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Antiviral agents for COVID-19: A post-pandemic systematic review of randomized controlled trials.

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Systematic Review

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Abstract

Background: After years of the pandemic of SARS-CoV-2 infection, some cases with severe symptoms of COVID-19 are still presenting. Therapeutic alternatives that provide a clear benefit for severe cases remain lacking.

Aim: To assess the best available evidence on the efficacy of antiviral therapy for severe COVID-19 and to synthesize the results.

Methodology: A systematic review was designed. PubMed publications until December 2025 were searched. Randomized clinical trials (RCTs) of interventions with antiviral agents, with control groups that received placebo or standard of care (SOC) in patients with severe COVID-19 hospitalized or in the intensive care unit (ICU), were selected. The primary outcome was all-cause mortality; other secondary results were considered.

Results: A total of 43 studies were identified, involving 12,052 patients. The severity distribution was 35.6%, 52.0%, and 12.4% for mild, moderate, and severe cases, respectively. Ten antiviral agents were evaluated. The results showed a decrease in mortality among patients treated with remdesivir (RR 0.83; 95% CI0.74-0.93; p=0.001), molnupiravir (RR 0.16; 95% CI 0.04-0.73; p=0.02), and nirmatrelvir (RR 0.05; 95% CI 0.00-0.91; p=0.04).

Conclusions: According to the results, some antivirals (remdesivir, molnupiravir, nirmatrelvir) reduced all-cause mortality among patients with COVID-19 compared with placebo or SOC.

1. Introduction

The COVID-19 pandemic emerged three years ago, with millions of people affected in almost every country and thousands of deaths worldwide. Initially, experts proposed therapy alternatives based on theoretical considerations, with no evidence of practical results, but in the end, there is still no clear alternative for the management of new infections (1) other than vaccination (2).

Even when the number of cases has descended dramatically, including severe cases, and a minimum of current fatal events occur, there is no certainty on the course of the disease to an endemic presentation or if there is any chance for new peaks. Therefore, alternatives for treating such an infection remain necessary (3). The question was: In patients with SARS-CoV-2 infection (P), therapy with antivirals (I) compared with placebo (C) improved outcomes (O)? The study aimed to assess the best available evidence on the efficacy of antiviral therapy for COVID-19 and synthesize the results.

2. Methodology

2.1. Study design and protocol registration

This study was conducted as a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating antiviral therapies for severe COVID-19. The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (4). The protocol, which was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420233994294.

2.2. Eligibility criteria

Eligibility criteria were predefined using the PICO framework.

Types of studies: We included randomized controlled trials published in peer-reviewed journals. Both double-blind and open-label RCTs were eligible. Observational studies, non-randomized trials, preprints, conference abstracts, editorials, reviews, and vaccine studies were excluded. Retraction papers were also excluded from the review and meta-analysis, in accordance with PRISMA 2020 guidelines.

Types of participants: Eligible studies enrolled adult patients (≥18 years) with laboratory-confirmed SARS-CoV-2 infection, hospitalized with mild, moderate, or severe disease. Ambulatory patients, community- or home-based, non-severe, or post-exposure but asymptomatic status were excluded.

Types of interventions: Trials evaluating antiviral agents administered for the treatment of COVID-19 were included. Eligible interventions comprised, but were not limited to, remdesivir, lopinavir/ritonavir, favipiravir, molnupiravir, nirmatrelvir (with or without ritonavir), sofosbuvir, umifenovir, and other investigational antiviral compounds. Other antiviral therapies (immunomodulators, monoclonal antibodies, vaccines, and non-antiviral agents) were excluded.

Types of comparators: Comparator groups included placebo or standard of care (SOC), as defined within individual trials.

Outcomes: The primary outcome was all-cause mortality, reported as 14-day, 28-day, 30-day, or in-hospital mortality. Secondary outcomes included clinical recovery (defined as a lower NEWS-2 score or improvement), time to recovery, length of hospital stay, intensive care unit (ICU) admission, requirement for mechanical ventilation, and time to symptom resolution. Viral clearance, rebound, recurrence, sequelae, and long-term symptoms were excluded as outcomes.

2.3. Information sources and search strategy

A comprehensive literature search was conducted in Medline (via PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL), including searches in Embase. The search covered publications from January 1, 2020, to December 31, 2022, without geographic restrictions. Only articles published in English were considered.

Searched strategies combined controlled vocabulary terms (e.g., MeSH and Emtree) and free-text keywords related to SARS-CoV-2, COVID-19, Coronavirus Infections, and antiviral agents. The complete search strategies for all databases are provided in Supplementary Appendix 1.

Reference lists of relevant systematic reviews and included trials were manually screened to identify additional eligible studies.

2.4. Study selection

All retrieved records were imported into a reference management software, and duplicates were removed. Two reviewers independently screened titles and abstracts to assess eligibility. Full-text articles were subsequently reviewed for inclusion in accordance with the predefined criteria. Disagreements at any stage of the selection process were resolved through discussion, with adjudication by a third reviewer when necessary.

2.5. Data extraction

Data were independently extracted by two reviewers using a standardized data extraction form. Extracted information included:

- Study characteristics (first author, year of publication, country, journal).
- Participant characteristics (sample size, age, disease severity, clinical setting).
- Intervention details (antiviral agent, dosage, duration).
- Comparator characteristics.
- Outcome data for all predefined endpoints.
- Duration of follow-up.

For a multi-arm trial evaluation of more than one antiviral intervention, each eligible comparison was extracted and analyzed separately to avoid unit-of-analysis errors.

2.6. Risk of bias assessment

Methodological quality was assessed using the Cochrane Risk of Bias tool, version 2 (ROB 2), which evaluates bias across five domains:

- Randomization process.
- Deviations from intended interventions.
- Missing outcome data.
- Measurement of the outcome.
- Selection of the reported result.

Each study was categorized as having low risk of bias, some concerns, or high risk of bias. Assessment was conducted independently by two reviewers, with disagreements resolved by consensus.

2.7. Data synthesis and statistical analysis

Meta-analyses were performed when at least two studies reported comparable outcome data. For dichotomous outcomes, treatment effects were summarized as relative risks (RRs) with 95% confidence

intervals (CIs). A random-effects model (DerSimonian-Laird method) was used to account for anticipated clinical and methodological heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic, with values of approximately 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively.

Predefined subgroup analyses were conducted according to:

- Antiviral agent.
- Combinations.

All statistical analyses were performed using Review Manager (RevMan) version 5.4.1 (Cochrane Collaboration).

Formal assessment of publication bias (e.g., funnel plots) was not performed when fewer than ten studies were available for a given outcome.

The certainty of evidence for the primary outcome was assessed qualitatively, considering risk of bias, consistency of results, precision of effect estimates, and clinical relevance, in line with established systematic review methodology.

2.8. Ethical considerations

As this study synthesized data from previously published trials, ethical approval was not required.

3. Results

3.1. Studies selection

The study selection process is summarized in accordance with the PRISMA 2020 flow diagram (Figure X. PRISMA 2020 flow diagram of study identification and selection).

A total of [295] records were identified through database searches, including PubMed (n = 110) and Cochrane CENTRAL (n = 185). After removing duplicate records [190], 199 unique records remained for screening. No additional eligible studies were identified through manual reference screening. Title and abstract screening excluded [N4] records, primarily due to non-randomized study design, non-antiviral interventions, irrelevant outcomes, or non-COVID-19 populations. The full texts of [N5] articles were subsequently assessed for eligibility. Of these, [N6] articles were excluded following full-text review for the following reasons: retracted papers (n=), non-randomized design (n=), absence of relevant clinical outcomes (n=), inappropriate comparator (n=), duplicate or overlapping populations (n=), or insufficient for extraction (n=). Ultimately, [N7] randomized controlled trials met the inclusion criteria and were included in the qualitative synthesis. Of these, [N8] trials provided sufficient data to be included in the quantitative meta-analysis.

About 12,250 results were found in our search. After excluding publications without an abstract, published in English, and that were human studies, 9,849 studies remained from 2020 to 2025. About 278 of them were RCTs, 161 were meta-analyses, and 264 were systematic reviews. After reviewing the titles and abstracts, 110 references remained. Non-antiviral agents (monoclonal antibodies, steroids, interferon, plasma exchange, and chloroquine) were excluded. Mild, long, non-hospitalized, community-based, or asymptomatic patients were excluded. Subgroup analyses included vaccinated and unvaccinated patients, as well as combinations of antivirals and no combinations. The outcomes studied were mortality, ICU admission, acute respiratory failure, and hospital length of stay.

The search in CENTRAL (Cochrane Library) yielded 87 Cochrane reviews and 23,688 trials, and one clinical answer.

About 1891 citations were found in our search. After removing duplicate and irrelevant studies, 473 publications were identified and screened for relevance based on their titles and abstracts. 58 RCTs were assessed for eligibility; 49 studies from 43 journals were included in the systematic review and meta-analysis (Fig. 1). Some articles evaluated several options concomitantly or with combinations but in separate arms and were analyzed apart: baloxavir (BXV) and FPV (7); FPV alone or FPV/LPV/r; and LPV/r alone (8), LPV/r alone or combination with chloroquine (CLQ) (9); LPV/r and UFV (10); the WHO Solidarity trial evaluated concomitantly RDS alone, LPV/r alone among others (11).

According to editors' decisions, some publications were initially published and subsequently retracted due to inconsistencies in the results. Two studies with FPV were by the same authors (12, 13). Another study used SOF (14), and another used RDS (15). These studies were not considered in the analysis.

3.2. Population

Patients (12,052) were adults across a spectrum of clinical presentations, from asymptomatic individuals with a positive SARS-CoV-2 RT-PCR to severe COVID-19, either outpatients or hospitalized. Nearly 1,965 hospital or research settings were involved, ranging from 1 to 405 per trial. Some cases occurred in an institutional setting, such as a general ward or an ICU, with or without mechanical ventilation. Patients included in each range varied from 20 (7) to 5551 (11) across studies.

3.3. Risk of bias assessment

Twenty-five of the included clinical trials had a high methodological quality; nineteen had some concerns attributed mainly to issues with randomization or measurement of the outcome in open-label trials. Six studies found an increased risk of bias for doubts on the declaration of the randomization process, lack of blinding patients, caregivers, and researchers about the allocation of participants, or outcome measuring and final analyses (Fig. 2).

3.4. Severity

The distribution of study severity was predominantly moderate (52%), mild (35.6%), and severe (12.4%). Most trials had particularly mild cases (3 of 7 agent groups; Fig. 3). Severe cases were mainly tested for LPV/r, RDS, SOF, and UFV. Trials testing RDS included many moderate and severe cases (Fig. 4) (11, 16–23).

3.5. Intervention

Antiviral regimens included LPV/r (7 trials), RDS (10 trials), FPV (13 trials), MPV (3 trials), SOF (7 trials), and UFV (3 trials). In some cases, different doses and the duration of therapy (5 vs. 10 days) were tested. Antiviral agents were evaluated in only one trial, like atazanavir, baloxavir, ensitrelvir, and nirmatrelvir (7, 24–26).

3.6. Comparator

In the included studies, a placebo or standard of care (SOC) was used as a comparator. Sometimes, therapies in the SOC included additional antivirals, corticosteroids, immunotherapy, and chloroquine.

3.7. Outcomes

The primary efficacy outcome considered was mortality. Some studies evaluated it at 14, 28, or 30 days after hospital admission for hospital mortality (9, 11, 29–31, 16, 18, 19, 22, 24, 26–28). In some cases, recovery rates were extracted from studies as frequencies under the term “improvement” or as scores on a clinical scale (32, 33).

Some studies considered evaluating secondary outcomes in their follow-up, including the need for hospitalization, ICU admission, and mechanical ventilation. Others measured clinical improvement scales (e.g., the WHO scale) or viral clearance in daily or interval tracking (25, 34).

3.8. Synthesis of the results

The included clinical trials recruited 28840 patients from 29 to 11330 (Table I). One study evaluated several options (WHO Solidarity): 2750 were assigned to receive RDS, 1411 to LPV/r alone, and 2063 to LPV/r with interferon (11). Several trials tested some antiviral agents (FPV = 13; LPV/r = 7; RDS = 10; SOF = 7).

3.9. Efficacy

3.9.1. Mortality

According to the results, treatment with RDS for ten days significantly decreased the mortality rate compared to the control group, with an RR of 0.83 (95%IC 0.74–0.93; p = 0.001). These are the pooled results from six clinical trials with moderate and high severity (Fig. 5) (11, 16–18, 22, 31). Most of the positive effects on mortality were found in the ACTT-1 trial, especially in moderate cases or scores of 5 (Fig. 6) (18). In one study, the death rate was also lower in patients treated with SOF (RR 0.17; 0.04–0.73; p = 0.02) (35). Patients treated with molnupiravir also had lower mortality (RR 0.16; 0.04–0.73; p = 0.02)

(36). One additional study reported a reduction in mortality among patients treated with nirmatrelvir (RR 0.05; 0.00–0.91; p = 0.04) (26). Contrarily, the combination of LPV/r with chloroquine showed increased mortality in one study (Fig. 7) (9).

3.9.2. Clinical improvement

The ACTT-1 trial (RDS) also showed a reduced risk of progression to higher severity (score 6 or 7; invasive or noninvasive ventilation) in moderate, but not mild, cases (18). According to five studies, the recovery rate was higher in patients treated with SOF (RR 1.45; 1.25–1.67; p < 0.00001) (33, 35, 37–39). Clinical cure was also higher in patients treated with SOF compared to oseltamivir according to one study (RR 1,80; 1.41–2.29; p < 0.00001) (39); the time of cure was also shorter in the same study (Mean difference [MD] -10.00; -7.52 to -12.48; p = 0.00001).

3.9.3. Need and duration of ICU stay.

Patients treated with LPV/r showed a significant decrease in ICU and hospital length of stay (5 days; 2.36–7.64 and 2 days; 0.47–3.53, respectively), even when no effect was found in mortality (40). Moderate cases treated with RDS had a decreased need for ICU admission (RR 0.66; 0.42–1.05) (18, 31). Studies have reported a lower need for ICU admission among patients treated with SOF (RR 0.30; 0.13–0.67; p = 0.003) (35, 38).

3.9.4. Need and duration of mechanical ventilation.

Five studies found that patients treated with RDS had a lower need for mechanical ventilation (RR 0.86; 0.75–0.98; p = 0.022) and a shorter duration of mechanical ventilation (-8.50 days; -4.68 to -12.32) (41).

3.9.5. Need and duration of hospitalization.

Patients treated with RDS had a decrease in the need for hospitalization, although the difference was not significant (RR 0.82; 0.65–1.05; p = 0.12) (20, 22). Contrarily, these patients also had a lower rate of discharge (RR 0.69; 0.59–0.81; p < 0.0001) (22). The hospitalization rate was also lower in patients treated with nirmatrelvir (RR 0.12; 0.06–0.25; p < 0.00001) (26).

In patients treated with SOF, the length of stay was shorter according to one study (MD = -4.00; -2.00 to -6.00; p < 0.0001) (35). This was consistent with the results from another study (MD -9.00; -7.43 to -10.57; p < 0.00001) (39). Hospitalization length was also shorter in patients treated with UFV than in those treated with LPV/r, according to one study (MD = -2.40; -0.46 to -4.34; p = 0.02) (42).

3.9.6. Viral clearance

Viral clearance was primarily studied in non-severe cases and had a higher proportion on days 5, 8, 11, and 14 in patients treated with SOF (RR 1.54; 95% CI 1.23–1.93; p = 0.0002) (33, 39, 43, 44). Similar results were found with UFV (RR 1.52; 1.18–1.98; p = 0.001) (42, 45, 46) and MPV (RR 1.18; 1.04–1.33; p = 0.01) (47). A lower viral load positivity rate by day 3 with a higher MPV dose was observed in the latter study (RR 0.11; 0.01–0.86; p = 0.04).

3.10. Subgroup analysis

First, the effects of the repurposed antivirals differed. Efficacy varied widely among some, with no effect on others.

3.10.1. Lopinavir/ritonavir

Most studies of LPV/r showed no benefit on mortality (**Error! Reference source not found.**), need or duration of mechanical ventilation, hospital stay, clinical improvement or worsening, or viral clearance (8–11, 40, 48). However, some studies showed that ICU and hospital lengths of stay were shorter, and clinical improvement was higher on days 7 and 28 (40).

3.10.2. Remdesivir

The results showed decreased mortality in patients treated with RDS (RR 0.88; 95% CI 0.79–0.99; p = 0.03) (Fig. 5). The effect was observed in moderate cases (Fig. 6) (11, 18). Some studies have shown shorter hospital stays (20), fewer ICU admissions (18), and shorter mechanical ventilation durations (17, 22).

3.10.3. Favipiravir

Three studies showed no benefit on mortality with FPV, mechanical ventilation, or ICU admission (27, 29, 34); two other studies found higher clinical improvement (RR 2.45; 1.45–4.15), a shorter time to sustained clinical improvement (2.14 days shorter; 0.76–3.52), and viral clearance (49, 50). Another trial reported a shorter time to viral clearance (50), whereas another found no difference in viral clearance, length of stay, or clinical improvement (32, 51, 52). A study found no benefit in viral clearance by day 14, time to clinical improvement, incidence of mechanical ventilation, or ICU transfer (7). Two more studies combined FPV with interferon (IF) and found no benefit on mortality or viral load compared to placebo, LPV/r alone, or combined with IF (8, 28). The combination of FPV with LPV/r showed antagonism on viral clearance.

Other RCTs found FPV superior in shortening the duration of viral shedding in SARS-CoV-2 RNA positivity after discharge (53).

3.10.4. Sofosbuvir

Several trials evaluated the effect of SOF in combination with daclatasvir (DCV) or others. An RCT found increased mortality, hospital length of stay, and the need for and duration of mechanical ventilation (54). Other investigators found no benefit in hospital admission or clinical improvement for outpatients with mild COVID-19 treated with SOF/DCV (37). Additionally, an RCT showed no benefit in mortality, need for, or duration of mechanical ventilation, hospital stay, clinical improvement, time to clinical improvement, or viral clearance for severe cases with SARS-CoV-2 infection (33). One more RCT showed a higher viral clearance rate in non-severe COVID-19 patients (43).

An RCT compared SOF/DCV with ribavirin (RBV) and found a lower risk of death (p = 0.02), ICU admission (p = 0.01), and shorter hospital stays, and a higher proportion of patients recovered. However, other RCTs found no benefit in mortality, ICU admission, mechanical ventilation, or hospital length of stay with SOF/DTV + RBV (38).

One more RCT compared SOF/LPV (ledipasvir) with a combination of oseltamivir, CLQ, and azithromycin (AZT) (39). The results showed a higher cure rate with shorter hospital stays; however, differences in mortality and viral clearance were not significant.

3.10.5. Umifenovir

In an RCT with UFV, authors found a higher proportion of viral clearance by day 5 (p = 0.004) but no difference after day 7 in the mild-asymptomatic group (45). Clinical improvement was faster in the mild-asymptomatic group by day 5 (p = 0.019) but not in the moderate group. Other RCTs showed no less mortality, ICU admission, or viral clearance, but the duration of hospitalization was lower in patients treated with UFV in contrast with LPV/r.

3.10.6. Molnupiravir

An RCT showed a faster viral clearance in non-severe patients treated with high doses of MPV (47). Another study showed a lower risk of hospitalization or death (RR 0.16; 95% CI 0.04–0.73; p = 0.02) (36).

3.10.7. Nirmatrelvir

In a multicenter RCT granted by Pfizer® on non-hospitalized patients with SARS-CoV-2 infection mortality, there were no deaths in the arm treated with nirmatrelvir/ritonavir compared to placebo (RR 0.05; 95% CI 0.00-0.91; p = 0.04) (26). A decrease in hospitalization rate was also significant (0.38 vs. 3.17%; RR 0.12; 95% CI 0.02–0.25; p < 0.0001).

3.10.8. Ensitrelvir

An RCT found higher viral clearance by day 4 in patients with mild-to-moderate COVID-19 treated with ensitrelvir (25).

3.10.9. Atazanavir

The study of atazanavir used in combination with other antivirals and chloroquine was compared with various LPV/r regimens with CLQ; no placebo arm was included (24). No benefit was found in mortality, ICU admission, or mechanical ventilation.

3.10.10. Baloxavir

An RCT evaluated baloxavir in symptomatic individuals with COVID-19 and found no difference in viral clearance, viral clearance rate, time to clinical improvement, need for mechanical ventilation, or ICU admission (7).

4. Discussion

This study gathers a comprehensive analysis of the current evidence on outcomes for antiviral agents in patients with COVID-19 provided by RCTs. Treatment for SARS-CoV-2 infection has been symptomatic for mild cases and supportive for severe cases. There have been reports of widespread use of antiviral agents, even when the World Health Organization (WHO) has not recommended their use (42). Several publications have evaluated the efficacy of antiviral agents for treating SARS-CoV-2 infection from asymptomatic to critical cases. Only a few of them were revealed to be efficacious in modifying outcomes. Even after the pandemic, patient numbers have declined worldwide, but some peaks persist in several countries. There is currently no certainty about which therapies are beneficial and which outcomes are modified by treatment.

The evaluation of outcomes varied among studies. Some considered mortality the primary outcome (24, 29); even in these cases, there was a disparity among studies: some monitored the effect at 14 days (55), whereas others monitored it at 28 days (31, 48).

Although RDS showed a decrease in mortality, these findings were based primarily on two large RCTs (6613 patients) (11, 18); both included patients with mild to severe disease, and the beneficial effect was observed in moderate cases. SOF, MPV, and nirmatrelvir also reduced mortality among patients with mild and moderate disease (26, 35, 36). No studies with LPV/r or FPV showed a decrease in mortality (9, 11, 48, 56), and the combination with chloroquine was deleterious (9).

Viral clearance is a major concern during pandemics. High viral counts were associated with disease severity and the likelihood of infectivity. Several studies have focused on the viral shedding effects of antiviral agents as primary or secondary outcomes in outpatients (51) or hospitalized (7, 21), including those with mild to moderate symptoms (25, 50, 52). Antiviral agents with efficacy in reducing the duration or extent of viral shedding were SOF (33, 39), UFV (45), and MPV (47).

A search of the PROSPERO register of systematic reviews (57) identified 1631 records on COVID-19. Approximately 316 included antiviral agents: 94 with LPV, 141 with RDS, 45 with FPV, and 10 with SOF. Our review is dedicated exclusively to evaluating the effect of antiviral agents on experimental studies.

4.1. Limitations

One of the main limitations of the analysis of the results is the heterogeneity of subjects allocated to the studies, including differences in severity (Fig. 4), age, and other risk factors, as well as additional therapies included in the SOC arm. In this context, the efficacy of RDS may differ across mild, moderate, and severe cases. The impact of RDS on mortality was observed in the moderate-severity group but not in the other severity groups (Fig. 6). This result was observed in the ACTT-1 trial (18) but not in the WHO Solidarity trial (11), which had a higher proportion of moderate cases.

There were also differences in outcomes studied, from mortality to viral clearance. When interpreting an antiviral agent, caution should be exercised regarding the severity and the desired clinical outcome.

Pharmaceutical companies sponsored some studies on new alternatives, the external results of which have yet to be confirmed. Most allocations included mild cases, and the benefit was limited to viral clearance.

Another limitation is the lack of a placebo arm in some studies and the use of SOC in the control group, which included some therapeutic alternatives, even when some showed no beneficial effects in other trials. There is no certainty that such a combination could have a biased impact.

A small number of allocations might have an impact on the capacity to detect a beneficial effect with the therapy; even when affecting a considerable amount of the population, COVID-19 had a low frequency of severe cases and mortality; ACTT-1 study had a small proportion of deaths in both groups (near six vs. 12%) (18). An experiment should have at least 358 cases assigned to each arm to find a (50%) difference in the effect, and maybe 1640 in each group if the impact was less (a 25% decrease in mortality). The studies with sufficient patient numbers included FPV (27), LPV/r (9, 11, 48), MPV (36), nirmatrelvir (26), RDS (11, 16–22), and SOF (54).

Finally, heterogeneity in trials evaluating mortality with LPR/r was low ($I^2 = 0$); RDS was moderate ($I^2 = 40\%$), and FPV was intermediate ($I^2 = 37\%$).

5. Conclusion

Several antiviral agents demonstrated benefits in specific patient populations with SARS-CoV-2 infection. The benefits were observed in reduced mortality, ICU admission, mechanical ventilation, hospitalization, the rate of clinical improvement, and viral load. The overall certainty of evidence remains moderate to low, and results should be interpreted in the context of disease severity, treatment timing, and evolving standards of care. The effect was highly variable among studies and agents. Precaution is advised to adjudicate the impact of a specific agent on others.

Declarations

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Conflicts of interest

The authors declare that they have no competing interests. None of the authors were members of the research teams for any of the selected trials included in this review; we were not members of the advisory boards of any drug or technology agency, nor were we participants in any pharmaceutical company or biotechnology enterprise. The authors received no financial support for this article's

research, authorship, or publication. The opinions expressed in this document are those of the authors and do not reflect the official position of any agency.

Availability of data and other material

A dataset of the registers included in the review was stored in the Mendeley Data repository (DOI: 10.17632/4RK2KFBJVT.1). The study protocol was registered in the PROSPERO register (University of York, Centre for Reviews and Dissemination) under the code CRD24023394294.

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Tables

Tables 1 and 2 are available in the Supplementary Files section.

Figures

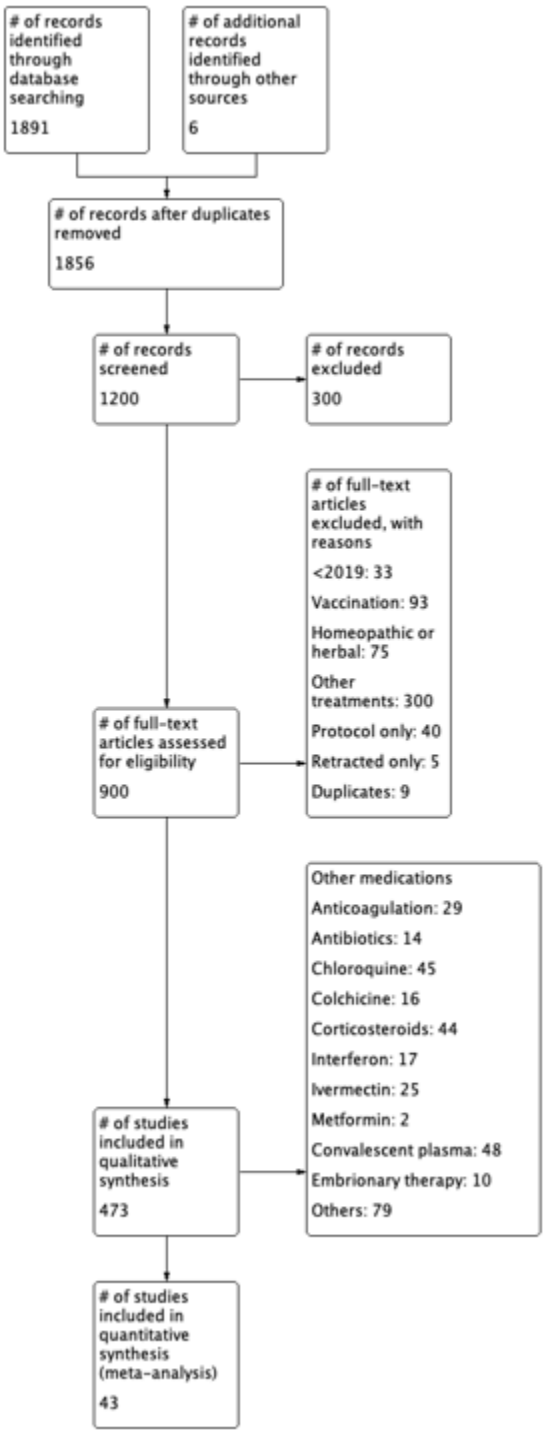
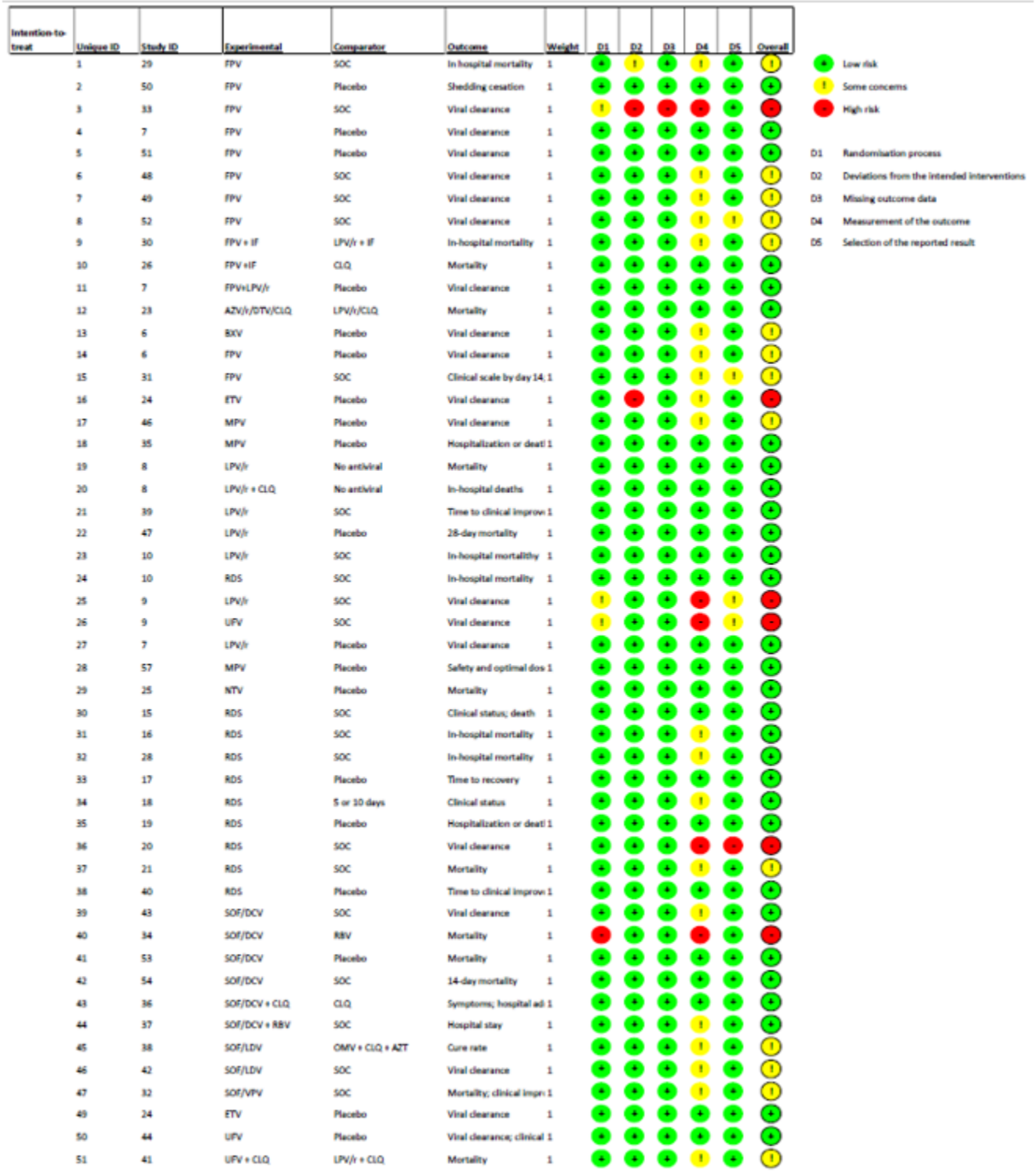


Figure 1

PRISMA Flow diagram of the included studies.



Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	1	29	FPV	SOC	In-hospital mortality	1	+	!	+	!	+	!
	2	50	FPV	Placebo	Shedding cessation	1	+	+	+	+	+	+
	3	33	FPV	SOC	Viral clearance	1	!	-	-	-	+	-
	4	7	FPV	Placebo	Viral clearance	1	+	+	+	+	+	+
	5	51	FPV	Placebo	Viral clearance	1	+	+	+	+	+	+
	6	48	FPV	SOC	Viral clearance	1	+	+	+	!	+	!
	7	49	FPV	SOC	Viral clearance	1	+	+	+	!	+	!
	8	52	FPV	SOC	Viral clearance	1	+	+	+	!	!	!
	9	30	FPV + IF	LPV/r + IF	In-hospital mortality	1	+	+	+	!	+	!
	10	26	FPV +IF	CLQ	Mortality	1	+	+	+	+	+	+
	11	7	FPV+LPV/r	Placebo	Viral clearance	1	+	+	+	+	+	+
	12	23	AZV/r/DTV/CLQ	LPV/r/CLQ	Mortality	1	+	+	+	+	+	+
	13	6	BXV	Placebo	Viral clearance	1	+	+	+	!	+	!
	14	6	FPV	Placebo	Viral clearance	1	+	+	+	!	+	!
	15	31	FPV	SOC	Clinical scale by day 14;	1	+	+	+	!	!	!
	16	24	ETV	Placebo	Viral clearance	1	+	-	+	!	+	-
	17	46	MPV	Placebo	Viral clearance	1	+	+	+	!	+	!
	18	35	MPV	Placebo	Hospitalization or deat	1	+	+	+	+	+	+
	19	8	LPV/r	No antiviral	Mortality	1	+	+	+	+	+	+
	20	8	LPV/r + CLQ	No antiviral	In-hospital deaths	1	+	+	+	+	+	+
	21	39	LPV/r	SOC	Time to clinical improv	1	+	+	+	+	+	+
	22	47	LPV/r	Placebo	28-day mortality	1	+	+	+	+	+	+
	23	10	LPV/r	SOC	In-hospital mortalithy	1	+	+	+	+	+	+
	24	10	RDS	SOC	In-hospital mortality	1	+	+	+	+	+	+
	25	9	LPV/r	SOC	Viral clearance	1	!	+	+	-	!	-
	26	9	UFV	SOC	Viral clearance	1	!	+	+	-	!	-
	27	7	LPV/r	Placebo	Viral clearance	1	+	+	+	+	+	+
	28	57	MPV	Placebo	Safety and optimal dos	1	+	+	+	+	+	+
	29	25	NTV	Placebo	Mortality	1	+	+	+	+	+	+
	30	15	RDS	SOC	Clinical status; death	1	+	+	+	+	+	+
	31	16	RDS	SOC	In-hospital mortality	1	+	+	+	!	+	+
	32	28	RDS	SOC	In-hospital mortality	1	+	+	+	!	+	+
	33	17	RDS	Placebo	Time to recovery	1	+	+	+	+	+	+
	34	18	RDS	5 or 10 days	Clinical status	1	+	+	+	!	+	+
	35	19	RDS	Placebo	Hospitalization or deat	1	+	+	+	+	+	+
	36	20	RDS	SOC	Viral clearance	1	+	+	+	-	-	-
	37	21	RDS	SOC	Mortality	1	+	+	+	!	+	!
	38	40	RDS	Placebo	Time to clinical improv	1	+	+	+	+	+	+
	39	43	SOF/DCV	SOC	Viral clearance	1	+	+	+	!	+	+
	40	34	SOF/DCV	RBV	Mortality	1	-	+	+	-	+	-
	41	53	SOF/DCV	Placebo	Mortality	1	+	+	+	+	+	+
	42	54	SOF/DCV	SOC	14-day mortality	1	+	+	+	+	+	+
	43	36	SOF/DCV + CLQ	CLQ	Symptoms; hospital ad	1	+	+	+	+	+	+
	44	37	SOF/DCV + RBV	SOC	Hospital stay	1	+	+	+	!	+	+
	45	38	SOF/LDV	OMV + CLQ + AZT	Cure rate	1	+	+	+	!	+	!
	46	42	SOF/LDV	SOC	Viral clearance	1	+	+	+	!	+	!
	47	32	SOF/VPV	SOC	Mortality; clinical impr	1	+	+	+	!	+	!
	49	24	ETV	Placebo	Viral clearance	1	+	+	+	+	+	+
	50	44	UFV	Placebo	Viral clearance; clinical	1	+	+	+	+	+	+
	51	41	UFV + CLQ	LPV/r + CLQ	Mortality	1	+	+	+	!	+	!

Figure 2

Risk of bias assessment. (*) low risk of bias; (-) high risk of bias; (!) some concerns.

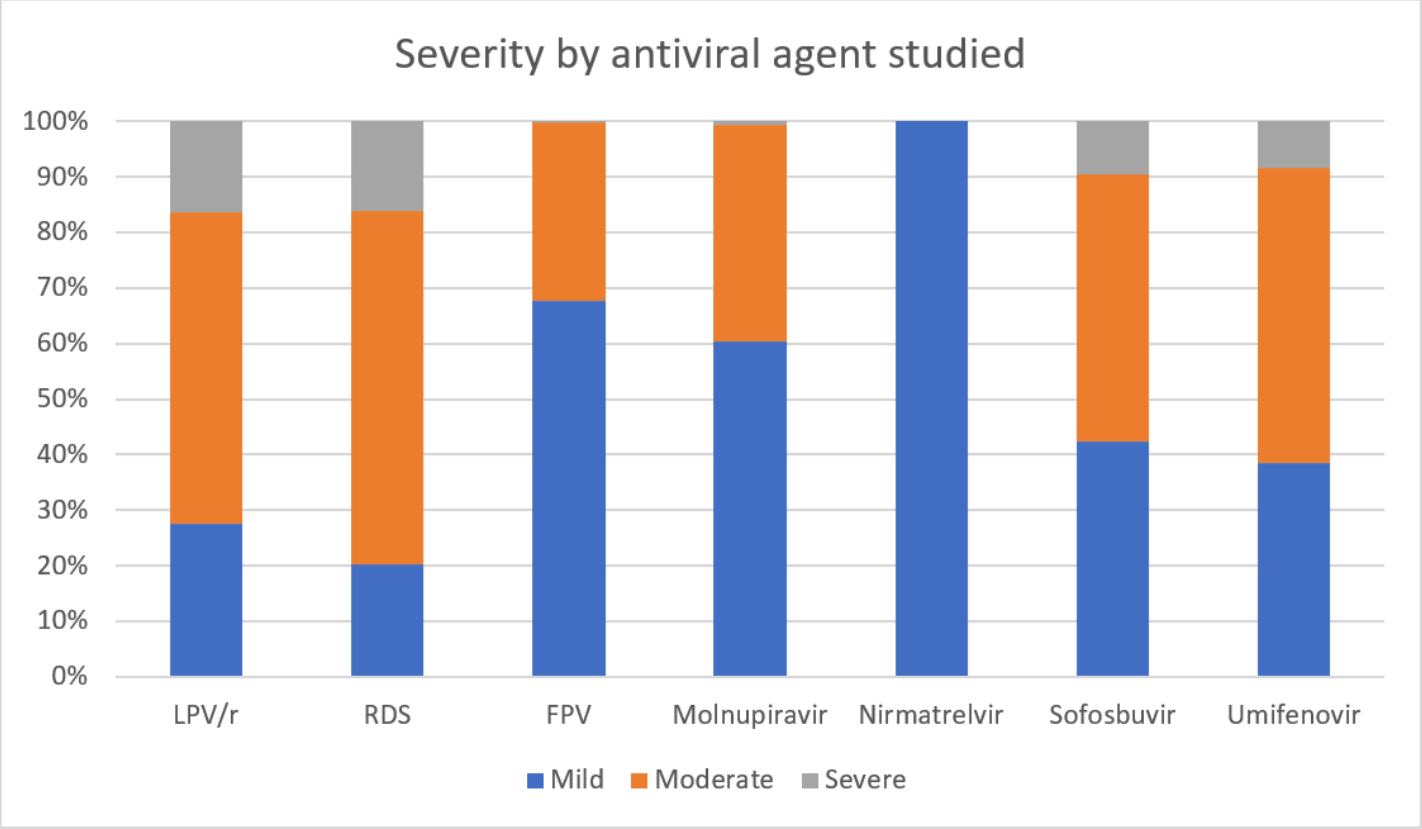


Figure 3

Proportion of patients with COVID-19 allocated by severity in studies evaluating the efficacy of antivirals.

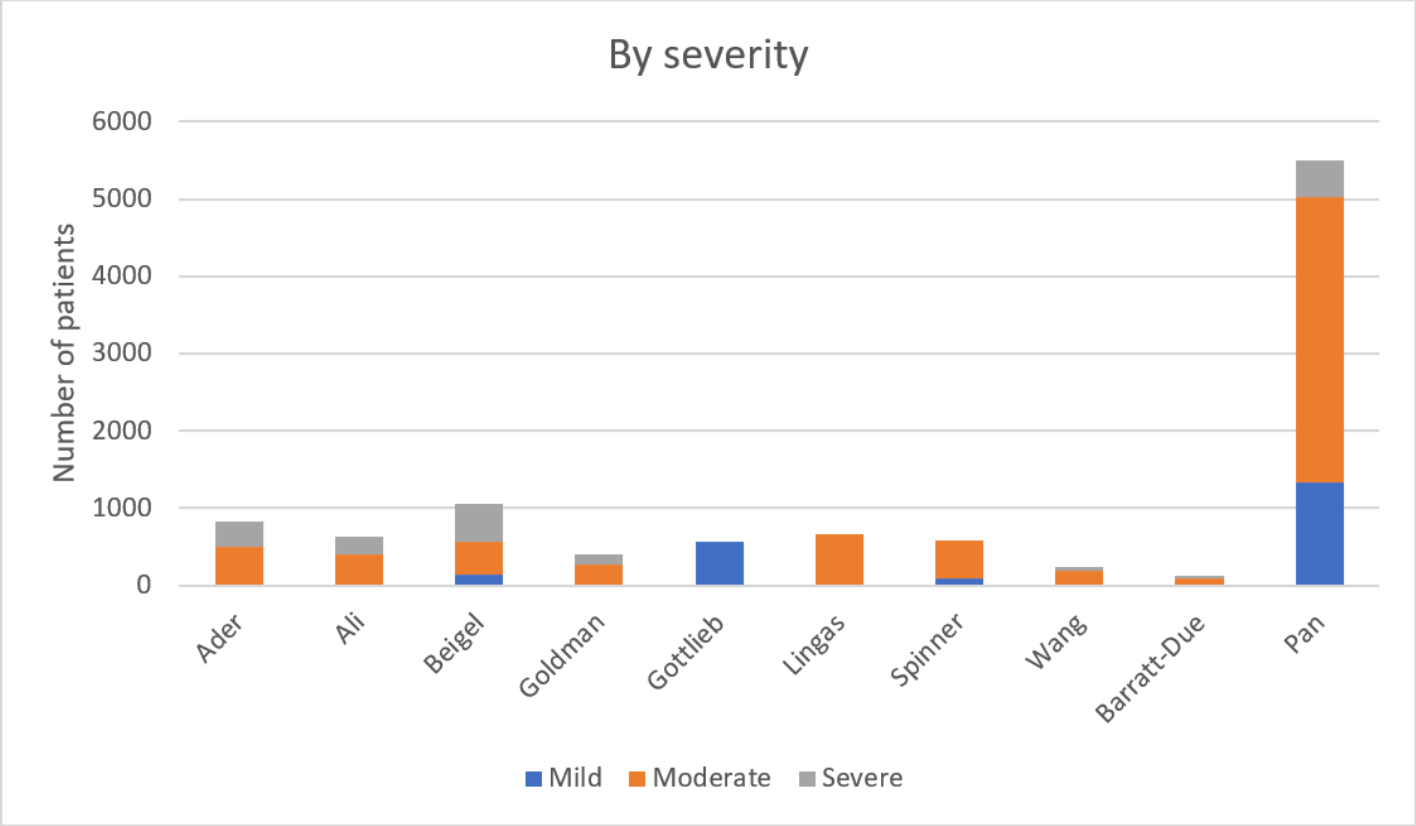


Figure 4

Number of patients with COVID-19 allocated by author and by severity in studies evaluating the efficacy of remdesivir.

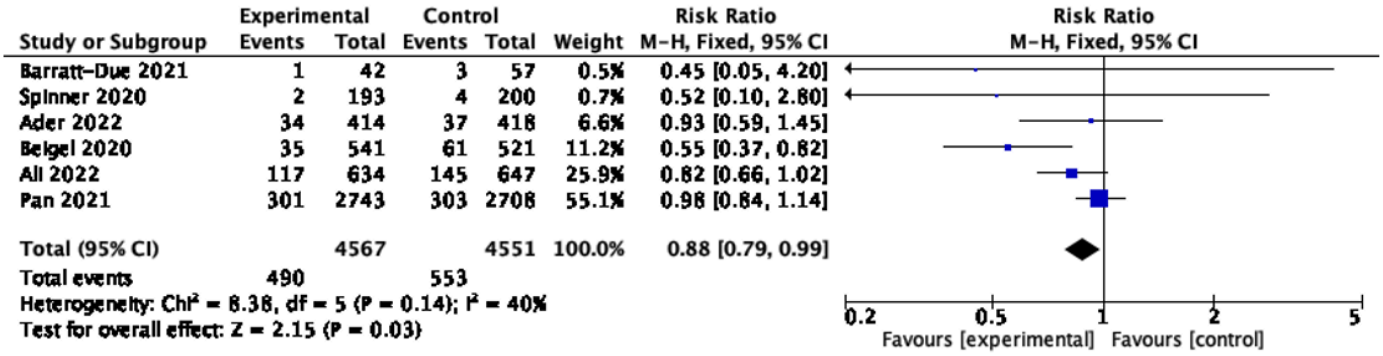


Figure 5

Effect of remdesivir on mortality of patients with COVID-19.

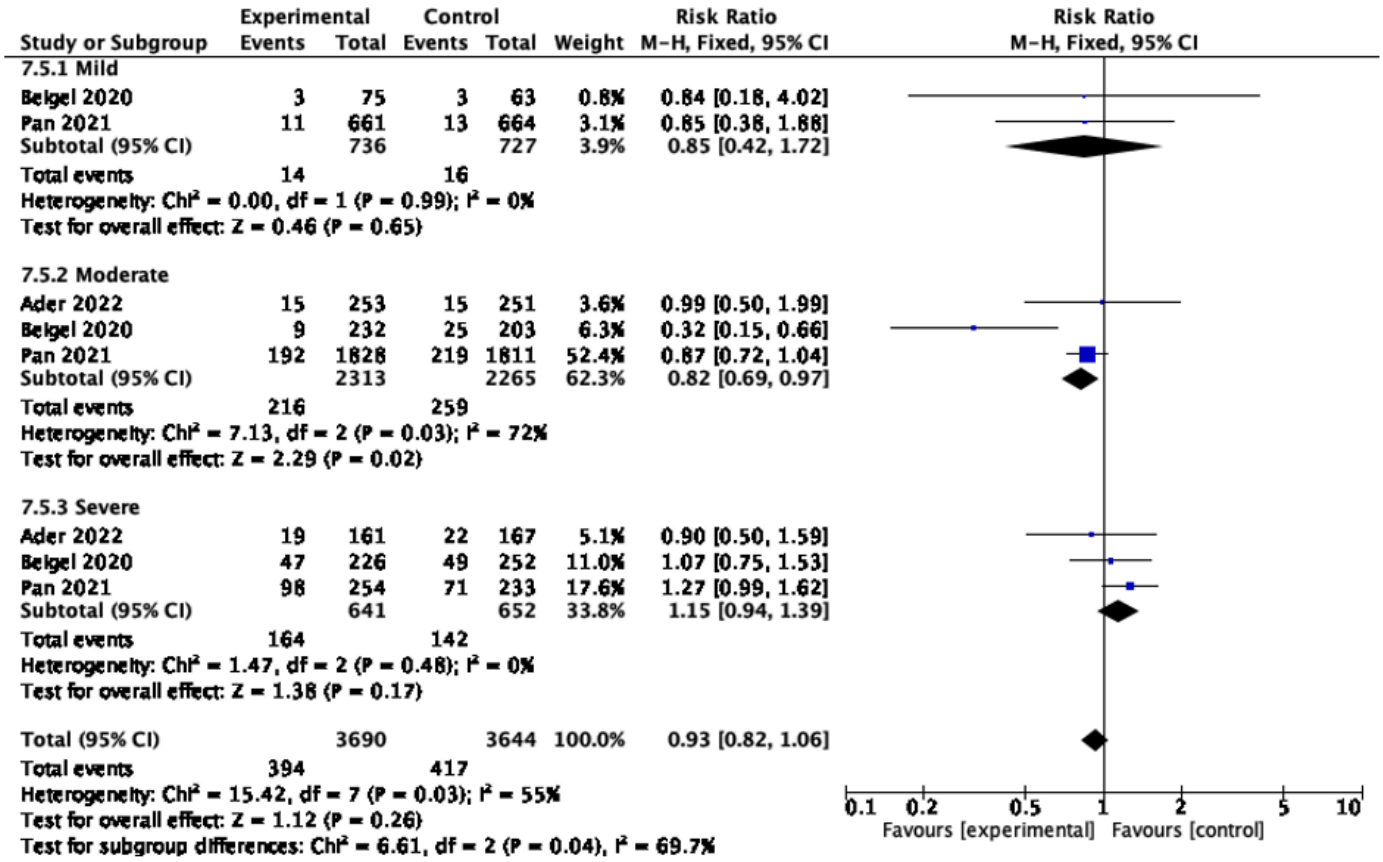


Figure 6

Effect of remdesivir on mortality of patients with COVID-19 by severity.

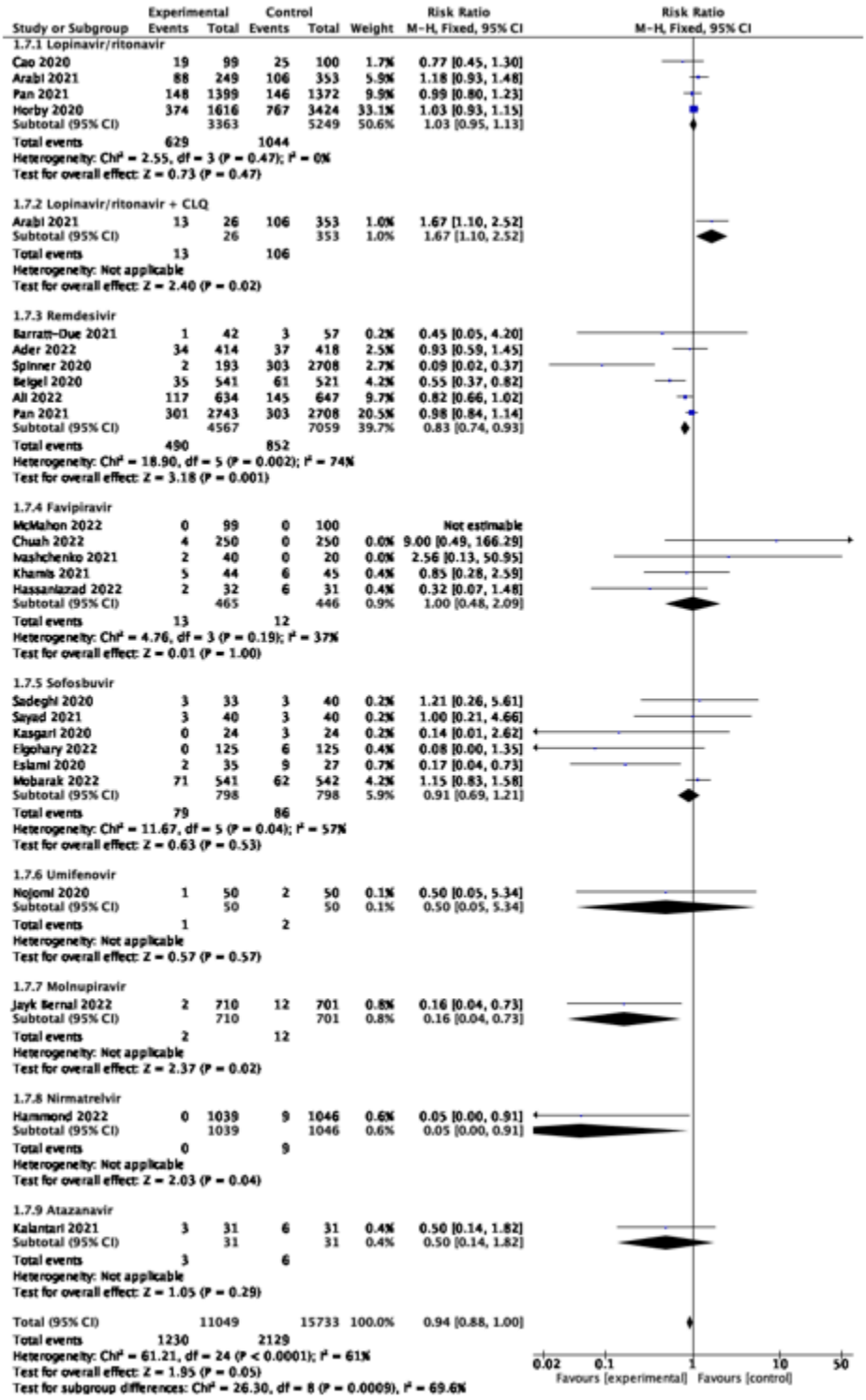


Figure 7

Mortality of patients with COVID-19 treated with antiviral agents.

Supplementary Files

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- Tables.docx