The intervention group in the ELACOI trial[15] received oral LPVR (400 mg lopinavir, 100 mg ritonavir) twice daily for seven to 14 days plus standard of care. One of the comparator groups received arbidol (200 mg), orally, three times a day for seven to 14 days plus standard of care, and the control group received standard care but did not receive any antivirals. The mean length of treatment was not reported, nor was it reported how the investigators determined whether patients were treated for seven days or up to 14 days.[15] In this trial, standard care included supportive care and oxygen therapy, but was not otherwise described.[15]

Outcomes

The primary outcome in the LOTUS trial[14] was time to clinical improvement, which was defined as an improvement of two or more points on a seven category ordinal scale (previously used in studies of severe influenza), or time to discharge from the hospital, whichever came first. Other outcomes reported in the LOTUS trial were clinical status, mortality, duration of ventilation, length of stay, viral load, and adverse events.[14] For the ELACOI trial,[15] the primary outcome was the rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid on day 21, assessed through pharyngeal swabs and RT-PCR. The secondary outcomes reported in the ELACOI trial were the rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid on day 14, reduction of fever, cough alleviation, improvement in chest CT, clinical status, and adverse events.[15]

Summary of Critical Appraisal

The critical appraisal of the included studies is summarized below and additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 3.

Randomized Controlled Trials

Both RCTs[14,15] had detailed descriptions of the objective of the study, the eligibility criteria, the baseline characteristics of the patients, and the adverse events. The length of follow-up was short (i.e., less than 30 days) in both RCTs,[14,15] which was appropriate for the viral RNA load outcomes, but may not have been sufficient time to observe a change in clinical status, and neither study reported losing any patients to follow up. The reporting was well done in the LOTUS trial.[14] This RCT described how the primary and secondary outcomes would be measured and the time points of assessment, and provided clear explanations of the treatments received by the patients.[14] This trial[14] also provided simple outcome data for all outcomes, an actual probability value for the primary outcome, and 95% confidence intervals for the secondary outcomes, improving the transparency and interpretation of the findings. In the ELACOI trial[15] some details were poorly reported reducing certainty of the findings. For instance, the primary and secondary outcomes were listed in the methods, but there was some uncertainty in the outcome definitions and how they would be measured (e.g., no additional description provided for the outcome of 'improvement rate of chest CT').[15] Insufficient information was also reported with regard to what constituted 'standard of care', and it was unclear which other treatments the patients received in the ELACOI trial.[15] In addition, the primary outcome in the ELACOI trial[15] was reported with a figure with

no accompanying numerical results, and it was unclear which statistical test was used to compare the findings, thus this finding was associated with some uncertainty. Both RCTs reported the source of funding and the authors declared that they did not have any conflicts of interest.[14,15]

Both RCTs[14,15] used appropriate methods for randomizing the participants and concealing treatment allocation to reduce selection bias. The LOTUS trial[14] was an open-label trial and did not report whether the outcome assessors were blinded to the intervention, and it is unclear whether this would have influenced the results. Most of the outcomes in the LOTUS trial[14] were objective outcomes (e.g., length of stay), however, the primary outcome (i.e., time to improvement in clinical status) consists of a seven-category ordinal scale which has a subjective aspect to it. The ELACOI trial[15] reported that the participants and the outcome assessors were blinded to the treatment allocation. All patients received their allocated intervention in the ELACOI trial[15] and there were five people who did not receive the intervention in the LOTUS trial[14] (three due to death prior to treatment, and two due to the physician refusing to prescribe it [reasons for refusal not provided]).

The statistical methods used in LOTUS trial[14] were well described and appropriate for the outcomes assessed. The main analysis was an intention-to-treat analysis (i.e., included all patients who were randomized), and supplemental modified intention-to-treat analyses (i.e., excluded the three patients who died within 24 hours of randomization) were also conducted; similar findings were observed with both statistical approaches.[14] The authors stated that they did not adjust for multiplicity in the statistical analysis plan, and therefore reported a P value for the primary analysis and reported 95% confidence intervals for the other analyses (with the caveat that these findings should be interpreted with caution).[14] This study[14] exceeded the original calculated sample size (i.e., N = 160), as the initial calculation was later determined by the authors to be insufficient, but the re-calculated sample size was not reported and the trial was halted early (when another potential treatment became available) and it was not reported whether the study was adequately powered (N = 199) upon completion.

It was unclear whether all of the statistical tests used in the ELACOI trial[15] were appropriate. For the main outcome, a graph was provided but it is unclear which statistical test was used to compare the treatment groups.[15] In addition, although this RCT[15] had three groups of patients, some of the statistical tests reported in the methods section are tests primarily used for comparing two groups (i.e., Mann-Whitney test, chi square test, and Fisher's exact test) and it is possible that different statistical tests designed for determining whether differences exist across three groups may have been more appropriate (e.g., Kruskal-Wallis test). Furthermore, the statistical analysis plan did not adjust for multiplicity, increasing the possibility of a false positive result from conducting multiple statistical tests.[15] The sample size for this three-arm trial was small (N = 86), and the trial failed to reach the estimated sample size (i.e., N = 125) due to a reported drop in cases of COVID-19 in the area.[15]

Summary of Findings

Relevant findings are summarized below, and a detailed summary of the findings and authors' conclusions are presented Appendix 4, Table 4.

Clinical Effectiveness of Lopinavir–Ritonavir

Two RCTs[14,15] were identified regarding the clinical effectiveness of LPVR for the treatment of COVID-19.

Clinical Status

In the LOTUS trial[14] there was no difference in the time to clinical improvement, or in the percentage of patients with clinical improvement at day 7, between those receiving LPVR plus standard care compared to those receiving standard care alone. The percentage of patients with an improvement in clinical status at day 14 was higher in the LPVR group (45.5%) compared to the standard care group (30.0%), however, the difference between groups was associated with a wide confidence interval which was not adjusted for multiplicity, limiting inferences that can be drawn from this finding. In the ELACOI trial[15] the deterioration of the clinical status from mild/moderate to severe/critical occurred in a greater proportion of patients in the LPVR group (23.5%), compared the those treated with arbidol (8.6%) or standard of care (11.8%), but the difference was not statistically significant across the three groups.

SARS-CoV-2 RNA

There was no difference between the LPVR and the standard of care groups in the percentage of patients with detectable viral RNA on day 14 or day 28 in the LOTUS trial.[14] In the ELACOI trial[15] there was no difference in the rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid at day seven, day 14 or day 21, across all three groups (i.e., LPVR vs. arbidol vs. standard care). The number of days for positive-to-negative conversion of SARS-CoV-2 nucleic acid was also similar across the three groups in this trial.

Mortality

There was no difference in mortality on day 28, and no difference in the time between randomization and death between the LPVR and the standard of care groups in the LOTUS trial.[14]

Length of Stay

In the LOTUS trial[14] there was no difference in the length of say in the hospital (i.e., time to discharge) or in the length of stay in the ICU between the LPVR and the standard of care groups.

Duration of Mechanical Ventilation

There was no difference in the duration of mechanical ventilation between the LPVR and the standard of care groups in the LOTUS trial.[14]

Fever

In the ELACOI trial[15] there was no difference between the three groups with regard to the percentage of patients with a reduction in fever on day seven or on day 14.

Cough

The percentage of patients whose cough was alleviated after treatment initiation was not statistically different between the three groups (i.e., LPVR, arbidol, standard care) in the ELACOI trial[15] on day seven or day 14.

Improvement in Chest CT

The percentage of patients with an improvement seen in their chest CT was not different between the three groups (i.e., LPVR, arbidol, standard care) in the ELACOI trial[15] on day seven or day 14.

Adverse Events

In the LOTUS trial,[14] a similar proportion of patients experienced any adverse event in the LPVR group (48.4%) as those receiving standard care (49.5%), whereas in the ELACOI trial,[15] the number of patients experiencing an adverse event was higher in the LPVR (35.3%) and arbidol (14.3%) groups, compared to those receiving standard care alone (0%), but no statistical tests were conducted in either trial. In the LOTUS trial,[14] more patients receiving standard care alone experienced a serious adverse event (32.3%) in compared to the LPVR group (20.0%), but no statistical test was conducted for this analysis. In contrast, one patient treated with LPVR experienced a serious adverse event in the ELACOI trial, and no other serious adverse events were reported.[15]

Limitations

The main limitation of the evidence for this report was the small quantity of research on LPVR for the treatment of patients with COVID-19. Two RCTs[14,15] were identified that used LPVR to treat patients with COVID-19, and no studies were identified that used LPVR to prevent COVID-19. One of the RCTs identified, the ELACOI trial,[15] was a three arm trial, and the statistical analyses reported whether a difference existed across all three groups, but did not report whether a difference existed between any two groups (i.e., LPVR versus arbidol, or LPVR versus standard of care), which would have been more relevant to this report. Both RCTs in this report also had small sample sizes. The LOTUS trial[14] was the larger of the two RCTs, with 199 patients randomized, however, it was unclear whether the study was adequately powered as the recalculated sample size was not reported by the authors. The ELACOI trial,[15] which was a three arm trial, did not reach their estimated sample size (86 of 125 patients recruited), limiting the certainty in the findings. These underpowered studies limit the ability to draw conclusions from the evidence. This report also identified 13 non-randomized studies that examined the clinical effectiveness of LPVR compared to a variety of alternative treatments in patients with COVID-19. These studies are listed in Appendix 5, as non-randomized studies do not meet the inclusion criteria for study design for this report (i.e., RCTs needed due to stronger methodological quality). Given that COVID-19 is a new disease, as more evidence is published from larger, high quality RCTs it may add more certainty with regards to the effectiveness and safety of LPVR for treating patients with COVID-19.

The body of evidence was also limited by the heterogeneity across the two RCTs, which may affect the certainty of the evidence, and the generalizability of these findings to the clinical context. Three of the nine outcomes summarized in this report (i.e., clinical status, SARS-CoV-2 RNA, and adverse events) overlapped across the two RCTs,[14,15] although they were measured and reported differently limiting the ability to compare findings between trials. The patient populations also differed across RCTs; the LOTUS trial[14] had additional criteria for the severity of COVID-19 (i.e., confirmed pneumonia, and oxygen saturation at or below 94%), whereas the ELACOI trial[15] may have had a less sick population as it recruited patients with mild (e.g., no signs of pneumonia) or moderate (e.g., fever with respiratory symptoms) clinical status and excluded multiple underlying conditions. The median number of days between the onset of COVID-19 symptoms and the

randomization/treatment of the patients was also higher in the LOTUS trial[14] (13 days) compared to ELACOI trial[15] (LPVR 3.5 days; arbidol 6 days; standard care 5 days). It is unknown whether the longer period of time between symptom onset and treatment affected the effectiveness of the treatment in the LOTUS trial.[14] Furthermore, while both RCTs administered LPVR in combination with standard care, what was considered standard was poorly described care in the ELACOI trial,[15] thus it is unclear if there were differences in standard care between the trials.

In addition, both RCTs[14,15] were conducted in China. It is unknown if studies conducted out of Canada are generalizable to the Canadian clinical practice.

Conclusions and Implications for Decision or Policy Making

This report was comprised of two RCTs[14,15] regarding the clinical effectiveness of LPVR for the treatment of patients with COVID-19. No relevant evidence regarding LPVR for the prevention of COVID-19 was identified.

Overall, neither trial demonstrated a clinical benefit of LPVR plus standard care for treating patients with COVID-19 when compared to standard care alone[14] or when compared to arbidol plus standard care or standard care alone (i.e., a three arm trial).[15] The evidence in this report suggests that treatment with LPVR resulted in no difference between groups in clinical status,[14,15] SARS-CoV-2 viral load,[14,15] length of stay in the hospital or ICU,[14] reduction in fever,[15] alleviation of cough,[15] improvement of a chest CT,[15] or mortality.[14] In one RCT[14] there was a higher percentage of patients with improved clinical status at day 14 for those treated with LPVR compared to standard care alone, however, this finding had a large confidence interval, and the trial was not designed to infer definitive treatment effects for this outcome. There are methodological limitations with both trials that affect the certainty of these findings. There were concerns as to whether either trial was adequately powered to detect a difference between treatment groups, and it is unclear whether the open-label design may have biased the outcomes in the LOTUS trial. In addition, the ELACOI trial lacked clarity on some of the interventions and outcome measures and did not adjust the statistical analysis for multiple comparisons.

In regard to the safety of LPVR for treating patients with COVID-19, the findings were mixed, and neither trial[14,15] was designed to test for statistical differences between groups for the number of adverse events. In one RCT[14] there was no difference between groups in the number of patients who experienced an adverse events, whereas in the other RCT[15] a greater proportion of patients treated with LPVR experienced an adverse event (compared to those treated with arbidol or standard care alone), however, no statistical tests were reported with either finding. Adverse events experienced by those in the LPVR groups that were not experienced by the standard care groups included nausea,[14] vomiting,[14] and diarrhea,[14,15] which are commonly reported adverse events to LPVR.[9] Concerning serious adverse events, fewer patients treated with LPVR experienced a serious adverse event in one RCT[14] and a single serious adverse event was reported in the other RCT[15] in a patient treated with LVPR.

Both trials[14,15] used the same dose of LPVR (i.e., 400 mg lopinavir, 100 mg ritonavir, orally, twice daily), which is the recommended dosage used for patients with HIV,[9] although the length of treatment was potentially shorter in the ELACOI trial[15] (i.e., seven to 14 days) compared to the 14 day treatment used in the LOTUS trial.[14] The patients in both trials[14,15] had confirmed COVID-19, although the LOTUS trial[14] recruited patients with more severe COVID-19 and there was a longer time between symptom onset and treatment in this trial.

Despite these differences and the methodological limitations associated with the trials, neither study demonstrated a benefit for treatment with LPVR compared to standard care alone,[14,15] or to arbidol plus standard care.[15]

There are a number of ongoing trials regarding the effectiveness of LPVR for the treatment of patients with COVID-19 (see Appendix 5), however, some trials investigating treatments for COVID-19 have recently discontinued the LPVR treatment arm due to a lack of an observed benefit. The RECOVERY trial (Randomized Evaluation of COVID-19 Therapy),[16] a large RCT designed to test multiple different treatments for COVID-19, discontinued the LPVR treatment arm on June 29, 2020 following a review of the data which showed no benefit of LPVR (N = 1596) on 28-day mortality compared to usual care alone (N = 3376).[17] In addition, the WHO discontinued the LPVR treatment arm of the Solidarity Trial (an international clinical trial for COVID-19) on July 4, 2020 after failing to see a reduction in mortality when compared to standard of care (no additional details available).18 The results of these trials have not been published at the time this report was written and are not included in this report. The lack of an observed benefit of LPVR for treating patients with COVID-19 reported in the discontinued treatment arms of these trials reflects the findings described in this CADTH report (i.e., no difference in clinical effectiveness of LPVR plus standard care compared to standard care alone).

This report is based on a two underpowered RCTs[14,15] that are associated with clinical heterogeneity and statistical uncertainty, and these limitations should be considered when interpreting the finding in this report. Nonetheless, the findings consistently demonstrated no additional clinical benefit of LPVR in patients with COVID-19 compared to standard care alone, or when compared to arbidol or standard care. These findings reflect what was observed in two large, unpublished RCTs investigating treatments for COVID-19[17,18] and was the reason given for discontinuing the LPVR treatment arms of these trials. It is also possible that patients treated with LPVR experience more adverse events, although these findings were mixed with a high amount of uncertainty. Published findings from additional well designed and adequately powered studies examining LPVR for the treatment of patients with COVID-19 is needed to support the conclusions of this report.

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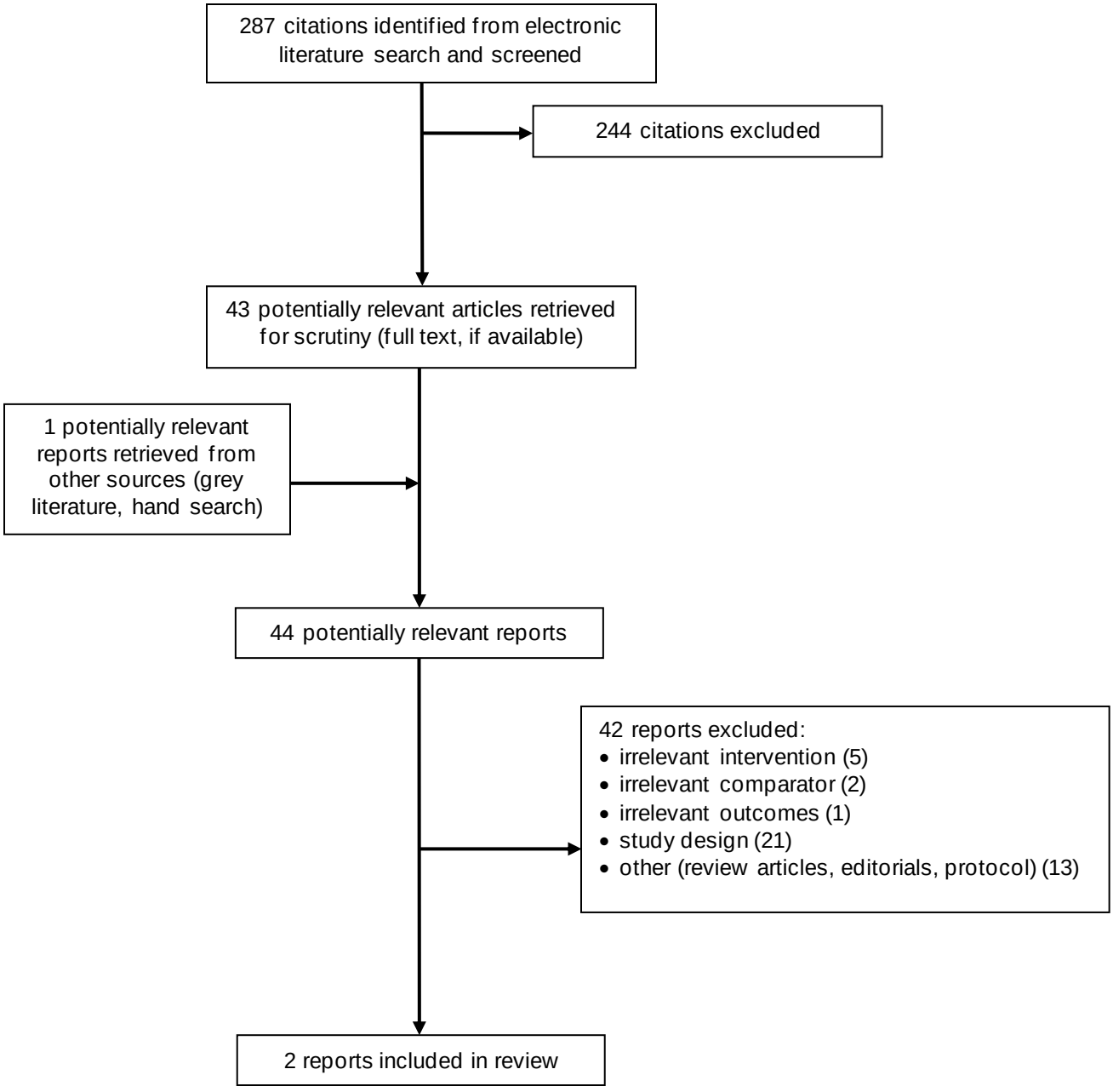
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Cao et al. (2020)[14] China **Funding**: Major Projects of National Science and Technology on New Drug Creation and Development; the Chinese Academy of Medical Sciences Emergency Project of COVID-19; and a National Science Grant for Distinguished Young Scholars	RCT, open-label trial. Intention-to-treat analysis. 1:1 randomization Randomization stratified based on the need for respiratory support at time of enrollment. LOTUS trial (Lopinavir Trial for Suppression of SARS-Cov-2) Setting: Conducted at one hospital in China between January 18 and February 3, 2020.	**Inclusion criteria**: Adults (18 or older) with COVID-19 (confirmed by positive RT-PCR specimen, pneumonia by chest imaging, oxygen saturation ≤ 94%) **Excludes**: People with allergies to LPVR, severe liver disease, use of contraindicated medications, pregnancy or breastfeeding, HIV infection **Number of patients**: LPVR, n = 99 (includes 5 who did not receive LPVR) Control, n = 100 **Median age (IQR):** 58 (49 to 68) **Days between symptom onset and treatment, median (IQR):** 13 (11 to 16)	**Intervention**: LPVR (400 mg lopinavir, 100 mg ritonavir; orally) twice daily plus standard care **Comparator**: Standard of care alone. **Length of treatment**: 14 days Standard care included: oxygen support, ventilation (invasive or noninvasive), antibiotics, vasopressors, and renal replacement therapy (as needed)	**Primary outcome**: time to clinical improvement (i.e., time from randomization to an improvement of 2 points on a 7 category ordinal scale, or time to discharge, whichever comes first). **Secondary outcomes**: - clinical status on days 7 and 14 - mortality on day 28 - duration of mechanical ventilation - length of stay - time from treatment initiation to death - viral load - adverse events **Follow-up**: 28 days
Li et al. (2020)[15] China **Funding**: Chinese 13th Five-Year National Science and technology major project and Infectious Disease Specialty of Guangzhou High-level Clinical Key Specialty	RCT, 3 arm trial 2:2:1 randomization (LPVR: arbidol: standard care) ELACOI trial (Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection) Setting: conducted at a single hospital in China from February 1 to March 28, 2020	**Inclusion criteria:** Adults 18 to 80 years, with COVID-19 (confirmed by RT-PCR), mild or moderate clinical status, and creatinine, eGFR, AST, ALT, and TBIL within specific ranges. **Excludes:** allergic to LPVR or arbidol, severe gastrointestinal symptoms that affect absorption, serious underlying conditions (e.g., heart, lung, liver, or kidney disease), pregnant or breastfeeding. **Number of patients:** LPVR, n = 34 Arbidol, n = 35 Standard care, n = 17 **Mean age (range)**: 49.4 (19 to 79)	**Intervention**: LVPR (200 mg lopinavir boosted by 50 mg ritonavir; two tablets each) orally, twice daily, plus standard care **Comparators**: 1. Arbidol: 200mg, orally, three times daily, plus standard care 2. Control: no antiviral plus standard of care **Length of treatment**: 7 to 14 days Standard care included: supportive	**Primary outcome**: rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid at day 21 **Secondary outcomes**: - rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid at day 14 - reduction of fever (i.e., temperature ≤ 37.3 ° C for > 72 hours since treatment initiation) - rate of cough alleviation - improvement in chest CT at days 7 and 14 - deterioration rate of clinical status (from mild/moderate to severe/critical) - adverse events

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Days between symptom onset and treatment, median (IQR): LPVR:3.5 (2 to 6) Arbidol: 6 (2 to 8) Standard care: 5 (2 to 8)	care and oxygen therapy	**Follow-up**: up to 21 days

ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = coronavirus disease; eGFR = creatinine clearance rate; IQR = interquartile range; LPVR = lopinavir/ ritonavir; RCT = randomized controlled trial; RT-PCR = reverse-transcriptase–polymerase-chain-reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TBIL = total bilirubin.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[12]

Strengths	Limitations
Cao et al. (2020)[14]	
• Detailed descriptions of the objection, primary and secondary outcomes, and eligibility criteria were provided • Intervention was well described, including the dose of LPVR, and a description of the treatment components included in 'standard of care' was provided, including a breakdown of how many patients received each component • All patients recruited from the same hospital over the same period of time • Baseline demographic and clinical characteristics of both groups provided • Outcome data was clearly reported, including adverse events • 95% confidence intervals were reported for primary and secondary outcomes • An actual probability value (P value) was reported for the primary outcome; P values not reported for secondary outcomes (as the statistical plan did not adjust for multiplicity) • No patients were lost to follow up • Transparent and appropriate statistical methods were followed • Appropriate methods for randomization and allocation concealment were used to reduce bias • All authors declared no conflicts of interest, and the sources of funding were reported	• Two patients did not receive the intervention due to refusal of the physician to prescribe it • Patients were not blinded to the intervention, but unlikely that this would have influenced the outcomes • Unclear whether those measuring the main outcomes were blinded, and unclear whether this would have influenced the primary outcome (i.e., time to clinical improvement) • Statistical methods did not adjust for multiplicity, but the authors acknowledge this, and only report a P value for the primary outcome, and state that the 95% confidence intervals of the should be interpreted with caution • Unclear whether study was sufficiently powered; study exceeded the sample size as the authors determined the study to be underpowered, but do not report whether final sample size was sufficient
Li et al. (2020)[15]	
• Detailed descriptions of the objective and eligibility criteria were provided • Primary and secondary outcomes were listed in the methods • All patients recruited from the same hospital over the same period of time • Baseline clinical characteristics for all 3 groups described • Simple outcome data was reported for the secondary outcomes • Adverse events were reported appropriately • No patients were lost to follow up • Actual probability values (P values) were reported • Patients were blinded to the intervention • Team members reviewing the data and radiological images were blinded to the intervention • All patients received the allocated intervention • Appropriate methods for randomization and allocation concealment were used to reduce bias	• Supportive care was not fully described, and the details of the supportive care provided to the 3 groups of patients was not reported • The definitions for some of the outcomes were unclear • Reporting of the primary outcome was not clear. A graph was presented, but not accompanying numbers or results of a statistical test • Some outcomes were reported at timepoints not listed in the methods • Unclear whether appropriate statistical tests were • Statistical analysis did not adjust for multiplicity, and there may be a risk of false positive results due to conducting multiple statistical tests • Study did not reach its estimated sample size and may not have been adequately powered to detect differences between groups

Strengths	Limitations
• All authors declared no conflicts of interest, and the sources of funding were reported	

LPVR = lopinavir/ritonavir;

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings Included Randomized Controlled Trials

Main Study Findings	Authors' Conclusion
Cao et al. (2020)[14]	
Time to clinical improvement: LPVR vs. standard of care HR = 1.31, 95% CI, 0.95 to 1.31, P = 0.09 **Mortality, at day 28**: LPVR (19.2%) vs. standard of care (25.0%) Difference: –5.8%, 95% CI, –17.3 to 5.7 **Improvement in Clinical Status, day 7:** LPVR (6.1%) vs. standard of care (2.0%) Difference: 4.1%, 95% CI, –1.4 to 9.5 **Improvement in Clinical Status, day 14**: LPVR (45.5%) vs. standard of care (30.0%) Difference: 15.5%, 95% CI, 2.2 to 28.8 **ICU length of stay, days, median**: LPVR (6) vs. standard of care (11) Median difference: –5 days, 95% CI, –9 to 0 **Duration of mechanical ventilation, days, median**: LPVR (4) vs. standard of care (5) Median difference: –1 day, 95% CI, –4 to 2 **Time from randomization to discharge, days**: LPVR (12) vs. standard of care (14) Difference: 1 day, 95% CI, 0 to 3 **Time from randomization to death, days**: LPVR (9) vs. standard of care (12) Difference: –3 days, 95% CI, –6 to 2 **Viral load, patients with detectable viral RNA (%)**: Day 14: LPVR (55.2%) vs. standard of care (57.1%) Day 28: LPVR (60.3%) vs. standard of care (58.6%) **Adverse events, n (%)**: Any adverse event: LPVR, 46 (48.4) vs. standard of care 49 (49.5) Any serious adverse event: LPVR, 19 (20.0) vs. standard of care, 32 (32.3)	"This randomized trial found that lopinavir–ritonavir treatment added to standard supportive care was not associated with clinical improvement or mortality in seriously ill patients with COVID-19 different from that associated with standard care alone." (p. 8) "The question of whether earlier lopinavir–ritonavir treatment in COVID-19 could have clinical benefit is an important one that requires further study." (p. 8) "We did not find that adding lopinavir–ritonavir treatment reduced viral RNA loads or duration of viral RNA detectability as compared with standard supportive care alone" (p. 8) "In conclusion, we found that lopinavir–ritonavir treatment did not significantly accelerate clinical improvement, reduce mortality, or diminish throat viral RNA detectability in patients with serious COVID-19." (p.10)
Li et al. (2020)[15]	
Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid, %: Day 7: LPVR (35.5) vs. Arbidol (37.1) vs. Standard care (41.2), P = 0.966 Day 14: LPVR (85.3) vs. Arbidol (91.4) vs. Standard care (76.5), P = 0.352	"The results showed that LPVR and arbidol did not shorten the time of positive-to-negative conversion of COVID-19 nucleic acid in respiratory specimens (9.0 versus 9.1 versus 9.3 days), and they did not improve the symptoms of COVID-19 or pneumonia on lung CT imaging at 7 days and 14 days. Moreover, more patients treated with LPVR progressed from mild/moderate to

Main Study Findings	Authors' Conclusion
Day 21: no statistical difference in cumulative incidence of conversions (reported in a figure only) **Days for positive-to-negative conversion of SARS-CoV-2 nucleic acid, mean (SD)**: LPVR, 9.0 (5.0) vs. Arbidol, 9.1 (4.4) vs. Standard care, 9.3 (5.2), P = 0.981 **Reduction of fever, %**: Day 7: LPVR (74.1) vs. Arbidol (81.8) vs. Standard care (88.9), P = 0.579 Day 14: LPVR (88.9) vs. Arbidol (95.5) vs. Standard care (100), P = 0.343 **Rate of cough alleviation, %**: Day 7: LPVR (42.9) vs. Arbidol (28.0) vs. Standard care (22.2), P = 0.432 Day 14: LPVR (76.2) vs. Arbidol (56.0) vs. Standard care (44.4), P = 0.180 **Rate of improvement in chest CT, %:** Day 7: LPVR (39.3) vs. Arbidol (39.4) vs. Standard care (42.9), P = 0.971 Day 14: LPVR (75.0) vs. Arbidol (69.7) vs. Standard care (92.9), P = 0.089 **Deterioration of clinical status from mild/ moderate to severe/ critical status, n (%)**: Day 7: LPVR, 8 (23.5) vs. Arbidol, 3 (8.6) vs. Standard care, 2 (11.8), P = 0.206 **Adverse events, n (%)** Any adverse event: LPVR, 12 (35.3) vs. Arbidol, 5 (14.3) vs. Standard care 0 (0) Serious adverse events: LPVR = 1	severe/ critical status than patients from the other two groups" (p. 7) "In conclusion, our study found that LPVR or arbidol monotherapy presents little benefit for improving the clinical outcome of hospitalized patients with mild/moderate COVID-19 beyond symptomatic and supportive care, causing instead more adverse events." (p. 8)

CI = confidence interval; COVID-19 = coronavirus disease; LPVR = lopinavir/ ritonavir; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation.

Appendix 5: Additional References of Potential Interest

Systematic Reviews

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Ongoing Work – Randomized Controlled Trials

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NCT04328285. Chemoprophylaxis of SARS-CoV-2 infection (COVID-19) in exposed healthcare workers (COVIDAXIS). Centre Hospitalier Universitaire de Saint Etienne; June 2020.
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