Lopinavir/Ritonavir

Section last reviewed and updated 2/16/2022

Last literature search conducted 1/31/2022

Recommendation 1 (NEW): In persons exposed to COVID-19, the IDSA guideline panel recommends against post-exposure prophylaxis with lopinavir/ritonavir. (Strong recommendation, Moderate certainty of evidence)

Recommendation 2 (NEW): Among ambulatory patients with mild-to-moderate COVID-19, the IDSA guideline panel recommends against the use of lopinavir/ritonavir. (Strong recommendation, Moderate certainty of evidence)

Recommendation 3: Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against the use of the combination lopinavir/ritonavir. (Strong recommendation, Moderate certainty of evidence)

Why is lopinavir plus ritonavir considered for treatment?

Lopinavir/ritonavir is a protease inhibitor that was U.S. Food and Drug Administration (FDA)-approved for the treatment of HIV in September 2000. Ritonavir is added to the combination as a pharmacokinetic enhancer due to its strong inhibition of cytochrome P450 3A4, a metabolic pathway for lopinavir metabolism. Lopinavir/ritonavir demonstrated in vitro inhibition of SARS-CoV-1 and MERS-CoV replication [1-3]. A trial of lopinavir/ritonavir and ribavirin *versus* historical controls in SARS-CoV-1 patients, showed a reduced rate of acute respiratory distress syndrome and mortality in those receiving lopinavir/ritonavir. This study had limitations including a control group from early in the outbreak when management strategies likely differed significantly [4]. During the MERS outbreak, case reports cited efficacy of lopinavir/ritonavir with interferon in the management of MERS patients [5, 6]. During the early phase of COVID-19, triple combination of interferon beta-1b, lopinavir/ritonavir, and ribavirin shortened the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19 in an open-label, randomized, phase II trial [7].

Summary of the evidence

One randomized controlled trial (RCT) reported on post-exposure prophylaxis with combination lopinavir/ritonavir or placebo for ambulatory persons exposed to COVID-19 [8]. During the follow up period of 21 days, the investigators reported on symptomatic SARS-CoV-2

infection (COVID) either independent of baseline PCR/serology or among those who had a negative PCR test/serology at baseline.

One RCT reported on treatment with combination lopinavir/ritonavir or placebo for ambulatory patients with mild-to-moderate COVID-19 [9]. During the follow up of 90 days, COVID-19-related hospitalizations as well as mortality were recorded.

Three RCTs reported on treatment with combination lopinavir/ritonavir or placebo for hospitalized patients with COVID-19 [10-12] (**Table 3**). The trials reported on the following outcomes: mortality, failure of clinical improvement (measured using a 7-point scale or hospital discharge), need for mechanical ventilation, and adverse events leading to treatment discontinuation.

Benefits

Among persons exposed to COVID-19, prophylactic treatment with lopinavir/ritonavir failed to show or exclude a beneficial effect on symptomatic SARS-CoV-2 infection, either independent of baseline PCR/serology or among those with a negative polymerase chain reaction (PCR) and serology at baseline (hazard ratio [HR]: 0.60; 95% confidence interval [CI]: 0.29, 1.26; moderate certainty of evidence [CoE] and HR: 0.59; 95% CI: 0.17, 2.02; moderate CoE, respectively).

Among ambulatory patients with mild-to-moderate COVID-19, lopinavir/ritonavir failed to show or excluded a beneficial effect on COVID-19-related hospitalizations or deaths (HR: 1.16; 95% CI: 0.53, 2.56; moderate CoE and HR: 1.86; 95% CI 0.17 to 20.4; low certainty evidence, respectively).

Among hospitalized patients with COVID-19, treatment with lopinavir/ritonavir failed to show or exclude a beneficial effect on mortality or need for invasive mechanical ventilation (risk ratio [RR]: 1.00; 95% CI: 0.89, 1.13; moderate CoE and RR: 1.12; 95% CI: 0.93, 1.34; low CoE). Similarly, lopinavir/ritonavir may reduce failure of clinical improvement at 14 days, but it is uncertain (RR: 0.78; 95% CI: 0.63, 0.97; very low CoE).

Harms

Prophylactic treatment of persons exposed to SARS-CoV-2 with lopinavir/ritonavir compared to placebo increases the risk of adverse events (RR: 2.74; 95% CI: 2.05, 3.66; moderate CoE). The most common adverse events were nausea/vomiting, diarrhea, abdominal pain, lack of appetite, itching and bloating.

Treatment of COVID-19 in ambulatory persons with lopinavir/ritonavir rather than placebo may increase the risk of serious adverse events (RR: 1.58; 95% CI: 0.79, 3.16; moderate CoE). RECOVERY reported 1/1588 serious adverse event due to treatment with

lopinavir/ritonavir [11]; however, nearly 14% of lopinavir/ritonavir recipients in Cao 2020 were unable to complete the full 14-day course of administration. This was due primarily to gastrointestinal adverse events, including anorexia, nausea, abdominal discomfort, or diarrhea, as well as two serious adverse events, both acute gastritis. Two recipients had self-limited skin eruptions. Such side effects, including the risks of hepatic injury, pancreatitis, more severe cutaneous eruptions, and QT prolongation, and the potential for multiple drug interactions due to CYP3A inhibition, are well documented with this drug combination. The side effect profile observed in these trials raise concerns about the use of higher or more prolonged lopinavir/ritonavir dose regimens in efforts to improve outcomes.

Other considerations

The panel determined the certainty of evidence to be moderate due to concerns with imprecision for most critical outcomes across indications. The guideline panel made a strong recommendation against treatment with the combination of lopinavir/ritonavir for post-exposure prophylaxis, and ambulatory as well as hospitalized patients with COVID-19.

Conclusions and research needs for this recommendation

The guideline panel recommends against treatment with lopinavir/ritonavir across patient groups at risk for or with COVID-19.

Table 1. GRADE evidence profile, Recommendation 1

Question: Prophylactic lopinavir/ritonavir compared to no prophylactic lopinavir/ritonavir for persons exposed to COVID-19

New evidence profile developed 2/16/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	prophylactic lopinavir/ ritonavir	no prophylactic lopinavir/ ritonavir	Relative (95% CI)	Absolute (95% CI)		
Symptomatic SARS-COV-2 infection (COVID-19) regardless of baseline PCR/serology (follow-up: 21 days)												
1[1]	randomized trials	not serious	not serious	not serious	serious [a]	none	35/209 (16.7%)	13/109 (11.9%)	**HR 0.60** (0.29 to 1.26) [b]	**46 fewer per 1,000** (from 83 fewer to 29 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Symptomatic SARS-COV-2 infection (COVID-19), negative PCR and serology at baseline (follow-up: 21 days)												
1[1]	randomized trials	not serious	not serious	not serious	serious [a]	none	8/159 (5.0%)	7/90 (7.8%)	**HR 0.59** (0.17 to 2.02)	**31 fewer per 1,000** (from 64 fewer to 73 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Adverse events (follow-up: 29 days)												
1[1]	randomized trials	serious [c]	not serious	not serious	not serious	none	175/207 (84.5%) [d]	33/107 (30.8%)	**RR 2.74** (2.05 to 3.66)	**537 more per 1,000** (from 324 more to 820 more)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that has not been peer reviewed or published.

CI: Confidence interval; **HR:** Hazard ratio; **PCR:** Polymerase chain reaction; **RR:** Risk ratio

Explanations

a. Few events, unable to exclude benefits as well as harms
b. This pre-specified primary endpoint adjusted analysis is a mixed model analysis adjusted for baseline imbalance
c. Participants not blinded to lopinavir/ritonavir
d. Two serious adverse events occurred and both judged by the author as unrelated to lopinavir/ritonavir

Reference

1. Labhardt ND, Smit M, Petignat I, et al. Post-exposure Lopinavir-Ritonavir Prophylaxis versus Surveillance for Individuals Exposed to SARS-CoV-2: The COPEP Pragmatic Open-Label, Cluster Randomized Trial. EClinicalMedicine **2021**; 42: 101188.

Table 1. GRADE evidence profile, Recommendation 2

Question: Lopinavir/ritonavir compared to no lopinavir/ritonavir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

New evidence profile developed 2/16/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	lopinavir/ ritonavir	no lopinavir/ ritonavir	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 90 days)												
1[1]	randomized trials	not serious	not serious	not serious	very serious [a]	none	2/244 (0.8%)	1/227 (0.4%)	**RR 1.86** (0.17 to 20.40)	**4 more per 1,000** (from 4 fewer to 85 more)	⨁⨁◯◯ LOW	CRITICAL
COVID-19-related hospitalizations (follow-up: 90 days)												
1[1]	randomized trials	not serious	not serious	not serious	serious [a]	none	14/244 (5.7%)	11/227 (4.8%)	**HR 1.16** (0.53 to 2.56)	**8 more per 1,000** (from 22 fewer to 71 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (follow-up: 90 days)												
1[1]	randomized trials	not serious	not serious	not serious	serious [a]	none	20/232 (8.6%)	12/220 (5.5%)	**RR 1.58** (0.79 to 3.16)	**32 more per 1,000** (from 11 fewer to 118 more)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that has not been peer reviewed or published.

CI: Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio

Explanations

a. Sparse data, few events, unable to excluded harms as well as benefits

References

1. Reis G, Moreira Silva E, Medeiros Silva DC, et al. Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial. JAMA Netw Open **2021**; 4(4): e216468.

Table 3. GRADE evidence profile, Recommendation 3

Question: Lopinavir/ritonavir compared to no lopinavir/ritonavir for hospitalized patients with severe COVID-19

Last reviewed and updated 11/22/2020

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	lopinavir/ ritonavir	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
3 [1,2,3]	randomized trials	not serious [a]	not serious	not serious	serious [b]	none	538/3111 (17.3%) [c]	938/4896 (19.2%)	**RR 1.00** (0.89 to 1.13)	**0 fewer per 1,000** (from 21 fewer to 25 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Invasive mechanical ventilation (follow up: 28 days)												
2 [1,3]	randomized trials	serious [a,d]	not serious	not serious	serious [b]	none	166/1655 (10.0%)	297/3380 (8.8%)	**RR 1.12** (0.93 to 1.34)	**11 more per 1,000** (from 6 fewer to 30 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events leading to treatment discontinuation												
1 [1]	randomized trials	serious [a]	not serious	not serious	very serious [e]	none	Nearly 14% of lopinavir–ritonavir recipients were unable to complete the full 14-day course of administration. This was due primarily to gastrointestinal adverse events, including anorexia, nausea, abdominal discomfort, or diarrhea, as well as two serious adverse events, both acute gastritis. Two recipients had self-limited skin eruptions. Such side effects, including the risks of hepatic injury, pancreatitis, more severe cutaneous eruptions, and QT prolongation, and the potential for multiple drug interactions due to CYP3A inhibition, are well documented with this drug combination. The side-effect profile observed in the current trial arouses concern about the use of higher or more prolonged lopinavir–ritonavir dose regimens in efforts to improve outcomes.				⨁◯◯◯ VERY LOW	IMPORTANT
Failure of clinical improvement at 14 days (follow up: 14 days)												
1 [1]	randomized trials	serious [a]	not serious	not serious	very serious [f]	none	54/99 (54.5%)	70/100 (70.0%)	**RR 0.78** (0.62 to 0.97)	**154 fewer per 1,000** (from 266 fewer to 21 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings are derived from evidence that has not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unblinded studies which can affect outcomes that require judgment, such as how investigators judge clinical improvement or decide to stop the treatment in patients with side effects.
b. 95% CI may not include a meaningful difference.
c. Modified intention to treat data from Cao 2020 used for this outcome; some deaths were excluded when drug was not given.
d. One patient randomized to the lopinavir/ritonavir arm in Cao 2020 was mechanically ventilated at baseline.
e. Small number of events making estimates highly uncertain
f. The upper boundary of the 95% confidence interval crosses the threshold of meaningful improvement as the worst case estimate is a 3% RRR.

References

1. 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): 1787-99.
2. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med **2021**; 384: 497-511.
3. RECOVERY Collaborative Group, Horby PW, Mafham M, et al. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet **2020**; 396(10259): 1345-52.

References

1. 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.
2. 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): 10012-7.
3. Chan JF, Yao Y, Yeung ML, et al. Treatment With Lopinavir/Ritonavir or Interferon-beta1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. J Infect Dis **2015**; 212(12): 1904-13.
4. 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): 252-6.
5. Spanakis N, Tsiodras S, Haagmans BL, et al. Virological and serological analysis of a recent Middle East respiratory syndrome coronavirus infection case on a triple combination antiviral regimen. Int J Antimicrob Agents **2014**; 44(6): 528-32.
6. Kim UJ, Won EJ, Kee SJ, Jung SI, Jang HC. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-alpha for Middle East respiratory syndrome. Antivir Ther **2016**; 21(5): 455-9.
7. 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): 1695-704.
8. Labhardt ND, Smit M, Petignat I, et al. Post-exposure Lopinavir-Ritonavir Prophylaxis versus Surveillance for Individuals Exposed to SARS-CoV-2: The COPEP Pragmatic Open-Label, Cluster Randomized Trial. EClinicalMedicine **2021**; 42: 101188.
9. Reis G, Moreira Silva E, Medeiros Silva DC, et al. Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial. JAMA Netw Open **2021**; 4(4): e216468.
10. 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): 1787-99.
11. RECOVERY Collaborative Group, Horby PW, Mafham M, et al. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet **2020**; 396(10259): 1345-52.
12. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med **2021**; 384: 497-511.

Supplementary Materials

Study characteristics

- **Table s1.** Should persons exposed to or with COVID-19 receive treatment with lopinavir/ritonavir vs. no lopinavir/ritonavir?

Forest plots

- **Figure s1a.** Outcome of mortality at 28 days for lopinavir/ritonavir vs. no lopinavir/ritonavir in hospitalized patients with severe COVID-19
- **Figure s1b.** Outcome of invasive mechanical ventilation for lopinavir/ritonavir vs. no lopinavir/ritonavir in hospitalized patients with severe COVID-19

Risk of bias

- **Table s2.** Randomized controlled studies (lopinavir/ritonavir vs. no lopinavir/ritonavir)

Table s1. Should persons exposed to or with COVID-19 receive treatment with lopinavir/ritonavir vs. no lopinavir/ritonavir?

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Cao/ 2020 [1]	China/ Jin Yin-Tan Hospital	RCT	199 (99/100)	39.7	Median: 58 (49-68)	Severe COVID: had pneumonia confirmed by chest imaging, and had oxygen saturation of 94% or less while breathing ambient air or a ratio of partial pressure of oxygen to the fraction of inspired oxygen at or below 300 mg Hg	Lopinavir/ritonavir 400/100mg orally twice daily x 14 days	(1) SoC	N/A	Mortality at day 28 Clinical improvement at days 7, 14, 28 Adverse events	Major Projects of National Science and Technology on New Drug Creation and Development The Chinese Academy of Medical Sciences (CAMS) Emergency Project of Covid-19 National Science Grant for Distinguished Young Scholars
Labhardt / 2021 [2]	Brazil and Switzerland/4 centers	RCT	318 (209/109)	49.4	Median: 39 (28-50)	Asymptomatic with documented exposure as a close contact with a person with confirmed SARS CoV-2 infection	Lopinavir 400 mg/ritonavir 100 mg twice daily for 5 days	Surveillance and no PeP	None	Incidence of COVID-19 at day 21 Severity of COVID-19 Serious adverse events	Swiss National Science Foundation Private Foundation of Geneva University Hospitals

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										Acceptability of PeP Adherence Drug levels at day 5	
RECOVERY Collaborative Group (Horby)/ 2020 [3]	United Kingdom / 176 hospitals	RCT	5040 (1616/3424)	N/A	N/A	Clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial	Lopinavir/ritonavir 400/100mg orally every 12 hrs x 10 days or until discharge	(1) SoC	N/A	Mortality at day 28 Discharged from hospital within 28 days Invasive mechanical ventilation Adverse events	UK Research and Innovation and NIHR NIHR Oxford Biomedical Research Centre Wellcome The Bill & Melinda Gates Foundation UK Department for International Development Health Data Research UK Medical Research Council (MRC) Population

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
											Health Research Unit NIHR Health Protection Unit in Emerging and Zoonotic Infections NIHR Clinical Trials Unit Support Funding
Reis/ 2021 [4]	Brazil/10 cities	RCT	685 (244/227) Additional 214 patients randomized to HCQ alone	55%	Median: 53 (18-94)	Adults with symptom onset of flu-like symptoms within 8 days or CT chest consistent with COVID-19 AND one criterion for high risk to progression to severe disease	Lopinavir 800 mg/ritonavir 200 mg, then lopinavir 400 mg/ritonavir 100 mg every 12 hours for an additional 9 days	Placebo	None	Mortality COVID-associated hospitalization Hospital admissions Proportion of patients with negative swab at days 3, 7, and 14 Treatment-emergent adverse events	Bill and Melinda Gates Foundation
WHO Solidarity Trial Consortium	30 countries/ 405 hospitals	RCT	2771 (1399/1372)	38.0	N/A	≥18 years, hospitalized with a diagnosis of COVID-19, not known to	Lopinavir/ritonavir 400/200mg orally every 12 hrs x 14 days	(1) SoC	N/A	Mortality Ventilation	N/A

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
(Pan)/ 2020 [5]						have received any study drug, without anticipated transfer elsewhere within 72 hours, and, in the physician's view, with no contra-indication to any study drug					

Figure s1a. Forest plot for the outcome of mortality at 28 days for lopinavir/ritonavir vs. no lopinavir/ritonavir in hospitalized patients with severe COVID-19

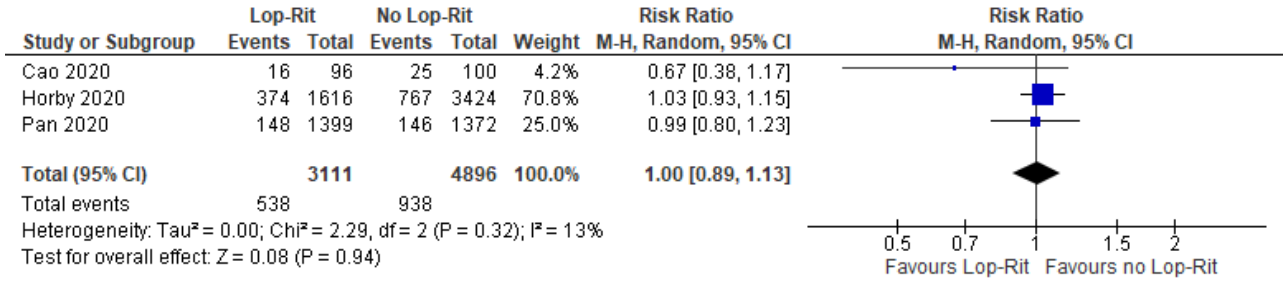

Figure s1b. Forest plot for the outcome of invasive mechanical ventilation for lopinavir/ritonavir vs. no lopinavir/ritonavir in hospitalized patients with severe COVID-19

Table s2. Risk of bias for randomized controlled studies (lopinavir/ritonavir vs. no lopinavir/ritonavir)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Cao 2020 [1]							
Labhardt 2021 [2]							
RECOVERY Collaborative Group (Horby) 2020 [3]							
Reis 2021 [4]							
WHO Solidarity Trial Consortium (Pan) 2020 [5]							

Low	High	Unclear

References for Supplementary Materials

1. 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): 1787-99.
2. Labhardt ND, Smit M, Petignat I, et al. Post-exposure Lopinavir-Ritonavir Prophylaxis versus Surveillance for Individuals Exposed to SARS-CoV-2: The COPEP Pragmatic Open-Label, Cluster Randomized Trial. EClinicalMedicine **2021**; 42: 101188.
3. RECOVERY Collaborative Group, Horby PW, Mafham M, et al. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet **2020**; 396(10259): 1345-52.
4. Reis G, Moreira Silva E, Medeiros Silva DC, et al. Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial. JAMA Netw Open **2021**; 4(4): e216468.
5. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med **2021**; 384: 497-511.