Efficacy and safety of antivirals for Covid-19: A systematic review and meta-analysis

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ABSTRACT

Background. Coronavirus disease 2019 (Covid-19) has led to a severe medical, social and economic crisis globally. Use of antivirals has given inconsistent results; thus systematic summaries of available evidence are required for any recommendations for treatment. We conducted a systematic review and meta-analysis on the use of antivirals for Covid-19.

Methods. The databases we searched were—Medline, Embase, Cochrane CENTRAL and Medrxiv. Title/abstract screening, full-text screening and data abstraction were carried out in duplicate by two researchers. Pooled effect sizes and 95% confidence intervals (CI) were calculated using the Mantel–Haenszel method of random effects for meta-analysis.

Results. Twenty studies were found eligible for inclusion: 6 randomized controlled trials, 9 cohort studies and 5 case series. Moderate-quality evidence suggests a likely clinical benefit from the use of remdesivir in improving the number of recoveries (RR 1.18; 95% CI 1.07–1.31; $I^2=0\%$) and time to recovery in days (median −3.02; 95% CI −4.98 to −1.07; $I^2=97\%$). A possibility of lower mortality is suggested by low-quality evidence with remdesivir (RR 0.74; 95% CI 0.40–1.37, $I^2=58\%$). Moderate-quality evidence suggests no certain benefit of using lopinavir/ritonavir for Covid-19 compared to arbidol, lopinavir/ritonavir combined with arbidol or other medications used as controls.

Conclusion. Further evidence from randomized controlled trials is required for all antivirals to treat Covid-19. At present, remdesivir seems more promising than other antivirals.

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INTRODUCTION

The pandemic of coronavirus disease 2019 (Covid-19), the illness caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), poses an unprecedented threat to human health. As of 28 May 2020, Covid-19 had resulted in more than 357 377 deaths worldwide.[1] The pandemic has left many parts of the world grappling with severe medical, social and economic crises.[2,3]

The huge potential for adverse health consequences from this pandemic has led to a desperate need for interventions that can reduce morbidity and mortality. Research is ongoing to develop vaccines and identify therapeutics for Covid-19, including repurposing of medications.[4] However, research has so far been limited by short follow-up, exclusion of in-patients and small sample size.

The use of medications without proven efficacy may result in avoidable harm to patients, diversion of investment in other resources and erosion of public trust in the medical community.[5,6]

Antivirals used so far to treat Covid-19 have given inconsistent results. Thus, systematic summaries of available evidence are required to guide clinicians and policy-makers on use of antivirals. We conducted a systematic review and meta-analysis on the use of antivirals for Covid-19 to assess their efficacy and safety in patients.

METHODS

We adhered to the statements of the preferred reporting items for systematic reviews and meta-analyses (PRISMA)[7] and meta-analyses and systematic reviews of observational studies in epidemiology (MOOSE)[8] and developed a protocol for systematic review.

Inclusion criteria

Type of participants: Studies on patients with severe and non-severe Covid-19.

Type of interventions: Studies that assessed any of the following drugs—ribavirin, remdesivir, umifenovir (arbidol), favipiravir and lopinavir–ritonavir

Type of outcomes: Studies that reported the following outcomes: (i) *primary outcome:* overall mortality and (ii) *secondary outcomes:* clinical recovery (as defined by authors), rate of admission to the intensive care unit (ICU), length of stay in ICU, length of hospital stay, need for mechanical ventilation, viral clearance and adverse events.

Type of studies: Randomized controlled trials (RCTs), cohort studies and case series. (Editorials, letters, news, reviews,

expert opinions, case reports and studies without original data were excluded.)

Data sources and searches

We searched the following databases for articles published till 15 May 2020: Medline, Embase, Cochrane CENTRAL and PubMed (for articles not yet indexed in Medline). We also searched Medrxiv for pre-print articles.

Reference lists of retrieved articles and pertinent reviews were also searched for relevant articles. No language restriction was imposed. Appendix 1 (available at *www.nmji.in*) gives details of the search strategy.

Selection of studies

Titles and abstracts were screened in duplicate by two researchers (MP, S). Full texts of articles that either researcher considered potentially eligible were obtained. The eligibility of articles was determined from the full texts. Similarly, data were abstracted by two researchers independently and risk of bias was assessed. For all phases of the project, disagreement was resolved by discussion.

Data extraction

The data extracted from each study were author's name, publication year, study design, setting/inclusion criteria, number of patients, patient characteristics, dose, duration and timing of antiviral therapy, co-medications, outcomes reported and method of adjustment (for cohort studies and case series).

Risk of bias assessment

Risk of bias was assessed using the modified version of the Cochrane Risk of Bias tool for RCTs, the revised version of Newcastle Ottawa Scale for Cohort studies and the Joanna Briggs Institute (JBI) checklist for case series.[9–11]

Data synthesis and statistical analysis

We calculated pooled risk ratio or risk difference and 95% CI using the Mantel–Haenszel method. The random effects model was used for meta-analysis. We carried out all statistical analyses using Review Manager 5.3. Heterogeneity was assessed using visual inspection of forest plot and the I^2 statistic.

Grade

We used the GRADE methodology to rate certainty of evidence for each outcome as high, moderate, low or very low. We used detailed GRADE guidance to assess overall risk of bias, imprecision, inconsistency, indirectness and publication bias, and summarized results in an evidence profile.[12]

RESULTS

Study selection

Our search yielded 1328 titles and abstracts—all were identified from the electronic database search. We excluded 1256 articles based on a review of the title and abstract, leaving 72 articles for full review. Of these, 52 were excluded—24 were case reports or reviews, 10 had an inappropriate study design, 15 reported irrelevant outcomes and 3 had an inappropriate comparison. Twenty studies were found eligible on full-text screening; 5 of these were pre-print articles that had not been peer-reviewed. These 20 studies were included in the systematic review[13–32] and 12 studies were included in the meta-analysis (Fig. 1).[13–20,27,29,30,32]

Study characteristics and estimates reported

The studies included were 6 RCTs, 9 cohort studies and 5 case series.[13–32] All studies included patients hospitalized with Covid-19. Three trials[13–15] and two case series[25,26] included mostly patients with severe Covid-19. The other three trials included patients with mild-to-moderate Covid-19.[16,27,32]

Two RCTs and two case series studied the drug remdesivir for Covid-19.[13,14,25,26] Two retrospective cohort studies compared lopinavir/ritonavir to lopinavir/ritonavir along with arbidol,[17,30] and three retrospective cohort studies and one RCT compared lopinavir/ritonavir to only arbidol.[18,20,27,30] Three RCTs and two retrospective cohort studies compared lopinavir/ritonavir to other medications used as controls.[15,16,19,27,30] One RCT each compared arbidol to placebo and favipiravir.[27,32] One prospective cohort study compared lopinavir/ritonavir with favipiravir[21] (Tables I and II).

The outcomes reported by various studies are summarized in Appendix II (available at *www.nmji.in*).

Risk of bias assessment

All RCTs except one mentioned adequate generation of random sequence and blinding. However, only two trials mentioned adequate blinding. Missing outcome data were infrequent for all trials and two trials possibly had other sources of bias (Appendix III–I; available at *www.nmji.in*).

For all outcomes in the cohort studies, risk of bias was low for selection of exposed and non-exposed population and assessment of exposure. All cohort studies were assessed to have low risk of bias from outcome being present at the start of the study. Adequate adjustment and assessment of prognostic factors were carried out by only two studies. Follow-up was adequate for all outcomes in the cohort studies; however, only one study documented similar co-interventions in both groups (Appendix III–II; available at *www.nmji.in*).

Most case series had well-defined criteria for inclusion and

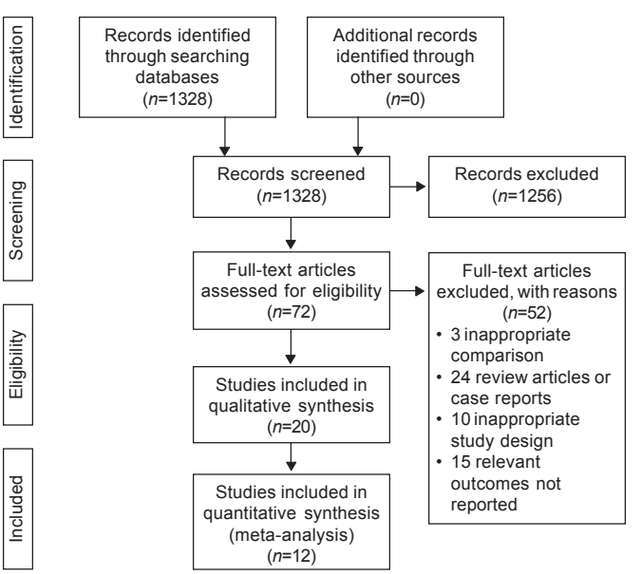

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FIG 1. PRISMA flow diagram for study selection[7]

TABLE I. Characteristics of included randomized controlled trials

Author (year)	Setting, country	Patient characteristics	Intervention group	Control group	Intervention dose/ timing/duration	Outcomes reported
Beigel *et al.* (2020)[14]	60 trial sites and 13 subsites in the USA (45 sites), Denmark (8), the UK (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1) and Singapore (1)	Patients with Covid-19 admitted to hospital with lower respiratory tract infection, 89% severe	Remdesivir (*n*=541)	Placebo (*n*=522)	Intravenous remdesivir as a 200 mg loading dose on day 1, followed by a 100 mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death	Recovery, time to recovery, mortality, ordinal score at day 15, adverse events
Wang *et al.* (2020)[13]	Beijing, China	Patients with Covid-19 pneumonia with O_2 saturation of 94% or lower on room air or a ratio of arterial O_2 partial pressure to fractional inspired O_2 of $\leq$300 mmHg and within 12 days of symptom onset	Remdesivir (*n*=158)	Placebo (*n*=78)	Intravenous remdesivir 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions	Time to clinical improvement, mortality at day 28, frequency of invasive mechanical ventilation, duration of O_2 therapy, length of stay, nosocomial infection, viral clearance
Cao *et al.* (2020)[15]	Jin Yin-Tan Hospital, Hubei, China	Patients with Covid-19 pneumonia with O_2 saturation <94% or PaO_2/FiO_2<300	Lopinavir+ ritonavir (*n*=99)	Standard of care (*n*=100)	Lopinavir–ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days	Time to clinical improvement, clinical recovery, proportions with viral RNA detection
Hung *et al.* (2020)[16]	Queen Mary Hospital, Hong Kong	Patients with mild to moderate Covid-19 (national early warning score 2 [NEWS2] of at least 1)	Lopinavir+ ritonavir+ ribavirin+ interferon beta-1b (*n*=86)	Lopinavir+ ritonavir (*n*=41)	Lopinavir 400 mg and ritonavir 100 mg every 12 h, ibavirin 400 mg every 12 h, and three doses of 8 million i.u. of interferon beta-1b on alternate days (combination group) or to 14 days of lopinavir 400 mg and ritonavir 100 mg every 12 h (control group)	Time to viral clearance, time to resolution of symptoms; length of hospital stay; 30-day mortality
Li *et al.* (2020)[27] (pre-print)	Eight People's Hospital, Guangzhou Medical University, Guangzhou, China	Patients with mild/ moderate Covid-19	Lopinavir+ ritonavir (*n*=34) Arbidol (*n*=35)	Placebo (*n*=17)	Group A (lopinavir/ritonavir group): 34 patients were given lopinavir (200 mg) boosted by ritonavir (50 mg) (orally twice daily, 500 mg, each time for 7–14 days); in group B (arbidol group), 35 patients were given arbidol (100 mg) (orally, 200 mg three times daily for 7–14 days); in group C (control group) 17 patients were not given any antiviral therapy	Viral conversion till day 21, viral conversion on days 7 and 14; deterioration of clinical status from mild/moderate to severe/critical status (follow-up 21 days)
Chen *et al.* (2020)[32] (pre-print)	Zhongnan Hospital of Wuhan University, Wuhan, China	Patients with Covid-19 pneumonia within 12 days of initial symptoms; clinical classification of 89% of patients was moderate	Favipiravir (*n*=116)	Arbidol (*n*=120)	Favipiravir (1600 mg, twice on day 1 followed by 600 mg, twice daily, for the following days) or Arbidol (200 mg, three times daily) plus standard care for 7 days	Clinical recovery rate at day 7; latency to relief for pyrexia and cough, rate of auxiliary O_2 therapy or non-invasive mechanical ventilation

TABLE II. Characteristics of included cohort studies/case series

Study	Country, region and hospital	Study design	Population	Intervention(s)	Adjustment	Outcomes
Deng *et al.* (2020)[17]	The Fifth Affiliated Hospital of Sun Yat-Sen University, China	Retrospective cohort study	Patients with Covid-19 pneumonia without invasive or non-invasive ventilation; 33% had lung 'total severity score' in '4'.	Lopinavir+ ritonavir (*n*=17); lopinavir+ ritonavir+arbidol (*n*=16)	None	Viral clearance at days 7 and 14, pneumonia progression on day 7
Zhu *et al.* (2020)[18]	Jiangsu, Third People's Hospital of Changzhou, China	Retrospective cohort study	Patients with Covid-19 diagnosed as per the Chinese guideline for diagnosis and treatment of Covid-19; most patients had bilateral pneumonia in both groups (79.4% and 68.8%); none of the patients developed severe pneumonia or ARDS	Lopinavir/ ritonavir (*n*=34); arbidol (*n*=16)	None	Development of severe pneumonia, reduction of viral load, duration of positive RNA test
Ye *et al.* (2020)[19]	Ruian, Ruian People's Hospital, China	Retrospective cohort study	Patients with Covid-19 admitted to hospital	Lopinavir+ ritonavir (*n*=47): oral liquid contained 80 mg lopinavir and 20 mg ritonavir; control (*n*=5): adjuvant treatment with interferon aerosol inhalation/arbidol/ methoxyphenamine capsules/eucalyptol limonene and pinene enteric soft capsules/ moxifloxacin	None	Change in body temperature, blood parameters, viral clearance
Lian *et al.* (2020)[20]	Fujian, The First Affiliated Hospital, China	Retrospective cohort study	Patients with Covid-19 admitted in non-ICU (37% severe cases)	Arbidol (*n*=45); control (*n*=36)	None	Viral clearance, disease progression, need for mechanical ventilation
Cai *et al.* (2020)[21]	National Clinical Research Center for Infectious Diseases (The Third People's Hospital of Shenzhen), Shenzhen, China	Prospective cohort study	Patients with Covid-19 admitted to hospital	Favipiravir (*n*=35); lopinavir/ritonavir (*n*=45)	Cox proportional hazards regression	Viral clearance, chest CT changes
Lan *et al.* (2020)[29] (pre-print)	Lishui Hospital of Zhejiang University, China	Retrospective cohort study	Patients hospitalized with Covid-19	Lopinavir+ ritonavir (*n*=34); Lopinavir+ ritonavir+arbidol (*n*=39)	None	Rate of cure (discharge from hospital); hospital stay; viral clearance
Yan *et al.* (2020)[31] (pre-print)	The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China	Retrospective cohort study	Patients with Covid-19 infection with available RNA viral data; 32% severe	Lopinavir+ ritonavir (*n*=78); Standard treatment (*n*=42)	None	Duration of viral shedding;length of hospital stay
Wen *et al.* (2020)[30]	Guangzhou Eighth People's Hospital Infectious Disease Center, China	Retrospective cohort study	Patients hospitalized with Covid-19 for at least 14 days	Lopinavir+ ritonavir (*n*=59); Arbidol (*n*=36); Lopinavir+ ritonavir+arbidol (*n*=25); Standard treatment (*n*=58)	None	Viral clearance

contd.

TABLE II. Characteristics of included cohort studies/case series *(contd.)*

Study	Country, region and hospital	Study design	Population	Intervention(s)	Adjustment	Outcomes
Shi *et al.* (2020)[28] (pre-print)	Shanghai Public Health Clinical Center, Fudan University, Shanghai, China	Retrospective cohort study	Patients with Covid-19 pneumonia	Symptomatic treatment group (*n*=17); Arbidol group (*n*=30); Lopinavir/ritonavir group (*n*=27); Arbidol+lopinavir/ritonavir (*n*=25); Interferon (*n*=41); Interferon+ lopinavir/ritonavir (*n*=21); Interferon+ darunavir group (*n*=23)	None	Proportion of improvement in pneumonia volume; length of hospital stay
Wang *et al.* (2020)[22]	Union Hospital, Wuhan, China	Case series	Patients with Covid-19: SpO_2 ≥90% group (*n*=55), SpO_2<90% group (*n*=14)	Arbidol (*n*=67) Co-interventions: other antivirals, interferon, moxifloxicin	None	Mortality
Young *et al.* (2020)[23]	Singapore	Case series	Patients with Covid-19: febrile, on O_2	Lopinavir+ ritonavir (n=5)	None	Requirement of mechanical ventilation
Wang *et al.* (2020)[24]	Shanghai Public Health Clinical Center, Shanghai, China	Case series	Patients hospitalized with Covid-19 pneumonia	Lopinavir/ ritonavir, arbidol and SFJDC (n=4)	None	Clinical recovery; viral clearance; need for mechanical ventilation
Grein *et al.* (2020)[25]	USA/Europe/Canada	Case series	Patients with Covid-19, O_2 saturation <94% while breathing ambient air or receiving O_2 support. Majority of patients (34 [64%]) were receiving invasive ventilation at baseline	Remdesivir (*n*=53)	Cox proportional hazard analysis	Clinical improvement (median follow-up 18 days); requirement of ventilation; extubation; death; hospital discharge
Antinori *et al.* (2020)[26]	Luigi Sacco Hospital, University of Milan, Milan, ltaly	Case series	Patients with Covid-19 pneumonia on mechanical ventilation or O_2 saturation <94% or NEWS2 of ≥4	Remdesivir (*n*=35)	None	Hospitalization status on days 10 and 28 of treatment; adverse events leading to premature treatment discontinuation (median follow-up 39 days)

ARDS acute respiratory distress syndrome ICU intensive care unit SFJDC Shufeng Jiedu Capsule, a Chinese traditional medicine

the condition measured in a standard, reliable way and clear reporting of the demographics of participants. However, most case series did not mention consecutive and complete inclusion of participants (Appendix III–III; available at *www.nmji.in*).

Pooled effects of antivirals on safety and efficacy outcomes

Remdesivir versus placebo: Moderate-quality evidence from two RCTs[13,14] (1295 participants) suggested a significantly greater number of clinical recoveries with remdesivir compared to placebo with no statistical heterogeneity (RR 1.18; 95% CI 1.07–1.31; I^2=0%; Fig. 2, Table III).

Moderate-quality evidence from two RCTs[13,14] suggested a statistically significant shorter time to recovery with remdesivir when compared to placebo (mean deviation –3.02; 95% CI –4.98 to –1.07; I^2=97%; Fig. 3, Table III).

Low-quality evidence from two RCTs[13,15] (1295 participants) raised the possibility of a reduction in mortality with remdesivir (RR 0.74; 95% CI 0.40–1.37, I^2= 58%; Fig. 4, Table III).

Moderate-quality evidence from two RCTs[13,14] (1295 participants) raised the possibility of no increase in adverse events due to remdesivir (RR 0.94; 95% CI 0.80–1.11; Fig. 5, Table III).

Lopinavir/ritonavir versus arbidol

One RCT[27] (69 participants) gave inconclusive results for viral clearance at day 7 (RR 0.95; 95% CI 0.51–1.78) and raised the

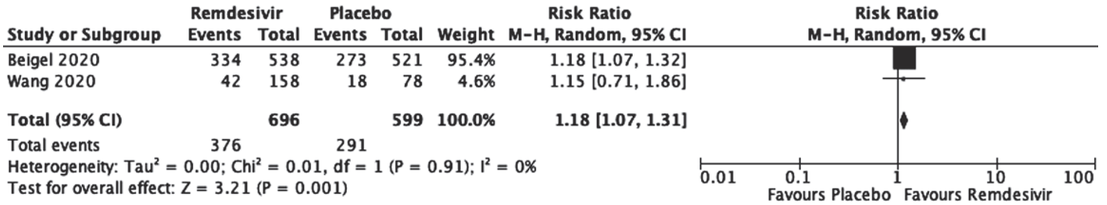

FIG 2. Effect of remdesivir on clinical recovery as compared to placebo

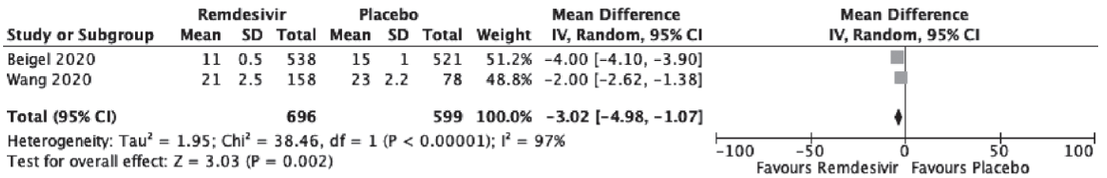

FIG 3. Effect of remdesivir on time to recovery as compared to placebo

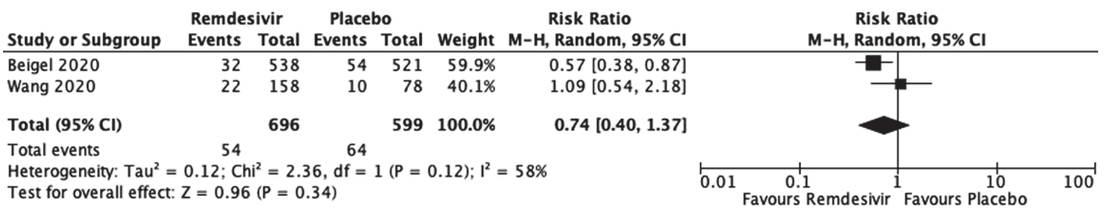

FIG 4. Effect of remdesivir on mortality as compared to placebo

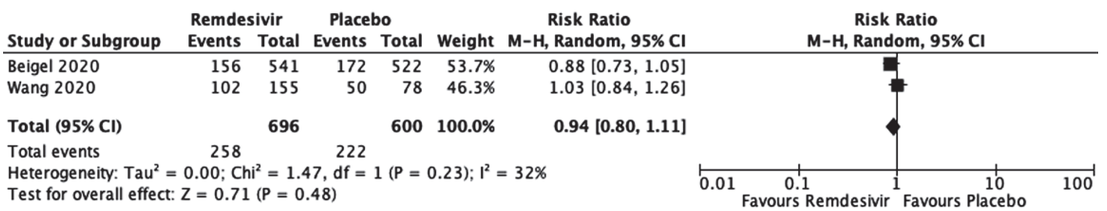

FIG 5. Effect of remdesivir on adverse events as compared to placebo

TABLE III. Summary of findings: Remdesivir compared to placebo for Covid-19

Outcome	Relative effect (95% CI)‡	Anticipated absolute effects (95% CI)			Certainty
		Baseline risk for control group	Risk with remdesivir (95% CI)	Difference	
Recovery	RR 1.18 (1.07–1.31)	48.6%*	57.3% (52–63.6)	8.7% more (3.4 more to 15.1 more)	⨁⨁⨁◯ MODERATE (Serious risk of bias)
Time to recovery		Median 7 days†	–	Median 3.02 lower (4.98 lower to 1.07 lower)	⨁⨁⨁◯ MODERATE (Serious inconsistency)
Mortality	RR 0.74 (0.40–1.37)	10.7%*	7.9% (4.3–14.6)	2.8% fewer (6.4 fewer to 4 more)	⨁⨁◯◯ LOW (Serious imprecision and serious inconsistency)
Adverse events	RR 0.94 (0.80–1.11)	37.0%*	34.8% (29.6–41.1)	2.2% fewer (7.4 fewer to 4.1 more)	⨁⨁⨁◯ MODERATE (Serious imprecision)

* baseline risk was obtained from Covid-19 patients who had not been administered remdesivir in studies included in the meta-analysis for the outcome
† baseline risk from a study of Covid-19 patients without remdesivir use: Guan *et al. N Engl J Med* 2020;**382:**1708–20. doi: 10.1056/NEJMoa2002032
‡ based on data from 1295 participants in two randomized trial

possibility of an increase in adverse events (RR 2.47; 95% CI 0.97–6.26) with lopinavir/ritonavir compared to arbidol.

Very low-quality evidence from three cohort studies[18,20,30] (226 participants) suggested possible but uncertain effects of reduction in viral clearance at day 7 with lopinavir/ritonavir compared to arbidol (RR 0.65; 95% CI 0.35–1.22; Fig. 6, Table IV).

Lopinavir/ritonavir versus lopinavir/ritonavir combined with arbidol

One RCT[30] (84 participants) suggested a possible but uncertain reduction in viral clearance at day 7 with lopinavir/ritonavir compared to lopinavir/ritonavir plus arbidol (RR 0.51; 95% CI 0.17–1.51; Fig. 7).

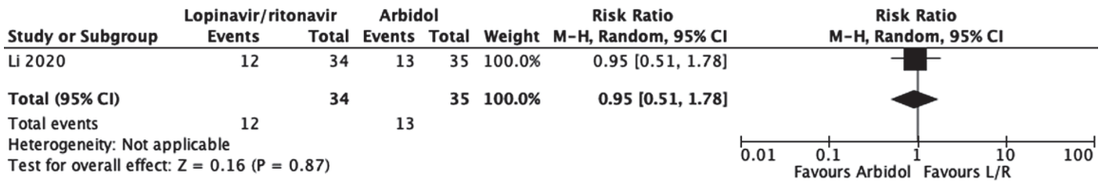

FIG 6a. Effect of lopinavir/ritonavir (L/R) on viral clearance as compared to arbidol: Evidence from randomized controlled trial

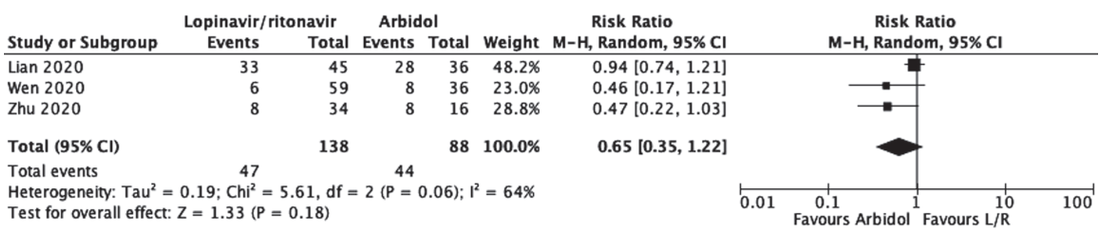

FIG 6b. Effect of lopinavir/ritonavir (L/R) on viral clearance as compared to arbidol: Evidence from cohort studies

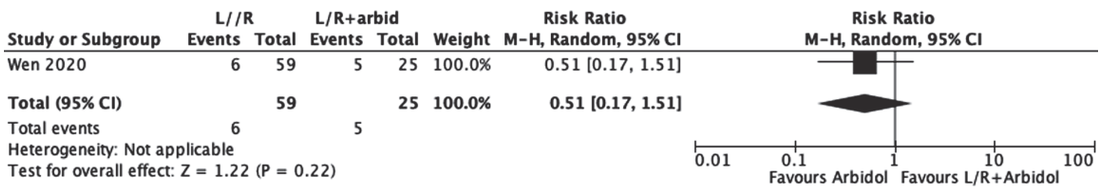

FIG 7a. Effect of lopinavir/ritonavir (L/R) on viral clearance as compared to L/R combined with arbidol (arbid): Evidence from randomized controlled trial

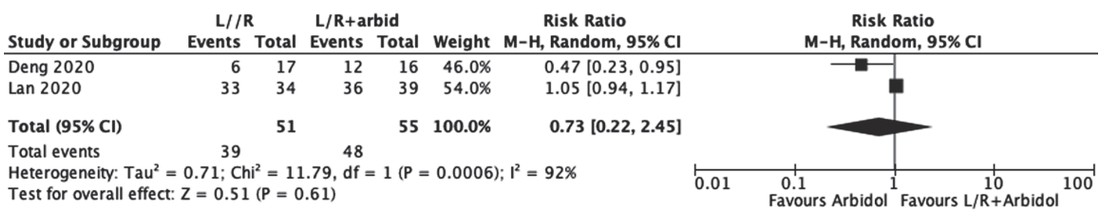

FIG 7b. Effect of lopinavir/ritonavir (L/R) on viral clearance as compared to L/R combined with arbidol (arbid): Evidence from cohort studies

TABLE IV. Summary of findings: Lopinavir/ritonavir compared to arbidol for Covid-19

Outcome	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Baseline risk for control group	Risk with remdesivir (95% CI)	Difference	
Viral clearance	RR 0.65 (0.35–1.22) Based on 226 participants in three cohort studies	50%*	32.5% (17.5–61)	17.5% fewer (32.5 fewer to 11 more)	⨁◯◯◯ VERY LOW (serious imprecision and risk of bias)

* baseline risk was obtained from Covid-19 patients who had been administered arbidol in studies included in the meta-analysis for the outcome.

TABLE V. Summary of findings: Lopinavir/ritonavir compared to lopinavir/ritonavir+arbidol for Covid-19

Outcome	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Baseline risk for control group	Risk with remdesivir (95% CI)	Difference	
Viral clearance	RR 0.73 (0.22 to 2.45) Based on 106 participants in two cohort studies	87.3%*	63.7% (19.2–100)	23.6% fewer (68.1 fewer to 126.5 more)	⨁◯◯◯ VERY LOW (serious imprecision and risk of bias)

* baseline risk was obtained from Covid-19 patients who had been administered lopinavir/ritonavir+arbidol in studies included in the meta-analysis for the outcome.

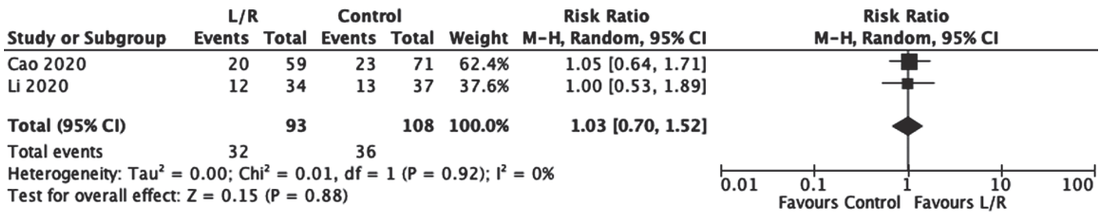

FIG 8. Effect of lopinavir/ritonavir (L/R) on viral clearance as compared to control

TABLE VI. Summary of findings: Lopinavir/ritonavir compared to other controls for COVID-19

Outcome	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Baseline risk for control group	Risk with remdesivir (95% CI)	Difference	
Viral clearance	RR 1.03 (0.70–1.52); based on 201 participants in two RCTs	33.3%*	34.3% (23.3–50.7)	1.0% more (10 fewer to 17.3 more)	⨁⨁⨁◯ MODERATE (serious imprecision)
Mortality	RR not estimable (no event in either group); based on 326 participants in two cohort studies	17.7%*	0.0% (0–0)	17.7% fewer (17.7 fewer to 17.7 fewer)	⨁⨁◯◯ LOW (serious inconsistency and risk of bias)

* baseline risk was obtained from Covid-19 patients who had not been administered lopinavir/ritonavir in studies included in the meta-analysis for the outcome.

Moderate-quality evidence from two cohort studies[17,29] (106 participants) gave inconclusive results regarding a reduction in viral clearance at day 7 with lopinavir/ritonavir compared to lopinavir/ritonavir and arbidol (RR 0.73; 95% CI 0.22–2.45; Fig. 7 and Table V).

Lopinavir/ritonavir versus no antiviral

Moderate-quality evidence from two RCTs[15,27] (201 participants) suggested no statistically significant reduction in viral clearance at day 7 with lopinavir/ritonavir compared to the control medication (RR 1.03; 95% CI 0.70–1.52; Fig. 8 and Table VI).

Favipiravir versus lopinavir/ritonavir

One cohort study[21] compared favipiravir to lopinavir/ritonavir and found a shorter viral clearance time for the favipiravir arm versus lopinavir/ritonavir: median 4 *v*. 11 days (p<0.001). The favipiravir arm also showed significant improvement in chest imaging compared with the control arm, with an improvement rate of 91.43% *v*. 62.22% (p=0.004).

Favipiravir versus arbidol

One RCT[32] that had not been peer-reviewed reported no statistically significant difference in the clinical recovery rate at day 7 in the favipiravir (61%) and arbidol (52%) groups.

Combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin versus lopinavir/ritonavir alone

One RCT[16] compared the combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin with lopinavir/ritonavir alone. The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 *v*. 12 days; hazard ratio 4.37; 95% CI 1.86–10.24, p=0.001).

Studies without a comparator

A case series[25] of patients who received remdesivir reported clinical improvement in 36 of 53 patients (68%) and mortality in 7 (13%). Another case series[26] of patients who received remdesivir reported clinical recovery at day 28 for 22 of 35 patients (63%).

In a series of 5 patients who received lopinavor/ritonavir, the fever resolved and supplemental oxygen requirement was reduced within 3 days for 3 patients, whereas the condition of 2 deteriorated with progressive respiratory failure. Four of 5 patients treated with lopinavir–ritonavir developed nausea, vomiting, and/or diarrhoea, and 3 developed abnormal liver function as shown by test results.[23]

DISCUSSION

This systematic review provides moderate-quality evidence for the use of remdesivir in Covid-19 for improving the number of recoveries and time to recovery, and low-quality evidence for a possible reduction in mortality. Moderate-quality evidence suggests no benefit of using lopinavir/ritonavir in Covid-19 compared to arbidol, lopinavir/ritonavir combined with arbidol or other controls.

The clinical benefit in recovery with remdesivir, as reported by Beigel *et al.,*[14] is from the trial results published on the basis of a partial dataset. The data safety and monitoring board made a recommendation to unblind the results in view of the significant benefit. Thus, the imprecise estimates for the efficacy of remdesivir in reducing overall mortality, which this meta-analysis has yielded, are subject to change from the anticipated complete trial results.

In their preliminary report, Beigel *et al*. observed the reduction in time to recovery particularly for patients with severe disease (12 days in remdesivir recipients, compared with 18 days in recipients of placebo).[14] On the other hand, patients with mild or moderate disease experienced a time to recovery similar to those in the placebo group (5 days).

Wang *et al.*[13] have reported results that are consistent with those of Beigel *et al*. Their trial, which took place in China, could only enrol two-thirds of the intended patients since the outbreak had considerably diminished by that time, which explains the lack of precision in their estimates. The two trials reported mortality at different follow-up periods (14 days in Beigel *et al*. and 28 days in Wang *et al.*), which may have contributed to the heterogeneity.

Considering that both trials did observe mortality in a considerable proportion of participants receiving remdesivir (7%–8%), the question of discovering the best treatment for Covid-19 seems far from being resolved. It is also under investigation whether this mortality was due to the advanced stage of disease in these patients or they needed additional therapy. Additional concerns are the intravenous route of this drug, which precludes wider use. An endeavour to produce an oral formulation that can be taken by patients with moderate disease severity should be made.

Another trial compared the duration of remdesivir therapy and concluded no significant difference between a 5-day versus a 10-day course. The efficacy could not be determined due to the lack of placebo.[33]

The present systematic review has several strengths. It incorporates a robust and comprehensive search that covers three major databases in addition to unindexed and pre-print articles. The steps of screening and data abstraction, including risk of bias assessment, were conducted independently by two researchers. Lastly, we used the GRADE approach to rate the certainty in the evidence as very low, low, moderate or high. This enabled us to pay close attention to methodological issues such as imprecision, inconsistency and risk of bias.

The limitations of the present review are largely because only primary studies were included. The number of RCTs are so far, understandably, very few. Most cohort studies did not report using adjustment or assessment of prognostic factors, which resulted in rating down of the certainty in evidence.

There are, to the best of our knowledge, no previous systematic reviews that have incorporated all the studies included in the present review. A systematic review by Zhang *et al*.[34] found that treatment with lopinavir–ritonavir showed no significant benefit in the rates of mortality and ARDS, which is consistent with our observations. Another systematic review[35] combined indirect evidence from SARS and MERS to some studies on Covid-19 and reported very low-quality evidence of a possible reduction in mortality from a combination of ribavirin and corticosteroids. A systematic review by Lui *et al*. did not study remdesivir and found only very low-quality evidence with little or no suggestion of benefit for most other treatments and outcomes in both non-severe and severe Covid-19.[36] Rios *et al*. included all the known antiviral treatments and antibodies for their potential treatment for Covid-19 and searched for all types of studies including preclinical (animal) studies. They summarized the results as inconclusive; however, they did not apply the GRADE approach.[37]

Limitations of the existing evidence make it imperative that researchers cooperate in conducting high-quality studies of efficacy, particularly RCTs.

In the light of these findings, remdesivir seems more promising than other medications. The medical community must commit to generating and implementing interventions with proven efficacy and safety, while discouraging the use of medications with very low-quality evidence.

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Appendix I. Search strategy

Umifenovir

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed

Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp Coronavirus/
2 exp Coronavirus Infections/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 or/1-3
5 arbidol.mp.
6 umifenovir.mp.
7 5 or 6
8 4 and 7

Database: Embase

Search Strategy:

1 exp coronavirinae/
2 exp Coronavirus infection/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4 or/1-3
5 arbidol/
6 arbidol.mp.
7 umifenovir.mp. or umifenovir/
8 5 or 6 or 7
9 4 and 8

Cochrane Library

1 MeSH descriptor: [Coronavirus] explode all trees
2 MeSH descriptor: [Coronavirus Infections] explode all trees
3 (coronavir* or coronovir* or " SARS-COV-2 " or COV or NCOV or " 2019 nCOV " or " 2019-nCOV " or " COVID-19 "): ti, ab, kw
4 1 or 2 or 3
5 arbidol or umifenovir
6 4 AND 5

PubMed

Search (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019 nCOV or 2019-nCOV or COVID-19) AND (arbidol or umifenovir) AND (publisher[sb] OR inprocess[sb] OR pub med not med line [sb] OR pub status ahead of print)

Favipiravir

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed

Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp Coronavirus/
2 exp Coronavirus Infections/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 or/1-3
5 (favipiravir or avigan or favipivavir or t 705 or t705).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6 4 and 5

Database: Embase

Search Strategy:

1 exp coronavirinae/
2 exp Coronavirus infection/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4 or/1-3
5 favipiravir/
6 (favipiravir or avigan or favipivavir or t 705 or t705).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7 5 or 6
8 4 and 7

Cochrane Library

1 MeSH descriptor: [Coronavirus] explode all trees
2 MeSH descriptor: [Coronavirus Infections] explode all trees
3 (coronavir* or coronovir* or " SARS-COV-2 " or COV or NCOV or " 2019 nCOV " or " 2019-nCOV " or " COVID-19 "): ti, ab, kw
4 1 or 2 or 3
5 favipiravir or avigan or favipivavir or t 705 or t705
6 4 and 5

PubMed

Search ((((coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19))) AND (favipiravir OR avigan OR favipiravir OR t 705 OR t705)) AND ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint))

Lopinavir plus Ritonavir

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed

Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp Coronavirus/
2 exp Coronavirus Infections/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 or/1-3
5 (lopinavir adj2 ritonavir).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6 (aluvia* or kaletra).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7 5 or 6
8 4 and 7

Database: Embase

Search Strategy:

1 exp coronavirinae/
2 exp Coronavirus infection/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4 or/1-3
5 lopinavir plus ritonavir/
6 (lopinavir adj2 ritonavir).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7 (aluvia* or kaletra).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8 5 or 6 or 7
9 4 and 8

Cochrane Library

1 MeSH descriptor: [Coronavirus] explode all trees
2 MeSH descriptor: [Coronavirus Infections] explode all trees
3 ((coronavir* or coronovir* or "SARS-COV-2" or COV or NCOV or "2019nCOV" or "2019-nCOV" or "COVID-19")):ti,ab,kw
4 1 or 2 or 3
5 lopinavir NEAR/2 ritonavir
6 aluvia* or kaletra
7 5 or 6
8 4 and 7 in Trials

PubMed

Search (((((coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19))) AND ((((lopinavir) AND ritonavir)) OR ((aluvia* or kaletra)))) AND ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))

Ribavirin

MEDLINE

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed

Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp Coronavirus/
2 exp Coronavirus Infections/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 or/1-3
5 Ribavirin/
6 (Rebetol or ribamide or ribamidil or ribamidyl or ribasphere or ribavirin or tribavirin or vilona or viramide or virazide or virazole).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7 or/5-6
8 4 and 7

Database: Embase

Search Strategy:

1 exp coronavirinae/
2 exp Coronavirus infection/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4 or/1-3
5 ribavirin/
6 (Rebetol or ribamide or ribamidil or ribamidyl or ribasphere or ribavirin or tribavirin or vilona or viramide or virazide or virazole).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7 5 or 6
8 4 and 7

Cochrane Library

1 MeSH descriptor: [Coronavirus] explode all trees
2 MeSH descriptor: [Coronavirus Infections] explode all trees
3 ((coronavir* or coronovir* or "SARS-COV-2" or COV or NCOV or "2019nCOV" or "2019-nCOV" or "COVID-19")):ti,ab,kw
4 1 or 2 or 3
5 MeSH descriptor: [Ribavirin] explode all trees
6 Rebetol or ribamide or ribamidil or ribamidyl or ribasphere or ribavirin or tribavirin or vilona or viramide or virazide or virazole
7 5 or 6
8 4 and 7 in Trials

PubMed

Search (((((coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19))) AND ((Rebetol or ribamide or ribamidil or ribamidyl or ribasphere or ribavirin or tribavirin or vilona or viramide or virazide or virazole))) AND ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))

Remdesivir

MEDLINE

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed

Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp Coronavirus/
2 exp Coronavirus Infections/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 or/1-3
5 Remdesivir/
6 (remdesivir or GS-5734 or GS 5734).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7 or/5-6
8 4 and 7

Database: Embase

Search Strategy:

1 exp coronavirinae/
2 exp Coronavirus infection/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4 or/1-3
5 remdesivir/
6 (remdesivir or GS-5734 or GS 5734).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7 5 or 6
8 4 and 7

Cochrane Library

1 MeSH descriptor: [Coronavirus] explode all trees
2 MeSH descriptor: [Coronavirus Infections] explode all trees
3 ((coronavir* or coronovir* or "SARS-COV-2" or COV or NCOV or "2019nCOV" or "2019-nCOV" or "COVID-19")):ti,ab,kw
4 1 or 2 or 3
5 MeSH descriptor: [Remdesivir] explode all trees
6 remdesivir or GS-5734 or GS 5734
7 5 or 6
8 4 and 7 in Trials

PubMed

Search (((((coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19))) AND ((remdesivir or GS-5734 or GS 5734))) AND ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))

Medrxiv search strategy (for all interventions) 'coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019- nCOV or COVID' https://www.medrxiv.org/search/coronavir%252A%252Bor%252Bcoronovir%252A%252Bor%252BSARS-COV-2%252Bor%252BCOV%252Bor%252BNCOV%252Bor%252B2019nCOV%252Bor%252B2019-nCOV%252Bor%252BCOVIDprint)))

Favipiravir

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed

Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp Coronavirus/
2 exp Coronavirus Infections/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 or/1-3
5 (favipiravir or avigan or favipivavir or t 705 or t705).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6 4 and 5

Database: Embase

Search Strategy:

1 exp coronavirinae/
2 exp Coronavirus infection/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4 or/1-3
5 favipiravir/
6 (favipiravir or avigan or favipivavir or t 705 or t705).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7 5 or 6
8 4 and 7

Cochrane Library

1 MeSH descriptor: [Coronavirus] explode all trees
2 MeSH descriptor: [Coronavirus Infections] explode all trees
3 (coronavir* or coronovir* or "SARS-COV-2" or COV or NCOV or "2019nCOV" or "2019-nCOV" or "COVID-19"):ti,ab,kw
4 1 or 2 or 3
5 favipiravir or avigan or favipivavir or t 705 or t705
6 4 and 5

PubMed

Search ((((coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19))) AND (favipiravir OR avigan OR favipiravir OR t 705 OR t705)) AND ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint))

Lopinavir plus Ritonavir

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed

Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp Coronavirus/
2 exp Coronavirus Infections/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 or/1-3
5 (lopinavir adj2 ritonavir).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6 (aluvia* or kaletra).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7 5 or 6
8 4 and 7

Database: Embase

Search Strategy:

1 exp coronavirinae/
2 exp Coronavirus infection/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title,

abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4 or/1-3
5 lopinavir plus ritonavir/
6 (lopinavir adj2 ritonavir).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7 (aluvia* or kaletra).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8 5 or 6 or 7
9 4 and 8

Cochrane Library
1 MeSH descriptor: [Coronavirus] explode all trees
2 MeSH descriptor: [Coronavirus Infections] explode all trees
3 ((coronavir* or coronovir* or "SARS-COV-2" or COV or NCOV or "2019nCOV" or "2019-nCOV" or "COVID-19")):ti,ab,kw
4 1 or 2 or 3
5 lopinavir NEAR/2 ritonavir
6 aluvia* or kaletra
7 5 or 6
8 4 and 7 in Trials

PubMed
Search (((((coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19))) AND ((((lopinavir) AND ritonavir)) OR ((aluvia* or kaletra)))) AND ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))

Ribavirin

MEDLINE

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed

Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:
1 exp Coronavirus/
2 exp Coronavirus Infections/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 or/1-3
5 Ribavirin/
6 (Rebetol or ribamide or ribamidil or ribamidyl or ribasphere or ribavirin or tribavirin or vilona or viramide or virazide or virazole).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7 or/5-6
8 4 and 7

Database: Embase

Search Strategy:
1 exp coronavirinae/
2 exp Coronavirus infection/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4 or/1-3
5 ribavirin/
6 (Rebetol or ribamide or ribamidil or ribamidyl or ribasphere or ribavirin or tribavirin or vilona or viramide or virazide or virazole).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7 5 or 6
8 4 and 7

Cochrane Library
1 MeSH descriptor: [Coronavirus] explode all trees
2 MeSH descriptor: [Coronavirus Infections] explode all trees
3 ((coronavir* or coronovir* or "SARS-COV-2" or COV or NCOV or "2019nCOV" or "2019-nCOV" or "COVID-19")):ti,ab,kw
4 1 or 2 or 3
5 MeSH descriptor: [Ribavirin] explode all trees
6 Rebetol or ribamide or ribamidil or ribamidyl or ribasphere or ribavirin or tribavirin or vilona or viramide or virazide or virazole
7 5 or 6
8 4 and 7 in Trials

PubMed
Search ((((((coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19))) AND ((Rebetol or ribamide or ribamidil or ribamidyl or ribasphere or ribavirin or tribavirin or vilona or viramide or virazide or virazole))) AND ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))

Remdesivir

MEDLINE

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed

Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:
1 exp Coronavirus/
2 exp Coronavirus Infections/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 or/1-3
5 Remdesivir/
6 (remdesivir or GS-5734 or GS 5734).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7 or/5-6
8 4 and 7

Database: Embase

Search Strategy:
1 exp coronavirinae/
2 exp Coronavirus infection/
3 (coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

4 or/1-3
5 remdesivir/
6 (remdesivir or GS-5734 or GS 5734).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7 5 or 6
8 4 and 7

Cochrane Library

1 MeSH descriptor: [Coronavirus] explode all trees
2 MeSH descriptor: [Coronavirus Infections] explode all trees
3 ((coronavir* or coronovir* or "SARS-COV-2" or COV or NCOV or "2019nCOV" or "2019-nCOV" or "COVID-19")):ti,ab,kw
4 1 or 2 or 3
5 MeSH descriptor: [Remdesivir] explode all trees
6 remdesivir or GS-5734 or GS 5734
7 5 or 6
8 4 and 7 in Trials

PubMed

Search (((((coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19))) AND ((remdesivir or GS-5734 or GS 5734))) AND ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))

Medrxiv search strategy (for all interventions) 'coronavir* or coronovir* or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID'

https://www.medrxiv.org/search/coronavir%252A%252Bor%252Bcoronovir%252A%252Bor%252BSARS-COV-2%252Bor%252BCOV%252Bor%252BNCOV%252Bor%252B2019nCOV%252Bor%252B2019-nCOV%252Bor%252BCOVID

Appendix II. Outcomes reported

Study (year)	Mortality (28 days)	Mechanical ventilation	Days to clinical recovery	Clinical improvement (day 7)	Clinical improvement (day 14)	Clinical improvement (day 28)	Viral clearance (7 days)	Viral clearance (28 days)	Adverse events (overall)	Adverse events (Grades 3–4)
Wang *et al.* (2020)[13]	Remdesivir 22/158 Placebo 10/78	Remdesivir 11/158 Placebo 10/78	Remdesivir median 21 (13–28) Placebo median 23 (15–28)	Remdesivir 4/158 Placebo 2/78	Remdesivir 42/158 Placebo 18/78	Remdesivir 103/158 Placebo 45/78	Remdesivir: 66/131 Placebo 32/65	Remdesivir 99/131 Placebo 54/65	Remdesivir 102/155 Placebo 50/78	Remdesivir 13/158 Placebo 11/78
Beigel *et al.* (2020)[14]	(14 days) Remdesivir 32/538 Placebo 54/521	nr	nr	nr	Remdesivir 334/538 Placebo 273/521	nr	nr	nr	Remdesivir 156/541 Placebo 172/522	Remdesivir 114/541 Placebo 141/522
Cao *et al.* (2020)[15]	Lopinavir/ ritonavir 19/99 Standard care 25/100	Lopinavir/ ritonavir 14/99 Standard care 18/100	Lopinavir/ ritonavir median 16 (15–17) Standard care 16	Lopinavir/ ritonavir 6/99 Standard care 2/100	Lopinavir/ ritonavir 45/99 Standard care 30/100s	Lopinavir/ ritonavir 78/99 Standard care 70/100	nr	Lopinavir/ ritonavir 35/59 Standard care 41/71	Lopinavir/ ritonavir 46/95 Standard care 49/99	Lopinavir/ ritonavir 20/95 Standard care 11/99
Hung *et al.* (2020)[16]	Triple therapy 0/86 Lopinavir/ ritonavir 0/41	Triple therapy 0/86 Lopinavir/ ritonavir 1/41	Triple therapy median 4 (3–8) Lopinavir/ ritonavir 8 (7–9)	nr	nr	nr	nr	nr	Triple therapy 41/86 Lopinavir/ ritonavir 20/41	Triple therapy 0/86 Lopinavir/ ritonavir 1/41
Zhu *et al.* (2020)[18]	Lopinavir/ ritonavir 0/34 Arbidol 0/16	Lopinavir/ ritonavir 0/34 Arbidol 0/16	nr	nr	nr	nr	Lopinavir/ ritonavir 8/34 Arbidol 8/16	nr	nr	nr
Li *et al.* (2020)[27]	Lopinavir/ ritonavir Arbidol Placebo	nr	nr	nr	nr	nr	Lopinavir/ ritonavir 12/34 Arbidol 7/17 Placebo 13/35	Lopinavir/ ritonavir 29/34 Arbidol 13/17 Placebo 32/35	Lopinavir/ ritonavir 12/34 Arbidol 0/17 Placebo 5/35	nr
Cai *et al.* (2020)[21]	nr	nr	nr	nr	nr	nr	nr	nr	Favipiravir 4/35 Lopinavir/ ritonavir 25/45	nr
Lan *et al.* (2020)[29]	Lopinavir/ ritonavir 1/34 Lopinavir/ ritonavir+ Arbidol 1/39	Lopinavir/ ritonavir: Lopinavir/ ritonavir+ Arbidol	nr	nr	nr	nr	Lopinavir/ ritonavir 33/34 Lopinavir/ ritonavir+ Arbidol 36/39	nr	nr	nr
Chen *et al.* (2020)[32]	Favipiravir 0/116 Arbidol 0/120	nr	nr	Favipiravir 71/116 Arbidol 62/120	nr	nr	nr	nr	Favipiravir 37/116 Arbidol 28/120	nr
Deng *et al.* (2020)[17]	nr	Lopinavir/ ritonavir 0/17 Lopinavir/ ritonavir+ Arbidol 0/16	nr	nr	nr	nr	Lopinavir/ ritonavir 6/17 Lopinavir/ ritonavir+ Arbidol 12/16			

(contd.)

Appendix II. Outcomes reported *(contd.)*

Study (year)	Mortality (28 days)	Mechanical ventilation	Days to clinical recovery	Clinical improvement (day 7)	Clinical improvement (day 14)	Clinical improvement (day 28)	Viral clearance (7 days)	Viral clearance (28 days)	Adverse events (overall)	Adverse events (Grades 3–4)
Wang *et al.* (2020)[24]	nr	Lopinavir/ ritonavir, arbidol and SFJDC 1/4	nr	Lopinavir/ ritonavir, arbidol and SFJDC 3/4	nr	nr	Lopinavir/ ritonavir, arbidol and SFJDC 2/4	nr	nr	nr
Lian *et al.* (2020)[20]	Arbidol 0/45 Control 0/36	nr	nr	nr	nr	nr	Arbidol 33/45 Control 28/36	nr	Arbidol 5/45 Control 3/36	Arbidol 0/45 Control 0/36
Grein *et al.* (2020)[25]	Remdesivir 7/53	nr	nr	nr	nr	Remdesivir 74%	nr	nr	Remdesivir 32/53	Remdesivir 12/53
Antinori *et al.* (2020)[26]	nr	nr	nr	Remdesivir 10/35	nr	Remdesivir 22/35	nr	nr	nr	nr
Wang *et al.* (2020)[22]	Arbidol 0/36 No arbidol 5/31	nr	nr	nr	nr	nr	nr	nr	nr	nr
Young *et al.* (2020)[23]	nr	Lopinavir/ ritonavir 1/5	nr	nr	nr	nr	nr	nr	nr	nr

nr not recorded SFJDC Shufeng Jiedu Capsule, a Chinese traditional medicine

Appendix III–I. Risk of bias in included randomized controlled trials

Study (year)	Sequence generation	Allocation sequence concealment	Blinding	Missing outcome data	Other bias
Beigel *et al.* (2020)[14]	Definitely yes[1]	Probably yes[2]	Definitely yes[4]	Definitely yes[7]	Probably no[8]
Wang *et al.* (2020)[13]	Definitely yes[1]	Definitely yes[2]	Definitely yes[4]	Definitely yes[7]	Probably yes
Cao *et al.* (2020)[15]	Definitely yes[1]	Definitely yes[2]	Definitely no[5]	Definitely yes[7]	Probably yes
Hung *et al.* (2020)[16]	Definitely yes[1]	Definitely yes[2]	Definitely no[5]	Definitely yes[7]	Probably yes
Li *et al.* (2020)[27]	Definitely yes[1]	Definitely yes[2]	Probably no[6]	Definitely yes[7]	Probably yes
Chen *et al.* (2020)[32]	Probably yes[1]	Probably no[3]	Probably no[6]	Definitely yes[7]	Probably no[9]

1 Computer-generated random number sequence 2 Central allocation 3 Central allocation not reported 4 Placebo-controlled trial 5 Open-label trial 6 Blinding not reported 7 No missing outcome data or reasons for missing outcome data unlikely to be related to outcome 8 Primary outcome changed midway and preliminary results available 9 Balance of co-interventions not reported

Appendix III–II. Risk of bias in included cohort studies

Study (year)	From the same population	Assessment of exposure	Outcome not present at start	Adjustment	Assessment of prognostic factors	Assessment of outcome	Adequate follow-up	Co-interventions similar
Lan *et al.* (2020) (pre-print)[29]	Definitely yes	Probably yes	Definitely yes	Probably no	Probably no	Yes	Yes	Probably no
Zhu *et al.* (2020)[18]	Definitely yes	Probably yes	Definitely yes	Definitely no	Probably no	Yes	Probably yes	Probably no
Ye *et al.* (2020)[19]	Definitely yes	Probably yes	Definitely yes	Definitely no	Probably no	Yes	Probably yes	Probably no
Lian *et al.* (2020)[20]	Definitely yes	Probably yes	Definitely yes	Definitely no	Probably no	Yes	Probably yes	Probably no
Deng *et al.* (2020)[17]	Definitely yes	Probably yes	Probably yes	Definitely no	Probably no	Yes	Probably yes	Definitely no
Wang *et al.* (2020)[22]	Definitely yes	Probably yes	Probably yes	Definitely no	Probably no	Yes	Probably yes	Definitely no
Cai *et al.* (2020)[21]	Definitely yes	Probably yes	Probably yes	Definitely yes	Probably yes	Probably no	Probably yes	Probably yes
Yan *et al.* (2020)[31]	Definitely yes	Probably yes	Probably yes	Probably yes	Probably yes	Yes	Probably yes	Definitely no
Shi *et al.* (2020)[28]	Definitely yes	Probably yes	Probably yes	Definitely no	Probably no	Yes	Probably yes	Definitely no
Wen *et al.* (2020)[30]	Definitely yes	Probably yes	Probably yes	Definitely no	Probably no	Yes	Probably yes	Definitely no

Appendix III–III. Risk of bias in included cohort studies

Study (year)	Criteria for inclusion	Condition measured in a standard, reliable way	Valid methods used for identification of the condition	Consecutive inclusion of participants	Complete inclusion of participants	Clear reporting of the demographics of the participants	Clear reporting of clinical information	Outcomes or follow-up results of cases clearly reported	Clear reporting of the presenting site(s)/ clinic(s) demographic information	Statistical analysis appropriate
Young *et al.* (2020)[23]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Grein *et al.* (2020)[25]	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	Yes	Unclear
Zhou *et al.* (2020)	No	Yes	Yes	No	No	Yes	No	Unclear	Unclear	Yes
Antinori *et al.* (2020)[26]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Wang *et al.* (2020)[24]	Unclear	Unclear	Unclear	No	No	No	Unclear	Unclear	Unclear	Yes