



Antiviral Treatment for COVID-19: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author FAA designed the study. Author PTC performed the statistical analysis. Authors FAA and PTC wrote the protocol and wrote the first draft of the manuscript. Author ARO managed the literature searches. Authors AMP and DFO individually extracted each of the selected articles and wrote the results. All authors read and approved the final manuscript.

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ABSTRACT

Aim: In December 2019, there were reports of a new type of coronavirus that affects the different health systems of the world. We have carried out a systematic review of the possible antivirals studied that could be useful in this public health catastrophe.

Data Sources: A search strategy with MESH terms was performed in PubMed, Web of Science, and Scopus. Also, RCTs published in clinicaltrials.gov were reviewed. The databases were searched between April and June 2020.

Study Selection: We selected all Randomized Controlled Trials evaluating the effects of antivirals and 5 studies were included from a research database of 280 articles collected between. After removing duplicated articles, 43 were selected for review. Finally, 5 articles were eligible for full-text review and included in the article.

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Results: Current randomized controlled trial data showed no clinical improvement in terms of mortality, need for oxygen support or need for intubation in patients who used antivirals versus those who did not. No clinical improvement was demonstrated. It was observed that there is difficulty in calculating clinical improvement, this large difference makes the eligible studies difficult to compare.

Conclusion: These predictors, however, need further work to validate reliability. More clinical trials involving antivirals are needed to observe a relationship between clinical improvement or mortality from SARS-CoV-19.

Keywords: Systematic review; COVID-19; treatment; clinical improvement; mortality.

ABBREVIATIONS

AHF	: Acute Heart Failure
AKI	: Acute kidney injury
ALT	: Alanine Aminotransferase
AMOX-CLAV	: Amoxicillin-clavulanate
CHD	: Coronary heart disease
CID	: Disseminated Intravascular Coagulation
CVA	: Cerebrovascular disease
DM	: Diabetes Mellitus
HT	: Hypertension
ICU	: Intensive Care Unit.
LVX	: Levofloxacin
MA	: Meta-analysis
N-RA	: Meta-Regression
PTX	: Pneumothorax
RCT	: Randomized Controlled Trial
SR	: Systematic Review
TZP	: Tazobactam-Piperacillin

1. INTRODUCTION

In early December 2019, we received reports of pneumonia cases caused by a new virus in Wuhan, China, taking only 3 months to spread worldwide. Since then, this pandemic has affected health systems worldwide to varying degrees. The World Health Organization (WHO) named this new condition as coronavirus-19 (Covid-19) disease caused by SARS-CoV-2. This new virus, belonging to the extensive family of coronaviruses, already had a history of a previous presentation about severe acute respiratory syndrome (SARS) in 2003 also in China [1].

The fatal case index (CFR) is one of the important measures of impact during outbreaks, epidemics, or pandemics, it is defined as "the proportion of cases of a specified condition that are fatal within a specified time" [2]. What has been reported in studies of SARS-Cov 2 infection in China so far exhibit an approximate CFR of 4.0% [3,4]. In addition to the need for properly

equipped intensive care units and their high contagion capacity, the search for an accurate and efficient treatment became a priority in the scientific community.

When the first patient arrived in the United States, experts recommended Remdesivir treatment, and its application was even approved by the Food and Drug Administration (FDA).³ But the lack of information that will prove its efficacy and validity in the use of Covid-19 cases was quickly questioned [4,5].

In 2003, one trial of Lopinavir-ritonavir and Ribavirin demonstrated reduced mortality and lesser complications in patients with SARS-CoV-1; for this reason, researchers are performing these medications in context on Covid-19 pandemic [6].

In the meantime, several studies have just appeared, and suggest treatments with former results for other viral diseases; but what we do not have is plenty of clinical evidence to apply these for patients with SARS-CoV-2. Besides Remdesivir, Lopinavir-ritonavir, Chloroquine and Hydroxychloroquine, Favipiravir, Umifenovir, Ribavirin, and Interferon have been proven in a sort of trials [7-13].

The main reason for this systematic review is to organize the recent data from COVID-19 and to compare the available antiviral therapies used in this new disease

2. METHODS

2.1 Search Strategy

A systematic review of RCT's evaluating the effect of antiviral medications (remdesivir, oseltamivir, favipiravir, lopinavir, ritonavir) was performed. A search strategy with MESH terms was performed in PubMed, Web of Science, and Scopus. Also, RCTs published in clinicaltrials.gov

were reviewed. The databases were searched between April and June 2020. The search strategy was done using the following MESH terms: Coronavirus 2019 OR COVID 19 OR 2019-nCov OR SARS COV-2 OR nCOV disease OR COVID19 OR coronavirus disease 2019 OR novel coronavirus) AND (Antiviral OR treatment OR (Lopinavir AND Ritonavir) OR Umifenovir OR Remdesivir OR Oseltamivir OR Favipiravir OR Ribavirin AND Mortality AND Adverse effects. There were no limitations in language and the time of publication was limited from 2019 to the moment when the search was performed. The search strategy is available in the appendix.

2.2 Study Selection

We Selected all RCT's evaluating the effects of antivirals (Remdesivir, Oseltamivir, favipiravir, Lopinavir, ritonavir,) on mortality, rate of the need of mechanical ventilation, acute coronary syndrome, and harmful events in patients with a severe or moderate case of COVID. We included studies in any language or with any sample size. We excluded case reports, reviews, editorials, letters to editors, and retrospective studies. Abstracts from all engines were centrally collected in myendnoteweb.com, and duplicates were removed. The selection of abstracts was done independently by two investigators and any discrepancies were solved with a third investigator.

2.3 Data Extraction

Two investigators independently extracted the information from full texts of selected studies, and any discrepancies were solved by a third investigator. Extracted information included the year of publication, length of the study, place where the study was taken, trial phase, the population included, intervention drug, control, trial therapy, and time of follow-up. Also, data from the outcomes were extracted.

2.4 Outcomes

The main outcome considered in the study was mortality, while the secondary outcomes were clinical improvement as defined by the NEWS-2 score, severe respiratory failure (defined by the requirement of mechanical ventilation), the presence of Disseminated Intravascular Coagulation (defined by the increment of levels of D dimer and systemic organ failure) and Acute Heart Failure (defined by acute heart symptoms of fluid overload, acute pulmonary edema and/or

left ventricular ejection fraction <40%). Finally, the most common side effects in studies are presented (ALT increase, Lymphopenia, Thrombocytopenia, Rash, Acute Kidney Injury, and Pneumothorax). All the definitions will be described in Table 2.

2.5 Risk of Bias Assessment

Two investigators evaluated the risk of bias of each eligible RCT using the Cochrane collaboration tool for assessing the risk of bias for randomized clinical trials [14]. Any discrepancies were solved by a third investigator. The following criteria were included in the evaluation: Randomness of Allocation sequence, Concealment of Allocation sequence, Blinding of the patient, the investigator and of the outcome, selective reporting, incomplete outcome, and any other biases. Each item was described for each study as Low, high or uncertain risk of bias.

2.6 Additional Analyses

A meta-analysis could not be performed due to the heterogeneity of the included studies. (Fig. 3)

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Selection of trials

We identified a total of 280 articles in the search engines specified. After removing duplicates, 43 articles left. These were screened by title and abstract, where 36 articles were excluded. Finally, a full-text review was taken for eligibility in 7 articles, where 2 of them were excluded due to not including the outcomes searched in this study (Fig. 1). The characteristics of the 5 studies included in this review are shown in Table 1.

3.1.2 Description of trials

Overall baseline characteristics are presented in Table 1. The largest study population was presented by Beigel et al where a total of 1063 participants were considered in the analysis, while the smallest population included was by Hung et al with 127 patients [12,13]. Baseline characteristics show that the highest average age comes from the study by Wang et al. with a median age of 66 and an IQR: 57-73, while the predominant gender in almost all studies was male, the only exception being the arbidol-treated group in the trial developed by Chen et al. which showed 57.5% of the female population

[7,11]. Diabetes [(30.6%) Beigel et al.], hypertension [(46%) Beigel et al.], cerebrovascular disease [(8%) Cao et al.], and coronary heart disease [(12%) Hung et al.] were the most frequent comorbidities [9,12,13] Patients in clinical trials by Wang et al. and Hung et al. received basal treatments before conducting the trial [15]. The longest follow-up was 28 days by Wang et al. while the shortest was 10 days by Beigel et al and Chen et al. [7,11,13].

3.1.3 Risk of bias assessment

In selection bias, the generation of both random sequence and allocation concealment showed a low risk of bias in all 5 selected articles.

However, Cao et al., Chen et al. and Hung et al. (60%) presented a high risk of bias in the assessment of performance, blinding of participants and personnel because of their nature as open-label studies [7,9,12]. In the setting of detection bias, Cao et al., Chen et al. and Hung et al. presented a high risk of detection bias due to lack of assessors blinding; while Beigel et al. and Wang et al. showed an unclear risk of bias since this information was not specified [7,9,11-13]. All articles presented a low risk of bias in reporting and attrition. Finally, only Beigel et al. showed a high risk of bias in the 'other' category because that study was sponsored by the pharmaceutical company producing Remdesivir [16] (Fig. 2).

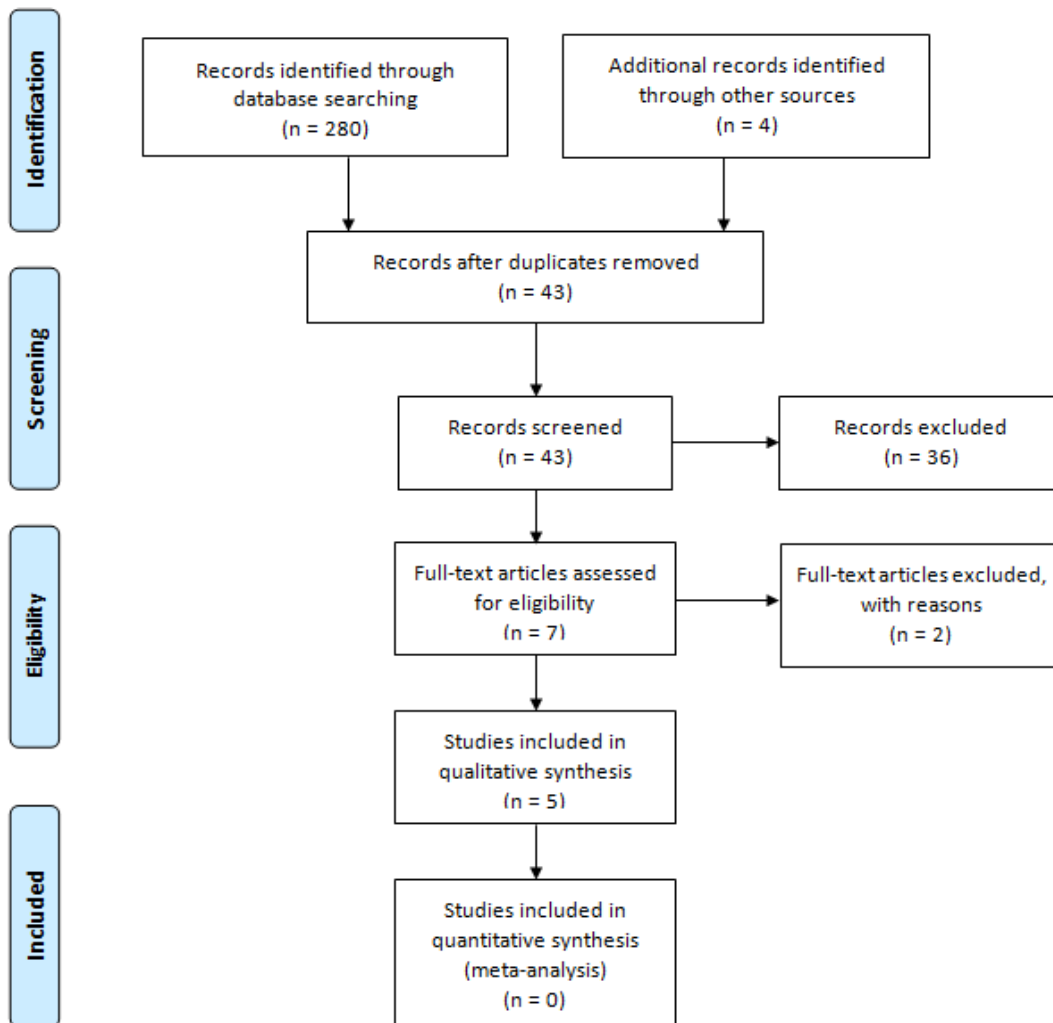


Fig. 1. Flowchart of included studies

Table 1. Clinical characteristics of the patients at baseline

	Chen C, et al. (N=236)		Cao B, et al. (N=199)		Wang Y, et al. (N=237)		Hung I, et al. (N=127)		Beigel JH, et al. (N=1063)	
	Favipiravir (N=120)	Arbidol (N=116)	Lopinavir– Ritonavir (N=99)	Control (N=100)	Remdesivir (N=158)	Placebo (N=79)	Interferon beta-1b, lopinavir–ritonavir, and ribavirin (N=86)	Lopinavir– ritonavir (N=41)	Remdesivir (EV) (N=541)	Placebo (N=522)
Mean age (years)*			58(50-68)	58(48-68)	66(57-73)	64(53-70)	51(31-61)	52(33.5-62.5)	58.6(43.9-73.2)	59.2(43.8 - 74.6)
Women (%)	49.1	57.5	38.4	41	44	35	48	44	34.9	36.1
Comorbidities										
DM (%)	14 (12)	13 (10.8)	10 (10.1)	13 (13)	40 (25)	16 (21)	11 (13)	6 (15)	144 (30.6)	131 (28.7)
HT (%)	36 (31)	30 (25)			72 (46)	30 (38)	23 (27)	13 (32)	231 (49.3)	229 (49.9)
CVA (%)			5 (5.1)	8 (8)			1 (1)	1 (2)		
CHD (%)					15 (9)	2 (3)	5 (6.0)	5 (12)		
Treatments received before enrolment no. of patients (%)										
Antibiotic					121 (77)	63 (81)	44 (51)	25 (61)		
AMOX-CLAV							29 (34)	21 (51)		
Azithromycin							7 (8)	4 (10)		
Ceftriaxone							12 (14)	8 (20)		
Doxycycline							13 (15)	8 (20)		
TZP							5 (6)	0		
LVX							11 (13)	3 (7)		
Corticosteroids therapy					60 (38)	31 (40)	6 (7)	2 (5)		
Interferon alfa-2b					29 (18)	15 (19)				
Lopinavir–ritonavir					27 (17)	15 (19)				
Vasopressors					25 (15.8)	13 (16.4)				
Treatment characteristics										
Drug dose frequency	1600 mg 2/first day followed by 600 mg 2/day	200 mg 3/day	400 mg-100 mg/day	-	200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions	-	Lopinavir 400 mg and Ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate days	Lopinavir 400 mg and ritonavir 100 mg every 12 h	200-mg loading dose on day 1, followed by a 100- mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death.	-

Median time hospitalized*		14(12-17)	16(13-18)	25(16-38)	24(18-36)	9 (7–13)	14(9.3–16)	9 (6–12)	9 (7–13)
Follow-up (days)	10	14		28		14		10	
Outcomes	Mortality and Increase ALT	Clinical Improvement, Mortality, Severe Respiratory Failure, CID, AHF, Lymphopenia, Thrombocytopenia, Increase ALT, Rash, AKI and PTX		Clinical Improvement, Mortality, Severe Respiratory Failure, CID, AHF, Thrombocytopenia, Increase ALT, Rash and AKI		Mortality and Increase ALT		Clinical Improvement and mortality	

*Numerical variables were presented with IQR (interquartile range). AHF: Acute Heart Failure AKI: Acute kidney injury ALT: Alanine Aminotransferase AMOX-CLAV: Amoxicillin–clavulanate CHD: Coronary heart disease CID: Disseminated Intravascular Coagulation CVA: Cerebrovascular disease DM: Diabetes Mellitus HT: Hypertension ICU: Intensive Care Unit. PTX: Pneumothorax LVX: Levofloxacin TZP: Tazobactam-Piperacillin

Table 2. Clinical outcomes of included studies

	Chen C, et al (N=236)		Cao B, et al (N=199)		Wang Y, et al (N=237)		Hung I, et al (N=127)		Beigel JH, et al (N=1063)	
	Favipiravir (N=120)	Arbidol (N=116)	Lopinavir–Ritonavir (N=99)	Control (N=100)	Remdesivir (N=158)	Placebo (N=79)	Interferon beta-1b, lopinavir–ritonavir, and ribavirin (N=86)	Lopinavir–ritonavir (N=41)	Remdesivir (EV) (N=541)	Placebo (N=522)
Region	China		China		China		China		United States, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapor	
Hospital stay. Median. days (IQR)			15 (12-17)		25 (17-37)					
Clinical Improvement DAY 7 no. (%)			14 (12-17)	16 (13-18)	25 (16-38)	24 (18-36)	9 (7 to 13)		14.5 (9.3-16)	
Difference Improvement †			6 (6.1)	2 (2)	4 (3)	2 (3)				
			4.1 (-1.4 to 9.5)		0 (-4.3 to 4.2)					
Score on seven-category scale at day 7 — no. of patients (%)										
Not hospitalized, but unable to resume normal activities			4 (4)	0	4 (3)	2 (3)				
Hospitalization, not requiring supplemental oxygen			12 (12.1)	17 (17)	21 (14)	16 (21)				
Hospitalization, requiring supplemental oxygen			58 (58.6)	51 (51)	87 (56)	43 (56)				
Hospitalization, requiring HFNC or noninvasive mechanical ventilation			14 (14.1)	21(21)	26 (17)	8 (10)				

Hospitalization, requiring ECMO, invasive mechanical ventilation, or both	6 (6.1)	4 (4)	6 (4)	4 (5)		
Death	5 (5.1)	7 (7)	10 (6)	4 (5)		
Clinical Improvement DAY 14 no. (%)	45 (45.5)	30 (30)	42 (27)	18 (23)		
Difference Improvement †	15.5(2.2 to 28.8)		3.5 (−8.1 to 15.1)			
Score on seven-category scale at day 14 — no. of patients (%)						
Not hospitalized, but unable to resume normal activities	43 (43.4)	28 (28)	39 (25)	18 (23)	268 (61.7)§	209 (51)§
Hospitalization, not requiring supplemental oxygen	8 (8.1)	24 (24)	21 (14)	10 (13)	23 (5.3)*	20 (4.9)*
Hospitalization, requiring supplemental oxygen	25 (25.3)	20 (20)	61 (40)	28 (36)	34 (7.8)*	40 (9.8)*
Hospitalization, requiring HFNC or noninvasive mechanical ventilation	5 (5.1)	6 (6)	13 (8)	8 (10)	16 (3.7)*	14 (3.4)*
Hospitalization, requiring ECMO, invasive mechanical ventilation, or both	3 (3)	5 (5)	4 (3)	7 (9)	60 (13.8)*	72 (17.6)*
Death	15 (15.2)	17 (17)	15 (10)	7 (9)	33 (7.6)*	55 (13.4)*
Clinical Improvement DAY 28 no. (%)	78 (78.8)	70 (70)	103 (65)	45 (58)		
Difference Improvement †	8.8 (-3.3 to 20.9)		7.5 (−5.7 to 20.7)			
Score on seven-category scale at day 28 — no. of patients (%)						
Not hospitalized, but unable to resume normal activities			92 (61)	45 (58)		
Hospitalization, not requiring supplemental oxygen			14 (9)	4 (5)		
Hospitalization, requiring supplemental oxygen			18 (12)	13 (1)		
Hospitalization, requiring HFNC or noninvasive mechanical ventilation			2 (1)	2 (3)		
Hospitalization, requiring ECMO, invasive mechanical ventilation, or both			2 (1)	3 (4)		
Death			22 (15)	10 (13)		

Mortality no. of patients (%)	0	0	44 (22.1)	19 (19.2)	25 (25.0)	22 (15)	10 (13)	0	0	32	54
Entering ICU no. of patients(%)	2 (1.72)	2 (1.67)									
Severe Respiratory Failure - Intubation (no. of days and DS)			5 (3-9)	4 (3-7)	5 (3-9)	8 (5-17)	7 (3-13.5)	16 (8-21)			
CID no. of patients (%)			1(1.1)	1(1)	1(1)	1 (1)	1 (1)				
AHF no. of patients (%)			0	1(1)	1(1)	8 (5)	7 (9)				
Adverse Events no. of patients (%)											
Lymphopenia			16 (16.8)	12 (12.1)							
Thrombocytopenia			6 (6.3)	10 (10.1)	16 (10)	5 (6)					
Increase ALT	9 (7) [°]	12 (10) [°]	1 (1.1)	4(4)	2 (1)	0	11 (13)	7 (17)			
Rash			2 (2.1)	0	11 (7)	2 (3)					
AKI			3 (3.2)	6(6.1)	1 (1)	0					
PTX			0	0							

AKI: Acute kidney injury ALT: Alanine Aminotransferase AST: Aspartate Aminotransferase CID: Disseminated Intravascular Coagulation ICU denotes intensive care unit. PTX: Pneumothorax

† Differences were expressed as rate differences or median differences and 95% confidence intervals.

§ Beigle JH, et al, presents the following data divided into 3 different categories, which comprise the following classification: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons)

* Beigle HJ, et al presents the data of the score on day 15 (± 2 days) - no. of patients (%)

[°]ALT and/or AST were elevated

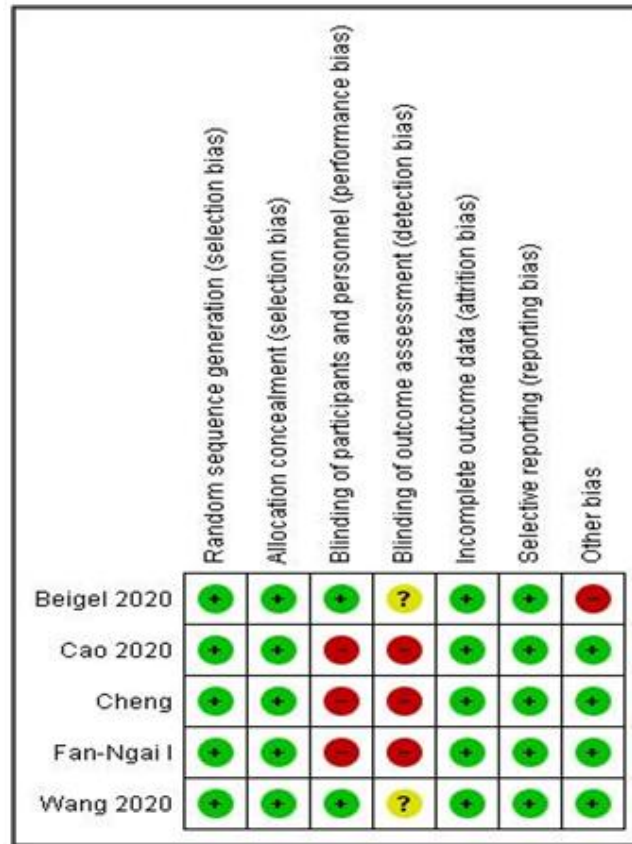


Fig. 2. Risk of bias table. Legend: Red (-) = high risk of bias; Yellow (?) = unknown risk of bias; Green (+) = low risk of bias

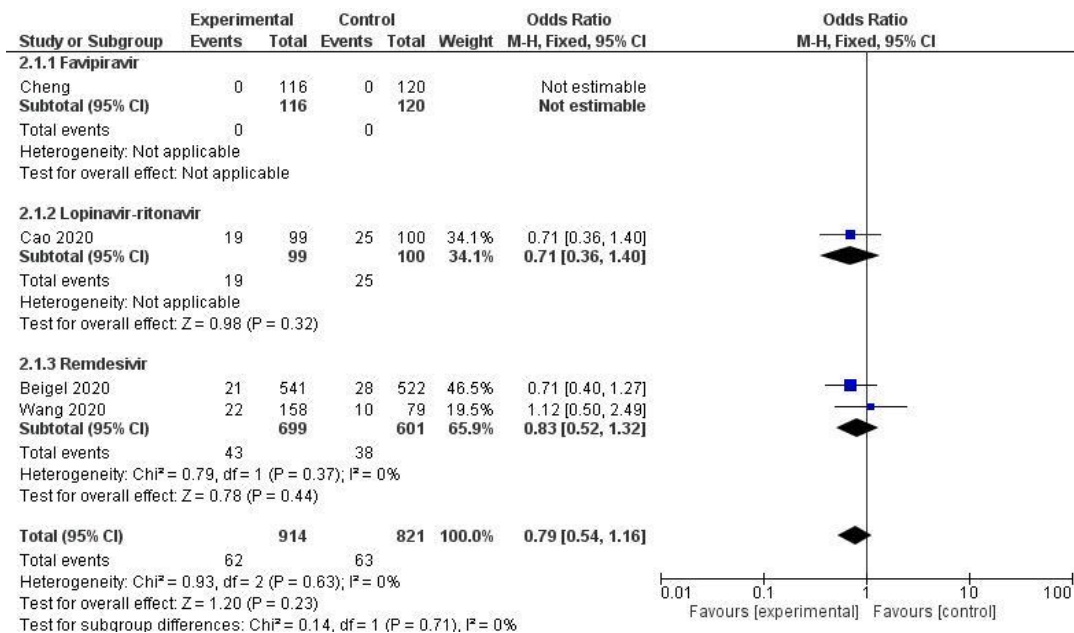


Fig. 3. Forest plot of included studies

3.1.4 Main findings

3.1.4.1 Mortality

In the randomized clinical trials (RTC's) analyzed, it was evidenced that the drugs used did not associate improvement in mortality in patients with COVID -19 compared to standard care, the need for invasive ventilation, hospitalization without oxygen, hospitalization with oxygen or non-invasive ventilation, or treatment discontinuation [9,11]. Besides, the highest mortality of RCTs was from Beigel et al. (54 %) in the control group compared to the rest of the trials, however, this also presented the largest study population (1063) from different nationalities, indicating that it included a larger and diverse population [13].

3.1.4.2 Clinical improvement

The studies that include the evaluation of clinical improvement as outcomes (Cao et al., Wang et al.) showed most patients that required hospitalization by day 14 were in the control subgroup, in comparison with the patients in the Lopinavir-Ritonavir subgroup [9,11]. Patients requiring Extracorporeal membrane oxygenation (ECMO) or mechanical ventilation were predominant in the control subgroup versus the patients receiving Remdesivir. There were no other major differences in the results reported. Remdesivir recently had proved better clinical outcomes in a phase 3 trial.

3.4.4.3 Severe Respiratory Failure, DIC, and AHF

One of the most outstanding results among secondary outcomes was the need for intubation due to severe respiratory failure, whose data were presented by Cao et al. and Wang et al. [9,11] They provide data on the number of days of intubation, and in addition to the IQR (Cao et al. 5 days, IQR: 3-9 and Wang et al. 8 days, IQR: 5-17); Regarding the trial developed by Wang et al, there was no significant difference between the different study groups, the following data being found in the group treated with remdesivir presented a median of 7 days with an IQR: 3-13.5; while the placebo group had a median of 16 days with an IQR: 8-21. [7,11] Regarding the presence of acute heart failure (ACI) Cao et al. it only showed 1% with this affection in the control group, Wang et al. presented 5% of cases of acute heart failure in the treatment group, and 9% of cases of acute heart failure in the placebo group. [9,11] Finally, disseminated intravascular

coagulation (DIC) occurred only in the trial developed by Cao et al., Showing no significant difference between the analyzed groups [9].

3.1.4.4 Side effects of medications

In the set of side effects observed in the articles included in this systematic review, we considered 6 of them as the most relevant. Five of the six articles included presented these side effects. Beigel et al. does not present any side effects in their population [13]. The increase of ALT (Alanine aminotransferase) is the side effect more commonly presented. Hung et al. showed the highest prevalence of increased ALT in their population. Despite this information, it is known that patients without antiviral treatment raise ALT and AST levels [12,16]. The treatment group (Interferon beta-1b, lopinavir-ritonavir, and ribavirin group with 13%; and Lopinavir-ritonavir alone group with 17%). The lowest prevalence of increased ALT was presented by Wang et al. with 1% in the treatment group, and 0% in the placebo group [11]. The rash, acute kidney injury and thrombocytopenia were showed by Cao et al and Wang et al. [9,11] In their treatment group, Wang et al. presented the highest prevalence of thrombocytopenia (10% versus 6.3% in the treatment group of Cao et al.) [9,11]. The rash was highest in the treatment group of Wang et al. with 7%, and the acute kidney injury was highest in prevalence in the control group of Cao et al. study (6.1% versus 3.2% of the treatment group) [9,11].

3.2 Discussion

3.2.1 What we know from the literature

Recently, FDA approved Remdesivir as a drug available for the treatment of COVID-19 [17]. Piscoya et al. demonstrated in a systematic review that Remdesivir had a significantly shorter time to recover from symptoms, and fewer adverse events than placebo groups; however, it does not reduce the all-cause mortality outcome [18]. Moreover, Musa et al concluded that there is limited evidence supporting that Remdesivir might be effective to treat COVID either in vitro or in vivo, so the use of this drug should be delayed until high-quality phase 3 RCT's studying it are completed. Its therapeutic potential is still to be determined [16,15,19].

On the other hand, Yousefifard et al. showed that Lopinavir-Ritonavir was ineffective in improving the patient's outcomes. While Zhang et al. in their SR, MA, and N-RA, did not found any

superiority of Lopinavir-Ritonavir when compared with other antivirals. But they found a relationship with the use of corticosteroids and the development of ARDS [20,21]. Several studies have been proposing different treatments in this context of the SARS-CoV-2 pandemic. For example, Chowdhury et al found that both chloroquine and hydroxychloroquine showed favorable outcomes in the recovery of COVID-19 patients. This was explained since the Viral Load was significantly reduced in the patients using this therapeutic. Also, they concluded that further research is required [22].

Another advance found was made by Cortegiani et al. presented in vitro evidence of chloroquine, showing its efficacy in reducing viral replication and its changes in the cell's pH level. However, unpublished clinical evidence is not robust to the recommendations; and the need for prior examinations before medication makes access difficult to use [23].

Heidary et al. found that even though Ivermectin is an effective antiviral agent in vitro, its effect has not been reproduced in living mice models with a different virus. Also, the antiviral activity of this drug is being noted while using concentrations around 1ugram/ml, the doses used in humans is way lower in the range of 20-80ng/ml [24].

Additionally, Liu et al. found in their SR and metanalyses that there was insufficient evidence that suggests any benefit from the treatments included (Lopinavir/Ritonavir, Ribavirin, Chloroquine, hydroxychloroquine, arbidol, favipiravir) in the clinical outcomes of the patients. Also, they found an increase in the GI adverse events with the use of Lopinavir/ritonavir [18].

Di Lorenzo et al. and Youseffard et al. concluded in their systematic reviews, that there is an urgent need for phase 3 RCT's to be completed and published, to find better associations between the clinical outcomes and the medications used [20,25].

Finally, it is well known that patients with SARS-CoV-2 with only supportive care presents some degree of liver damage, with a rise in AST and ALT levels, with no clinical manifestations [17].

3.2.2 What's new on our study

This study adds Clinical improvement as an outcome using the NEWS-2 Score, which was

not included in previous systematic reviews. Also, this paper includes the evaluation of specific side effects of the antivirals; and besides, it includes the evaluation of some of the complications commonly associated with COVID-19. These outcomes were not included in most of the previously published systematic reviews. In this systematic review, the latest updates in clinical improvement of patients focused only on antivirals are studied.

4. LIMITATIONS

The main limitation of this study is that the data included was recollected from other studies. Furthermore, only a limited number of eligible published RCTs on the subject could be chosen, which did not have validation. Most of them also have a very small population included. Another limitation is the population from the studies are different from each other, and not all of them consider the same outcomes for their RCTs.

5. CONCLUSION

It is important to consider that the use of the antivirals mentioned in the study may cause certain adverse effects. Among them, the elevation of alanine aminotransferase was evident in all antivirals in this systematic review. The use of clinical improvement scales, as in the case of NEWS-2 Score, helps the follow-up of the patients included in the trials and allows us to have quick and understandable reading data. Some more serious side effects like CID and AHF are mentioned in 2 of these studies. Also, other adverse effects are mentioned in studies such as acute kidney damage, thrombocytopenia, among others. More clinical trials involving antivirals are needed to observe a relationship between clinical improvement or mortality from SARS-CoV-19.

DECLARATION

The Authors declare that they have taken extreme care with the handling of data and identity since it is a bibliometric study, no people have been surveyed or their data has been obtained, so we have not violated any normal ethics.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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