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Systematic Review

Comparative efficacy and safety of anti-infective drugs for patients with mild to severe COVID-19: A systematic review and network meta-analysis of randomized controlled trials

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Abstract

Background: *Different anti-infective drugs have been proposed for the treatment of patients with COVID-19. We carried out a network meta-analysis to assess their relative efficacy and safety.*

Methods*: We searched relevant databases for all randomized controlled trials that reported the efficacy and or safety of any anti-infective drugs published up to April 30, 2022 for different outcomes. We did both pairwise and network meta-analysis with 95% confidence intervals using a fixed-effect model. We assessed studies for quality of evidence using an extension of the standard Grading of Recommendations, Assessment, Development and Evaluation approach considering P<0.05 to be statistically significant.*

Results*: We included 68 RCTs for 27,680 participants on 22 anti-infective drugs. For clinical recovery at 14 days Ivermectin (OR= 3.00, 95%CI: [1.82; 4.96]; p < 0.0001; moderate certainty evidence), Baricitinib plus Remdesivir (OR= 2.20, 95%CI: [1.35; 3.53]; p = 0.005; low certainty evidence), and Favipiravir (OR= 2.16, 95%CI: [1.27; 3.68]; p = 0.004; moderate certainty evidence) were statistically effective than standard of care. There was no statistically significant difference between treatments for the viral clearance at 14 days outcome and standard of care. In terms of death outcome, only combined therapy of Baricitinib and Remdesivir showed statistically significant risks of ratio (RR= 0.47, 95%CI: [0.23; 0.99]; p = 0.03). Arbidol (RR= 0.46, 95% CI: [0.23; 0.95]; p = 0.04) was statistically safe drug than standard of care.*

Conclusion*: This Network Meta-analysis suggests that Baricitinib plus Remdesivir is more effective than the other anti-infective drugs in treating patients with COVID-19 in terms of clinical recovery at 14 days, mortality and adverse events outcomes.*

Keywords*: COVID-19, SARS-CoV-2, treatment, network meta-analysis, systematic review, randomized controlled trials.*

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Introduction

COVID-19 is a respiratory illness caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS CoV-2)(1) and it was labeled a pandemic of international concern by the World Health Organization on March 11, 2020(2). Its major mode of transmission is from human to human through respiratory droplets(3-5) and its clinical presentations can be from subclinical with mild to severe infections(6-9). As of 16 July 2021, there were 189,749,287 confirmed cases and 4,083,256 (2.15%) deaths globally(10). Currently, many anti-infective drugs are being repurposed for patients with COVID-19 including remdesivir (used to treat Ebola virus disease and Marburg virus infections (11), lopinavir and ritonavir (used to treat HIV/ AIDS (12), chloroquine phosphate or hydroxychloroquine (used to treat malaria (13), tocilizumab (used to treat rheumatoid arthritis (14), corticosteroids, stem cells, among others.

Anti-infective drugs act on SARS-CoV-2 by inhibiting its replication(15). Their effect is higher in the early stages of the disease because of active replication of the virus in the early courses of infection(16). Remdesivir, a broad-spectrum antiviral medication of nucleotide prodrug adenosine analog, inhibits viral replication by binding to the viral RNA-dependent RNA polymerase and terminating RNA transcription (17). Chloroquine and hydroxychloroquine inhibiting the fusion of SARS-CoV-2 and the host cell membranes by increasing the endosomal pH.(18) Both have immunomodulatory effects which are potential mechanisms of action for the treatment.(19) Lopinavir/ritonavir, a protease inhibitor that may inhibit the action of 3CLpro, leads to disruption of SARS-CoV-2 replication and appears to be highly conserved (20). Ivermectin, a well-known anti-helminthic agent from the late-1970s, eliminate SARS-CoV-2 by inhibiting importin α/β1 mediated transport of viral proteins in and out of the nucleus(21).

Several randomized clinical trials are underway and currently, there are about 2868 trials registered worldwide for the treatment of COVID-19(22). Yet, the only US Food and Drug Administration (FDA)-approved anti-infective drug is Remdesivir. It has been approved for the treatment of hospitalized patients (aged ≥12 years and weighing ≥40 kg)(23). Its administration was associated with clinical improvements(24) and significantly lower serious adverse drug reactions (ADRs) when compared to control groups(25). Mortality was decreased in hospitalized COVID-19 patients treated with only hydroxychloroquine combined with azithromycin(26). Remdesivir, hydroxychloroquine, and lopinavir regimens had little or no effect on hospitalized patients with COVID-19 in decreasing overall mortality(27). Recent studies showed that Ivermectin had beneficial effects in COVID-19 by reduction of mortality, higher negativity rate, and higher symptoms alleviations rate(28). One network meta-analysis done by mixing observational and RCT studies revealed that anti-inflammatory agents and remdesivir were associated with improved outcomes of hospitalized COVID-19 patients(29).

There have been efforts underway to identify effective drugs for the treatment of COVID-19 there were a couple of systematic reviews combined with meta-analysis and/or network meta-analysis carried out to systematically synthesis the efficacy and safety of such drugs. However, currently available reviews did not recommend the best drugs in terms of clinical recovery, viral clearance, and tolerability; besides, some are already outdated as new findings are emerging. There were two such potential reviews. One was published in April 2021 that reviewed 33 articles published up to February 2021(30), and the second was a living review published in May 2021 that included articles published up to December 2020(31).

Therefore, our systematic review and network meta-analysis aimed to compare the efficacy and safety of anti-infective drugs for patients with mild to severe COVID-19.

Methods

The systematic review and network meta-analysis was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for network meta-analysis (PRISMA-NMA)(32) (Supplementary material 2). The protocol was prospectively registered with PROSPERO2021 (ID: CRD42021230919)(33).

Eligibility

The PICOS (participants, interventions, comparison, outcomes, and study designs) description model was used to set eligibility criteria of the study

- Participants: patients with mild, moderate and severe COVID 19, confirmed by laboratory RT-PCR or imaging (chest CT scan or chest x-ray).
- Intervention: any anti-infective drug tested to evaluate its efficacy or safety in patients diagnosed with COVID-19. Different dosages and durations of anti-infective drugs were taken as individual treatments but separately evaluated for subgroup analysis.
- Comparator: standard of care or placebo.
- Outcomes: Primary outcomes were time to clinical recovery and treatment-emergent serious adverse events. Secondary outcomes were rate of viral clearance, all-cause mortality, and adverse events.
- Study design: RCTs, published in the English language.

Search strategy and study selection

We searched PubMed, Cochrane Central Register of Controlled Trials, COVID-evidence, Cochrane COVID-19 Study Register, Embase, and clinical trial registration sites in the US (ClinicalTrials.gov), Europe (clinicaltrialsregister.eu), and China (chictr.org.cn) up to 30 April 2022 for all RCTs that evaluated the efficacy or safety of any anti-infective drugs. For the PubMed database, we used the MeSH terms “Antiviral Agents” OR “specific drugs” AND “COVID-19” OR “SARS-COV-2” limited to human studies and published in English languages**.** Paper was included if it is RCT investigating anti-infective drug treatment and clinical outcomes in confirmed COVID-19 disease with at least one of the outcomes. Additional potential papers were considered from reference lists of included articles and other relevant

systematic reviews. The title/abstract was initially as well as full text screened by two independent reviewers and disagreements were resolved by third authors.

Table 1: Summary characteristics of studies included in the systematic review and network meta-analysis

SN	Authors/ year	Setting/ Country; registration number	Study design; sample size; arms	Mean age years; sex ratio (M to F)	Intervention (name, dose, frequency, route etc.)	Comparator (name, dose, frequency, route etc.)	Outcomes (primary; secondary)
1	Chen L,2020	Single center/ China; ChiCTR2000030054	RCT; 67; 3 (2:2:1)	45.22/45.67/51.33; 39/44/58	1.Hydroxychloroquine 200mg orally BID for 10 days 2. Chloroquine 1000mg orally QD for the first day, then 500 mg QD for additional 9 days	Standard of care	time to clinical recovery (TTCR); time to SARS-CoV-2 RNA negativity, 2. length of hospital stay 3. Changes on chest CT scan; 4. duration (days) of supplemental oxygenation; 5. frequency of adverse events; 6. clinical status; 7. all-cause mortality;
2	Abd-Elsalam S,2020	Multicenter/Egypt; NCT04353336	RCT; 194; 2 (1:1)	40.35/41.09; 57.7/59.8	HCQ 400 mg BID in day 1 followed by 200 mg BID for 15 days	Standard of care	1.recovery within 28 days 2. need for mechanical ventilation, 3. death;
3	Abd-Elsalam S2,2020	multicenter/Egypt; NCT04447534	RCT; 191; 2 (1:1)	43.48/43.64; 54.2/67.4	Hydroxychloroquine 400 mg BID on day 1, then 200 mg BID for 5 days PLUS zinc sulfate 220 mg BID	Hydroxychloroquine 400 mg BID on day 1, then 200 mg BID for 5 days	1.recovery within 28 days, 2.the need for mechanical ventilation, and 3. death
4	Babalola OE,2020	Nigerian; ISRCT-N40302986	RCT; 62; 3 (1:1:1)	48.3/39.7/44.8; 71.4/66.7/70	1.Ivermectin 6mg twice a week. 2. Ivermectin 12mg twice a week for 2 weeks	lopinavir / ritonavir daily for 2 weeks	time to SARS-CoV-2 negativity;
5	Beigel J,2020	Multicenter/ multi-county; NCT04280705	RCT; 1062; 2(1:1)	58.6/59.2; 65.1/63.7	Remdesivir 200 mg loading dose on day 1, followed by 100 mg daily for up to 9 days	Placebo	Time to recovery; clinical status at day 15, time to discharge, days of hospitalization, mortality at 14 and 28 days
6	Cao B,2020	China; ChiCTR2000029308	RCT; 199; 2 (1:1)	58/58*; 61.6/59	lopinavir–ritonavir 400 mg-100 mg orally BID for 14 days	Standard of care	time to clinical improvement; Mortality at 28 days, adverse events, the duration of mechanical ventilation, the duration of hospitalization

7	**Cavalcanti A,2020**	**Multicenter/ Brazil; NCT04322123**	**RCT; 665; 3 (1:1:1)**	**49.6/51.3/49.9; 56.7/64.3/54.2**	**1.hydroxychloroquine 400mg BID plus azithromycin 500 mg daily for 7 days. 2.hydroxychloroquine 400 mg BID for 7 days**	**Standard of care**	**Clinical status at 15 days; clinical status at 7 days, duration of hospital stays, hospital death**
8	Doi Y,2020	Japan; jRCTs041190120	RCT; 88; 2 (1:1)	48.0/51.0*; 52.3/70.5	Favipiravir 1,800mg orally BID at least 4 h apart on the first day, followed by 800mg BID for a total of up to 19 doses over 10 days	Favipiravir 1,800mg orally BID at least 4 h apart on the six day, followed by 800mg orally BID for a total of up to 19 doses over 10 days	Time to SARS-CoV-2 clearance; SARS-CoV-2 clearance by day 10, death
9	Furtado R,2020	Brazil; NCT04321278	RCT; 447; 2 (1:1)	59·4 /60·2*; 65/67	Azithromycin 500 mg orally, nasogastric, or intravenous administration once daily for 10 days	Standard of care	clinical status at day 15; mortality at 29 days, length of hospital stays
10	Goldman J,2020	Multi-county; NCT04292899	RCT; 397; 2 (1:1)	61/62*; 60/68	Remdesivir 200 mg on day 1, followed by 100 mg of Remdesivir once daily for the subsequent 4 days.	Remdesivir 200 mg on day 1, followed by 100 mg of Remdesivir once daily for the subsequent 9 days	clinical status on day 14; adverse events, time to clinical improvement, time to recovery, time to modified recovery, death
11	Horby P and Landray M,2020	Multicenter/UK; ISRCTN50189673, NCT04381936	RCT; 5040; 2(1:2)	66/66.4; 60/61	lopinavir–ritonavir 400 mg-100 mg orally for 10 days	Standard of care	28-day all-cause mortality; time to discharge
12	Horby P,2020	Multicenter/UK; SRCTN50189673; NCT04381936	RCT; 4716; 2(1:2)	65.2/65.4; 61.5/62.6	hydroxychloroquine sulfate 800 mg at baseline and at 6 hours, followed by 400 mg starting at 12 hours after the initial dose and then every 12 hours for the next 9 days	Standard of care	28-day mortality; time until discharge, initiation of invasive mechanical ventilation
13	Hung I,2020	multicenter/Hong Kong; NCT04276688	RCT; 127; 2 (2:1)	51·0/52·0*; 52/56	lopinavir 400 mg/ ritonavir 100 mg every 12 h PLUS ribavirin 400 mg every 12 h PLUS three doses of 8 million international units of interferon beta-1b on alternate days for 14 days	lopinavir 400 mg/ ritonavir 100 mg every 12 h for 14days	time to a nasopharyngeal swab negative; time to resolution of symptoms, length of hospital stays; and 30-day mortality

14	Ivashchenko A,2020	Multicenter/ Russia; NCT04434248	RCT; 60; 3 (1:1:1)	Comparable	1.AVIFAVIR 1600 mg BID on Day 1, followed by 600 mg BID on Days 2–14 (1600/600 mg). 2. AVIFAVIR 1800 mg BID on Day 1, followed by 800 mg BID on Days 2–14 (1800/800 mg)	Standard of care	Elimination of SARS-CoV-2 by Day 10; rate of viral clearance by Day 5, time to normalization of clinical symptoms, adverse events
15	Kamran M,2020	Single center / Pakistan; NCT04491994	RCT; 500; 2 (2:1)		HCQ 400 orally BID for day one followed by 200 mg BID for next 5 days	Standard of care	disease progression within 5 days; viral clearance
16	Kasgari H,2020	single center/ Iran; IRCT20200328046886N1	RCT; 48; 2 (1:1)	45/60*; 46/29	400mg sofosbuvir, 60mg daclatasvir and 1200mg ribavirin	Standard of care	length of hospital stays; frequency of ICU admission, invasive mechanical ventilation, duration of ICU admission, mechanical ventilation, frequency and
17	Khamisa F,2020	single/ Oman; NCT04385095	RCT; 89; 2 (1:1)	56/54; 53/64	Favipiravir 1600 mg on day 1 followed by 600 mg BID for a maximum of 10 days, and interferon beta-1b at a dose of 8 million IU (0.25 mg) BID for 5 days	HCQ 400 mg BID on day 1, then 200mg BID for 7 days	time to clinical recovery; intensive care unit (ICU) admission rate, mortality within 14 days
18	Nojomi M,2020	single/ Iran; IRCT20180725040596N2	RCT; 100; 2 (1:1)	56.6/56.2; 66/54	hydroxychloroquine (400mg on first day) followed by 400 mg KALETRA (Lopinavir/ ritonavir)	Hydroxychloroquine (400 mg BD on first day) followed by ARB (200mg TDS) 7 to 14 days	hospitalization duration and clinical improvement 7 days; death during the 30 days of treatment, duration of hospitalization, need for invasive mechanical ventilation
19	Ruzhentsova T,2020	multicenter/ Russia; NCT04501783	RCT; 168; 2 (2:1)	41·7/42.0; 43.8/53·6	Favipiravir 1800 mg BID on day 1, followed by 800 mg BID for up to 9 days	Standard of care	time to clinical improvement and the time to viral clearance; rate of clinical improvement at Day 7 and the rate of viral clearance at Day 5
20	Sadeghi A,2020	multicenter/Iran; IRCT20200128046294N2	RCT; 66; 2 (1:1)	58/62*; 61/42	400mg sofosbuvir and 60mg daclatasvir daily for 14days	Standard of care	clinical recovery within 14days; all-cause mortality, requirement for mechanical ventilation, duration of hospital stay and time to hospital discharge
21	Sekhavati E,2020	Single center/ Iran	RCT; 111; 2 (1:1)	54.38/59.89; 50/41	Oral AZM 500 mg daily, oral LPV/r 40 0/100 mg twice daily and oral HCQ 400 mg daily for 5 days	oral LPV/r 400/ 100 mg twice daily and oral HCQ 400 mg daily for 5 days	mortality, duration of hospitalization and need for intensive care unit (ICU) admission

23	Spinner C,2020	multicenter/United States, Europe, and Asia; NCT04292730	RCT;584;3 (1:1:1)	56/58/57*; 61/60/63	Remdesivir 200mg intravenously on day 1, followed by 100mg once daily for the subsequent days, infused over 30 to 60 minutes (5 and 10 days)	Standard of care	clinical status on day 11; adverse events, time to recovery, time to clinical improvement, all-cause mortality
24	Tang W,2020	multicenter/ China; ChiCTR2000029868	RCT; 150; 2 (1:1)	48.0/44.1; 42/40	Hydroxychloroquine loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily (total treatment duration: two or three weeks	Standard of care	Negative conversion by 28 days; all cause death
25	Udwadia Z,2020	multicenter/ India; CTRI/2020/05/025114	RCT; 147; 2 (1:1)	43.6/43.0; 51/57	oral favipiravir (1800 mg BID loading dose on day 1; 800 mg BID maintenance dose thereafter) for 14 days	Standard of care	time to the cessation of oral shedding of the SARS-CoV-2 virus, hospital discharge; time to clinical cure, ventilation (noninvasive or mechanical), time to hospital discharge
26	Wang Y,2020	multicenter/China; NCT04257656	RCT; 237; 2 (2:1)	66·0/64.0*; 56/65	intravenous Remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions)	Placebo	time to clinical improvement; all-cause mortality at day 28, frequency of invasive mechanical ventilation, duration of hospital admission
27	Yueping L,2020	single-center/ Guangzhou, China; NCT04252885	RCT; 86; 3 (2:2:1)	50.7/50.5/44.3*; 50/45.7/41.2	lopinavir (200mg)/ ritonavir (50mg) orally BID, 500 mg, each time for 7-14 days), arbidol (100mg) (orally TID, 200mg daily for7-14 days)	Standard of care	rate of positive-to-negative to day 21; rate of positive-to-negative to day 14
28	Ahmeda S,2021	Single center/ Bangladesh	RCT; 72; 3 (1:1:1)	42; 46	1.oral ivermectin12 mg once daily for 5 days. 2. oral ivermectin plus doxycycline (12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h	Placebo	time required for virological clearance, remission of fever (37.5 C) and cough within 7 days; duration of hospitalization, all-cause mortality, Drug safety
29	Dabbous H,2020	multicenter/ Egypt; NCT04351295	RCT; 96; 2 (1:1)	36.15/34.86; 52.1/45.5	chloroquine 600 mg tablets twice daily for 10 days;	1600 mg of favipiravir twice a day on the first day and 600 mg twice a day from the 2 to 10 day	Death, hospitalization, need mechanical ventilation
30	Ader F, 2021	multicenter/ France; unpublished/ NCT04315948	RCT; 583; 5 (1:1:1:1:1)	65/63/62*; 71.7/73.1/70.9	1.lopinavir/ritonavir (400 mg lopinavir and 100 mg ritonavir every 12h for 14 days). 2.hydroxychloroquine (400 mg twice on day 1 then 400 mg once daily for 9 days)	Standard of care	clinical status at day 15; SARS-CoV-2 quantification in respiratory specimens, safety analyses

31	Beltran G. J,2021	unpublished/ NCT04391127	RCT; 106; 3 (1:1:1)	48.9/56/53.8; 66.6/58.3/62.1	1.Hydroxychloroquine, 400 mg BID on the first day and subsequently, 200 mg BID for 4 days. 2.ivermectin, 12 mg or 18 mg	Placebo	duration of hospitalization, the total duration of hospitalization, and the safety
32	Brown S,2021	NCT04329832	RCT; 85; 2 (1:1)	51/58; 44/33	hydroxychloroquine 400mg BID on the first day, followed by 200 mg BID for the following 4 days (total dose,2.4 gm	Azithromycin loading dose of 500 mg on the first day, followed by 250 mg daily for the next 4 days (total dose, 1.5 gm)	Day 14 COVID ordinal outcomes scale; hospital-free, ventilator-free, and intensive care unit (ICU)–free days
33	Dabbous HM,2021	Egypt; NCT04349241	RCT; 100; 2 (1:1)	36.3/36.4; 50/50	favipiravir 3200mg at day1 followed by 600mg twice (day2-day10)	hydroxychloroquine 800mg at day1 followed by 200mg twice (day2- 10) and oral oseltamivir 75mg/12hour/day for 10 days	SARS-CoV-2 viral clearance on days 3, 7, and 14; clinical outcomes on days 3, 7 and 14
34	Dubée V,2020	multicenter/ France; unpublished/ NCT04325893	RCT; 250; 2 (1:1)	76/78*; 52/44.8	800mg hydroxychloroquine on Day 0 followed by 400mg per day for 8 days	Placebo	death or tracheal intubation within 14 days; mortality and clinical evolution at Day 14 and 28, viral shedding at Day 5 and 10
35	Elgazzar A,2020	multicenter/ Egypt; unpublished/ NCT04668469	RCT; 600; 2 (1:1)	57.45/56.7; 70/70.5	Ivermectin 0.4mg/kg body weight maximum 4 tablets (6mg /tablet) once daily dose	hydroxychloroquine (400 mg every 12 hours for one day followed by 200 mg every 12 hours for 5 days)	clinical, laboratory improvement; adverse events
36	Galan L ,2021	Brazil	RCT; 168; 3 (1:1:1)	54.8/51.9/53.2; 56.8/57/8/60.7	1.CQ diphosphate (450 mg, BID on day 0, and once daily from day 1 to day 4, total dose 2.7 g). 2.HCQ sulfate (400 mg twice on day 0, and once daily from day 1 to day 4, total dose 2.4 g)	ivermectin (14 mg once at day 0 + 1 placebo tablet at day 0, and once daily from day 1 to day 2, + 1 placebo tablet daily from day 3 to 4, total dose 42 mg)	need of supplemental O2, invasive ventilation, admission in ICU, death
37	Hernandez-Cardenas C, 2021	Mexico; Unpublished/ NCT04315896	RCT; 214; 2 (1:2)	50/49; 82/68	HCQ orally or by nasogastric tube, 200 mg BID for 10 days	Placebo	Mortality; days of mechanical ventilation, days of hospitalization and cumulative incidence of serious adverse events

38	Horby P and Land-ray M,2021	Multi-center/ UK; NCT04381936/ ISRCT-N501896	RCT; 7763; 2 (1:2)	65·4/65.2; 62/62	Azithromycin 500 mg daily by mouth or intravenously for 10 days or until dis-charge	Standard of care	28-day all-cause mortality
39	Huang Y-Q,2020	single-center/ China; ChiCTR2000029387	RCT; 101; 3 (1:1:1)	40.3/43.3/43.8; 55/53/28	1.RBV loading dose of 2g, followed by oral doses of 400–600mg TID depending on patients' body weight, for 14 days. 2. LPV/r orally at a dose of 400 mg/100 mg per dose BID for 14 days	RBV plus LPV/r	median interval to SARS-CoV-2 nu-cleic acid negativi-ty, the proportion of patients with SARS-CoV-2 nu-cleic acid negativity at day 14, the mor-tality at day 28, the proportion of pa-tients re-classified as severe cases, and adverse events
40	Kalil A,2021	Multi-county; NCT04401579	RCT; 1033; 2 (1:1)	55.8/55; 64.3/61.9	Remdesivir intravenously 200-mg loading dose on day 1, followed by a 100-mg maintenance dose ad-ministered daily on days 2 through 10	Baricitinib 4-mg daily dose (either orally [two 2-mg tablets] or through a nasogastric tube) for 14 day	time to recovery; clinical status at day 15
41	Lou Y,2020	China; ChiCTR2000029544	RCT;29; 3 (1:1:1)	53.5/58/52.5; 70/77/70	1. Baloxavir marboxil 80 mg once a day orally on Day 1 and Day 4; for pa-tients who are still positive in virological test, they can be given again on Day 7. 2. Favipiravir 1600 mg or 2200mg orally, followed by 600 mg each time, three times a day, and the dura-tion of administration was not more than 14 days	Standard of care	percentage of sub-jects with viral negative by Day 14 and the time from randomization to clinical improve-ment; adverse events, death
42	Medina E,2021	single center/ Colom-bia; NCT04405843	RCT;400; 2 (1:1)	37/37*; 39/44.9	Ivermectin 300 μg/kg per day for 5 days	Placebo	time to resolution of symptoms within a 21-day; adverse event

Data extraction

Data extraction was performed by two independent reviewers and disagreements were resolved by third authors. The data collection format was adapted from the Cochrane data extraction tool(34). Extracted information was included the first author's name and year of publication, setting, country, study design, follow-up duration, age (mean/median), the proportion of male participants, treatment characteristics (name, dose, route, frequency, duration), sample size, study funder, type of statistical analysis, proportion or number of participants with clinical improvement, proportion or number of participants with viral clearance, death, and adverse events

Data synthesis and analysis

We summarized the included articles with a descriptive table. We did direct pairwise meta-analyses using standard inverse-variance fixed-effect by meta command of RStudio Version 1.2.5019 for studies reported in head-to-head comparisons for all supposed primary outcomes. We computed the odds ratio (OR) and risks ratio (RR) and its 95%confidence interval (CI) for the dichotomous variables and mean difference (MD) for continuous outcomes. We tested between-study heterogeneity in each pairwise using I^2 statistics (35).

A network meta-analysis (NMA) was performed using the netmeta commands in the RStudio Version 1.2.5019 to combine all direct and indirect comparisons (36). The geometry network maps were drawn to give an overview of the relationships between each pair of treatments (37). We have checked the major assumptions: (1) similarity, (2) inconsistency (disagreement between the different sources of evidence), and (3) intransitivity (38, 39). The network forest to summarize an effect size as pooled OR and RR with a 95% confidence interval (CI) setting a p-value of less than 0.05. We used the league tables to display the relative efficacy and safety outcomes(40). Inconsistency was quantified using the global Q test and locally using the so-called node-splitting (SIDDE) (41, 42). The surface under the cumulative ranking area (SUCRA) and P-score were used to show the hierarchy of superiority among interventions(43).

Quality assessment

We used the version 2 risk of bias Cochrane assessment tool (RoB2) for evaluating each selected RCT (44) and for each outcome. The tool is structured into five domains: the randomization process; deviations from intended interventions; missing outcome data; measurement of the outcome and selection of the reported result. We assessed the quality of evidence using an extension of the standard GRADE-NMA (Grading of Recommendations, Assessment, Development and Evaluation extension to network meta-analysis) approach which is based on the contributions of the direct comparisons to the estimation in the network meta-analysis(45). We downgraded evidence based on the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) and categorized into four levels: high, moderate, low, and very low.

Sensitivity and subgroup analysis and publication bias

We performed a sensitivity analysis on the impact of high risk of bias studies. Subgroup analysis was done among different severity of disease (mild, moderate and severe COVID 19). The publication bias was assessed by a comparison-adjusted funnel plot to identify small study publication bias.

Results

Study characteristics

From the total 1,017 articles retrieved, 68 studies met the eligibility criteria, of which 16 excluded from the main analysis because of risk of bias. A total of 42 studies were included in the systematic review and network meta-analysis (Figure 1). The selected studies involved a total of 37,429 participants, with a mean age of 50.1years and 77% male. The details of study characteristics are given in (Table 1).

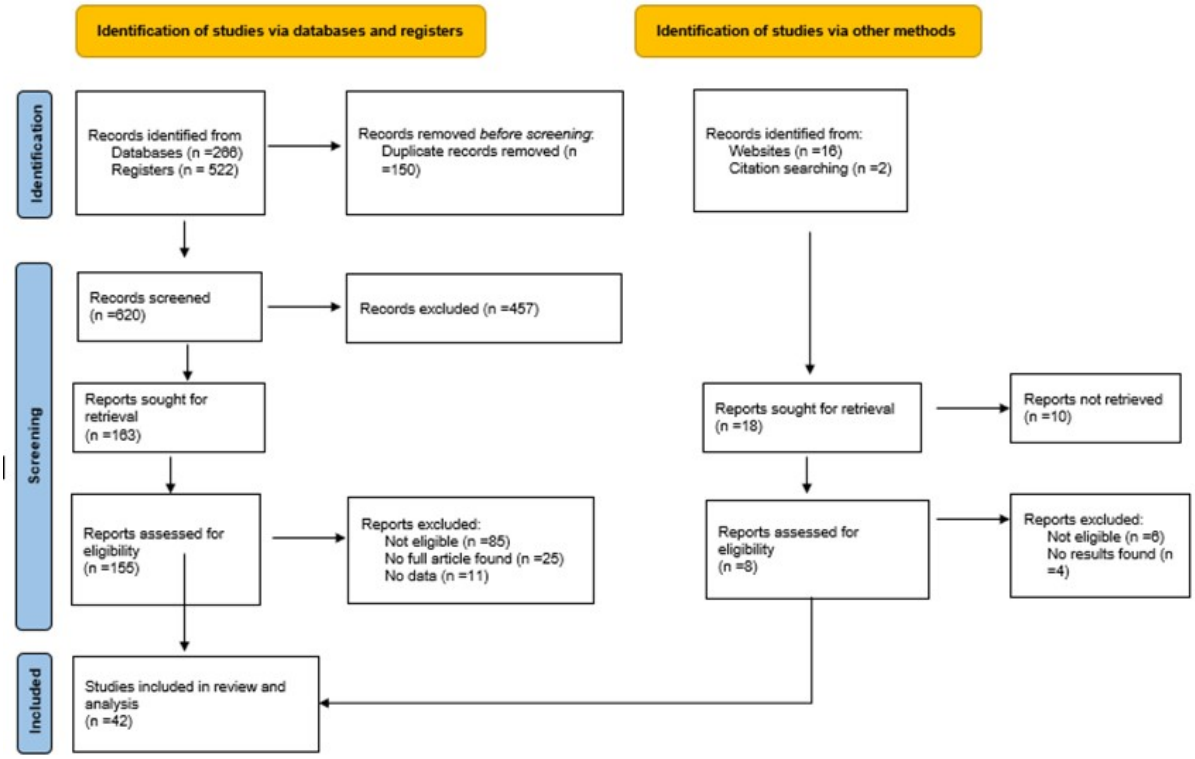

Figure 1: PRISMA flow chart of study selection for inclusion in the systematic review and network meta-analysis

The geometry network maps presentation of all treatment compaisons for each outcome is presented below **(**Figure 2**)**.

There were more than 22 different anti-infective drugs including Arbidol, Azithromycin, Baloxavir Marboxil, Baricitinib, Chloroquine, Daclatasvir, Favipiravir, Hydroxychloroquine, Ivermectin, Lopinavir–Ritonavir, Ribavirin, Sofosbuvir, Remdesivir, Placebo, Standard of care and their combinations. Standard of care treatment is selected as reference therapy for the analysis of NMA.

As per RoB2 risk of bias evaluation using the Excel tool ROB2_IRPG_beta_v7, 42 studies had some concern of risk of bias (62%). 18 studies were found to have a low risk of bias (27%), while the remaining eight studies had a high risk of bias (11%) (Figure 3).

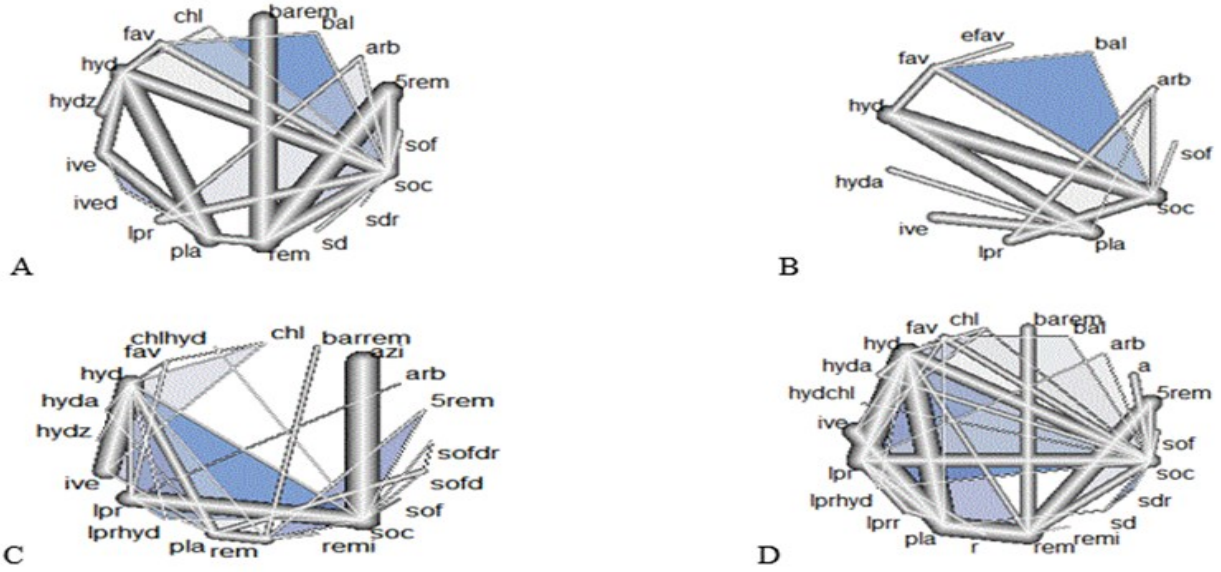

Figure 2: Network graph of eligible articles of anti-infective drugs for patients with mild to severe COVID-19. (A) Clinical recovery rate at 14 days; (B) Viral clearance rate at 14 days; (C) Mortality rate; (D) Adverse events. The thickness of the lines proportional to the number of studies evaluating each direct comparison and shaded triangle represents multi-arm trial.

5rem: remdesivir for 5 days; arb: arbidol; a: azithromycin; bal: baloxivir; barem: baricinib plus remdesivir; chl: chloroquine; fav: favipiravir; hyd: hydroxychloroquine; hydz: hydroxychloroquine plus azithromycin; ive: ivermectin; iverd: ivermectin plus doxycycline; lpr: lopinavir-ritonavir; pla: placebo; rem: remdesivir; sd: sofosbuvir plus daclatasvir; sdr; sofosbuvir/ daclatasvir/ ribavirin; soc: standard of care.

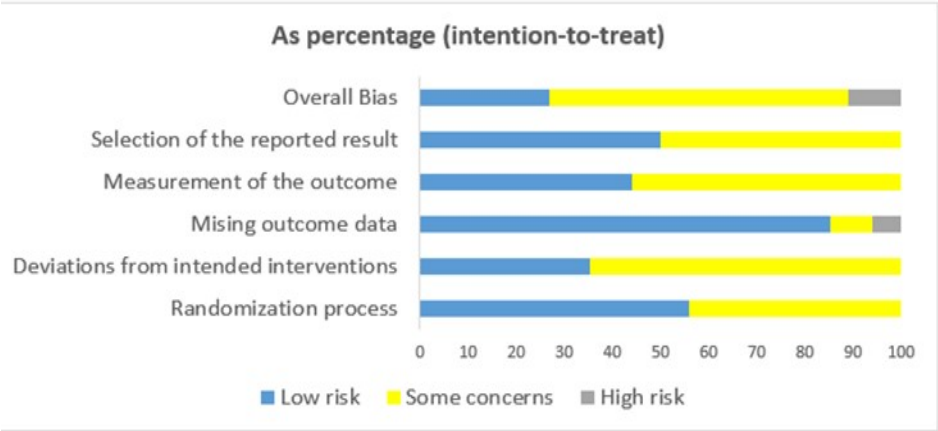

Figure 3: risks of bias diagram for all eligible studies assessed

Meta-analysis

Pairwise meta-analysis had shown higher statistically significance odds of clinical recovery rate at 14 days when Favipiravir (OR= 2.20; 95%CI: (1.22; 3.97); 4RCT) than standard of care but Hydroxychloroquine (OR= 1.28 95%CI: (0.83;1.97); 3RCTs) has low odds of clinical recovery rate at 14 days than standard of care **(**Supplementary material 3**, Table 1**). No drug had no statistically significant difference in direct comparison to the standard of care treatments for viral clearance rate at 14 days: Favipiravir (OR =1.94; 95%CI: (0.97; 3.86), 5RCTs), Hydroxychloroquine (OR= 0.86; 95%CI: (0.62; 1.20), 5RCTs) and Lopinavir/Ritonavir (OR= 1.02; 95%CI: (0.61; 1.73), 2RCTs) (Supplementary material 3**, Table 2**). Reduction in death rate due to COVID-19 was not better for Sofosbuvir plus Daclatasvir (OR= 0.36; 95%CI: (0.13; 1.04); 3RCTs) and Lopinavir/Ritonavir (OR= 1.08; 95%CI: (0.95; 1.23); 3RCTs) than standard of care (Supplementary material 3**, Table 3**). Favipiravir (OR= 1.35; 95%CI: (1.08; 1.70); 3RCTs), Lopinavir/ Ritonavir (OR= 1.15; 95%CI: (1.02; 1.29); 4RCTs), and Hydroxychloroquine (OR= 1.17; 95%CI: (1.03; 1.32); 5RCTs) were less tolerable than standard of care in treating COVID-19 (Supplementary material 3**, Table 4**).

Network meta-analysis
Clinical recovery rate at 14 days

The network meta-analysis with 35 papers investigating 17 treatment drugs in 6,228 participants identified more than five drugs statistically significant in increasing the clinical recovery at 14 days than standard of care (Supplementary material 3, Table 1). In general, network forest plot by frequentist approach has shown that Ivermectin (OR= 3.01; 95%CI: (1.82; 5.00); p-value < 0.0001, moderate certainty of evidence), Remdesivir for 5 days (OR= 1.86; 95%CI: (1.27; 2.74); p-value 0.0016, low certainty of evidence), combined Remdesivir and Baricinib for 10 days (OR= 2.20; 95%CI: 1.34; 3.53; p-value 0.002, low certainty of evidence), Favipiravir (OR= 2.20; 95%CI:(1.32; 3.60); p-value 0.002), Remdesivir for 10 days (OR= 1.50; 95%CI:(1.03; 2.20); p-value 0.03, low certainty of evidence) and Sofosbuvir plus Daclatasvir (OR 3.63; 95%CI 1.02; 12.93; p-value 0.05, low certainty of evidence) were more effective than standard of care in clinical recovery at 14 days (Figure 5). Hierarch by frequentist P-score ranked Ivermectin drug (83.3%) as the best top followed by Sofosbuvir plus Daclatasvir (80.7%), combined Remdesivir and Baricinib for 10 days (68.8%) and Favipiravir (67%) (Figure 4). The total global heterogeneity for this network overall was statistically significant low heterogeneity (I^2 = 53% (15.6%; 73.9%); p value = 0. 008). Then the node splitting method (Separate indirect from direct design evidence (SIDDE)) revealed that there was evidence of local inconsistency identified in several pair of closed loops of networks comparison in clinical recovery at 14 days outcome.

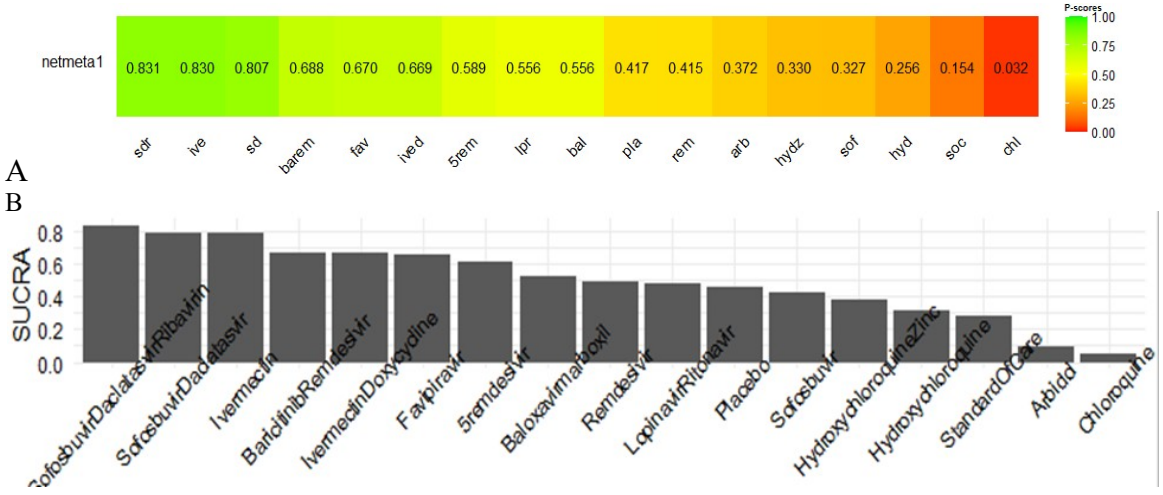

Figure 4: Hierarchy rank plot of network meta-analysis of Anti-infective drugs for clinical recovery at 14 days: P-score (A) and SUCRA (B)

5rem: remdesivir for 5 days; arb: arbidol; a: azithromycin; bal: baloxivir; barem: baricinib plus remdesivir; chl: chloroquine; fav: favipiravir; hyd: hydroxychloroquine; hydz: hydroxychloroquine plus azithromycin; ive: ivermectin; iverd: ivermectin plus doxycycline; lpr: lopinavir-ritonavir; pla: placebo; rem: remdesivir; sd: sofosbuvir plus daclatasvir; sdr; sofosbuvir/ daclatasvir/ ribavirin; soc: standard of care.

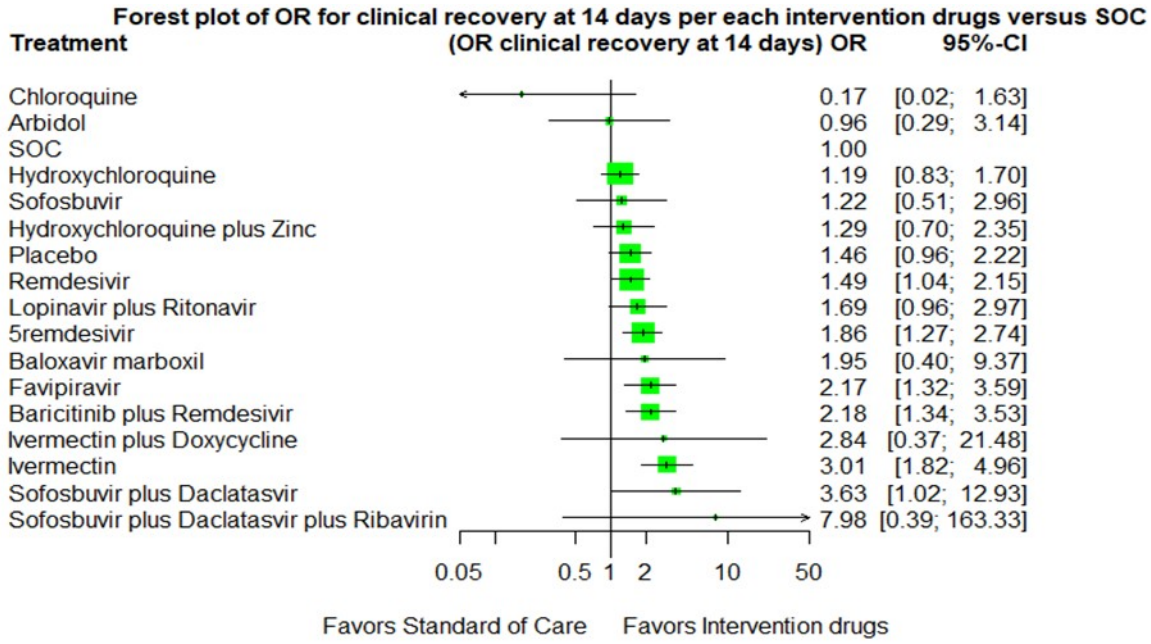

Figure 5: Forest plot. Network meta-analysis estimates of drug-level versus standard of care for the clinical recovery at 14days outcomes.

Viral clearance rate at 14 days

19 papers reporting on 11 treatment drugs involved 1,759 participants were presented by frequentist approach network graph (Figure 2) and relative estimates of effective by Netleague table (Supplementary material 3, Table 2). There was no statistically significant difference between an anti-infective drug in terms of viral clearance at 14days comparing to the standard of care: Arbidol (OR 1.55; 95%CI 0.65; 3.72), Favipiravir early treatment (OR 1.51; 95%CI 0.42; 5.49), Lopinavir/ Ritonavir (OR 1.29; 95%CI 0.68; 2.47) and Sofosbuvir (OR 1.59; 95%CI 0.37; 6.76) (Figure 6). Surface under the cumulative ranking curve (SUCRA) hierarchy ranked Arbidol best top safe drug (SUCRA = 74.2%) followed by Sofosbuvir (SUCRA = 68%) and Favipiravir (SUCRA = 67.6%) as third best drug (Figure 7). Global heterogeneity/ inconsistency was revealed with wide confidence interval (heterogeneity: I^2 = 24.7% (0.0%; 61.7%); Q = 14.6; p-value = 0.20).

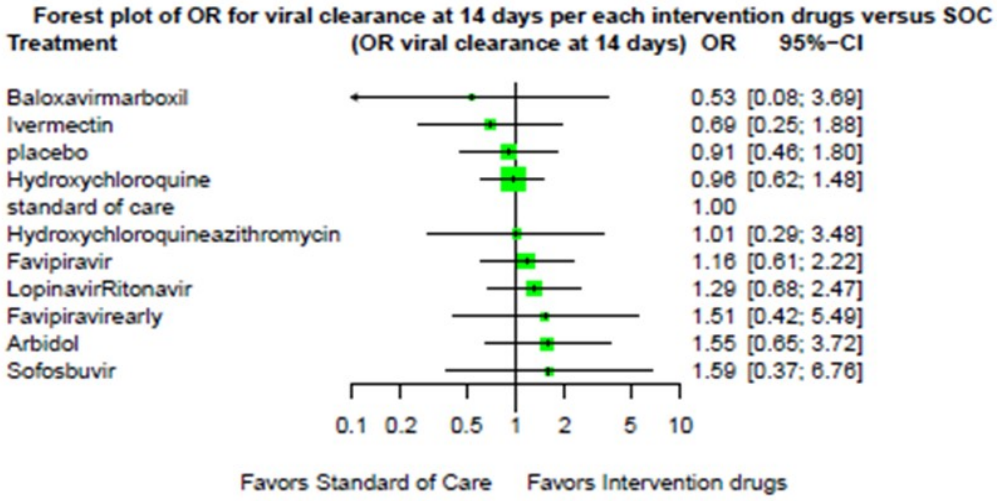

Figure 6: Forest plot. Network meta-analysis estimates of drug-level versus standard of care for the viral clearance at 14 days outcomes

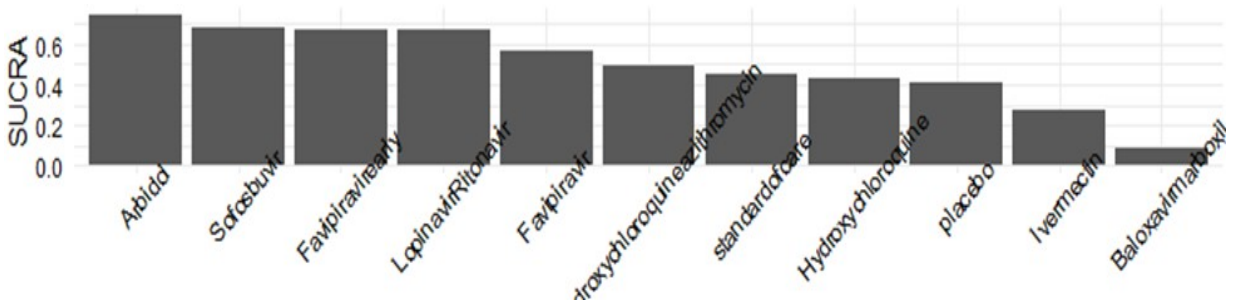

Figure 7: Sucra plot of network meta-analysis of Anti-infective drugs for viral clearance at 14

Mortality rate

The network meta-analysis of 47 studies examining 20 treatment drugs involved 34,461 participants was plotted by network graph (Figure 2) and their relationship by a league table (Supplementary material 3, Table 3). Statistically significant lower risks of mortality were shown for combined Baricitinib with Remdesivir therapy than standard of care therapy (RR= 0.47; 95%CI: (0.24; 0.94); P-value 0.03; very low certainty of evidence). Remdesivir for five days (RR= 0.53; 95%CI: (0.25; 1.13); P-value 0.10; low certainty of evidence), Ivermectin (RR= 0.75; 95% CI: (0.49; 1.14); P-value 0.18; low certainty of evidence), Remdesivir for 10 days (RR= 0.75; 95%CI: (0.47; 1.16); P-value 0.19; low certainty of evidence) and Hydroxychloroquine plus Azithromycin (RR= 0.61; 95%CI: (0.22; 1.73); P-value 0.35; very low certainty of evidence) decrease death but statistically not significant (Figure 8). Ranking analysis for mortality performed with surface under the cumulative ranking curves (SUCRA) strongly suggested that combined Baricitinib with Remdesivir therapy was the first top best (effective) treatment (SUCRA =85.4%) followed by remdesivir for 5 days second best drug (SUCRA = 79.3%), and Ivermectin third best drug (SUCRA = 68%) in decreasing mortality and P-score of frequentists also suggest similar hierarchy (Figure 9). The heterogeneity tau for this network overall was 0.10, which we considered low heterogeneity (Heterogeneity I^2 = 7.2% (0.0%; 36.5%)) and Q statistic was used to assess consistency under the assumption of a full design-by-treatment (consistency between designs) revealed no inconsistency seen with Q = 12.06 (p value 0.84).

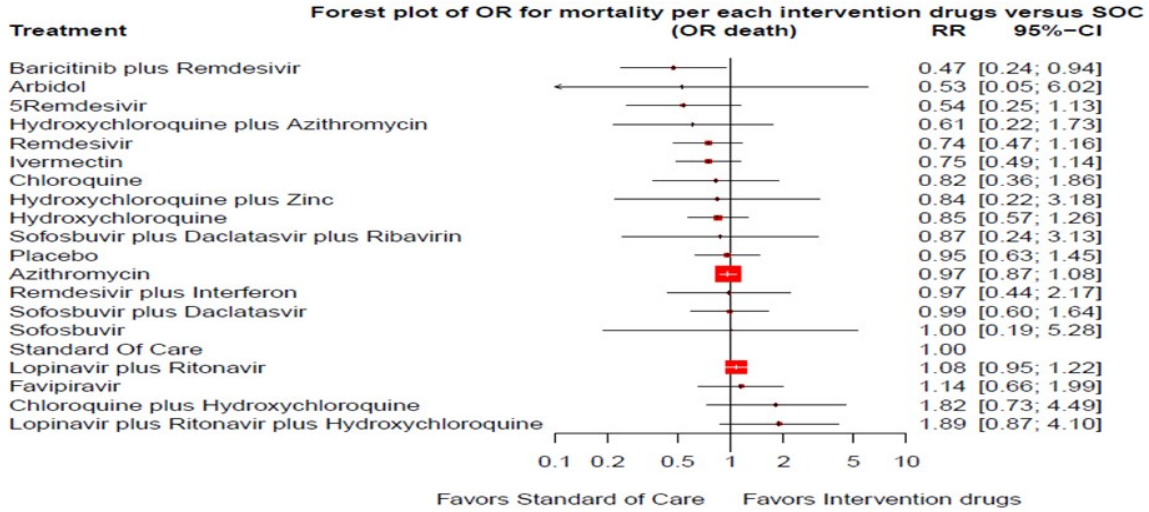

Figure 8: Forest plot. Network meta-analysis estimates of drug-level versus standard of care for the Mortality outcomes. *5Remdesivir-Remdesivir for five days; Remdesivir- Remdesivir for ten days*

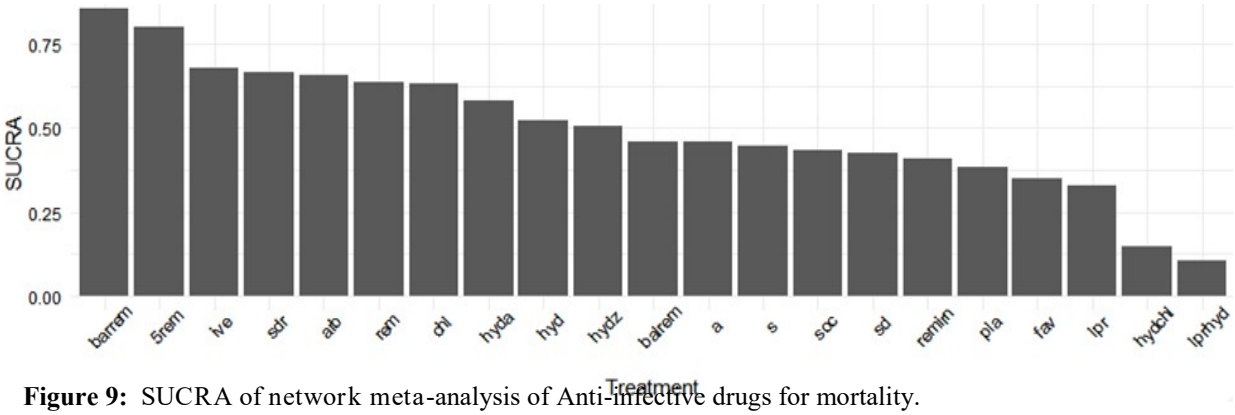

Figure 9: SUCRA of network meta-analysis of Anti-infective drugs for mortality.

Adverse events

An adverse event outcome was reported by 42 studies involving 22 treatment agents on 9,790 patients with COVID19 infection and have been shown by network geometry (Figure 2). Arbidol therapy results statistically significant low risks ratio than the standard of care therapy (RR= 0.46; 95%CI: (0.23; 0.95); p-value 0.04; very low certainty of evidence), and Sofosbuvir/Daclatasvir (RR= 0.40; 95%CI: (0.12; 1.03); p-value 0.056), but Hydroxychloroquine (OR= 1.17; 95%CI: (1.06; 1.29); p-value 0.002), lopinavir-ritonavir versus standard of care (OR= 1.26; 95%CI: (1.15; 1.38); p-value < 0.0001), and remdesivir versus standard of care (OR= 1.20; 95%CI: (1.20; 1.34); p-value 0.002) had statistically significant high risks ratio in developing adverse events Figure 10, Figure 11, Supplementary material 3). (Ranking analysis for adverse event was performed with P-Score probability strongly suggested that Sofosbuvir/Daclatasvir (P-Score = 95.4%) as top safe drug and Arbidol (P-Score = 94.1%) the second safe drug and standard of care (P-Score = 76.3%) as third safe drug in treatment of COVID-19. We quantified the heterogeneity with I^2 as moderate (heterogeneity I^2 = 61.9% (45.1%; 73.6%) and global inconsistency was found assessed by Q statistic after detaching of single designs and SIDDE approach (Cochran's Q= 60.23; p-value < 0.0001) and identified on several network loops comparison.

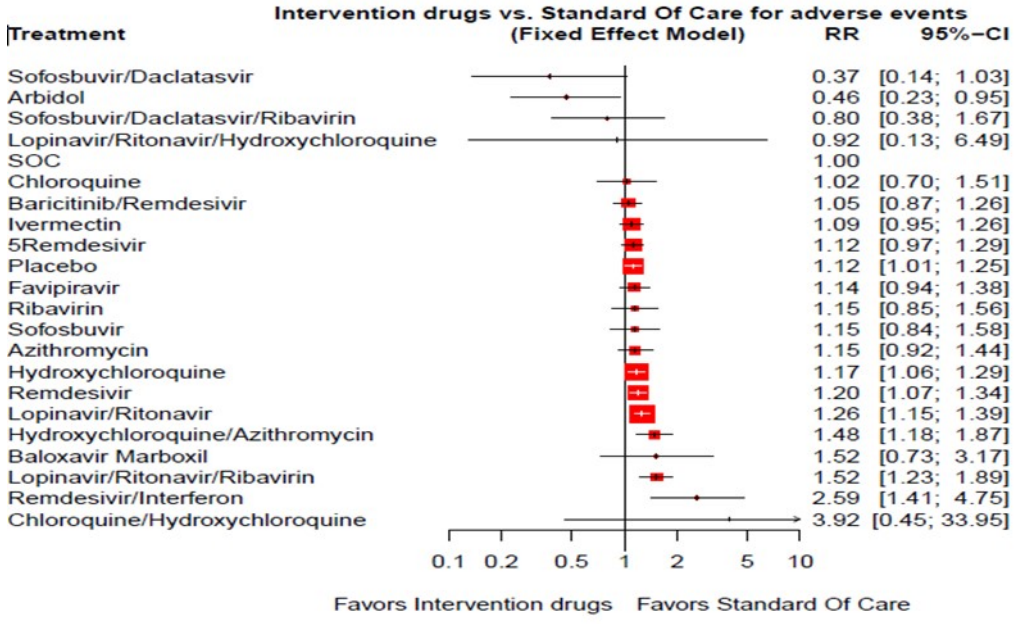

Figure 10: Forest plot. Network meta-analysis estimates of drug-level versus standard of care for the adverse event outcomes. *CI: Credible interval; SOC: standard of care; RR: Risk Ratio*

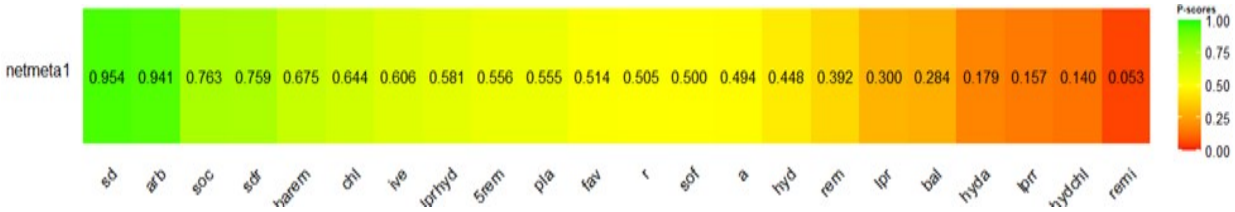

Figure 11: Netmeta P-Score hierarchy probability of network meta-analysis of Anti-infective drugs for any adverse events.

Sensitivity and subgroup analysis

The result of sensitivity analysis on the low risks of bias articles found that Ivermectin (OR= 3.00; 95% CI: (1.81; 5.00); p-value < 0.0001, low certainty of evidence), Remdesivir for 5 days (OR= 1.87; 95%CI: (1.27; 2.75); p-value 0.002, low certainty of evidence), combined Remdesivir and Baricinib for 10 days (OR= 2.20; 95%CI: (1.34; 3.53); p-value 0.002, low certainty of evidence), Remdesivir for 10 days (OR= 1.50; 95%CI: (1.03; 2.20); p-value 0.03, low certainty of evidence) and Sofosbuvir plus Daclatasvir (OR= 3.63; 95%CI: 1.02; 12.93; p-value 0.05, low certainty of evidence) were more effective than standard of care in clinical recovery at 14 days (Supplementary file). Subgroup analysis found Remdesivir for 10 days caused statistically significant serious adverse events (RR= 1.43; 95%CI: (1.16; 1.75); p-value 0.0009), Lopinavir-Ritonavir (RR= 1.52; 95%CI: 1.22; 1.90); p-value 0.0002), Hydroxychloroquine (RR= 1.35; 95%CI: (1.06; 1.70); p-value 0.01), and Placebo (RR= 1.80; 95%CI: (1.40; 2.35); p-value <0.0001) (Supplementary file).

Publication bias

According to the comparison-adjusted funnel plots, there was no sign of asymmetry found in three outcomes. But, we identified publication bias for adverse events outcome which indicates that there are small-study effects in our network (p = 0.06) (Supplementary file, D).

Discussion

In this latest systematic review and network meta-analysis, we have analyzed 13anti-infective drugs pooled from 68 RCTs up to 30 April 2022. We found that our NMA showed several drugs including Ivermectin, Remdesivir, combined Remdesivir and Baricinib, Favipiravir and Sofosbuvir plus Daclatasvir are statistically significant in increasing the rate of clinical recovery at 14 days than standard of care. However, there was no statistically significant difference between assessed drugs versus standard of care interms of clinical recovery rate but there are drugs like Arbidol, Favipiravir, Lopinavir/Ritonavir and Sofosbuvir revealed high odds of increased viral clearance at 14 days. This review also found that treating with combined Baricitinib with Remdesivir, Remdesivir, Ivermectin, and Hydroxychloroquine plus Azithromycin had lower risks of ratio in terms of mortality than treating with standard of care. We revealed from this NMA Arbidol and Sofosbuvir/Daclatasvir were the highly tolerable drugs (statistically significant low risks ratio) than the standard of care therapy.

We have evaluated from our NMA that ivermectin was the best top drug in terms of increasing clinical recovery rate at 14 days, while sofosbuvir plus daclatasvir was second-best and a combination of remdesivir and baricinib was third-best compared to the standard of care therapy.

A systematic review and meta-analysis on ivermectin with random effect model revealed that ivermectin led to significant clinical improvement compared to usual therapy (OR=1.98, 95% CI: (1.11, 3.53); P=0.02) similar to a previous meta-analysis (OR= 1.38; 95%CI: (0.85, 2.24); p-value 0.187).(46) However, the meta-analysis only included three studies in the meta-analysis and all were deemed to provide low certainty evidence. A previous systematic review and meta-analysis on efficacy of remdesivir found that remdesivir did not decrease all-cause mortality (RR= 0.71, 95%CI: (0.39 to 1.28), I^2 = 43%)(47) which contradicts our result (OR= 0.61 95%C:I(0.42; 0.88); p-value 0.009; I^2= 23%). However, another meta-analysis published in June 2021 reported a significantly reduced mortality rate with the use of remdesivir (RR= 0.39; 95% CI: (0.27, 0.56); p < 0.00001).(48)

A previous systematic review and meta-analysis on favipiravir group for the treatment of patients with COVID-19 revealed significant clinical improvement on day 14 (OR 3.03; 95%CI 1.17, 7.80) but no difference for rate of viral clearance (OR= 2.19; 95%CI 0.69, 6.95), (49) and our result is in agreement (OR= 2.04; 95%CI: (1.25, 3.33); p-value 0.0042, I^2 = 0%). An updated systematic review and network meta-analysis of 25 RCTs published in January 2021 reported that remdesivir for 10-day compared to standard care were associated with a higher clinical improvement rate.(50) Our finding is similar to the previous finding in that remdesivir showed an increased clinical recovery rate by 49% (OR= 1.51; 95%CI: (1.04, 2.18); p-value 0.03). Another updated article with 196 trials enrolling 76, 767 patients reported reduces deaths with remdesivi compared with

standard care (OR= 0.90; 95%CI: (0.72,1.11); low certainty) (51), which is comparable to our finding (OR= 0.70; 95%CI: (0.35,1.38); low certainty) (Supplementary material 3).

This review may have possible limitations that would serve as an important opportunity for future reviews. Though we included more than seven databases in our search to make the meta-analysis the largest, there were still some databases that the review did not include and this may affect the comprehensiveness of the study. We included 68 articles that had sufficient evidence for analysis. The COVID-19 therapeutic options are moving very quickly and active candidates are emerging that this review may not have covered. Anti-inflammatory drugs or monoclonal antibodies are shown to have promising effects that this review did not include.

Conclusions

Baricitinib plus Remdesivir is more effective than the other 22 anti-infective drugs in the rate of clinical recovery at 14 days and mortality outcomes of patients with COVID-19, while no statistically significant difference in viral clearance at 14 days and safety outcomes. Arbidol drug is the tolerable treatment and Ivermectin had statistically significant in clinical recovery at 14 days. We recommend there will be more and multinational studies to identify the effect of Ivermectin and Arbidol on treatment of COVID-19.

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Supplementary materials
Supplementary material 1 https://bit.ly/3Zu9B3U
Supplementary material 2 https://bit.ly/3JT7AZg
Supplementary material 3 https://bit.ly/3lVKtoZ

Reference

1. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine. 2020;382(18):1708-20.
2.Organization WH. Novel Coronavirus (2019-nCoV): situation report, 3. 2020.
3.Covid C, COVID C, COVID C, Bialek S, Gierke R, Hughes M, et al. Coronavirus Disease 2019 in Children—United States, February 12–April 2, 2020. Morbidity and Mortality Weekly Report. 2020;69(14):422.
4.Ali M, Shah STH, Imran M, Khan A. The role of asymptomatic class, quarantine and isolation in the transmission of COVID-19. Journal of Biological Dynamics. 2020;14(1):389-408.
5. Organization WH. Report of the WHO-China Joint Mission on coronavirus disease 2019 (COVID-19). 2020. Significant account of fatality rates and comorbidities in reports from China related to COVID-19 infection. 2020.
6. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine. 2020.
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497-506.
8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020;395 (10223):507-13.
9. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama. 2020;323(11):1061-9.
10.Organization WH. Coronavirus disease (COVID-19) outbreak. 2020. URL https://www who int/emergencies/diseases/novel-coronavirus-2019. 2020.
11.Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, et al. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo [2, 1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. ACS Publications; 2017.
12.Chandwani A, Shuter J. Lopinavir/ritonavir in the treatment of HIV-1 infection: a review. Therapeutics and clinical risk management. 2008;4(5):1023.
13.Tanenbaum L, Tuffanelli DL. Antimalarial agents: chloroquine, hydroxychloroquine, and quinacrine. Archives of Dermatology. 1980;116(5):587-91.

14. Scott LJ. Tocilizumab: a review in rheumatoid arthritis. Drugs. 2017;77(17):1865-79.
15. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. Jama. 2020;323(18):1824-36.
16. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. The journal of heart and lung transplantation. 2020;39(5):405.
17. Malin JJ, Suárez I, Priesner V, Fätkenheuer G, Rybniker J. Remdesivir against COVID-19 and other viral diseases. Clinical microbiology reviews. 2020;34(1):e00162-20.
18. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell research. 2020;30(3):269-71.
19. Maisonnasse P, Guedj J, Contreras V, Behillil S, Solas C, Marlin R, et al. Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates. Nature. 2020;585(7826):584-7.
20. ul Qamar MT, Alqahtani SM, Alamri MA, Chen L-L. Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. Journal of pharmaceutical analysis. 2020;10(4):313-9.
21. Gupta D, Sahoo AK, Singh A. Ivermectin: potential candidate for the treatment of Covid 19. Brazilian Journal of Infectious Diseases. 2020;24(4):369-71.
22. Global Coronavirus COVID-19 Clinical Trial Tracker [Internet]. 2021 [cited 19/4/21]. Available from: https://www.covid19-trials.org/.
23. Food U, Administration D. FDA Approves First Treatment for COVID-19. 2020.
24. Jiang Y, Chen D, Cai D, Yi Y, Jiang S. Effectiveness of remdesivir for the treatment of hospitalized Covid-19 persons: a network meta-analysis. Journal of medical virology. 2021;93(2):1171-4.
25. Rezagholizadeh A, Khiali S, Sarbakhsh P, Entezari-Maleki T. Remdesivir for treatment of COVID-19; an updated systematic review and meta-analysis. European journal of pharmacology. 2021;897:173926.
26. Fiolet T, Guihur A, Rebeaud M, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y. Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a systematic review and meta-analysis. Clinical Microbiology and Infection. 2020.
27. Consortium WHOST, Pan H, Peto R, Henao-Restrepo A-M, Preziosi M-P, Sathiyamoorthy V, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. The New England journal of medicine. 2021;384(6):497-511.
28. Hariyanto TI, Halim DA, Rosalind J, Gunawan C, Kurniawan A. Ivermectin and outcomes from Covid-19 pneumonia: A systematic review and meta-analysis of randomized clinical trial studies. Reviews in Medical Virology. 2021:e2265.
29. Kim MS, An MH, Kim WJ, Hwang T-H. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis. PLoS medicine. 2021;17 (12):e1003501.
30. Qiu R, Li J, Xiao Y, Gao Z, Weng Y, Zhang Q, et al. The therapeutic effect and safety of the drugs for COVID-19: A systematic review and meta-analysis. Medicine. 2021;100(16):e25532.
31. De Crescenzo F, Amato L, Cruciani F, Moynihan LP, D'Alò GL, Vecchi S, et al. Comparative Effectiveness of Pharmacological Interventions for Covid-19: A Systematic Review and Network Meta-Analysis. Frontiers in Pharmacology. 2021;12(1009).
32. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Annals of internal medicine. 2015;162(11):777-84.
33. Dejene Tolossa KD. Comparing the effectiveness of anti-infectious drugs for the treatment of laboratory-confirmed Covid-19 patients: a systematic review and network meta-analysis of randomized clinical trials. PROSPERO. 2021.
34. Cochrane C. Data collection form for intervention reviews: RCTs only. The Cochrane Collaboration, community cochrane org. 2015.
35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002;21 (11):1539-58.
36. Shim SR, Kim S-J, Lee J, Rücker G. Network meta-analysis: application and practice using R software. Epidemiology and health. 2019;41.
37. Salanti G, Ades A, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology. 2011;64(2):163-71.
38. Dias S, Welton NJ, Caldwell D, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Statistics in medicine. 2010;29(7-8):932-44.
39. Brignardello-Petersen R, Mustafa RA, Siemieniuk RA, Murad MH, Agoritsas T, Izcovich A, et al. GRADE approach to rate the certainty from a network meta-analysis: addressing incoherence. Journal of clinical epidemiology. 2019;108:77-85.
40. Yepes-Nuñez JJ, Li S-A, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the summary of findings table for network meta-analysis. Journal of clinical epidemiology. 2019;115:1-13.

41. Schwarzer G, Carpenter JR, Rücker G. Meta-analysis with R: Springer; 2015.
42. van Valkenhoef G, Dias S, Ades A, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Research synthesis methods. 2016;7(1):80-93.
43. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC medical research methodology. 2015;15(1):1-9.
44. Eldridge S, Campbell M, Campbell M, Drahota-Towns A, Giraudeau B, Higgins J, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2.0): additional considerations for cluster-randomized trials. 2016.
45. Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. Bmj. 2014;349.
46. Padhy BM, Mohanty RR, Das S, Meher BR. Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques. 2020;23:462-9.
47. Piscoya A, Ng-Sueng LF. Efficacy and harms of remdesivir for the treatment of COVID-19: A systematic review and meta-analysis. 2020;15(12):e0243705.
48. Timotius Ivan H, Felix K, Karunia Valeriani J, Vika D, Andree K. The Effectiveness and Safety of Remdesivir for the Treatment of Patients With COVID-19: A Systematic Review and Meta-Analysis. Anti-Infective Agents. 2021;19(3):333-40.
49. Manabe T, Kambayashi D, Akatsu H, Kudo K. Favipiravir for the treatment of patients with COVID-19: a systematic review and meta-analysis. BMC infectious diseases. 2021;21(1):489.
50. Diallo A, Carlos-Bolumbu M, Traoré M, Diallo MH, Jedrecy C. An updated systematic review and network meta-analysis of 25 randomized trials assessing the efficacy and safety of treatments in COVID-19 disease. Journal of Public Health Research. 2021;10(1).
51. Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Kum E, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ (Clinical research ed). 2020b;370:m2980.