Appendix 3: Included, excluded and ongoing studies - Lopinavir/ritonavir for COVID-19: A living systematic review

Included randomised trials

LOTUS China (1,2)	Details or comments
REFERENCES Chen et al (1) ChiCTR2000029387 (2)	**Publication thread for LOTUS China** Epistemonikos Type: Journal article Epistemonikos | DOI Type:Trial registry (Chinese Clinical Trial Registry) Epistemonikos | DOI (not available)
STUDY DESIGN ☑Randomised trial ☐Comparative, non-randomised ☐Non-comparative study	QUOTE: Single centre , open-label, individually randomized, controlled trial; Eligible patients were randomly assigned in a 1:1 ratio; To balance the distribution of oxygen support between the two groups as an indicator of severity of respiratory failure, randomization was stratified on the basis of respiratory support methods at the time of enrollment: no oxygen support or oxygen support with nasal duct or mask, or high-flow oxygen, noninvasive ventilation, or invasive ventilation including ECMO. The permuted block (four patients per block) randomization sequence, including stratification, was prepared by a statistician not involved in the trial, using SAS software, version 9.4 (SAS Institute).
POPULATION: INCLUSION CRITERIA ☐COVID-19 ☑COVID-19 pneumonia ☐Severe COVID-19 pneumonia	QUOTE: Patients were assessed for eligibility on the basis of a positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay) for SARS-CoV-2 in a respiratory tract sample Male and nonpregnant female patients 18 years of age or older were eligible if they had a diagnostic specimen that was positive on RT-PCR, had pneumonia confirmed by chest imaging, had an oxygen saturation of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen to the fraction

	of inspired oxygen at or below 300 mg Hg.
INTERVENTION ☑Lopinavir/ritonavir ☐lopinavir	QUOTE: ...to receive either lopinavir–ritonavir (400 mg and 100 mg, orally; freely provided by the national health authority) twice daily, plus standard care, or standard care alone, for 14 days
COMPARISON ☐Placebo (plus standard care) ☑No treatment (standard care)	Standard care comprised supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and ECMO for 14 days.
OUTCOMES ☑All-cause mortality ☑Mechanical ventilation ☑Extracorporeal membrane oxygenation ☑Length of hospital stay ☑Respiratory failure ☑Serious adverse events ☐Time to SARS-CoV-2 RT-PCR negativity ☑Acute respiratory distress syndrome ☑Total adverse events	All-cause mortality: Quote: This outcome was measured at 7, 14 and 28 days of follow-up. In this study, 3 patients assigned to receive lopinavir–ritonavir died within 24 hours of randomization and did not receive lopinavir/ritonavir. However, we included these events in the intervention group (intention-to treat-analysis). Mechanical ventilation: This outcome was measured at 28 days of follow-up. One patient received ECMO or invasive mechanical ventilation at the enrollment. This event was not considered in the analysis. Extracorporeal membrane oxygenation: This outcome was measured at 28 days of follow-up. One patient received ECMO or invasive mechanical ventilation at the enrollment. This event was not considered in the analysis. Length of hospital stay: This outcome was measured at 28 days of follow-up. Respiratory failure: This outcome was measured combined with ARDS after randomization through day 28 (longer follow-up). Serious adverse events: This outcome included: Respiratory failure or ARDS, acute kidney injury, secondary infection, shock, severe anemia, acute gastritis, hemorrhage of lower digestive tract, pneumothorax, unconsciousnes among others. This outcome was measured after randomization through day 28 (longer follow-up). Time to SARS-CoV-2 RT-PCR negativity: This outcome was not measured.

	Other outcomes Total adverse events: This outcome included: Lymphopenia, nausea, tthrombocytopenia, leukopenia, vomiting, increased aspartate, aminotransferase, abdominal discomfort, diarrhea, stomach ache, neutropenia among others, This outcome was measured after randomization through day 28 (longer follow-up).
RISK OF BIAS	
Risk of bias arising from the randomisation process	**Low risk for all outcomes.** Cao et al. randomisation process was stratified on the basis of respiratory support methods at the time of enrollment (no oxygen support or oxygen support with nasal duct or mask, or high-flow oxygen, noninvasive ventilation, or invasive ventilation including ECMO) and performed allocation concealment with an interactive Web-based response system until randomization was finished on the system through a computer or phone.
Risk of bias due to deviations from intended interventions	**Some concern for all outcomes** The study was not blinded to investigators or participants.
Risk of bias due to missing outcome data	**Low risk of bias** Total of 199 participants were randomised to Lopinavir/ritonavir (n = 99) or placebo (n = 100); 194 patients (97.4%) completed the study. Reasons for missing outcome data provided by study authors are unlikely to be related to true outcomes.
Risk of bias in measurement of outcomes	**Low risk of bias for some outcomes. Some concern for others.** The study was not blinded to outcome assessors. We judged risk of bias as low for the outcomes of mortality, adverse events and length of hospital stay. We judged risk of bias as 'some concern' for development of respiratory failure, acute respiratory distress syndrome and need of mechanical ventilation or ECMO, as knowledge of the assigned intervention could influence the assessments of these outcomes.

Risk of bias in selection of reported results	**Low risk of bias** All outcomes were listed as pre-planned outcomes and were analysed in accordance with a pre-specified analysis plan according to the protocol published in the Chinese clinical trial registry (ChiCTR2000029308).

ELACOI (3-5)	Details or comments
REFERENCES Li et al (3) NCT04252885 (4) Li et al, 2020 (5)	**Publication thread for ELACOI** Epistemonikos Type: Preprint article Epistemonikos | DOI:10.1101/2020.03.19.20038984 Type:Trial registry Epistemonikos | DOI (not available) Type:Journal article Epistemonikos | DOI 10.1016/j.medj.2020.04.001
STUDY DESIGN ☑Randomised trial ☐Comparative, non-randomised ☐Non-comparative study	Single-center, randomized and controlled trial. Three arms: Lopinavir/ritonavir, umifenovir, control.
POPULATION: **INCLUSION CRITERIA** ☑COVID-19 ☐COVID-19 pneumonia ☐Severe COVID-19 ☐Severe COVID-19 pneumonia	• Age between 18 and 80 years • SARS-CoV-2 infection confirmed by real-time PCR (RT-PCR) from pharyngeal swab • Mild clinical status, defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging • Lab findings: creatinine ≤110μmol/L, creatinine clearance rate (eGFR) ≥60 ml/min/1.73m2, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 × ULN, and total bilirubin (TBIL) ≤2 × ULN; 5)

POPULATION: **BASELINE CHARACTERISTICS**	**Setting:** Hospital **Mean age:** 49.4 years (includes data from umifenovir arm) **Females in study:** 52.9% **Pneumonia:** 82.4% **Time from onset:** 3.5 vs 5.0 days (LPV/control). **Comorbidities:** None of the enrolled patients had chronic lung disease, chronic kidney disease, autoimmune disease or immunodeficiency disease. Underlying chronic diseases (LPV/control): 20.6% vs 35.3%. **Laboratory findings (LPV/control):** WBC < 4,000: 23.5 vs 17.6%; >10,000 2,9 vs 0%; Lymphocyte count: <1,100 26.5 vs 23.5%; Neutrophil count: 14.7 vs 11.8%; C-reactive protein >10 mg/L 50 vs 35.3%; Procalcitonin >0.05 ng/ml 47.1 vs 29.4% **Co-interventions (LPV/control):** Gamma globulin 8.8 vs 5.9%; corticosteroids 20.6 vs 17.6%; High flow oxygen.20.6 vs 11.8%
INTERVENTION ☑Lopinavir/ritonavir ☐lopinavir	Lopinavir (200mg) boosted by ritonavir (50mg), orally administered, twice daily, 500 mg, each time for 7-14 days.
COMPARISON ☐Placebo (plus standard care) ☑No treatment (standard care)	No treatment. Standard care comprised supportive care and effective oxygen therapy if in need.
OUTCOMES ☑All-cause mortality ☑Mechanical ventilation ☑Extracorporeal membrane oxygenation ☑Length of hospital stay ☑Respiratory failure ☑Serious adverse events ☐Time to SARS-CoV-2 RT-PCR negativity ☑Acute respiratory distress syndrome ☑Total adverse events	All-cause mortality: This outcome was measured after randomization through day 21 (longer follow-up). Mechanical ventilation: This study reported that two patients required mechanical ventilation, but there is no information about the trial group that these patients were enrolled. It was not possible to extract the data. Extracorporeal membrane oxygenation: This study reported that one patient required mechanical ventilation, but there is no information about the trial group that patient was enrolled in. It was not possible to extract the data. Length of hospital stay: This outcome was not reported.

	Respiratory failure: This outcome was not reported. Serious adverse events: Any unexpected, medical occurrence resulting in death, prolonged hospitalization, persistent or significant disability or incapacity, which is judged to be causally related to the study intervention. This outcome was measured after randomization through day 21 (longer follow-up). Time to SARS-CoV-2 RT-PCR negativity: This outcome was measured at 28 days of follow-up. Other outcomes Acute respiratory distress syndrome:This outcome was not measured. Total adverse events: This outcome included: Diarrhea, nausea, loss of appetite, elevation of ALT over 2.5-fold above the normal limit. This outcome was measured after randomization through day 21 (longer follow-up).
RISK OF BIAS	
Risk of bias arising from the randomisation process	**Low risk for all outcomes.** Randomization process was computer-generated and allocation concealment was achieved using a centralized web-based randomization system. No differences were observed in baseline demographic data, clinical manifestations, clinical status or baseline laboratory test result.
Risk of bias due to deviations from intended interventions	**Some concern for all outcomes** The study was not blinded to clinicians and research staff. Also, there was no information whether deviations arose because of the trial context. Participants and researchers who reviewed the data and radiological images were blinded

Risk of bias due to missing outcome data	**Low risk of bias** All randomized patients completed the study.
Risk of bias in measurement of outcomes	**Low risk of bias for all reported outcomes.** The study was blind to participants, those physicians and radiologists who reviewed the data and radiological images, but open-label to clinicians who recruited patients and research staff. However, the outcomes "Time to SARS-CoV-2 RT-PCR negativity", all-cause mortality, and "adverse events" is unlikely to be influenced by the assigned intervention.
Risk of bias in selection of reported results	**Low risk of bias** All outcomes were listed as pre-planned outcomes and were analysed in accordance with a pre-specified analysis plan according to the protocol published in Clinical Trial Register (NCT04252885)

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Excluded studies

Study name	Reason for exclusion
Alalwan et al	Wrong study design
Bai K et al	Wrong comparison
Bartiromo M et al	Wrong study design
Cai Q et al	Wrong outcomes
Cai et al	Wrong comparison
Cheng CY et al	Wrong study design
Chong VH et al	Wrong study design
Dan Yan et al	Wrong study design
Deng L et al	Wrong comparison
Diurno F et al	Wrong study design
Fan Z et al	Wrong outcomes
Fang Zheng et al	Wrong comparison
Fernández-Ruiz M et al	Wrong study design
Gheysarzadeh A et al	Wrong study design
Ghiasvand F et al	Wrong study design

Gérard A et al	Wrong comparison
Hong KS et al	Wrong study design
Huang M et al	Wrong comparison
Huang Q et al	Wrong study design
Hung IF et al	Wrong comparison
Jiang Y et al	Wrong study design
Kato Het al	Wrong comparison
Kim UJ et al	Wrong study design
Kim Y et al	Wrong study design
Kim et al	Wrong study design
Lichao Fan et al	Wrong comparison
Lim J et al	Wrong study design
Liu F et al	Wrong study design
Liu W et al	Wrong comparison
Mohammad Ali Ashraf et al	Wrong comparison
Nakamura K et al	Wrong study design

Nham E et al	Wrong study design
Park SY et al	Wrong population
Park et al	Wrong population
Qibin Liu et al	Wrong comparison
Qiu H,et al	Wrong study design
Qiu L et al	Wrong study design
Righi Get al	Wrong study design
Robustelli et al	Wrong study design
Schoergenhofer et al	Wrong study design
Spanakis et al	Wrong study design
Sun Jet al	Wrong comparison
Sánchez-Álvarez et al	Wrong comparison
Taghizadieh et al	Wrong study design
Testa S et al	Wrong study design
WEI et al	Wrong comparison
Wan S et al	Wrong study design

Wang L et al	Wrong study design
Wang Z et al	Wrong study design
Wang et al	Wrong comparison
Xiu Lan et al	Wrong comparison
Xiufeng Jiang et al	Wrong study design
Yan Lou et al	Wrong comparison
Young B et al	Wrong study design
Yuan J et al	Wrong comparison
Zhang P et al	Wrong study design
Zhenyu Fan et al	Wrong outcomes
Zhichao Feng et al	Wrong comparison
Zhu Z et al	Wrong comparison

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