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Potential Effectiveness and Safety of Antiviral Agents in Children with Coronavirus Disease 2019: A Rapid Review and Meta-Analysis

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Abstract

Background: The COVID-19 outbreak presents a new, life-threatening disease. Our aim was to assess the potential effectiveness and safety of antiviral agents for COVID-19 in children.

Methods: Electronic databases from their inception to March, 31 2020 were searched for randomized controlled trials, clinical controlled trials and cohort studies of interventions with antiviral agents for children (less than 18 years of age) with COVID-19.

Results: A total of 23 studies of indirect evidence with 6008 patients were included. The risks of bias in all studies were moderate to high in general. The effectiveness and safety of antiviral agents for children with COVID-19 is uncertain: For adults with COVID-19, lopinavir/ritonavir had no effect on mortality (risk ratio [RR]= 0.77, 95% confidence interval [CI] 0.45 to 1.30) and probability of negative PCR test (RR=0.98, 95 CI% 0.82 to 1.18). Arbidol had no benefit on probability of negative PCR test (RR=1.27, 95% CI 0.93 to 1.73). Hydroxychloroquine was not associated with increasing the probability of negative PCR result (RR=0.93, 95% CI 0.73 to 1.18). For adults with SARS, interferon was associated with reduced corticosteroid dose (weighted mean difference [WMD]=-0.14 g, 95% CI -0.21 to -0.07) but had no effect on mortality (RR=0.72, 95% CI 0.28 to 1.88); ribavirin did not reduce mortality (RR=0.68, 95% CI % 0.43 to 1.06) and was associated with high risk of severe adverse reactions; and oseltamivir had no effect on mortality (RR=0.87, 95% CI 0.55 to 1.38). Ribavirin

combined with interferon was also not effective in adults with MERS and associated with adverse reactions.

Conclusions: There is no evidence showing the effectiveness of antiviral agents for children with COVID-19, and the clinical efficacy of existing antiviral agents is still uncertain. We do not suggest clinical routine use of antivirals for COVID-19 in children, with the exception of clinical trials.

Keywords: Antiviral agents; children; COVID-19; meta-analysis; rapid review.

Background

A novel coronavirus, later named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first detected on December 8, 2019, when several cases of pneumonia of unknown etiology were reported in Wuhan, Hubei province, China. (1-3) Due to the rapidly increasing numbers of infections and deaths, World Health Organization (WHO) subsequently declared the outbreak as a Public Health Emergency of International Concern (PHEIC) on January 30, 2019 and officially named the disease as “Corona Virus Disease hyphen one nine” (COVID-19) on February 11, 2020.(4-6) As of April 12, a total of 1,696,588 confirmed cases had been reported in more than 200 countries, and the number of cases abroad was still rapidly increasing, creating global alarm and concerns about the impact on health care and economy of the affected areas (7). On February 28, WHO increased the level of risk of spread and impact of COVID-19 on the global level to very high and declared COVID-19 as a global pandemic on March 11, 2020. (8) However, there is so far no effective treatment or vaccine against the SARS-CoV-2.

At present, guidelines suggest that the use of lopinavir/ritonavir (LPV/r), interferon (IFN) and chloroquine may help to some extent against COVID-19 in adults.(9-11) Seven recently published systematic or rapid reviews suggested that LPV/r, IFN, chloroquine and hydroxychloroquine (HCQ) can be used as an experimental therapy for COVID-19 in adults as the initial treatment, (12-18) but the effectiveness and safety of other antiviral agents (such as ribavirin [RBV], remdesivir and oseltamivir) is uncertain.

Although the course of COVID-19 is usually milder in children than adults, children with undeveloped immune system, such as the youngest case confirmed only 30 hours after birth, are at substantial risk of severe infection. (19) Antiviral therapy against SARS-CoV-2 in children is therefore urgently needed, but so far the evidence and literature on the topic remain limited. (20-21)

The objective of this rapid review is to perform a comprehensive literature search and summarize the current evidence on effectiveness and safety of antiviral agents for children with COVID-19. The findings will provide evidence for the development of guideline and the clinical treatment of children with COVID-19.

Methods

Search Strategy

Two researchers (Q Shi and X Wang) searched the following electronic databases from their inception until March 31, 2020: MEDLINE (via PubMed), Embase, Web of Science, the Cochrane library, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), and Wanfang Data.(22) We also searched three clinical trial registry platforms (the WHO Clinical Trials Registry Platform, US National Institutes of Health Trials Register and the International Standard Randomized Controlled Trial Number [ISRCTN] Register), Google Scholar, the official websites of WHO and Centers for Disease Control (CDC), and the preprint platforms BioRxiv, MedRxiv, and SSRN. In addition, we searched the reference lists of the identified systematic reviews for further potential studies. Finally, we contacted experts in the

field to identify studies that may have been missed.

The search strategy was also peer reviewed by an external specialist. We systematically searched by combining the MeSH and free words. The keywords and terms in the MEDLINE including “COVID-19”, “SARS-CoV-2”, “Novel coronavirus”, “2019-novel coronavirus”, “2019-nCoV”, “antiviral agents”, “antiviral*”, “ribavirin”, “interferon”, “oseltamivir”, “remdesivir”, “lopinavir”, “ritonavir”, “LPV/r” and their derivatives. The details of the search strategy can be found in the *Supplementary Material 1*.

Inclusion and exclusion criteria

We primarily searched for studies on children less than 18 years of age diagnosed with COVID-19. We made no restrictions on gender, race, or geographical location or setting. COVID-19 was defined according to the WHO interim guidance. (23) If direct evidence on children was unavailable, we also searched indirect evidence from COVID-19 in adults, or from children or adults infected with severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) which have similar gene sequences with SARS-CoV-2.

We included all randomized controlled trials (RCTs), clinical controlled trials (CCTs) and cohort studies that compared the effectiveness and safety of antiviral agents (including but not limited to IFN, oseltamivir, LPV/r, RBV, HCQ and remdesivir) with placebo, or comparing the combination of antiviral agents and symptomatic treatment

with symptomatic treatment alone. Studies comparing different types and different administration mode of antiviral agents were also included. In vitro studies, animal experiments and basic researches were excluded. Duplicates, articles written in languages other than English or Chinese, conference abstracts and studies where full text could not be retrieved or data were missing were also excluded.

The primary outcomes were mortality and the risk of serious adverse effects (defined as hemolytic anemia, bradycardia and other side effects on cardiovascular system and drug-induced liver injury). The secondary outcomes included the probability of negative PCR test (defined as the rate of negative PCR of SARS-CoV-2 after discharge from the hospital or after receiving antiviral agents which differed in studies), mean or reduction in the dose of corticosteroids, remission of the main clinical symptoms, risk of Acute Respiratory Distress Syndrome (ARDS), duration of disease (defined as the duration (in days) of total stay from symptom onset to recovery), probability of admission to intensive care unit (ICU) and other adverse reactions. All the reasons for exclusion of ineligible studies were recorded, and the process of study selection was documented using a PRISMA flow diagram.

Study selection

After eliminating duplicates, two researchers (Q Shi and X Wang) independently screened first the titles and abstracts, and then the full-texts of potentially relevant articles, using pre-defined criteria. The specific bibliographic software EndNote was

used, and discrepancies were discussed, or solved with a third researcher (Q Zhou). The reasons for exclusion of ineligible studies were recorded. The process of study selection was documented using a PRISMA flow diagram. (23)

Data extraction

Four researchers (Q Shi, X Wang, Q Zhou and J Liao) extracted data independently in pairs with a pre-determined form, and disagreements were resolved by consensus. We extracted the following data: 1) basic information; 2) participants: baseline characteristics and inclusion/exclusion criteria; 3) details of the intervention and control strategies; and 4) outcomes (for dichotomous data, the number of events and total participants in per group; for continuous data, means, standard deviations (SD), and the number of total participants in per group).

Risk of bias assessment

Two researchers (Y Yu and Z Wang) independently assessed the potential bias in each included study. Discrepancies were resolved by discussion and consensus to a third researcher (S Lu). For RCTs we used the Cochrane Risk-of-Bias (RoB) assessment tool consisting seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. (24) We graded each potential source of bias as “Low”, “Unclear” or “High”. For included CCTs, we used

ROBINS-I tool, (25) which consists of seven domains: bias due to confounding, bias in selection of participants, bias in classification of interventions, bias due to departures from intended interventions, bias due to missing data, bias in outcome measurement, and bias in selective reporting. The risk of each type of bias was graded as “Low”, “Moderate”, “Serious”, “Critical”, and “No information”. For both RoB and ROBINS-I, the overall risk of bias within each study was based on the results of all the individual domains. For cohort studies, we used Newcastle-Ottawa Scale (NOS) consisting of three domains (selection of exposure, comparability and assessment of outcome). (26) The maximum score was nine, and scores of seven or more was graded as high quality while less than seven scores as low quality.

Data synthesis

We performed Meta-analyses of outcomes for which the data that were sufficiently compatible. For outcomes with too heterogeneous data, a qualitative synthesis was done. We processed the data according to the Cochrane Handbook by using a random-effects model. (27) For dichotomous data, we calculated risk ratios (RR) with 95% confidence intervals (CI); for continuous data, we calculated weighted mean difference (WMD) with 95% CI. Two-sided *P* values < 0.05 were considered statistically significant. (28) Analyses were performed by Stata 14 software (Stata Corp LLC).

For missing SDs, standard errors (SE) were converted to SDs when SE was presented, and if both were missing, we estimated SDs from *P* values or 95% CI. For

missing means, we estimated them from interquartile ranges and medians. (29) Statistical heterogeneity was assessed using the chi-square and the I^2 statistic, with $P <$ 0.10 was considered to be consistent with statistically significant heterogeneity and I^2 statistic > 50% indicating substantial heterogeneity. (28) If we detected heterogeneity, we performed subgroup analyses (route, dose, frequency or administration of antivirals) or sensitivity analyses (excluding studies with low-quality or high risk of bias; excluding studies in which mean or SD, or both of them were imputed for missing data) to explore the reasons. Publication bias was assessed by examining the symmetry of the funnel-plot.

Quality of the evidence assessment

We assessed the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, and classified the evidence quality as “high”, “moderate”, “low” and “very low”. (30-31) We also produced “Summary of Findings”tables. Direct evidence from RCTs starts at high quality, and evidence from observational studies at low quality. In the next step, the quality can be downgraded for five different reasons (study limitations, consistency of effect, imprecision, indirectness, and publication bias) and upgraded for three reasons (large magnitude of effect, dose-response relation and plausible confounders or biases).

Results

Study and Patient Characteristics

We identified 4095 references from the databases, and six records from additional searches. A total of 1216 records were excluded as duplicates, after screening for titles, abstract and full texts, no direct evidence for children with COVID-19 was found. Finally, a total of 23 studies (six RCTs and 17 cohort studies) with 6008 patients of indirect evidence were included (*Figure 1*) (32-54). These studies were published between 2003 and 2020 and the sample size ranged from 22 to 1701, of which, seven studies were on COVID-19, 13 studies on SARS and three studies on MERS. Another study of Cai 2020 was found but in temporary removal condition, therefore it was not included (55).

The risk of bias in the included three RCTs were high, as they did not perform allocation concealment and blindness for patients and clinicians. The other three RCTs had low risk of bias (n=3). More than half of the cohort studies (n=9) had a high risk of bias, the main reasons were being the lack of controlling for important factors that would influence the primary study results, lack of long enough follow-up for outcomes to occur, and inadequate outcome ascertainment. Study characteristics and risk of bias are illustrated in *Table 1*.

Efficacy and Safety of Existing Antiviral Agents

The results of the Meta-analysis for each type of antiviral agent are shown in *Table 2*. The details of primary data from each retrieved study can be found in *Supplementary*

Material 2. The details of GRADE for each outcome can be found in *Supplementary Material 3*. Due to the small number of studies for each outcome, we were unable to evaluate publication bias.

Lopinavir/ritonavir

Three studies with a total of 327 patients (32-34) reported the effectiveness and safety of LPV/r in adult patients with COVID-19. There was no statistically significant difference in the mortality (RR =0.77, 95% CI 0.45 to 1.30, low-quality evidence, *Figure 2*) and probability of negative PCR test (RR=0.98, 95 CI% 0.82 to 1.18, very low-quality evidence) between the intervention and control groups. There was also no statistically significant difference in the incidence of adverse reactions (RR=1.24, 95 CI% 0.67 to 2.28, very low-quality evidence) and serious adverse reactions (RR=0.62, 95 CI% 0.38 to 1.01, moderate-quality evidence) between the two groups, of which, the most common side effects were gastrointestinal reaction (including nausea and vomiting, diarrhea and abnormal liver function).

Two cohort studies with a total of 830 patients (35,36) reported the effectiveness and safety of LPV/r in adult patients of SARS. The results showed that LPV/r therapy decreased the risk of death (RR=0.16, 95% CI 0.03 to 0.77, low-quality evidence, *Figure 2*) and ARDS (RR=0.11, 95% CI 0.02 to 0.77, very low-quality evidence) compared with the control group. However, no statistically significant difference was found in the dose of corticosteroids (WMD=-0.82 g, 95% CI -2.03 to 0.40) with

considerable heterogeneity of the *I*-squared was 86.4%, because both means and SDs of the two studies were imputed from missing data. In addition, patients in the LPV/r group were more often nosocomially infected (RR=0.05, 95% CI 0.00 to 0.75), and had a higher risk of adverse reactions such as diarrhea (RR=0.39, 95% CI 0.23 to 0.69) or recurrent fever (RR=0.65, 95% CI 0.43 to 0.98). The overall quality of evidence was very low.

Arbidol

Three studies with a total of 138 patients (33-34,37) reported the effectiveness and safety of arbidol in adult patients of COVID-19. There was no statistically significant difference in the probability of having a negative PCR result (RR=1.27, 95% CI 0.93 to 1.73), probability of radiographic abnormalities remission (RR=1.23, 95% CI 0.63 to 2.40) and duration of disease (WMD=-1.70 days, 95% CI -3.28 to -0.12) between patients with arbidol therapy and control group. Because of the large heterogeneity in the radiographic abnormalities remission, we performed a subgroup analysis of study design, and we still found no significant association in neither cohort studies (RR=1.58, 95% CI 0.97 to 2.59) nor RCTs (RR=0.71, 95% CI 0.47 to 1.06). There was also no statistically significant difference in the incidence of adverse reactions (RR=1.06, 95% CI 0.25 to 4.43) between the two groups. The overall quality of evidence was very low.

Interferon

Four cohort studies with a total of 2013 patients (38-41) reported the effectiveness and safety of intramuscular or subcutaneous injection of IFN in adult patients with SARS. The results showed that IFN therapy decreased the dose of corticosteroids dose (WMD=-0.14 g, 95% CI -0.21 to -0.07) and promoted the remission of radiographic abnormalities. No statistically significant difference was found in mortality (RR=0.72, 95% CI 0.28 to 1.88, *Figure 2*). No obvious adverse reactions were reported in any of the above four studies. The quality of evidence was very low.

One cohort study with a total of 24 patients (43) compared the effectiveness of different types of IFN in adult patients with SARS. The results showed that there was no statistically significant difference in the risk of death (RR=1.33, 95% CI 0.80 to 2.20) between patients treated with IFN-α and IFN-β. The quality of evidence was very low.

Ribavirin

Six cohort studies with a total of 3481patients (40,43-47) reported the effectiveness and safety of RBV in adult patients with SARS. The results showed that RBV therapy significantly decreased the duration of corticosteroid use (WMD =-5.60 g, 95% CI -7.94 to -3.26, very low-quality evidence), and increased the duration of disease (WMD=1.04 d, 95% CI -0.44 to 2.52, very low-quality evidence) compared with the control group. There was no statistically difference in the risk of death (RR=0.68, 95% CI % 0.43 to 1.06, *Figure 2*). In addition, the use of RBV was associated with an increased risk of adverse reactions, including anemia (RR=1.67, 95% CI 1.07 to 2.61, low-quality

evidence), bradycardia (RR=2.02, 95% CI 1.30 to 3.12, low-quality evidence), and hypomagnesemia (RR=10.19, 95% CI 4.61 to 22.55, high-quality evidence).

Oseltamivir

Three cohort studies with a total of 2007 patients (40-41,48) reported the effectiveness and safety of oseltamivir in adult patients with SARS. The results showed that there was no statistically significant difference in the risk of death (RR=0.87, 95% CI 0.55 to 1.38, *Figure 2*) between oseltamivir therapy and the control group. The use of oseltamivir prolonged the duration of disease (WMD=3.91d, 95% CI 2.28 to 5.54, very low-quality evidence) and duration of fever (WMD=2.60 d, 95% CI 0.50 to 4.70, very low-quality evidence).

One RCT with a total of 127 patients (49) compared the effectiveness of oseltamivir between early use alone and use alone in adult patients with SARS. The results showed that early use alone was not associated with the risk of death (RR=1.62, 95% CI 0.33 to 8.05), ARDS (RR=2.60, 95% CI 0.30 to 22.57) or the duration of disease (WMD=-2.50 d, 95% CI -7.45 to 2.45). The quality of evidence was low.

Combination of ribavirin and interferon

Two cohort studies with a total of 393 patients (50-51) reported the effectiveness and safety of a combination of RBV and IFN for adult patients with MERS. The results showed that combination therapy of RBV and IFN could increase the mean reduction in

hemoglobin (WMD=2.18 g/L, 95% CI 0.86 to 3.50, very low-quality evidence) and the need of blood transfusion (RR=1.42, 95% CI 1.06 to 1.91, low-quality evidence). But there was no statistically significant difference in the risk of death (RR=1.04, 95% CI 0.74 to 1.46, *Figure 2*) between the two groups.

Favipiravir

One study with a total of 236 patients (52) reported the effectiveness and safety of favipiravir for adult patients with COVID-19. The results showed that when comparing to arbidol, favipiravir had lower incidence of dyspnea after taking medicine (RR=0.30, 95% CI 0.10 to 0.87), but there was no differnce in clinical recovery (RR=1.18, 95% CI 0.95 to 1.48) or the incidence of adverse reactions (RR=1.37, 95% CI 0.90 to 2.08). The overall quality of evidence was low.

Hydroxychloroquine

Two studies with a total of 92 patients (53-54) reported the effectiveness and safety of hydroxychloroquine for adult patients with COVID-19. The results showed that HCQ had no benefit on the negative PCR result (RR=0.93, 95% CI 0.73 to 1.18), but was effective for shortening the duration of fever (WMD=-0.90 days, 95% CI -1.48 to -0.31). In addition, there was no statistically significant difference in the incidence of adverse reactions (RR=1.65, 95% CI 0.50 to 5.50) between HCQ therapy and the control group. The overall quality of evidence was low.

Discussion

Our rapid review identified a total of 23 studies. No direct evidence for the effectiveness and safety of antiviral agents for children with COVID-19 was available. Based on the analysis of indirect evidence from adult patients with COVID-19, very low to low-quality evidence indicated that LPV/r, arbidol and hydroxychloroquine were not effective. For adult patients with SARS or MERS, very low to low-quality evidence indicated that LPV/r, IFN, RBV and oseltamivir had no clinical effectiveness on mortality, corticosteroids dose, or other main outcomes. Certain medications, such as LPV/r and RBV, were likely to lead to adverse reactions (such as gastrointestinal reaction, abnormal liver function, anemia, bradycardia, or hypoxemia).

Most viral diseases are self-limiting illnesses that do not require specific antiviral therapy. At present, no antiviral agent has been confirmed to be effective against COVID-19, and vaccination are currently under development, so symptomatic and supportive treatments are crucial. However, children are less likely than adults to have complications or develop into critical conditions, and their clinical manifestations are less atypical, complicating the diagnosis. (56-58) Guidelines recommend antiviral agents such as LPV/r, IFN, arbidol and chloroquine to treat COVID-19 in adults, while children (especially critically illness) can be treated reference to the regimen of adults. (9-11) Up to now, almost all COVID-19 patients (adults and children) have received antiviral therapy.(59) Several case reports or series (60-61) have also highlighted the

potential efficacy of antivirals in children with SARS-CoV-2 infection and found no obvious adverse reactions, but the number was too small to draw any conclusions. More studies are needed to further evaluate the risks and benefits that antiviral agents may bring.

LPV/r is one of the first medications that were taken into clinical practice after the beginning of the COVID-19 outbreak, and it is recommended for treatment of COVID-19 patients in the latest version of China national practice guideline (released on March 4, 2020) without any reference. (9) Our rapid review however demonstrates that LPV/r is unlikely to be effective for COVID-19 in adults with numerous obvious adverse reactions, which was the same as recent studies. (62-63) Two rapid reviews conducted in 2020 (12-13) examined that early use of LPV/r can reduce the mortality and steroid dosing in patients with SARS and MERS, and suggested that it could be used as a component for an experimental regimen to treat COVID-19. But no quantitative analysis or evidence grading was performed, and therefore the reliability of the conclusions is questionable. Although LPV/r could reduce the mortality of adult SARS patients, the quality of evidence was low. Therefore, LPV/r should not be recommended in clinical practice guidelines.

The results on other antivirals were similar to those identified in other systematic reviews. Among patients with COVID-19, the use of HCQ was effective for clinical recovery which is the same as published reviews (17-18), but we found HCQ had no benefit on probability of viral load disappearance, this is not the same as previous

studies due to the retraction of Philippe 2020 (64). All trials for HCQ included in this study had small sample size to draw robust conclusions. IFN had no benefit on mortality and the effect did not differ between IFN-α and IFN-β: the results are in line with another recent rapid review. (14) RBV and oseltamivir were not shown effective for treating adults with SARS, and the use of RBV was even related to a high risk of serious side effects, and oseltamivir prolonged the duration of disease. These results were also observed by recent and previous systematic reviews. (15, 65-66) One study demonstrated that the concentration of RBV required to effectively inhibit the activity of SARS-CoV or MERS-CoV was beyond the clinically acceptable range, so routine use of the drug would have no effect. (67) One recent case of COVID-19 in the United States suggested a promising clinical response to remdesivir, (68) and study by Wang et al. revealed that remdesivir was highly effective in the control of SARS-CoV-2 in vitro, (69) but the evidence quality was low and the newest results of clinical research suggested no significant effect for patients hospitalized of severe COVID-19, (70) and the clinical trials of remdesivir therapy are still ongoing. The outbreak of COVID-19 has imposed a great socioeconomic, public health, and clinical burden on the affected countries and regions, especially for the low-and middle-income countries. Therefore, priority should be given for the research and implementation of agents with promising outcomes.

Strengthens and Limitations

This study is to our knowledge the first systematic and comprehensive rapid review for

the effectiveness and safety of antiviral agents in children with COVID-19. It can therefore be considered the best evidence at the moment for the management of COVID-19 in children, and help to respond to the current public health emergency. Our study was also performed and reported in accordance with Cochrane Handbook and PRISMA checklist, and included Meta-analyses and grading of evidence to draw quantitative conclusions with scientific and rigorous methods. However, our study had also some limitations: First, this rapid review was unable to identify direct evidence for antiviral use in children with COVID-19 and only summarized the indirect evidence, mainly from adults patients with COVID-19, SARS or MERS. The reported treatment effects should be interpreted with caution due to the lack of high-quality RCTs and direct evidence. Second, due to the heterogeneity of the reviewed studies in terms of the wide range of treatment dosages, frequencies and routes of administration, we were unable to perform a quantitative analysis from these aspects for each antiviral. This is a major obstacle to a clear interpretation of the results of this review. Third, because of the specificity and urgency of PHEIC, our study protocol was not registered on the Prospective Register of Systematic Reviews Platform.

Further Suggestions

We suggest for the further actions on the basis of our study. First, high-quality clinical research should be carried out in a timely and effective manner, following the randomization, control and bind principles of evidence-based medicine, trying to adopt objective and representative outcomes for evaluation, so that unbiased research results

can be ensured. Second, health workers need high-quality, unbiased and evidence-based recommendations to guide clinical practice. Health workers should accumulate clinical experience and be encouraged to interpret the evidence with professionalism by cooperating with researchers, avoid conflicts of interest, and thus reduce the possibly harmful impact on children with COVID-19. Third, health policy decisions should be made based on the best available evidence and make full use of the limited resources to make decisions that are valid, rational and based on up-to-date scientific knowledge.

Conclusions

In conclusion, there is no direct evidence for antiviral agents in children with COVID-19 so far. Very low to low-quality indirect evidence indicated that antiviral agents were not effective for reducing mortality, and the effectiveness and safety of antivirals for children with COVID-19 are uncertain. Therefore, we cannot suggest routine use of these agents for the treatment of COVID-19 in children, with the exception of clinical trials after thorough ethical assessment.

Author contributions

(I) All the authors contributed to the conception and design of the study as follows; (II) Administrative support: Y Chen; (III) Provision of study materials or patients: Q Shi, Q Zhou and X Wang; (IV) Collection and assembly of data: Q Shi, Q Zhou, X Wang, J Liao; (V) Data analysis and interpretation: Q Shi, Q Zhou and X Wang, J Liao, Y Yu, Z

Wang, S Lu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary Material 1-Search strategy

PubMed

#1 "COVID-19" [Supplementary Concept]
#2 "Severe Acute Respiratory Syndrome Coronavirus" [Supplementary Concept]
#3 "Middle East Respiratory Syndrome Coronavirus" [Mesh]
#4 "Severe Acute Respiratory Syndrome" [Mesh]
#5 "SARS Virus" [Mesh]
#6 "COVID-19" [Title/Abstract]
#7 "SARS-COV-2" [Title/Abstract]
#8 "Novel coronavirus" [Title/Abstract]
#9 "2019-novel coronavirus" [Title/Abstract]
#10 "coronavirus disease-19" [Title/Abstract]
#11 "coronavirus disease 2019" [Title/Abstract]
#12 "COVID19" [Title/Abstract]
#13 "Novel CoV" [Title/Abstract]
#14 "2019-nCoV" [Title/Abstract]
#15 "2019-CoV" [Title/Abstract]
#16 "Wuhan-Cov" [Title/Abstract]
#17 "Wuhan Coronavirus" [Title/Abstract]
#18 "Wuhan seafood market pneumonia virus" [Title/Abstract]
#19 "Middle East Respiratory Syndrome" [Title/Abstract]
#20 "MERS" [Title/Abstract]
#21 "MERS-CoV" [Title/Abstract]
#22 "Severe Acute Respiratory Syndrome" [Title/Abstract]
#23 "SARS" [Title/Abstract]
#24 "SARS-CoV" [Title/Abstract]
#25 "SARS-Related" [Title/Abstract]
#26 "SARS-Associated" [Title/Abstract]
#27 #1-#26/ OR
#28 "Antiviral Agents" [Mesh]
#29 "Ribavirin" [Mesh]
#30 "Interferon" [Mesh]
#31 "GS-5734" [Supplementary Concept]
#32 "Oseltamivir " [Mesh]
#33 "Lopinavir" [Mesh]
#34 "Ritonavir" [Mesh]
#35 "lopinavir-ritonavir drug combination" [Supplementary Concept]
#36 "Antiviral*" [Title/Abstract]
#37 "Ribavirin" [Title/Abstract]
#38 "Virazole" [Title/Abstract]
#39 "Interferon" [Title/Abstract]
#40 "Remdesivir" [Title/Abstract]
#41 "GS-5734" [Title/Abstract]

#42 “Oseltamivir” [Title/Abstract]
#43 “Lopinavir” [Title/Abstract]
#44 “Ritonavir” [Title/Abstract]
#45 “Kaletra” [Title/Abstract]
#46 “LPV/r” [Title/Abstract]
#47 #28-#46/ OR
#48 #27 AND #47

Embase

#1 'middle east respiratory syndrome coronavirus'/exp
#2 'severe acute respiratory syndrome'/exp
#3 'sars coronavirus'/exp
#4 'COVID-19':ab,ti
#5 'SARS-COV-2':ab,ti
#6 'novel coronavirus':ab,ti
#7 '2019-novel coronavirus':ab,ti
#8 'coronavirus disease-19':ab,ti
#9 'coronavirus disease 2019':ab,ti
#10 'COVID19':ab,ti
#11 'novel cov':ab,ti
#12 '2019-ncov':ab,ti
#13 '2019-cov':ab,ti
#14 'wuhan-cov':ab,ti
#15 'wuhan coronavirus':ab,ti
#16 'wuhan seafood market pneumonia virus':ab,ti
#17 'middle east respiratory syndrome':ab,ti
#18 'middle east respiratory syndrome coronavirus':ab,ti
#19 'mers':ab,ti
#20 'mers-cov':ab,ti
#21 'severe acute respiratory syndrome':ab,ti
#22 'sars':ab,ti
#23 'sars-cov':ab,ti
#24 'sars-related':ab,ti
#25 'sars-associated':ab,ti
#26 #1-#25/ OR
#27 'Antiviral Agent'/exp
#28 Antiviral*[ti, ab]
#29 Ribavirin [ti, ab]
#30 Virazole [ti, ab]
#31 Interferon [ti, ab]
#32 Remdesivir [ti, ab]
#33 GS-5734 [ti, ab]
#34 Oseltamivir [ti, ab]

#35 Lopinavir [ti, ab]
#36 Ritonavir [ti, ab]
#37 Kaletra [ti, ab]
#38 "LPV/r"[ti, ab]
#39 #27-#38/ OR
#40 #26 AND #39
#41 [medline]/lim in #40
#42 #40 NOT #41

Web of science

#1 TOPIC: “COVID-19”
#2 TOPIC: “SARS-COV-2”
#3 TOPIC: “Novel coronavirus”
#4 TOPIC: “2019-novel coronavirus”
#5 TOPIC: “coronavirus disease-19” [Title/Abstract]
#6 TOPIC: “coronavirus disease 2019” [Title/Abstract]
#7 TOPIC: “COVID19” [Title/Abstract]
#8 TOPIC: “Novel CoV”
#9 TOPIC: “2019-nCoV”
#10 TOPIC: “2019-CoV”
#11 TOPIC: “Wuhan-Cov”
#12 TOPIC: “Wuhan Coronavirus”
#13 TOPIC: “Wuhan seafood market pneumonia virus”
#14 TOPIC: “Middle East Respiratory Syndrome”
#15 TOPIC: “MERS"
#16 TOPIC: “MERS-CoV"
#17 TOPIC: "Severe Acute Respiratory Syndrome"
#18 TOPIC: "SARS"
#19 TOPIC: "SARS-CoV"
#20 TOPIC: "SARS-Related"
#21 TOPIC: "SARS-Associated"
#22 #1-#21/OR
#23 TOPIC: (“Antiviral*”)
#24 TOPIC: (“Ribavirin”)
#25 TOPIC: (“Virazole”)
#26 TOPIC: (“Interferon”)
#27 TOPIC: (“Remdesivir”)
#28 TOPIC: (“GS-5734”)
#29 TOPIC: (“Oseltamivir”)
#30 TOPIC: (“Lopinavir”)
#31 TOPIC: (“Ritonavir”)
#32 TOPIC: (“Kaletra”)
#33 TOPIC: (“LPV/r”)

#34 #23-#33/ OR
#35 #22 AND #34

Cochrane Library

#1 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] explode all trees
#2 MeSH descriptor: [Severe Acute Respiratory Syndrome] explode all trees
#3 MeSH descriptor: [SARS Virus] explode all trees
#4 "COVID-19":ti,ab,kw
#5 "SARS-COV-2":ti,ab,kw
#6 "Novel coronavirus":ti,ab,kw
#7 "2019-novel coronavirus" :ti,ab,kw
#8 "Novel CoV" :ti,ab,kw
#9 "2019-nCoV" :ti,ab,kw
#10 "2019-CoV" :ti,ab,kw
#11 "coronavirus disease-19" :ti,ab,kw
#12 "coronavirus disease 2019" :ti,ab,kw
#13 "COVID19" :ti,ab,kw
#14 "Wuhan-Cov" :ti,ab,kw
#15 "Wuhan Coronavirus" :ti,ab,kw
#16 "Wuhan seafood market pneumonia virus" :ti,ab,kw
#17 "Middle East Respiratory Syndrome" :ti,ab,kw
#18 "MERS":ti,ab,kw
#19 "MERS-CoV":ti,ab,kw
#20 "Severe Acute Respiratory Syndrome":ti,ab,kw
#21 "SARS" :ti,ab,kw
#22 "SARS-CoV" :ti,ab,kw
#23 "SARS-Related":ti,ab,kw
#24 "SARS-Associated":ti,ab,kw
#25 #1-#24/ OR
#26 MeSH descriptor: [Antiviral agents] explode all trees
#27 ("Antiviral*"): ti, ab, kw
#28 ("Ribavirin"): ti, ab, kw
#29 ("Virazole"): ti, ab, kw
#30 ("Interferon"): ti, ab, kw
#31 ("Remdesivir"): ti, ab, kw
#32 ("GS-5734"): ti, ab, kw
#33 ("Oseltamivir"): ti, ab, kw
#34 ("Lopinavir"): ti, ab, kw
#35 ("Ritonavir"): ti, ab, kw
#36 ("Kaletra"): ti, ab, kw
#37 ("LPV/r"): ti, ab, kw
#38 #26-#37/ OR

#39 #25 AND #38

CNKI

#1 主题:("新型冠状病毒")

#2 主题:("COVID-19")

#3 主题:("SARS-COV-2")

#4 主题:("2019-nCoV ")

#5 主题:("2019-CoV ")

#6 主题:(" 武汉冠状病毒")

#7 主题:("中东呼吸综合征")

#8 主题:("严重急性呼吸综合征")

#9 主题:("SARS")

#10 主题:("MERS")

#11 主题:("MERS-CoV ")

#12 #1-#11/ OR

#13 主题:("抗病毒")

#14 主题:("干扰素")

#15 主题:("利巴韦林")

#16 主题:("病毒唑")

#17 主题:("三氮唑核苷")

#18 主题:("尼斯可")

#19 主题:("瑞德西韦")

#20 主题:("奥司他韦")

#21 主题:("达菲")

#22 主题:("特敏福")

#23 主题:("克流感")

#24 主题:("洛匹那韦")

#25 主题:("利托那韦")

#26 主题:("利托纳韦")

#27 主题:("克力芝")

#28 #13-#27/ OR
#29 #12 AND #28

CBM

#1 "新型冠状病毒"[常用字段:智能]

#2 "COVID-19"[常用字段:智能]

#3 "SARS-COV-2"[常用字段:智能]

#4 "2019-nCoV"[常用字段:智能]

#5 "2019-CoV"[常用字段:智能]

#6 "武汉冠状病毒"[常用字段:智能]

#7 "中东呼吸综合征冠状病毒"[不加权:扩展]

#8 "中东呼吸综合征"[常用字段:智能]

#9 "MERS"[常用字段:智能]

#10 "MERS-CoV"[常用字段:智能]

#11 "严重急性呼吸综合征"[不加权:扩展]

#12 "SARS 病毒"[不加权:扩展]

#13 "严重急性呼吸综合征"

#14 "SARS"[常用字段:智能]

#15 #1-#14 / OR

#16 "抗病毒药" [不加权:扩展]

#17 "抗病毒"[常用字段:智能]

#18 "干扰素"[常用字段:智能]

#19 "利巴韦林"[常用字段:智能]

#20 "病毒唑"[常用字段:智能]

#21 "三氮唑核苷"[常用字段:智能]

#22 "尼斯可"[常用字段:智能]

#23 "瑞德西韦"[常用字段:智能]

#24 "奥司他韦"[常用字段:智能]

#25 "达菲"[常用字段:智能]

#26 "特敏福"[常用字段:智能]

#27 "克流感"[常用字段:智能]

#28 "洛匹那韦"[常用字段:智能]

#29 "利托那韦"[常用字段:智能]

#30 "克力芝"[常用字段:智能]

#31 #16-#30/ OR
#32 #15 AND #31

Wanfang

#1 主题:("新型冠状病毒")

#2 主题:("COVID-19")

#3 主题:("SARS-COV-2")

#4 主题:("2019-nCoV ")

#5 主题:("2019-CoV ")

#6 主题:(" 武汉冠状病毒")

#7 主题:("中东呼吸综合征")

#8 主题:("严重急性呼吸综合征")

#9 主题:("SARS")

#10 主题:("MERS")

#11 主题:("MERS-CoV ")

#12 #1-#11/ OR

#13 主题:("抗病毒")

#14 主题:("干扰素")

#15 主题:("利巴韦林")

#16 主题:("病毒唑")

#17 主题:("三氮唑核苷")

#18 主题:("尼斯可")

#19 主题:("瑞德西韦")

#20 主题:("奥司他韦")

#21 主题:("达菲")

#22 主题:("特敏福")

#23 主题:("克流感")

#24 主题:("洛匹那韦")

#25 主题:("利托那韦")

#26 主题:("利托纳韦")

#27 主题:("克力芝 ")

#28 #13-#27/ OR
#29 #12 AND #28

Supplementary Material 2. Data extraction (Table 1-8)

1. Lopinavir/ ritonavir (LPV/r)

Table 1. Evidence summary of LPV/r

Study	Design	Size	Disease	Compare	Primary outcomes	Secondary outcomes	Conclusion
Cao 2020 (33)	RCT	199	COVID-19 (severe)	LPV vs no LPV	Mortality: 19.2% vs 25.0% Any adverse reactions (%): 48.4 vs 49.5 Serious adverse reactions (%): 20.0 vs 32.3	Negative PCR result (%) at 28 day: 59.3 vs 57.7 Time until clinical symptoms improved (d): 15 ±3 vs 16± 2 Duration of hospitalization (d): 14.3 ± 3.7 vs 15.7 ± 3.8	The use of LPV/r had no effects on mortality and negative PCR result for adult patients with severe COVID-19
Li 2020 (34)	RCT	28	COVID-19 (mild/moderate)	LPV vs no LPV	Adverse reactions: 5 vs 0 Negative PCR result at day 7 (%):42.9% vs 71.4% Negative PCR result at day 14 (%): 76.2 vs 71.4	Rate of received oxygen therapy: 18 (85.7%) vs 6 (85.7%) Rate of clinical symptoms improvement: 13/21 vs 6/7 Rate of improvement on chest CT (%):16/19(84.2%) vs 6/6 (100%)	LPV/r seems little benefit for improving the clinical outcome of COVID-19
Chen 2020 (35)	Cohort	134	COVID-19 (all)	LPV vs no LPV (both groups received Interferon and supportive treatment)	Duration of disease (d): 4.0 (2.5-7.0) vs 5 (3.0-8.5) P=0.20 Adverse reactions (%): 17.3 (n=9) vs 8.3 (n=4) P=0.33	Radiographic abnormalities remission (%): 42.3 (n=22) vs 52.1 (n=25) P=0.30 Negative PCR result (%): 71.8 (28/39) vs 77.1 (27/35) P=0.79 Median time to temperature normalization after admission (d): 6 vs 4 P=0.31	The use of LPV/r had no effects on relieving symptoms or accelerating virus clearance.
Chan 2003 (36)	Cohort	678	SARS	LPV vs no LPV (both	Mortality: 2.3 (0-6.8) vs 15.6 (9.8-22.8) (P <	Intubation (%): 0 vs 11.0 (7.7-15.3) (P < 0.005)	The addition of LPV to a standard treatment protocol

				groups received methylprednisolone and oral ribavirin)	0.005) Mean methylprednisolone dose (g): 1.6 (1.1-2.0) vs 3.0 (2.8-3.2) (P < 0.005)	Risk of oxygen desaturation episodes (%): 68.2(52.3-81.8) vs 84.5 (74.4-95.2) (P=NS) Elevated serum transaminase levels (%): 9.1 (0-18.2) vs 6.9 (4.5-9.9) (P=NS) Elevated serum amylase level (%): 5 (0-15) vs 2.4 (0-4.8) (P=NS)	for SARS could reduce overall death rate, intubation rate and the dose of methylprednisolone
Chu 2003 (37)	Cohort	152	SARS	LPV vs no LPV (both groups received methylprednisolone and ribavirin)	Mortality: 0 (0%) vs 7 (6.3%) (no P-value) Methylprednisolone does (g): 2.0 (0–3.0) vs 1.5 (1.0–3.0) (P=0.477)	ARDS: 1 (2.4%) vs 25 (22.5%) (no P-value) Radiographic abnormalities worsened:51.2% vs 81.1% (P < 0.001) Nosocomial infection:0% vs 25.2% (P=0.048) Diarrhea: 24.4% vs 62.2% (P < 0.001) Recurrent fever: 39% vs 60.4% (P = 0.0027)	There was no effect on the ARDS rate, mortality and dose of methylprednisolone in SARS with LPV, and it could cause adverse reactions.

PCR: Polymerase Chain Reaction

ARDS: Acute respiratory distress syndrome

2. Arbidol

Table 2. Evidence summary of Arbidol

Study	Design	Size	Disease	Compare	Primary outcomes	Secondary outcomes	Conclusion
Chen 2020 (35)	Cohort	82	COVID-19	Arbidol vs no Arbidol (both groups received Interferon and supportive treatment)	Duration of disease (d): 3.5 (2.0-6.0) vs 5 (3.0-8.5) P=0.20 Adverse reactions (%) 8.8 (n=3) vs 8.3 (n=4) P=0.33	Radiographic abnormalities remission (%): 35.3 (n=12) vs 52.1 (n=25) P=0.30 Negative PCR result (%) 82.6 (19/23) vs 77.1 (27/35) P=0.79 Median time to temperature normalization after admission (d): 6 vs 4 P=0.31	The use of Arbidol had no effects on relieving symptoms or accelerating virus clearance.

Deng 2020 (38)	Cohort	33	COVID-19	Arbidol plus LPV/r vs no LPV/r	Negative PCR result (%):15 /16 (94%) vs 9/17 (52·9%)	Improvement of chest CT scans: 11/16 (69%) vs 5/17 (29%)	Arbidol plus LPV/r could increase the rate of negative PCR and chest improvement
Li 2020 (34)	RCT	23	COVID-19	Arbidol vs no Arbidol	Adverse reactions: 0 vs 0 Negative PCR result at day 7 (%):62.5 vs 71.4 Negative PCR result at day 14 (%): 87.5 vs 71.4	Rate of received oxygen therapy: 11 (68.8%) vs 6 (85.7%) Rate of clinical symptoms improvement: 14/16 vs 6/7 Rate of improvement on chest CT (%):10/15(66.7%) vs 6/6 (100%)	Arbidol seems little benefit for improving the clinical outcome of COVID-19

PCR: Polymerase Chain Reaction

3. Interferon (IFN)

Table 3. Evidence summary of IFN

Study	Design	Size	Disease	Compare	Primary outcomes	Secondary outcomes	Conclusion
Loutfy 2003 (39)	Cohort	22	SARS	IFN-a plus corticosteroids vs corticosteroids alone (IFN was given by subcutaneous)	Mortality: 0 (0%) vs 2(15.39%) no P-value	Mechanical ventilation: 1 (11.1%) vs 3 (23.1%) no P-value Transferred to ICU: 3 (33.3%) vs 5 (38.5%) no P-value Median time of needing supplemental oxygen resolved (d): 10 vs 16 (P=0.02) Median time until 50% radiographic abnormalities resolved significantly (d): 4 vs 9 (P=0.001)	IFN-a plus corticosteroids could increase oxygen saturation, shorten the time for resolution of radiographic lung abnormalities, and improve clinical symptoms.
Li 2005 (40)	Cohort	87	SARS	IFN-a vs no IFN-a (2 groups all received antibiotic , and IFN was given by intramuscul	Corticosteroids dose (mg): 272.94 ± 154.59 vs 414.12 ± 192.32 (P < 0.05)	Duration of hospitalization (d): 16.06 ± 6.27 vs 20.47 ± 2.16 (P < 0.05) Time until X-ray results improved (d): 11.12 ± 2.86 vs 15.79 ± 1.35 (P < 0.05) Duration of fever (d):	IFN-a could reduce duration of hospitalization, time to X-ray results improved and dosage of corticosteroids, but without any effect on duration of fever.

				ar or subcutaneous)		5.7l ± 3.55 vs 6.64 ± 2.73 (P > 0.05)	
Liu 2009 (41)	Cohort	1701	SARS	IFN vs no IFN	Mortality: 2.0% vs 5.0% (P=0.504)	Duration of disease (d): 21.93 ± 11.61 vs 22.73 ± 14.83 (P= 0.799)	There was no effect of interferon on mortality and duration of disease in patients with SARS.
Xu 2003 (42)	Cohort	185	SARS	IFN-a vs no IFN-a (2 groups all received ribavirin)	Death(n): 4 vs 7 (P > 0.05)	Intubation (n): 3 vs 6 (P > 0.05) Time until clinical symptoms improved (d): 6.9 ± 2.8 vs 6.3 ± 2.6 (P > 0.05) Average duration of hospitalization (d) : 19.8 ± 6.9 vs 21.1 ± 7.3 (P > 0.05) Time of pulmonary shadow resolved significantly (d): 11.5 ± 4.1 vs 11.2 ± 3.9 (P > 0.05) Duration of fever (d): 7.2 ± 3.3 vs 6.5 ± 2.9 (P > 0.05)	IFN had no efficacy on mortality, duration of fever, clinical symptoms improvement, resolution of lung radiographic abnormalities, incidence of intubation.
Shalhoub 2015 (43)	Cohort	24	MERS	IFN-α vs IFN-β (2 groups all received ribavirin, and IFN was given by subcutaneous)	Mortality: 85% vs 64% (P=0.24).	Intubation: 10 (77%) vs 6 (55%) P=0.24 Survival days (d): 21.3 (95% CI 14.1-28.5) vs 21.4 (95% CI 12.4-30.4) (P =0.977)	There was no significant difference on intubation rate, mortality and survival days in MERS compared IFN-α with IFN-β.

ICU: Intensive care unit

4. Ribavirin (RBV)

Table 4. Evidence summary of RBV

Study	Design	Size	Disease	Compare	Primary outcomes	Secondary outcomes	Conclusion
Leong 2004 (44)	Cohort	229	SARS	RBV vs no RBV	Crude death rate: 10 (10.3%) vs 17 (12.9%) (P =0.679)	Admitted to ICU: 19 (19.6%) vs 27 (20.5%) (P >0.999)	There was no effect of ribavirin on crude death rate, numbers of

					Anemia: 24 (24.7%) vs 27 (20.5%) (P=0.521)	Myocardial injury: 3 (3.1%) vs 4 (3.0%) (P >0.999)	admitted to ICU, and adverse reaction in patients with SARS.
Chiou 2005 (45)	Cohort	51	SARS	RBV vs no RBV	Hypoxemia: 39% vs 14% (P =0.398) Anemia: 73% vs 14% (P= 0.006)	Peak CRP level (mg/dL): 10.3 ± 11.6 vs 5.8 ± 6.2 (P > 0.05) Peak LDH level (IU/L): 392.8 ± 307.5 vs 162.5 ± 98.0 (P=0.017)	Ribavirin could increase LDH levels and risk of anemia in SARS, but had no effect on CRP level and the occurrence of hypoxemia.
Lau 2009 (46)	Cohort	1104	SARS	RBV vs no RBV	Mortality (%): Hong Kong: 17.0 (95% CI 6.5-27.8) vs 15.4 (95% CI 13.2-17.6) (P=0.77); Toronto: 13.4 (95% CI 0-33.0) vs 16.6 (95% CI 0-44.9) (P=0.85)	None	Early treatment of SARS with ribavirin had no effect on mortality.
Wang 2005 (47)	Cohort	90	SARS	RBV vs no RBV	Duration of corticosteroids use (d): 21.5 ± 7.4 vs 2 7.1 ± 3.8 (P< 0. 0 1)	None	Ribavirin could reduce the duration of corticosteroids use, but the time length of ribavirin was not associated with the reduction.
Muller 2007 (48)	Cohort	306	SARS	RBV vs no RBV	Death: 20 (11%) vs 10 (8%) (P=0.42) Hemolytic anemia: 57% vs 30% (P <0.0001)	Mechanical ventilation: 15% vs 15% (P=0.88) Bradycardia: 34% vs 17% (P=0.0009) Hyperamylasemia: 11% vs 3% (P=0.032) Hypocalcemia: 55% vs 38% (P=0.0038) Hypomagnesemia: 50% vs 5% (P<0.0001)	High-dose ribavirin was associated with serious adverse reactions in SARS, but had no effect on mortality.
Liu 2009 (41)	Cohort	1702	SARS	RBV vs no RBV	Mortality: 4.4% vs 5.4% (P=0.340)	Duration of disease (d): 23.23±14.45 vs 22.19 ± 15.01 (P= 0.044)	Ribavirin cannot reduce the mortality, but prolong the duration of disease.

CRP: C-reactive protein

LDH: Lactate dehydrogenase

ICU: Intensive care unit

5. Oseltamivir

Table 5. Evidence summary of Oseltamivir

Study	Design	Size	Disease	Compare	Primary outcomes	Secondary outcomes	Conclusion
Xu 2011 (50)	Cohort	127	SARS	Oseltamivir (early use alone) vs Oseltamivir (use alone)	Mortality: 5(6.5) vs 2(4.0) (P > 0.05) ARDS: 4(5.2%) vs 1(2.0) (P > 0.05)	Duration of disease (d): 30.4 ± 11.2 vs 32.0 ± 15.4 (P > 0.05) Duration of fever (d): 11.17 ± 2.2 vs 12.6 ± 3.2 (P > 0.05)	Oseltamivir as initial treatment had no effect on mortality, reducing duration of fever, duration of disease and rate of ARDS.
Guo 2019 (49)	Cohort	103	SARS	Oseltamivir vs no Oseltamivir	Mortality: 3 (9%) vs 4 (6%) (P=0.682) ARDS: 7 (21%) vs 11 (16%) (P=0.588)	Mechanical ventilation: 25 (74%) vs 19 (28%) (P=0.000) Quality of life : (P > 0.05) Pulmonary artery (PA/mm): 21.00 ± 1.323 vs 19.31 ± 1.795 (P<0.001) Cardiopulmonary function: (P > 0.05) Radiological abnormalities : (P > 0.05) Cardiac ultrasound : (P > 0.05)	Oseltamivir could increase the rate of mechanical ventilation and PA, but had no effect on mortality, ARDS rate, other cardio-pulmonary function and quality of life.
Liu 2009 (41)	Cohort	1701	SARS	Oseltamivir vs no Oseltamivir	Mortality: 4.2% vs 5.2% (P=0.415)	Duration of disease (d): 25.55 ± 14 .30 vs 21.64 ± 14.77 (P= 0.000)	Oseltamivir cannot reduce mortality, but may prolong the duration of disease.
Xu 2003 (42)	Cohort	83	SARS	Oseltamivir vs no Oseltamivir (2 groups all received IFN and RBV)	Death (n): 1 vs 4 (P > 0.05)	Intubation (n): 0 vs 3 (P > 0.05) Average duration of hospitalization (d) : 12.2 ± 5.1 vs 19.8 ± 6.9 (P > 0.05) Time to clinical symptoms improved	Oseltamivir improved fever clearance time, but had no effect on mortality, intubation rate, duration of hospitalization and improvement of other symptoms and

					(d): 9.5 ± 6.0 vs 6. 9± 6.8 (P > 0.05) Time of pulmonary shadow resolved significantly (d): 12.2 ± 5.8 vs 11.5 ± 4.1 (P > 0.05) Duration of fever (d): 9.8 ± 4.2 vs 7.2 ± 3.3 (P < 0.05)	imaging.

ARDS: Acute respiratory distress syndrome

6. Combination of IFN and RBV

Table 6. Evidence summary of Combination

Study	Design	Size	Disease	Compare	Primary outcomes	Secondary outcomes	Conclusion
Omrani 2014 (51)	Cohort	44	MERS	RBV plus INF vs no RBV/IFN	14-day survival rate: 70% vs 29% (P=0.004) 28-day survival rate: 30% vs 17% (P=0.054)	Invasive ventilation: 95% vs 92% (P =1.0) Mean minimum absolute neutrophil count (×10□/L): 2.90 (1.87) vs 4.43 (1.89) (P=0.017) Mean drop in hemoglobin (g/L): 4.32 ± 2.47 vs 2.14 ± 1.9 (P=0.002)	Ribavirin combined with interferon could improve the 14-day survival rate and reduce hemoglobin level and neutrophil count in MERS, but had no effect on 28-day survival rate and other adverse effects.
Arabi 2019 (52)	Cohort	349	MERS	RBV plus IFN vs no RBV/IFN	Hospital mortality: 74.3% vs 63.4% (P=0.03) 28-d mortality: 67.4% vs 58.0% (P=0.08) 90-d mortality: 73.6% vs 61.5% (P =0.02) Adverse effects : no differences between groups	Mechanical ventilation: 58.3% vs 63.4% (P=0.34) Invasive ventilation: 87.5% vs 83.4% (P=0.29) Blood transfusions: 40.3 vs 28.3% (P =0 .02)	Ribavirin combined with interferon had no effect on 28-day mortality, rate of mechanical ventilation, invasive ventilation and adverse effects in MERS, but increased 90-day mortality and hospital mortality.

AST: Aspartate aminotransferase

ALT: Alanine aminotransferase

INR : International normalized ratio

WBC: White blood cell

7. Favipiravir

Table 7. Evidence summary of Favipiravir

Study	Design	Size	Disease	Compare	Primary outcomes	Secondary outcomes	Conclusion
Chen 2020 (53)[b]	RCT	236	COVID-19	Favipiravir vs Arbidol	clinical recovery rate of day 7: 61.21% (71/116) vs 51.67% (62/120) Adverse reactions: 37/116 vs 28/120	auxiliary oxygen therapy or noninvasive mechanical ventilation rate: 22.5% (27/120) vs 18.1% (21/116) new dyspnea: 4/116 vs 14/120 respiratory failure: 4/116 vs 4/120	favipiravir can be considered as a preferred treatment for moderate COVID-19

8. Hydroxychloroquine (HCQ)

Table 8. Evidence summary of HCQ

Study	Design	Size	Disease	Compare	Primary outcomes	Secondary outcomes	Conclusion
Chen 2020 (54)	RCT	30	COVID-19	Hydroxychloroquine vs none (two groups all received IGN)	Rate of virological cured at 7 days: 86.7 vs 93.3 Adverse reactions: 4 (26.7%) vs 3 (20.0%) $P > 0.05$	Time until negative result (d): 4 (1-9) vs 2 (1-4) $P > 0.05$ Duration of fever (d): 1(0-2) vs 1(0-3)	Hydroxychloroquine has little benefit for COVID-19 patients
Chen 2020 (55)	RCT	62	COVID-19	Hydroxychloroquine vs none	Adverse reactions: 2 vs 0	Duration of fever (d): 2.2 ± 0.4 vs 3.2± 1.3 Rate of improved pneumonia: 80.6%, (25/31) vs 54.8% (17 of 31) Incidence of clinical symptom improvement: 31 vs 27	HCQ can be considered as a preferred treatment for moderate COVID-19

Supplementary Material 3. GRADE evidence profile (Table 1-8)

Table 1. lopinavir/ ritonavir (LPV/r)

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
COVID-19										
Risk of death (%)										
RCT (1)	serious[1]	not serious	not serious	serious[3]	none	199	19/99	25/100	RR =0.77 (0.45 to 1.30)	⊕⊕◯◯ LOW
Negative PCR result (%)										
RCT (2) +CS (1)	serious[1]	not serious	not serious	serious[3]	none	232	79/119	73/113	RR 0.98 (0.82 to 1.18)	⊕◯◯◯ VERY LOW
Duration of disease (d)										
CS (1)	serious[1]	not serious	not serious	not serious	none	100	52	48	WMD -1.00 (-2.51 to 0.51)	⊕◯◯◯ VERY LOW
Adverse reactions (%)										
RCT (2) +CS (1)	serious[1]	not serious	not serious	serious[3]	none	322	60/168	53/154	RR 1.24 (0.67 to 2.28)	⊕◯◯◯ VERY LOW
Serious adverse reactions (%)										
RCT (1)	serious[1]	not serious	not serious	not serious	none	194	19/95	32/99	RR 0.62 (0.38 to 1.01)	⊕⊕⊕◯ MODERATE
Radiographic abnormalities remission (%)										
RCT (1) +CS (1)	serious[1]	not serious	not serious	serious[3]	none	125	46/71	29/54	RR 1.02 (0.70 to 1.48)	⊕◯◯◯ VERY LOW
Time until clinical symptoms improved (d)										
RCT (1)	serious[1]	not serious	not serious	serious[3]	none	199	99	100	WMD -1.00 (-1.71 to -0.29)	⊕⊕◯◯ LOW
Duration of hospitalization (d)										
RCT (1)	serious[1]	not serious	not serious	serious[3]	none	199	99	100	WMD -1.40 (-2.44 to -0.36)	⊕⊕◯◯ LOW
SARS										
Risk of death (%)										

Table 1. lopinavir/ ritonavir (LPV/r)

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
CS (2)	not serious	not serious	not serious	not serious	none	830	1/85	106/745	RR 0.16 (0.03 to 0.77)	⊕⊕◯◯ LOW
Corticosteroids dose (g)										
CS (2)	not serious	serious[2]	not serious	not serious	none	830	85	745	WMD -0.82 (-2.03 to 0.40)	⊕◯◯◯ VERY LOW
Intubation (%)										
CS (1)	not serious	not serious	not serious	not serious	none	678	0/44	70/634	RR 0.100 (0.01 to 1.59)	⊕⊕◯◯ LOW
ARDS (%)										
CS (1)	serious[1]	not serious	not serious	not serious	none	152	1/41	25/111	RR 0.11 (0.02 to 0.77)	⊕◯◯◯ VERY LOW
Elevated serum transaminase level (%)										
CS (1)	not serious	not serious	not serious	serious[3]	none	678	4/44	44/634	RR 1.31 (0.49 to 3.48)	⊕◯◯◯ VERY LOW
Elevated serum amylase level (%)										
CS (1)	not serious	not serious	not serious	serious[3]	none	678	2/44	15/634	RR 1.92 (0.45 to 8.14)	⊕◯◯◯ VERY LOW
Risk of oxygen desaturation episodes (%)										
CS (1)	not serious	not serious	not serious	not serious	none	678	30/44	536/634	RR 0.81 (0.66 to 0.99)	⊕⊕◯◯ LOW
Nosocomial infection (%)										
CS (1)	serious[1]	not serious	not serious	not serious	none	152	0/41	28/111	RR 0.05 (0.00 to 0.75)	⊕◯◯◯ VERY LOW
Diarrhea (%)										
CS (1)	serious[1]	not serious	not serious	not serious	none	152	10/41	69/111	RR 0.39 (0.23 to 0.69)	⊕◯◯◯ VERY LOW
Recurrent fever (%)										
CS (1)	serious[1]	not	not	not	none	152	16/41	67/111	RR 0.65	⊕◯◯◯

Table 1. lopinavir/ ritonavir (LPV/r)

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
		serious	serious	serious					(0.43 to 0.98)	VERY LOW
Radiographic abnormalities worsened (%)										
CS (1)	serious[1]	not serious	not serious	not serious	none	152	21/41	90/111	RR 0.63 (0.46 to 0.86)	⊕◯◯◯ VERY LOW

CI: Confidence Interval; RR: Risk Ratio; WMD: Weighted Mean Difference; CS: Cohort study;

PCR: Polymerase Chain Reaction; ARDS: Acute respiratory distress syndrome

Table 2. Arbidol

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
COVID-19										
Duration of disease (d)										
CS (1)	not serious	not serious	not serious	serious[3]	none	82	34	48	WMD -1.70 (-3.28 to -0.12)	⊕◯◯◯ VERY LOW
Negative PCR result (%)										
RCT (1) + CS (2)	not serious	serious[2]	not serious	not serious	none	114	48/55	41/59	RR 1.27 (0.93 to 1.73)	⊕◯◯◯ VERY LOW
Adverse reactions (%)										
CS (1)	not serious	not serious	not serious	serious[3]	none	82	3/34	4/48	RR 1.06 (0.25 to 4.43)	⊕◯◯◯ VERY LOW
Radiographic abnormalities remission (%)										
RCT (1) + CS (2)	not serious	not serious	not serious	serious[3]	none	136	43/65	34/71	RR 1.23 (0.63 to 2.40)	⊕◯◯◯ VERY LOW
Incidence of receiving oxygen therapy (%)										
RCT (1)	serious[1]	not serious	not serious	serious[3]	none	23	11/16	6/7	RR 0.80 (0.51 to 1.26)	⊕⊕⊕◯ MODERATE
Incidence of clinical symptoms improvement										
RCT (1)	serious[1]	not serious	not serious	serious[3]	none	23	14/16	6/7	RR 1.02 (0.72 to 1.46)	⊕⊕⊕◯ MODERATE

Table 2. Arbidol

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		

CI: Confidence Interval; RR: Risk Ratio; WMD: Weighted Mean Difference; CS: Cohort study;

Table 3. Interferon (IFN)

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
SARS (IFN vs None)										
Risk of death										
CS (3)	serious[1]	not serious	not serious	not serious	none	1908	5/125	92/1783	RR 0.72 (0.28 to 1.88)	⊕◯◯◯ VERY LOW
Duration of hospitalization (d)										
CS (2)	not serious	serious[2]	not serious	not serious	none	272	106	166	WMD -2.76 (-5.80 to 0.28)	⊕◯◯◯ VERY LOW
Duration of fever (d)										
CS (2)	not serious	serious[2]	not serious	not serious	none	272	106	166	WMD -0.04 (-1.64 to1.55)	⊕◯◯◯ VERY LOW
Corticosteroids dose (g)										
CS (1)	not serious	not serious	not serious	serious[3]	none	87	41	46	WMD -0.14 (-0.21 to -0.07)	⊕◯◯◯ VERY LOW
Duration of disease (d)										
CS (1)	serious[1]	not serious	not serious	not serious	none	1518	45	1473	WMD -0.80 (-4.28-2.68)	⊕◯◯◯ VERY LOW
Mechanical ventilation (%)										
CS (1)	not serious	not serious	not serious	serious[3]	none	22	1/9	3/13	RR 0.48 (0.06 to 3.92)	⊕◯◯◯ VERY LOW
Transferred to ICU (%)										
CS (1)	not serious	not serious	not serious	serious[3]	none	22	3/9	5/13	RR 0.87 (0.27 to 2.74)	⊕◯◯◯ VERY LOW
Intubation (%)										
CS (1)	not serious	not serious	not serious	serious[3]	none	185	3/65	6/120	RR 0.92 (0.24 to 3.57)	⊕◯◯◯ VERY LOW
Time of needing supplemental oxygen resolved (d)										

Table 3. Interferon (IFN)

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
CS (1)	not serious	not serious	not serious	serious[3]	none	22	9	13	WMD -4.00 (-9.05 to 1.05)	⊕◯◯◯ VERY LOW
Time until clinical symptoms improved (d)										
CS (1)	serious[1]	not serious	not serious	not serious	none	185	65	120	WMD 0.60 (-0.22 to 1.42)	⊕◯◯◯ VERY LOW
Time until 50% radiographic abnormalities resolved (d)										
CS (1)	not serious	not serious	not serious	serious[3]	none	22	9	13	WMD -5.00 (-6.46 to -3.54)	⊕◯◯◯ VERY LOW
Time of pulmonary shadow resolved significantly (d)										
CS (1)	serious[1]	not serious	not serious	not serious	none	185	65	120	WMD 0.30 (-0.92 to 1.52)	⊕◯◯◯ VERY LOW
Time until X-ray results improved (d)										
CS (1)	not serious	not serious	not serious	serious[3]	none	87	41	46	WMD -4.67 (-5.93 to -3.41)	⊕◯◯◯ VERY LOW
MERS (IFN-α vs IFN-β)										
Risk of death										
CS (1)	not serious	not serious	not serious	serious[3]	none	24	11/13	7/11	RR 1.33 (0.80 to 2.20)	⊕◯◯◯ VERY LOW
Intubation (%)										
CS (1)	not serious	not serious	not serious	serious[3]	none	24	10/13	6/11	RR 1.41 (0.76 to 2.61)	⊕◯◯◯ VERY LOW

CI: Confidence Interval; RR: Risk Ratio; WMD: Weighted Mean Difference; CS: Cohort study;

ICU: Intensive care unit

Table 4. Ribavirin (RBV)

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
SARS										
Risk of death										
CS (4)	not serious	serious[2]	not serious	not serious	none	2236	67/1116	74/1120	RR 0.68 (0.43 to 1.06)	⊕◯◯◯ VERY LOW

Table 4. Ribavirin (RBV)

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
Duration of corticosteroids use (d)										
CS (1)	serious[1]	not serious	not serious	not serious	none	90	53	37	WMD -5.60 (-7.94 to -3.26)	⊕○○○ VERY LOW
Duration of disease (d)										
CS (1)	serious[1]	not serious	not serious	not serious	none	1518	749	769	WMD 1.04 (-0.44 to 2.52)	⊕○○○ VERY LOW
Mechanical ventilation (%)										
CS (1)	not serious	not serious	not serious	serious[3]	none	306	27/183	19/123	RR 0.96 (0.56 to 1.64)	⊕○○○ VERY LOW
Admitted to ICU (%)										
CS (1)	not serious	not serious	not serious	serious[3]	none	229	19/97	27/132	RR 0.96 (0.57 to 1.62)	⊕○○○ VERY LOW
Anemia (%)										
CS (3)	not serious	not serious	not serious	not serious	none	586	160/324	65/262	RR 1.67 (1.07 to 2.61)	⊕⊕○○ LOW
Bradycardia (%)										
CS (1)	not serious	no serious	no serious	no serious	none	306	63/183	21/123	RR 2.02 (1.30 to 3.12)	⊕⊕○○ LOW
Hypoxemia (%)										
CS (1)	serious[1]	not serious	not serious	not serious	none	51	17/44	1/7	RR 2.71 (0.42 to 17.24)	⊕○○○ VERY LOW
Hyperamylasemia (%)										
CS (1)	not serious	not serious	not serious	not serious	none	306	20/183	5/123	RR 2.69 (1.04 to 6.97)	⊕⊕○○ LOW
Hypocalcemia (%)										
CS (1)	not serious	not serious	not serious	not serious	none	306	96/183	50/123	RR 1.29 (1.00 to 1.66)	⊕⊕○○ LOW
Hypomagnesemia (%)										

Table 4. Ribavirin (RBV)

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
CS (1)	not serious	not serious	not serious	not serious	large magnitude of effect[4]	306	91/183	6/123	RR 10.19 (4.61 to 22.55)	⊕⊕⊕⊕ HIGH
Myocardial injury (%)										
CS (1)	not serious	not serious	not serious	serious[3]	none	229	3/97	4/132	RR 1.02 (0.23 to 4.46)	⊕◯◯◯ VERY LOW
Peak CRP level (mg/dL)										
CS (1)	serious[1]	not serious	not serious	not serious	none	51	44	7	WMD 4.50 (-1.23 to 10.23)	⊕◯◯◯ VERY LOW
Peak LDH level (IU/L)										
CS (1)	serious[1]	not serious	not serious	not serious	none	51	44	7	WMD 230.30 (114.00 to 346.60)	⊕◯◯◯ VERY LOW

CI: Confidence Interval; RR: Risk Ratio; WMD: Weighted Mean Difference; CS: Cohort study;

CRP: C-reactive protein; LDH: Lactate dehydrogenase; ICU: Intensive care unit

Table 5. Oseltamivir

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
SARS (Oseltamivir vs None)										
Risk of death										
CS (3)	not serious	not serious	not serious	serious[3]	none	1887	23/502	73/1385	RR 0.87 (0.55 to 1.38)	⊕◯◯◯ VERY LOW
Mechanical ventilation (%)										
CS (1)	not serious	not serious	not serious	not serious	none	103	25/34	19/69	RR 2.67 (1.73 to 4.12)	⊕⊕◯◯ LOW
Intubation (%)										
CS (1)	serious[1]	not serious	not serious	not serious	none	83	0/18	3/65	RR 0.50 (0.03 to 9.19)	⊕◯◯◯ VERY LOW
ARDS (%)										

Table 5. Oseltamivir

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
CS (1)	not serious	not serious	not serious	serious [3]	none	103	7/34	11/69	RR 1.29 (0.55 to 3.03)	⊕◯◯◯ VERY LOW
Duration of disease (d)										
CS (1)	serious [1]	not serious	not serious	not serious	none	1518	413	1105	WMD 3.91 (2.28 to 5.54)	⊕◯◯◯ VERY LOW
Duration of hospitalization (d)										
CS (1)	serious [1]	not serious	not serious	not serious	none	83	18	65	WMD -7.60 (-10.49 to -4.71)	⊕◯◯◯ VERY LOW
Time until clinical symptoms improved (d)										
CS (1)	serious [1]	not serious	not serious	not serious	none	83	18	65	WMD 2.60 (-0.25 to 5.45)	⊕◯◯◯ VERY LOW
Duration of fever (d)										
CS (1)	serious [1]	no serious	no serious	no serious	none	83	18	65	WMD 2.60 (0.50 to 4.70)	⊕◯◯◯ VERY LOW
Pulmonary artery wide (mm)										
CS (1)	not serious	not serious	not serious	serious [3]	none	103	34	69	WMD 1.69 (1.08 to 2.30)	⊕◯◯◯ VERY LOW
Time of pulmonary shadow resolved significantly (d)										
CS (1)	serious [1]	not serious	not serious	not serious	none	83	18	65	WMD 0.70 (-2.16 to 3.56)	⊕◯◯◯ VERY LOW
SARS (Oseltamivir early use alone vs Oseltamivir use alone)										
Risk of death										
RCT (1)	serious [1]	not serious	not serious	serious [3]	none	127	5/77	2/50	RR 1.62 (0.33 to 8.05)	⊕⊕◯◯ LOW
ARDS (%)										
RCT (1)	serious [1]	not serious	not serious	serious [3]	none	127	4/77	1/50	RR 2.60 (0.30 to 22.57)	⊕⊕◯◯ LOW
Duration of disease (d)										
RCT (1)	serious [1]	not serious	not serious	serious [3]	none	127	77	50	WMD -2.50 (-7.45 to 2,45)	⊕⊕◯◯ LOW
Duration of fever (d)										
RCT (1)	serious [1]	not serious	not serious	serious [3]	none	127	77	50	WMD -0.90 (-1.91 to 0.11)	⊕⊕◯◯ LOW

Table 5. Oseltamivir

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		

CI: Confidence Interval; RR: Risk Ratio; WMD: Weighted Mean Difference; CS: Cohort study; RCT: Randomized controlled trial.

ARDS: Acute respiratory distress syndrome

Table 6. Ribavirin (RBV) plus Interferon (IFN)

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
MERS										
Risk of death										
CS (2)	not serious	serious[2]	not serious	not serious	none	393	120/164	146/229	RR 1.04 (0.74 to 1.46)	⊕○○○ VERY LOW
Invasive ventilation (%)										
CS (2)	not serious	not serious	not serious	serious[3]	none	393	145/164	193/229	RR 1.05 (0.97 to 1.13)	⊕○○○ VERY LOW
Mechanical ventilation (%)										
CS (1)	not serious	not serious	not serious	serious[3]	none	349	84/144	130/205	RR 0.92 (0.77 to 1.09)	⊕○○○ VERY LOW
Blood transfusions (%)										
CS (1)	not serious	not serious	not serious	not serious	none	349	58/144	58/205	RR 1.42 (1.06 to 1.91)	⊕⊕○○ LOW
Mean drop in haemoglobin (g/L)										
CS (1)	not serious	not serious	not serious	serious[3]	none	44	20	24	WMD 2.18 (0.86 to 3.50)	⊕○○○ VERY LOW
Mean minimum absolute neutrophil count (×10□/L)										
CS (1)	not serious	not serious	not serious	serious[3]	none	44	20	24	WMD -1.43 (-2.55 to -0.32)	⊕○○○ VERY LOW

CI: Confidence Interval; RR: Risk Ratio; WMD: Weighted Mean Difference; CS: Cohort study;

Table 7. Favipiravir

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
Favipiravir vs Arbidol (COVID-19)										
Rate of clinical recovery of day 7(%)										
RCT (1)	serious[1]	not serious	not serious	serious[3]	none	236	71/116	62/120	RR 1.18 (0.95 to 1.48)	⊕⊕◯◯ LOW
Adverse reactions (%)										
RCT (1)	serious[1]	not serious	not serious	serious[3]	none	236	37/116	28/120	RR 1.37 (0.90 to 2.08)	⊕⊕◯◯ LOW
Dyspnea after taking medicine (%)										
RCT (1)	serious[1]	not serious	not serious	serious[3]	none	236	4/116	12/120	RR 0.30 (0.10 to 0.87)	⊕⊕◯◯ LOW
Respiratory failure (%)										
RCT (1)	serious[1]	not serious	not serious	serious[3]	none	236	4/116	4/120	RR 1.03 (0.26 to 4.04)	⊕⊕◯◯ LOW

CI: Confidence Interval; RR: Risk Ratio; WMD: Weighted Mean Difference; CS: Cohort study;

Table 8. HCQ

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
COVID-19										
Negative PCR result (%)										
RCT (1)	serious[1]	not serious	not serious	serious[3]	none	30	13/15	14/15	RR 0.93 (0.73 to 1.18)	⊕⊕◯◯ LOW
Radiographic abnormalities remission (%)										
RCT (1)	serious[1]	not serious	not serious	serious[3]	none	62	25/31	17/31	RR 1.47 (1.02 to 2.11)	⊕⊕◯◯ LOW
Duration of fever (d)										
RCT (2)	serious[1]	not serious	not serious	serious[3]	none	69	37	32	WMD -0.90 (-1.48 to -0.31)	⊕⊕◯◯ LOW
Time until negative PCR result (d)										

Table 8. HCQ

№ of studies	Certainty assessment					№ of patients			Effect Value (95% CI)	Certainty
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sample	Intervention	Control		
RCT (1)	serious[1]	not serious	not serious	serious[3]	none	30	15	15	WMD 2.34 (-1.19 to 5.87)	⊕⊕◯◯ LOW
Adverse reactions (%)										
RCT (2)	serious[1]	not serious	not serious	serious[3]	none	92	6/46	3/46	RR 1.65 (0.50 to 5.50)	⊕⊕◯◯ LOW

CI: Confidence Interval; RR: Risk Ratio; WMD: Weighted Mean Difference; CS: Cohort study;

HCQ: hydroxychloroquine

Explanations

1. downgrade one level: The risk of bias is high due to the limitations of study design.
2. downgrade one level: Heterogeneity of data synthesis results, I^2> 50%.
3. downgrade one level: Sample size is less than optimal information sample (OIS).
4. upgrade two levels: Large magnitude of effect, RR>5.

FIGURE LEGENDS

Figure 1. Flow diagram of the literature search.

Abbreviations: CBM: China Biology Medicine; CNKI: China National Knowledge Infrastructure; WHO: World Health Organization; CDC: Centers for Disease Control; COVID-19: Corona Virus Disease hyphen one nine; SARS: Severe Acute Respiratory Syndrome ; MERS: Middle East respiratory syndrome; ARDS: Acute Respiratory Distress Syndrome.

Figure 2. Forest plot of mortality for included studies comparing antivirals with no antivirals.

Abbreviations: COVID-19: Corona Virus Disease hyphen one nine; SARS: Severe Acute Respiratory Syndrome ; MERS: Middle East respiratory syndrome.

The results of Meta-analysis indicated that lopinavir/ritonavir had no effect on mortality in adults with COVID-19 (risk ratio [RR]= 0.77, 95% confidence interval [CI] 0.45 to 1.30), but could decrease the mortality in adults with SARS (RR=0.16, 95% CI 0.03 to 0.77), and interferon (RR=0.72, 95% CI 0.28 to 1.88), ribavirin (RR=0.68, 95% CI % 0.43 to 1.06), oseltamivir (RR=0.87, 95% CI 0.55 to 1.38) did not reduce the mortality in adults with SARS, while combination of ribavirin and interferon was not efficeive for reducing the mortality in adults with MERS (RR=1.04, 95% CI 0.74 to 1.46).

Table 1. Baseline Characteristics of 23 Included Studies

Study	Country	Design	Sample	Disease	Sample size		Age (year)†		Sex (Male/Female)		Risk of bias
					Intervention	Control	Intervention	Control	Intervention	Control	
Cao 2020 (33)	China	RCT	199	COVID-19	99	100	58.7 ±13.5	58.0 ±15.0	61/38	59/41	High
Chen 2020 (53)	China	RCT	236	COVID-19	116	120	NR	NR	59/57	51/69	High
Li 2020 (34)	China	RCT	44	COVID-19	37	7	49.4 ±14.9		21/23		Low
Chen 2020 (54)	China	RCT	30	COVID-19	15	15	50.5 ± 3.8	46.7 ± 3.6	9/7	12/15	High
Chen 2020 (55)	China	RCT	62	COVID-19	31	31	44.1 ± 16.1	45.2 ± 14.7	14/17	15/16	Low
Xu 2011 (50)	China	RCT	127	SARS	77	50	44.4 ± 16.3	34.8 ± 12.8	59/68		Unclear
Chen 2020 (35)	China	Cohort	134	COVID-19	86	48	48 (35-62)		69/65		5
Deng 2020 (38)	China	Cohort	33	COVID-19	16	17	41.8 ±14.08	47.25 ± 17.25	7/9	10/7	7
Chan 2003 (36)	China	Cohort	678	SARS	44	634	NR	NR	12/32	NR	7
Chu 2003 (37)	China	Cohort	152	SARS	41	111	39.4 ± 15.2	42.1 ± 14.7	10/31	48/63	6
Loutfy 2003 (39)	Canada	Cohort	22	SARS	9	13	44.8 ± 9.7	46.5 ± 20.9	3/6	3/10	7
Leong 2004 (44)	Singapore	Cohort	229	SARS	97	132	34.4 ± 14.3	42.6 ± 17.7	22/75	51/81	7
Guo 2019 (49)	China	Cohort	103	SARS	34	69	29.9 ± 10.1	37.0 ± 13.2	11/23	33/36	7
Muller 2007 (48)	Canada	Cohort	306	SARS	183	123	44 (34–56)	45 (36–57)	73/110	41/82	7
Chiou 2005 (45)	China	Cohort	51	SARS	44	7	36.4 ± 15.7	49.8 ± 26.1	11/33	2/5	6
Lau 2009 (46)	China	Cohort	1104	SARS	309	795	NR	NR	125/184	395/400	6
Liu 2009 (41)	China	Cohort	1701	SARS	1200	501	42.3 ± 14.8		801/900		5
Wang 2005 (47)	China	Cohort	90	SARS	53	37	36.7 ± 13.7	39.6 ± 16.0	60/30		5
Li 2005 (40)	China	Cohort	87	SARS	41	46	29.3 ± 10.6	26.7 ± 8.2	8/33	8/38	7
Xu 2003 (42)	China	Cohort	203	SARS	83	120	41.1 ± 17.7		123/138		5
Omrani 2014 (51)	Saudi Arabia	Cohort	44	MERS	20	24	67.4 ± 18.5	64.0 ± 18.1	16/4	16/8	8
Arabi 2019 (52)	Saudi Arabia	Cohort	349	MERS	144	205	58 (47-70)	58.0 (41-70)	101/43	140/65	6
Shalhoub 2015 (43)	Saudi Arabia	Cohort	24	MERS	13	11	65 (33–84)	67 (25–88)	10/3	4/7	6

Abbreviations: NR: Not Reported; RCT: Randomized Controlled Trial; COVID-19: Corona Virus Disease hyphen one nine; SARS: Severe Acute Respiratory Syndrome; MERS: Middle East respiratory syndrome.

†Ages were reported either as mean ± standard deviation, or median (interquartile range); Sex (Male/Female) was reported as number

Table 2. Summary of evidence for the effectiveness and safety of antiviral agents

Outcome	No. of studies/ design	Sample size	Quality of the evidence	Relative effect (95% CI)
LPV/r vs no antivirals (COVID-19)				
Mortality	1 RCT	199	LOW	RR 0.77 (0.45 to 1.30)
Negative PCR result (%)	1 cohort study and 2 RCTs	232	VERY LOW	RR 0.98 (0.82 to 1.18)
Duration of disease (d)	1 cohort study	100	VERY LOW	WMD -1.00 (-2.51 to 0.51)
Adverse reactions (%)	1 cohort study and 2 RCTs	322	VERY LOW	RR 1.24 (0.67 to 2.28)
Serious adverse reactions (%)	1 RCT	194	MODERATE	RR 0.62 (0.38 to 1.01)
Radiographic abnormalities remission (%)	1 cohort study and 1 RCT	125	VERY LOW	RR 1.02 (0.70 to 1.48)
Time until clinical symptoms improved (d)	1 RCT	199	LOW	WMD -1.00 (-1.71 to -0.29)
Duration of hospitalization (d)	1 RCT	199	LOW	WMD -1.40 (-2.44 to -0.36)
LPV/r vs no antivirals (SARS)				
Mortality	2 cohort studies	830	LOW	RR 0.16 (0.03 to 0.77)
Corticosteroid dose (g)	2 cohort studies	830	VERY LOW	WMD -0.82 (-2.03 to 0.40)
Intubation (%)	1 cohort study	678	VERY LOW	RR 0.10 (0.01 to 1.59)
ARDS (%)	1 cohort study	152	VERY LOW	RR 0.11 (0.02 to 0.77)
Elevated serum transaminase level (%)	1 cohort study	678	VERY LOW	RR 1.31 (0.49 to 3.48)
Elevated serum amylase level (%)	1 cohort study	678	VERY LOW	RR 1.92 (0.45 to 8.14)
Risk of oxygen desaturation episodes (%)	1 cohort study	678	LOW	RR 0.81 (0.66 to 0.99)
Nosocomial infection (%)	1 cohort study	152	VERY LOW	RR 0.05 (0.00 to 0.75)
Diarrhea (%)	1 cohort study	152	VERY LOW	RR 0.39 (0.23 to 0.69)

Recurrent fever (%)	1 cohort study	152	VERY LOW	RR 0.65 (0.43 to 0.98)
Radiographic abnormalities worsened (%)	1 cohort study	152	VERY LOW	RR 0.63 (0.46 to 0.86)
Arbidol vs no antivirals (COVID-19)				
Duration of disease (d)	1 cohort study	82	VERY LOW	WMD -1.70 (-3.28 to -0.12)
Negative PCR result (%)	2 cohort studies and 1 RCT	114	VERY LOW	RR 1.27 (0.93 to 1.73)
Adverse reactions (%)	1 cohort study	82	VERY LOW	RR 1.06 (0.25 to 4.43)
Radiographic abnormalities remission (%)	2 cohort studies and 1 RCT	136	VERY LOW	RR 1.23 (0.63 to 2.40)
Incidence of receiving oxygen therapy (%)	1 RCT	23	MODERATE	RR 0.80 (0.51 to 1.26)
Incidence of clinical symptoms improvement	1 RCT	23	MODERATE	RR 1.02 (0.72 to 1.46)
IFN vs no antivirals (SARS)				
Death (%)	3 cohort studies	1980	VERY LOW	RR 0.72 (0.28 to 1.88)
Duration of hospitalization (d)	2 cohort studies	272	VERY LOW	WMD -2.76 (-5.80 to 0.28)
Duration of fever (d)	2 cohort studies	272	VERY LOW	WMD -0.04 (-1.64 to1.55)
Corticosteroid dose (g)	1 cohort study	87	VERY LOW	WMD -0.14 (-0.21 to -0.07)
Duration of disease (d)	1 cohort study	1518	VERY LOW	WMD -0.80 (-4.28 to -2.68)
Mechanical ventilation (%)	1 cohort study	22	VERY LOW	RR 0.48 (0.06 to 3.92)
Intubation (%)	1 cohort study	185	VERY LOW	RR 0.92 (0.24 to 3.57)
Admitted to ICU (%)	1 cohort study	22	VERY LOW	RR 0.87 (0.27 to 2.74)
Time of needing supplemental oxygen resolved (d)	1 cohort study	22	VERY LOW	WBD -4.00 (-9.05 to 1.05)
Time until clinical symptoms improved (d)	1 cohort study	185	VERY LOW	WMD 0.60 (-0.22 to 1.42)
Time until 50% radiographic abnormalities resolved (d)	1 cohort study	22	VERY LOW	WMD -5.00 (-6.46 to -3.54)
Time of pulmonary shadow resolved significantly (d)	1 cohort study	185	VERY LOW	WMD 0.30

				(-0.92 to 1.52)
Time until X-ray results improved (d)	1 cohort study	87	VERY LOW	WMD -4.67 (-5.93 to -3.41)
IFN-α vs IFN-β (MERS)				
Death (%)	1 cohort study	24	VERY LOW	RR 1.33 (0.80 to 2.20)
Intubation (%)	1 cohort study	24	VERY LOW	RR 1.41 (0.76 to 2.61)
RBV vs no antivirals (SARS)				
Death (%)	4 cohort studies	2236	VERY LOW	RR 0.68 (0.43 to 1.06)
Duration of corticosteroid use (d)	1 cohort study	90	VERY LOW	WMD -5.60 (-7.94 to -3.26)
Duration of disease (d)	1 cohort study	1518	VERY LOW	WMD 1.04 (-0.44 to 2.52)
Mechanical ventilation (%)	1 cohort study	306	VERY LOW	RR 0.96 (0.56 to 1.64)
Admitted to ICU (%)	1 cohort study	229	VERY LOW	RR 0.96 (0.57 to 1.62)
Anemia (%)	1 cohort study	586	LOW	RR 1.67 (1.07 to 2.61)
Bradycardia (%)	1 cohort study	306	LOW	RR 2.02 (1.30 to 3.12)
Hypoxemia (%)	1 cohort study	51	VERY LOW	RR 2.71 (0.42 to 17.24)
Hyperamylasemia (%)	1 cohort study	306	LOW	RR 2.69 (1.04 to 6.97)
Hypocalcemia (%)	1 cohort study	306	LOW	RR 1.29 (1.00 to 1.66)
Hypomagnesemia (%)	1 cohort study	306	HIGH	RR 10.19 (4.61 to 22.55)
Myocardial injury (%)	1 cohort study	229	VERY LOW	RR 1.02 (0.23 to 4.46)
Peak CRP level (mg/dL)	1 cohort study	51	VERY LOW	WMD 4.50 (-1.23 to 10.23)
Peak LDH level (IU/L)	1 cohort study	51	VERY LOW	WMD 230.30 (114.0 to 346.6)
Oseltamivir vs no antivirals (SARS)				
Death (%)	3 cohort studies	1887	VERY LOW	RR 0.87 (0.55 to 1.38)

Mechanical ventilation (%)	1 cohort study	103	LOW	RR 2.67 (1.73 to 4.12)
Intubation (%)	1 cohort study	83	VERY LOW	RR 0.50 (0.03 to 9.19)
ARDS (%)	1 cohort study	103	VERY LOW	RR 1.29 (0.55 to 3.03)
Duration of disease (d)	1 cohort study	1518	VERY LOW	WMD 3.91 (2.28 to 5.54)
Duration of hospitalization (d)	1 cohort study	83	VERY LOW	WMD -7.60 (-10.49 to -4.71)
Time until clinical symptoms improved (d)	1 cohort study	83	VERY LOW	WMD 2.60 (-0.25 to 5.45)
Duration of fever (d)	1 cohort study	83	VERY LOW	WMD 2.60 (0.50 to 4.70)
Pulmonary artery wide (mm)	1 cohort study	103	VERY LOW	WMD 1.69 (1.08 to 2.30)
Time of pulmonary shadow resolved significantly (d)	1 cohort study	83	VERY LOW	WMD 0.70 (-2.16 to 3.56)
Oseltamivir (early use alone) vs Oseltamivir (use alone) (SARS)				
Death (%)	1 cohort study	127	LOW	RR 1.62 (0.33 to 8.05)
ARDS (%)	1 cohort study	127	LOW	RR 2.60 (0.30 to 22.57)
Duration of disease (d)	1 cohort study	127	LOW	WMD -2.50 (-7.45 to 2,45)
Duration of fever (d)	1 cohort study	127	LOW	WMD -0.90 (-1.91 to 0.11)
RBV plus IFN vs no antivirals (MERS)				
Death (%)	2 cohort studies	393	VERY LOW	RR 1.04 (0.74 to 1.46)
Invasive ventilation (%)	2 cohort studies	393	VERY LOW	RR 1.05 (0.97 to 1.13)
Mechanical ventilation (%)	1 cohort study	349	VERY LOW	RR 0.92 (0.77 to 1.09)
Blood transfusion (%)	1 cohort study	349	LOW	RR 1.42 (1.06 to 1.91)
Mean drop in haemoglobin (g/L)	1 cohort study	44	VERY LOW	WMD 2.18 (0.86 to 3.50)
Mean minimum absolute neutrophil count (×10□/L)	1 cohort study	44	VERY LOW	WMD -1.43 (-2.55 to -0.32)

Favipiravir vs Arbidol (COVID-19)				
Rate of clinical recovery of day 7(%)	1 RCT	236	LOW	RR 1.18 (0.95 to 1.48)
Adverse reactions (%)	1 RCT	236	LOW	RR 1.37 (0.90 to 2.08)
Dyspnea after taking medicine (%)	1 RCT	236	LOW	RR 0.30 (0.10 to 0.87)
Respiratory failure (%)	1 RCT	236	LOW	RR 1.03 (0.26 to 4.04)
HCQ vs none (COVID-19)				
Negative PCR result (%)	1 RCT	30	LOW	RR 0.93 (0.73 to 1.18)
Radiographic abnormalities remission (%)	1 RCT	62	LOW	RR 1.47 (1.02 to 2.11)
Duration of fever (d)	2 RCTs	69	LOW	WMD -0.90 (-1.48 to -0.31)
Time until negative PCR result (d)	1 RCT	30	LOW	WMD 2.34 (-1.19 to 5.87)
Adverse reactions (%)	2 RCTs	92	LOW	RR 1.65 (0.50 to 5.50)

Abbreviations：

LPV/r: Lopinavir/ ritonavir; IFN: Interferon; RBV: Ribavirin. HCQ: hydroxychloroquine

CI: Confidence Interval; RR: Risk Ratio; WMD: Weighted Mean Difference; RCT: Randomized Controlled Trial;

COVID-19: Corona Virus Disease hyphen one nine; SARS: Severe Acute Respiratory Syndrome；MERS: Middle East respiratory syndrome ARDS: Acute Respiratory Distress Syndrome

PCR: Polymerase Chain Reaction; ICU: Intensive Care Unit; CRP: C-reactive Protein; LDH: Lactate Dehydrogenase

Figures

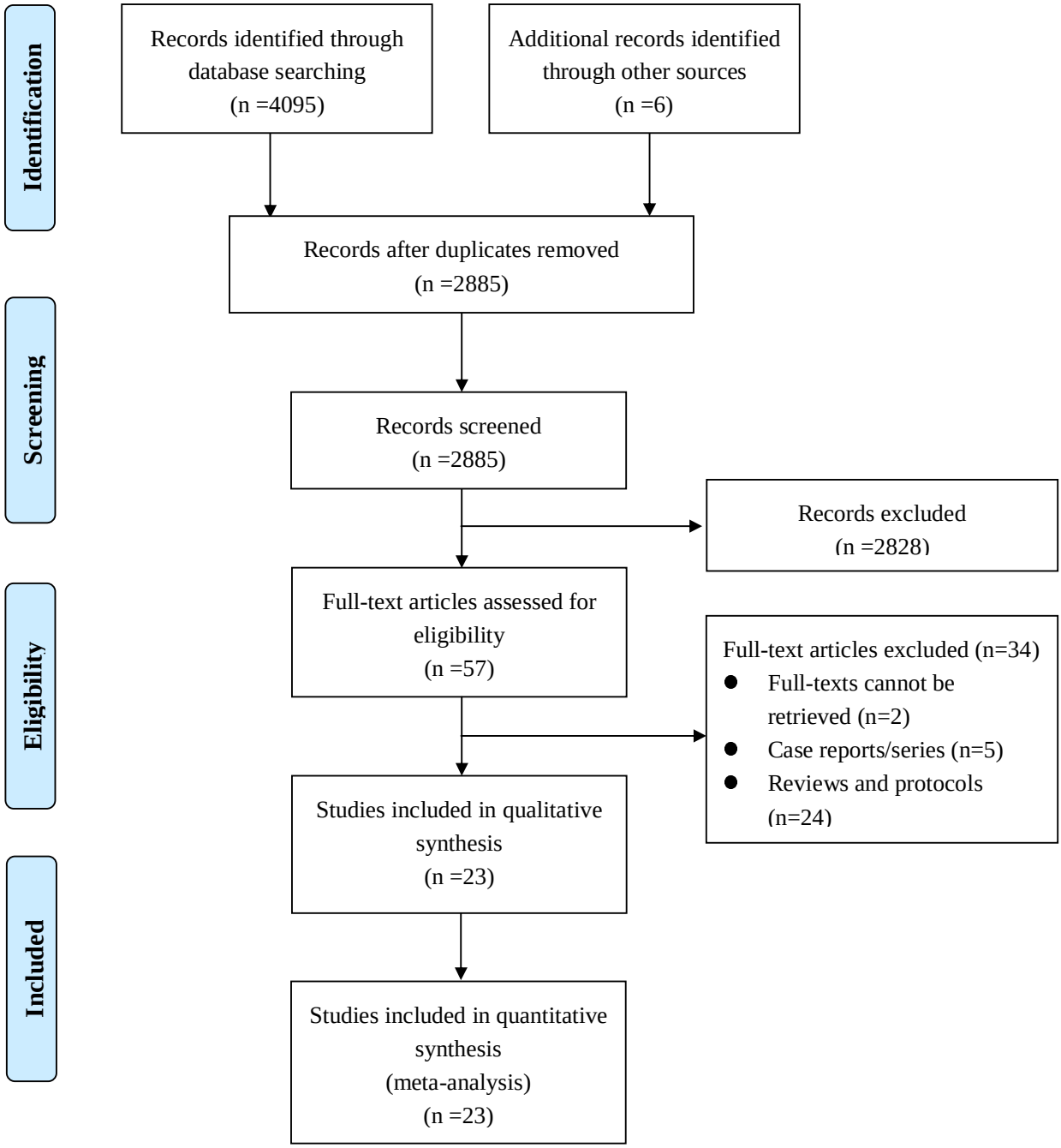

Figure 1. Flow diagram of the literature search.

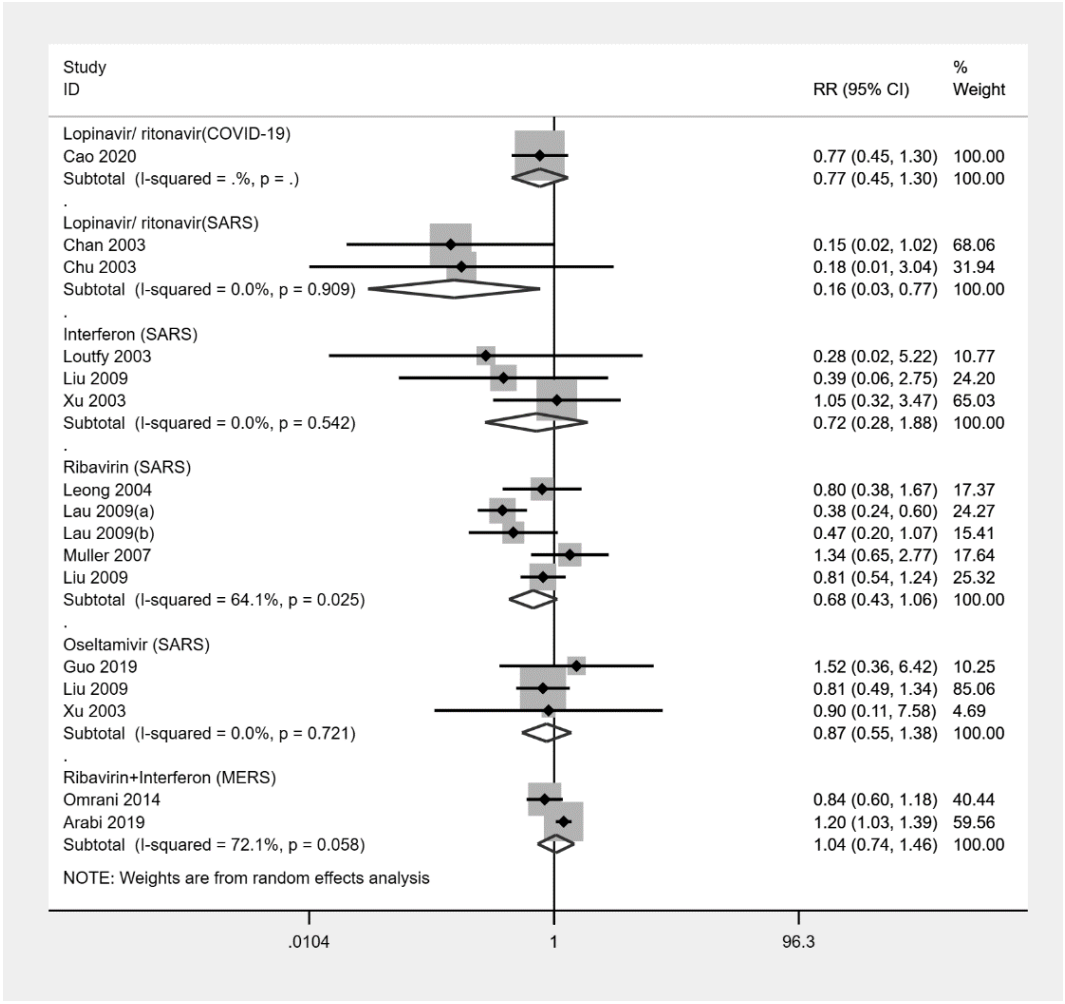

Figure 2. Forest plot of mortality for included studies comparing antivirals with no antivirals.