ORIGINAL RESEARCH ARTICLE

Lopinavir-Ritonavir in the Treatment of COVID-19: A Dynamic Systematic Benefit-Risk Assessment

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Abstract

Introduction and Objective COVID-19 is an ongoing, global public health crisis for which safe and effective treatments need to be identified. The benefit-risk balance for the use of lopinavir-ritonavir in COVID-19 needs to be monitored on an ongoing basis, therefore a systematic benefit-risk assessment was designed and conducted. A key objective of this study was to provide a platform for a dynamic systematic benefit-risk evaluation; although initially this evaluation is likely to contain limited information, it is required because of the urgent unmet public need. Importantly, it allows additional data to be incorporated as they become available, and re-evaluation of the benefit-risk profile.

Methods A systematic benefit-risk assessment was conducted using the Benefit-Risk Action Team (BRAT) framework. The exposure of interest was lopinavir-ritonavir treatment in severe COVID-19 compared to standard of care, placebo or other treatments. A literature search was conducted in PubMed and Embase to identify peer-reviewed papers reporting clinical outcomes. Two clinicians constructed a value tree and ranked key benefits and risks in order of considered clinical importance.

Results We screened 143 papers from PubMed and 264 papers from Embase for lopinavir-ritonavir; seven papers were included in the final benefit-risk assessment. In comparison to standard of care, data for several key benefits and risks were identified for lopinavir-ritonavir. Time to clinical improvement was not significantly different for lopinavir-ritonavir in comparison to standard of care (hazard ratio 1.31, 95% confidence interval 0.95–1.80). From one study, there were fewer cases of acute respiratory distress syndrome with lopinavir-ritonavir compared with standard of care (13% vs 27%). There also appeared to be fewer serious adverse events with lopinavir-ritonavir (20%) vs standard of care (32%). Limited data were available for comparison of lopinavir-ritonavir to other treatments.

Conclusions Based on currently available data, there was no clear benefit for the use of lopinavir-ritonavir compared to standard of care in severe COVID-19. Risk data suggested a possible decrease in serious adverse events. There was a reduction in acute respiratory distress syndrome with lopinavir-ritonavir in one study. Overall, the benefit-risk profile for lopinavir-ritonavir in severe COVID-19 cannot be considered positive until further efficacy and effectiveness data become available.

Key Points

COVID-19 is a global pandemic, for which lopinavir-ritonavir has been proposed as a possible treatment.

Based on currently available data, there is no clear benefit for the use of lopinavir-ritonavir compared to standard of care in severe COVID-19.

Ongoing clinical trial data can be incorporated into the framework when available to provide an updated benefit-risk assessment.

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1 Introduction

Coronaviruses have circulated in human and animal populations for many years and in humans they are a cause of respiratory tract infections [1]. More recently, severe acute respiratory syndrome coronavirus 2 emerged in Wuhan, China in December 2019 [2, 3]. Severe acute respiratory syndrome coronavirus 2 causes coronavirus disease (COVID-19) and this outbreak was declared a global pandemic by the World Health Organization in March 2020 [4]. Fever, cough and shortness of breath are the main reported symptoms of COVID-19 [5] but this disease also has a concerning case mortality rate among certain populations, such as older adults and those with underlying health conditions.

In the current COVID-19 pandemic, there is a need to identify effective safe treatments as rapidly as possible. Lopinavir-ritonavir (LPVr) is a combination protease inhibitor and nucleoside analogue used for the treatment of human immunodeficiency virus (HIV) type 1 [6]. The use of LPVr in severe acute respiratory syndrome has been examined previously and indicated a favourable clinical response, with a decreased incidence of adverse clinical outcomes at day 21, reduced viral load at 48 h, decreased steroid use and reduced incidence of nosocomial infections [7]. For this reason, multiple trials in COVID-19 are currently being conducted to determine if LPVr is an effective treatment, including the worldwide RECOVERY trial and the World Health Organization's SOLIDARITY trial [8–10]. It is essential to examine the benefit-risk profile of all medications, but ongoing monitoring is especially important where treatments may be used with limited evidence in new indications. Lopinavir-ritonavir is already being used as a standard treatment for COVID-19 in some countries. Systematic reviews have been conducted to examine the efficacy of LPVr in the treatment of COVID-19, though not all of these have been peer reviewed to date [11]; so far these have concluded that there is a lack of evidence of efficacy [11, 12]. However, a systematic benefit-risk assessment on the use of LPVr for COVID-19 treatment, based on currently available evidence, has not yet been conducted.

The Benefit-Risk Action Team (BRAT) uses a structured descriptive framework to outline the key benefits and risks of a medication within a defined disease context. If sufficient relevant data are available, an additional quantitative assessment can be used to further examine the benefit-risk profile [13]. The BRAT was also designed to assist communication with regulatory authorities [14]. The framework design allows for transparency in the decision-making process and assumptions can be explored further by sensitivity analyses using quantitative methods [15].

This dynamic approach to a benefit-risk assessment of potential treatments for COVID-19 has been previously applied to the anti-viral agent remdesivir [16].

The systematic benefit-risk assessment for LPVr was conducted based on publicly available data to 13 May, 2020. Because of continuous emerging data on the use of LPVr in COVID-19, the framework can be subsequently used to repeat the assessment as further data arise, allowing for rapid and dynamic evidence-based decision making as more relevant data become available. This assessment was conducted to aid clinicians and public health and regulatory authorities in the decision-making process on treatments for COVID-19.

2 Objectives

This study aimed to examine the benefit-risk profile of LPVr in patients with COVID-19 compared to standard of care, placebo or other treatments. A key objective of this study was to provide a platform for a dynamic systematic benefit-risk evaluation; although initially this evaluation is likely to contain limited information, it is required because of the urgent unmet public need. Importantly, it allows additional data to be incorporated as they become available, and re-evaluation of the benefit-risk profile.

3 Methods

3.1 Benefit-Risk Framework

The BRAT framework was used to assess the overall benefit-risk of using LPVr as a treatment for COVID-19 compared to standard of care, placebo or other treatments. The BRAT uses a six-step iterative process to support the decision and communication of a benefit-risk assessment: define decision context, identify outcomes, identify data sources, customise framework, assess outcome importance, and display and interpret key benefit-risk metrics [17]. Three settings of interest for use of COVID-19 treatments were identified; treatment for severe disease, treatment of mild disease in the community and prevention in healthcare professionals exposed to the virus. This assessment focuses on LPVr for the treatment of severe COVID-19 disease, which we defined as hospitalisation as a result of COVID-19 infection.

3.1.1 Population of Interest

Patients with COVID-19 who were treated with LPVr were the population of interest, while patients receiving standard of care, placebo or other treatments were the comparators of interest. Where standard of care was reported as the comparator group, this refers to no use of a specific pharmaceutical

treatment for COVID-19 but provision of standard supportive therapy within the hospital setting.

3.1.2 Outcomes of Interest

All potential benefits and risks related to LPVr were initially identified, regardless of their importance. Key benefits and risks were selected by clinician judgement, i.e. those considered to be of clinical importance or potentially serious, and included in the value tree, which provides a visual representation of these outcomes in the context of severe COVID-19 disease. These benefits and risks displayed in the value tree were ranked according to perceived importance (benefits) and potential seriousness (risks). Two clinicians performed this ranking after discussion of the importance of each benefit and risk. Risks were categorised according to which system organ class (SOC) they belonged to, and where multiple events were identified within the same SOC, the ranking was based on the most serious event(s) within that SOC, with the most serious event(s) in each SOC presented first.

3.1.3 Data Sources and Customisation of the Framework

A literature search was performed in PubMed and Embase using the following search strategy: (lopinavir AND ritonavir) AND (covid* OR SARS-CoV-2 OR n?CoV OR coronavirus). Two reviewers examined articles for eligibility and a third clinical reviewer made the final decision on inclusion. Papers were included in the data extraction tables if they reported quantitative data on effectiveness and/or safety of LPVr in patients with severe COVID-19. Case reports and case series were excluded from the data extraction tables, but were considered for construction of the value tree. Results were restricted to English language only (abstracts in English language were acceptable where sufficient data provided) and peer-reviewed publications from 2019 to 13 May, 2020. Data were extracted for each benefit and risk, for LPVr and the comparator (standard of care, placebo or other treatments), where available. EudraVigilance spontaneous reporting data (up to 8 May, 2020) for LPVr where used in COVID-19 were also examined. EudraVigilance data were examined because of the usefulness of identifying real-world reports of adverse events outside of the clinical trial setting and because the publicly available version of this specific data source is frequently updated. After data extraction, a second reviewer performed a quality-control check on the extracted data.

3.2 Outcome Assessment

Key benefits and risks associated with the use of LPVr were identified for inclusion in the value tree from available data sources, including the product information, regulatory assessment reports and published literature. Predicted key benefits (clinical endpoints) were derived from both the published literature and in the case of ongoing studies, available clinical trial protocols. These benefits and risks, as presented in the value tree, were derived from both qualitative and quantitative data. A summary benefit-risk table was created to allow visualisation of the magnitude of each benefit and risk. Risk differences and corresponding 95% confidence intervals (CIs) were calculated for each outcome where both numerator (number of events) and denominator (number of patients at risk) were available for both the treatment group (LPVr) and comparator group. No appropriate comparator groups were identified for LPVr within EudraVigilance owing to the recent nature of the pandemic and the lack of treatments made available for COVID-19 outside of the clinical trial setting. As such, adverse events reported for a comparison treatment in EudraVigilance were not available. Consequently, spontaneous reports are not included in the benefit-risk table and are presented in the text only.

Given the limited data at this point in time, further quantitative assessment was not considered appropriate. However, such methods can be used to account for both the importance of outcomes and the size of the study from which data were extracted by weighting outcomes. In anticipation of using further quantitative methods in the future when further data are made available, we have ranked the outcomes in the value tree by considered clinical importance.

4 Results

Figure 1 displays the value tree of the key benefits and risks related to LPVr treatment in COVID-19, which was constructed using a wide variety of data sources.

4.1 Benefits

Key benefits have been listed in the value tree in descending order of perceived clinical importance. At the current time, only one clinical trial was identified that provided empirical data for any of the clinical endpoints listed in the value tree [18]. Whilst the primary objective of this clinical trial was time to clinical improvement, additional data were provided for various endpoints including mortality risk, risk and duration of invasive mechanical ventilation, risk of non-invasive ventilation and oxygen requirement.

4.2 Risks

Key risks were identified for LPVr based on the current available evidence. It is acknowledged that this product is not licenced for use in the treatment of COVID-19 disease, and whilst safety data are available for its licenced use in
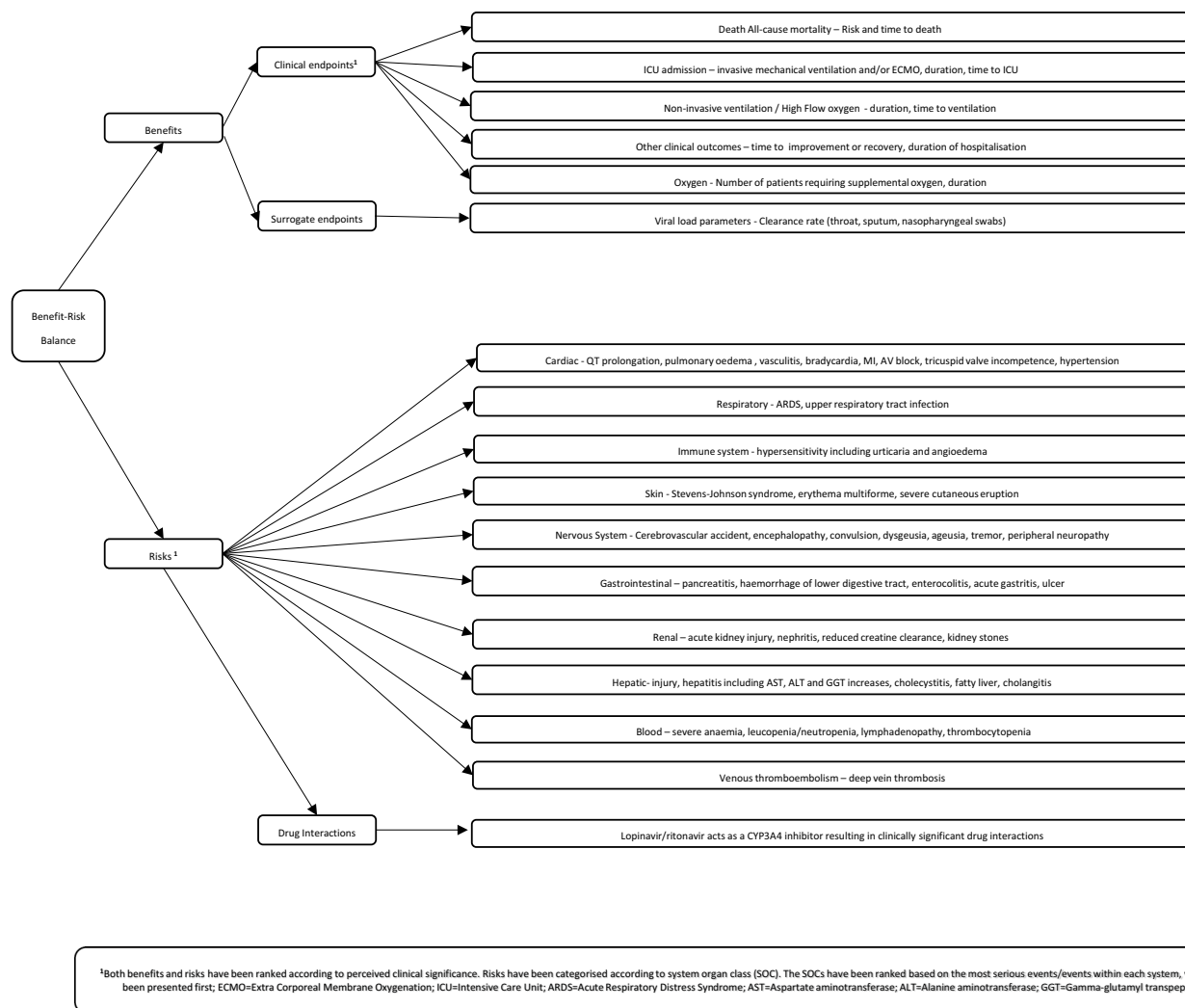
Fig. 1 Value tree of key benefits and risks identified for lopinavir/ritonavir, ranked by order of clinical significance. Superscript 1: both benefits and risks have been ranked according to perceived clinical significance. Risks have been categorised according to system organ class. The system organ classes have been ranked based on the most serious events/events within each system, which have been presented first. *ALT* alanine aminotransferase, *ARDS* acute respiratory distress syndrome, *AST* aspartate aminotransferase, *CYP* cytochrome P450, *ECMO* extracorporeal membrane oxygenation, *GGT* gamma-glutamyl transpeptidase, *ICU* intensive care unit, *MI* myocardial infarction

HIV type 1, its safety profile in the context of COVID-19 is largely unknown. Furthermore, for the limited safety data that are available for its use in COVID-19, it is often unclear whether the reported adverse event is due to the use of LPVr, or attributable to the underlying disease. Potentially serious risks that are likely to still pose a risk with the proposed short-term use of LPVr for COVID-19 have been summarised in the value tree and ranked according to perceived seriousness.

One of the most serious risks is prolongation of the QT interval, and the subsequent increased risk of sudden cardiac death [19–22]. Patients with COVID-19 are already predisposed to the development of cardiac arrhythmia owing to the effect of the virus on metabolic dysfunction, myocardial inflammation and the sympathetic nervous system

[20]. Additionally, it is important to note that LPVr is an inhibitor of cytochrome P450 3A4, and therefore it cannot be used with other medicines that are substrates of this enzyme, such as chloroquine, which itself can cause QT prolongation [21]. In addition to the effects on QT prolongation, LPVr has also been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects, with rare reports of second- or third-degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir), and therefore LPVr should be used with caution [23] in such patients.

Lopinavir/ritonavir are both inhibitors of the cytochrome P450 3A isoform, and therefore treatment is likely to

increase plasma concentrations of concomitant medicinal products that are primarily metabolised by cytochrome P450 3A [23]. Clinically significant drug interactions have been observed with LPVr use during treatment for COVID-19, including increased plasma concentrations of direct oral anticoagulants [24], and increased plasma concentrations of immunosuppressants in organ transplant recipients [25].

Certain risks factors and clinical characteristics have been associated with the development of acute respiratory distress syndrome (ARDS) amongst patients with COVID-19 [26]. Patients who developed COVID-19-related ARDS were likely to require admission to the intensive care unit. In the study by Cao et al., respiratory failure/ARDS was reported as a serious adverse event in both treatment groups [18]. Whilst causality in these cases is not known, it would seem likely that these cases were attributable to progression of the underlying COVID-19 disease.

Hypersensitivity reactions such as urticaria and angioedema are reported to occur commonly with the use of LPVr for the treatment of HIV, and rarely serious skin reactions such as Stevens–Johnson syndrome and erythema multiforme have been reported with its use in this treatment population [23]. Gastrointestinal side effects of LPVr are well recognised, and diarrhoea and nausea are very common. Serious gastrointestinal adverse effects included in the key risks for this assessment include pancreatitis, which has been associated with the use of LPVr [7, 23, 27]; most patients who developed pancreatitis during treatment for HIV had a prior history of this condition. Treatment with LPVr has been associated with an increase in triglycerides in patients treated for HIV [23], and amongst patients treated for COVID-19 [28–31], which is likely to be another contributory factor in the development of pancreatitis.

In the context of treatment for HIV, LPVr has been uncommonly associated with certain adverse renal outcomes, including a reduction in creatine clearance, nephritis and haematuria [23]. Cases of acute kidney injury have been reported in patients taking LPVr in COVID-19; however, it is unclear whether there is any association, as this outcome was reported more frequently amongst patients in the standard of care comparator group [18] in addition to overall limited safety data availability. Elevations of liver enzymes have also been commonly reported with the use of LPVr in the treatment of HIV [23], and liver injury has been reported in patients treated with LPVr for COVID-19 [32, 33]. Blood dyscrasias have also been associated with the use of LPVr during HIV treatment [23], with reports of severe anaemia amongst patients treated for COVID-19 [18].

4.3 Quantitative Data

Data for outcomes are presented in the data extraction table and key benefit-risk summary table (Tables 1 and 2,

respectively). From literature searching, we identified 143 papers from PubMed and 264 papers from Embase for LPVr. All papers were reviewed for information on the benefits and risks relating to LPVr, including both quantitative and qualitative data. After initial review and removal of duplicates, 43 papers were identified with information on safety of LPVr and 15 papers with efficacy information for LPVr. These papers were reviewed further to determine whether they met all inclusion criteria; seven papers were included in the final benefit-risk assessment.

In comparison to standard of care, data for several key benefits and risks for LPVr were identified. In the Cao et al. trial [18], the benefit of time to clinical improvement (intention-to-treat analysis) was not statistically significant after adjustment for other covariates in comparison to standard of care (16 vs 16 days, hazard ratio = 1.31, 95% CI 0.95–1.80). Other non-significant benefit data were identified in this trial including median duration of mechanical ventilation (risk difference = − 1 day, 95% CI − 4 to 2) and death at 28 days (risk difference = − 0.06, 95% CI − 0.17 to 0.06).

Risk data were mainly available from the Cao et al. trial, which reported fewer serious adverse events in patients taking LPVr (20%) compared to standard of care (32%). There were fewer cases of ARDS with LPVr compared to standard of care (13% vs 27%). The difference in the proportion of adverse events between groups was not tested statistically in the study and the study was also not powered to detect differences in adverse events.

Limited data were available for comparison of LPVr to other treatments. Viral clearance at day 14 for LPVr was lower compared with arbidol (85% vs 91%), and there was minimal difference in mean time to viral clearance (10.20 days vs 10.11 days, respectively). Data were only available for one risk in comparison to arbidol; a lower proportion of those patients treated with LPVr experienced increased ALT compared with arbidol (9% vs 19%, respectively).

In spontaneous reports from Eudravigilance, for LPVr used in COVID-19, there were 28 reports of hepatocellular injury, 15 reports of acute kidney injury, 17 reports of prolongation of the QT interval, six reports of ARDS and three reports of pancreatitis. Information on case reports was only available from the publicly available dataset and thus was limited; however, these data are useful in identifying real-world reports of adverse events outside of the clinical trial setting.

5 Discussion

The study aim was to examine the benefit-risk profile of LPVr in COVID-19 patients compared to standard of care, placebo or other treatments. A key objective of this study

Table 1 Data for key benefits and risks identified for lopinavir-ritonavir (L/R) from the peer-reviewed published literature

Outcome name	Study first author	Study primary outcome	Setting	L/R risk estimate	L/R number of patients	L/R number of events	Comparator type	Comparator risk estimate	Comparator number of patients	Comparator number of events	RD point estimate	RD lower 95% CI	RD upper 95% CI
Benefits													
Death at 28 days	Cao [18]	Time to clinical improvement	Hospital	0.19	99	19	Standard of care	0.25	100	25	−0.06	−0.17	0.06
Median duration of invasive mechanical ventilation (days)	Cao	Time to clinical improvement	Hospital	4	99		Standard of care	5	100		−1	−4	2
Invasive mechanical ventilation at day 14	Cao	Time to clinical improvement	Hospital	0.03	99	3	Standard of care	0.05	100	5	−0.02	−0.08[a]	0.04
Non-invasive ventilation at day 14	Cao	Time to clinical improvement	Hospital	0.05	99	5	Standard of care	0.06	100	6	−0.01	−0.07[a]	0.06
Median time to clinical improvement (days)	Cao	Time to clinical improvement	Hospital	16	99		Standard of care	16	100		0		
Clinical improvement at day 28	Cao	Time to clinical improvement	Hospital	0.79	99	78	Standard of care	0.7	100	70	0.09	−0.03	0.21
Oxygen support (days)	Cao	Time to clinical improvement	Hospital	12	99		Standard of care	13	100		0	−2	2
Supplemental oxygen at day 14	Cao	Time to clinical improvement	Hospital	0.25	99	25	Standard of care	0.2	100	20	0.05	−0.08[a]	0.18

Table 1 (continued)

Outcome name	Study first author	Study primary outcome	Setting	L/R risk estimate	L/R number of patients	L/R number of events	Comparator type	Comparator risk estimate	Comparator number of patients	Comparator number of events	RD point estimate	RD lower 95% CI	RD upper 95% CI
Viral load parameters: median time to viral clearance (days)	Cai [34]	Time to viral clearance	Hospital	11	45		Favipiravir	4	35		7.00		
Viral load parameters: viral clearance at day 14	Huang [35]	Viral clearance by day 14	Hospital	0.92	12	11	Chloroquine	1.00	10	10	−0.08	−0.91[a]	0.74
Viral load parameters: viral clearance at day 14	Li [36]	Viral clearance by day 21	Hospital	0.85	34	29	Arbidol	0.91	35	32	−0.06	−0.50[a]	0.38
Viral load parameters: viral clearance at day 14	Li	Viral clearance by day 21	Hospital	0.85	34	29	Standard of care	0.77	17	13	0.09	−0.43[a]	0.61
Viral load parameters: mean time to viral clearance (days)	Ye [37]	Time to viral clearance	Hospital	7.8	42		Standard of care	12.0	5		−4.2*		
Viral load parameters: viral detection at day 14	Zhu [38]	Not specified	Hospital	0.44	34	15	Arbidol	0.00	16	0	0.44*		

Table 1 (continued)

Outcome name	Study first author	Study primary outcome	Setting	L/R risk estimate	L/R number of patients	L/R number of events	Comparator type	Comparator risk estimate	Comparator number of patients	Comparator number of events	RD point estimate	RD lower 95% CI	RD upper 95% CI
Viral load parameters: mean time to viral clearance (days)	Wen [39]	Not specified	Hospital	10.20	59		Arbidol	10.11	36		0.09		
Viral load parameters: mean time to viral clearance (days)	Wen	Not specified	Hospital	10.20	59		Standard of care	8.44	58		1.76		
Risks													
Prolonged QT interval	Cao	Time to clinical improvement	Hospital	0.01	95	1	Standard of care	0.00	99	0	0.01	−0.01[a]	0.03
Acute heart failure	Cao	Time to clinical improvement	Hospital	0.00	95	0	Standard of care	0.01	99	1	−0.01	−0.03[a]	0.01
Acute respiratory distress syndrome	Cao	Time to clinical improvement	Hospital	0.13	95	12	Standard of care	0.27	99	27	−0.15	−0.27[a]	−0.02
Acute kidney injury	Cao	Time to clinical improvement	Hospital	0.03	95	3	Standard of care	0.06	99	6	−0.03	−0.09[a]	0.03
Liver and kidney injury	Cai	Time to viral clearance	Hospital	0.07	45	3	Favipiravir	0.03	35	1	0.04	−0.06[a]	0.13
Severe anaemia	Cao	Time to clinical improvement	Hospital	0.03	95	3	Standard of care	0.00	99	0	0.03	−0.01[a]	0.07

Table 1 (continued)

Outcome name	Study first author	Study primary outcome	Setting	L/R risk estimate	L/R number of patients	L/R number of events	Comparator type	Comparator risk estimate	Comparator number of patients	Comparator number of events	RD point estimate	RD lower 95% CI	RD upper 95% CI
Acute gastritis	Cao	Time to clinical improvement	Hospital	0.02	95	2	Standard of care	0.00	99	0	0.02	−0.01[a]	0.05
Haemorrhage lower GI tract	Cao	Time to clinical improvement	Hospital	0.02	95	2	Standard of care	0.00	99	0	0.02	−0.01[a]	0.05
Increase in ALT (<125 U/L)	Zhu	Not specified	Hospital	0.09	34	3	Arbidol	0.19	16	3	−0.10	−0.33[a]	0.14
Any serious adverse event	Cao	Time to clinical improvement	Hospital	0.20	95	19	Standard of care	0.32	99	32	−0.12	−0.27[a]	0.02

ALT alanine aminotransferase, *CI* confidence interval, *GI* gastrointestinal, *RD* risk difference

[a]95% CI calculated by authors and not provided in the original manuscript

*$p < 0.05$

Table 2 Benefit-risk summary table for key benefits and risks identified for lopinavir-ritonavir (L/R) compared to standard of care

Outcome name	L/R risk/1000 patients	Standard of care risk/1000 patients	RD (95% CI)/1000 patients	Hazard ratio (95% CI)
Benefits				
Death at 28 days	192	250	−58 (−173, 57)	
Invasive mechanical ventilation at day 14	30	50	−20 (−75, 36)[a]	
Non-invasive ventilation at day 14	51	60	−9 (−75, 56)[a]	
Time to clinical improvement				1.31 (0.95, 1.80)
Clinical improvement at day 28	788	700	88 (−33, 209)	
Supplemental oxygen at day 14	253	200	53 (−80, 185)[a]	
Viral load parameters: viral clearance at day 14	853	765	88 (−431, 607)	
Risks				
Prolonged QT interval	11	0	11 (−10, 31)[a]	
Acute heart failure	0	10	−10 (−30, 10)[a]	
Acute respiratory distress syndrome	126	273	−147 (−272, −21)	
Acute kidney injury	32	61	−29 (−89, 31)[a]	
Severe anaemia	32	0	32 (−4, 67)[a]	
Acute gastritis	21	0	21 (−8, 50)[a]	
Haemorrhage lower GI tract	21	0	21 (−8, 50)[a]	
Any serious adverse event	200	323	−123 (−267, 20)[a]	

CI confidence interval, *GI* gastrointestinal, *RD* risk difference

[a]95% CI calculated by authors and not provided in the original manuscript

was to provide a platform for a dynamic systematic benefit-risk evaluation; although initially this evaluation is likely to contain limited information, it is required because of the urgent unmet public need. Importantly, it allows additional data to be incorporated as they become available, and re-evaluation of the benefit-risk profile. This paper provides a systematic benefit-risk assessment using the BRAT methodology and is inclusive of the available literature up to and including 13 May, 2020. Therefore, this represents a snapshot of the data available to date and outlines a clear and transparent framework into which subsequent clinical trial and observational study data can be incorporated, and the benefit-risk profile re-assessed.

At the current time, data relating to the benefits of LPVr are limited, with efficacy data for clinical endpoints available from only one published clinical trial. This trial found no statistically significant difference in the primary outcome of time to improvement (intention-to-treat analysis) between the two groups (LPVr treatment in addition to standard supportive care vs standard care alone); however, the sample size was small. There was some evidence (though not statistically significant) that LPVr reduced mortality at 28 days (95% CI 19.2% vs 25.0%), difference of -5.8% (95% CI -17.3 to 5.7). It is of note that the median time interval between symptom onset and randomisation was 13 days (interquartile range, 11–16 days), therefore it is unknown whether more favourable results may have been seen if drug treatment had been initiated earlier in the course of the disease.

The safety profile of LPVr in the treatment of severe COVID-19 disease is largely unknown. We identified key risks from its usage in the treatment of HIV, in addition to the limited safety data available from its use in COVID-19. Comparator safety data revealed a lower incidence of all serious adverse events amongst patients receiving LPVr compared with standard of care (risk difference − 123 events per 1000 patients). Very small numbers of cases of some adverse events were reported in the study by Cao et al., including severe anaemia, acute gastritis and lower gastrointestinal bleeding, all of which were only reported amongst patients taking LPVr. The incidence of acute kidney injury was lower in the Cao et al. trial amongst patients taking LPVr compared with standard of care (3% vs 6%). The incidence of ARDS was also observed to be lower in patients using LPVr compared with standard of care (13% vs 27%). It is acknowledged that ARDS is a known outcome in COVID-19 and thus a reduction in risk could potentially be considered a benefit of LPVr treatment. Acute respiratory distress syndrome is included as a risk in the current value tree because it was considered an adverse event in all trials examined; however, the benefit-risk assessment may be updated if sufficient evidence becomes available to suggest it should be considered a benefit instead. Consequently, the incidence of ARDS with LPVr in COVID-19 should be intensively monitored as further data are made available to determine if this could potentially be a benefit of treatment.

Overall, there was a lack of efficacy data with no clear benefits identified for LPVr treatment compared with standard of care. Risk data, although limited, suggested a possible decrease in adverse events for some serious outcomes compared to standard of care. Further data are needed on the efficacy and effectiveness of LPVr for severe COVID-19. An update to this dynamic benefit-risk assessment will be published when sufficient data are made available from further peer-reviewed studies that impact significantly on the benefit-risk of LPVr.

5.1 Strengths and Limitations

A strength of this approach is the inclusion of all key benefits and risks in the same model and a transparent framework into which further data can be included as and when these become available. The method has a significant advantage compared with systematic reviews, which are equally comprehensive but focus only on efficacy or safety, rather than considering both together. When sufficient data are available, the methodology allows benefits and risks to be ranked, and weightings applied based on this ranking, with further quantitative analysis. The reproducibility of this assessment allows multiple treatments to be assessed using this approach, thereby allowing direct comparison between different treatments. This is of great significance during the current COVID-19 crisis, in which several potential interventions currently under evaluation need to be assessed and evaluated in real time, and where new data need to be incorporated quickly. Regulatory decision makers are also familiar with this framework, facilitating interpretation.

A limitation of the benefit-risk assessment presented at this time is the relative paucity of data that has been included in the model, as many clinical trials assessing LPVr are still ongoing. In addition, trials for which data were available had very small sample sizes and were likely to be underpowered when examining non-primary outcomes. Causality cannot be confirmed for many outcomes at this point in time but in general there is a need for further data regarding outcomes in COVID-19. It is anticipated that such data will become available in due course and allow us to comment further on the causal association between LPVr and outcomes included in the value tree. The dynamic nature of this benefit-risk assessment allows further updates in the future if sufficient data are made available to significantly impact the conclusion of the benefit-risk assessment.

Study quality was not considered in the assessment, although we only included peer-reviewed articles. The importance of each benefit and risk was assessed by two physicians and ranked accordingly based on their clinical judgement. Because of the dynamic nature of the benefit-risk assessment, other experts could be engaged in the future to reassess the importance of the benefits and risks and revise

the value tree. Outcomes displayed in the value tree were identified from a variety of sources and may therefore be related to different underlying diseases with different management including potentially different doses of LPVr. Efficacy outcomes could also be dependent on the time of administration of LPVr. Further, while we defined standard of care as no use of a specific pharmaceutical treatment for COVID-19 but provision of standard supportive therapy within the hospital setting, we acknowledge that standard of care may vary by setting and country.

6 Conclusions

Based on currently available data, there was no clear benefit for use of LPVr compared to standard of care in severe COVID-19. Risk data suggested a possible decrease in serious adverse events. There was a reduction in ARDS with LPVr in one study. Overall, the benefit-risk profile for LPVr in severe COVID-19 cannot be considered positive until further efficacy and effectiveness data become available.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability (software application or custom code) Not applicable.

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