

Systematic Reviews and Meta-Analysis

An updated systematic review and network meta-analysis of 25 randomized trials assessing the efficacy and safety of treatments in COVID-19 disease

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Abstract

To date, there is no definite effective treatment for the COVID-19 pandemic. We performed an update network meta-analysis to compare and rank COVID-19 treatments according to their efficacy and safety. Literature search was performed from MEDLINE and CENTRAL databases from inception to September 5, 2020. Randomized clinical trials (RCTs) which compared the effect of any pharmacological drugs versus standard care or placebo 28-day after hospitalization in adult patients with COVID-19 disease were included. Risk ratio (RR) and 95% CI were calculated for 28-day all-cause mortality, clinical improvement, any adverse event (AEs), and viral clearance. A total of 25 RCTs, evaluating 17 different treatments, and 11,597 participants were analyzed. Remdesivir for 10-day compared to standard care (RR 0.69, 95% CI [0.48–0.99]), and a low dose compared to a high dose of HCQ (0.38, [0.17–0.89]) were associated with a lower risk of death. A total of 2,766 patients experienced clinical improvement, a 5-day course of remdesivir was associated with a higher frequency of clinical improvement compared to standard care (RR 1.21, 95% CI [1.00–1.47]). Compared to standard care, remdesivir for both 5 and 10 days, lopinavir/ritonavir, and dexamethasone reduced the risk of any severe AEs by 52% (0.48, 0.34–0.67), 24% (0.77, 0.63–0.92), 40% (0.60, 0.37–0.98), and 50% (0.50, 0.25–0.98) respectively. In this study of hospitalized patients with COVID-19, administration of remdesivir for 10-day compared to standard care was associated with lower 28-day all-cause mortality and serious AEs, and higher clinical improvement rate.

Introduction

Despite more than 28 million cases and 900,000 deaths in early September caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, no definite effective treatment is available.¹ The urgency of this situation accelerated randomized trials of many repurposed drugs that had been shown to be effective in vitro or in or the therapeutic experience with SARS-CoV-1, and Middle East respiratory syndrome (MERS)-CoV infection.²

In this context, numerous meta-analyses were quickly carried out, in particular on the efficacy of hydroxychloroquine (HCQ). Data from Million *et al.*³ indicated the effectiveness of HCQ in reducing mortality in COVID-19 disease, while those of Singh *et al.*⁴ and Fiolet *et al.*⁵ concluded that HCQ was ineffective.

A recent prospective meta-analysis of seven clinical trials involving 1,703 critically ill patients with COVID-19 reported the benefit of routine administration of corticosteroids, compared with usual care or placebo, in to reducing 28-day all-cause mortality based only on the fixed-effect model.⁶ Overall, routine administration of corticosteroids is associated with a 34% reduction in mortality (summary OR, 0.66 [95%CI, 0.53–0.82]), and among corticosteroid drugs, only dexamethasone was beneficial (0.64 [0.50–0.82]). In the subgroup analysis, the greatest benefit of systematic corticosteroids was observed in patients who were not receiving vasoactive drugs (0.55 [0.34–0.88]) or invasive mechanical ventilation at randomization (0.41 [0.19–0.88]).

As there is no recommended treatment or vaccine to contain the disease to date, identifying the most effective treatment is an urgent medical need. To summarize data on promising treatments against COVID-19, we conducted a preliminary network meta-analysis (NMA) based on 14 randomized controlled trials (RCTs) evaluating 11 different treatments among 2,898 patients.⁷

Significance for public health

The current COVID-19 pandemic is the largest and deadliest coronavirus pandemic in history, leading to considerable global public health problems. To date more than 28 million cases and 900,000 deaths have been reported. This is an update of our previous systematic review and network meta-analysis to compare and rank COVID-19 treatments. Available data indicate that in hospitalized patients with SARS-CoV-2 infection, administration of remdesivir compared to standard care and low dose of HCQ compared to high dose were associated with lower risk of 28-day all-cause mortality. In the absence of compelling contraindication, a remdesivir regimen should be part of standard care for inpatients with COVID-19.

We found no difference between treatments in terms of reduced 28-day all-cause mortality. The aim of this update network meta-analysis of randomized trials was to compare and rank the efficacy and safety of treatments tested in patients with SARS-CoV-2 virus.

Design and Methods

Search strategy and selection criteria

In our previous report,⁷ search through MEDLINE and Cochrane library (CENTRAL) was performed from inception to June 30, 2020 and it identified 14 RCTs published in any language. Then, from July 1 to September 5, 2020, 11 additional RCTs were found and included in the current updated network meta-analysis. Data were collected as studies were identified; the latest date for this search was September 5, 2020. We included RCTs that compared in adult patients with COVID-19 (P) any pharmacologic drug (I) *versus* standard care or placebo (C) to evaluate both efficacy (mortality, clinical improvement, viral clearance) and safety (adverse event and serious adverse event) (O) 28-day (T) after hospitalization (S). Trials in which participant were non-randomly assigned to SARS-CoV-2 treatment were excluded. Using the search terms listed in the Supplementary Method, AD and MT identified all relevant studies, then independently reviewed their full texts, and in case of disagreement, differences were resolved through arbitration by another author (MCB). Extracted data included: first author name and year of publication, country, RCTs design, study follow-up, age (mean), proportion of male participants, treatment and dosing information, sample size, study sponsorship, proportion or number of participants with clinical improvement, all-cause mortality, and adverse events. The study protocol number is CRD42020176977 (PROSPERO).

Treatments exposure

We considered any pharmacological drugs tested to evaluate their efficacy and safety in patients infected with SARS-CoV-2. For randomized trials, patients were defined as receiving intervention or control if they were randomly allocated to receive either treatment. Almost all patients received supportive care according to the standard care at the trial site.

Primary and secondary outcomes

The primary outcome was 28-day all-cause mortality. Secondary outcomes were clinical improvement within 28-day after randomization, any reported Adverse Events (AEs), severe AEs, and viral clearance rate (negative conversion rate). Clinical improvement was defined as patient discharge or a reduction of 2 points on a 7-point disease severity scale. As these secondary outcomes were evaluated at different time-points across studies, we chose to consider only the latest in each trial.

Data analysis

The original clinical trials were described using summary table of study characteristics and forest plot. The Revised tool for Risk of Bias in randomized trials (Rob2 tool)⁸ was used to assess the risk of bias and to generate its number? We opted for a frequentist approach to compare the efficacy and safety of the treatments tested using a random-effects network meta-analysis (NMA) for binary endpoint. Summary estimates were reported as risk ratio (RR) with their reported 95% confidence intervals. For clinical improvement and decreased viral load, beneficial effects are described by

RRs >1, while for 28-day mortality and AEs, beneficial effects are described by RRs <1. To display the relative efficacy and safety outcomes of all available pairwise comparisons between treatments, league tables were used. To choose the preferred regimen, the P-score ranging from 0 (worse treatment) to 1 (best treatment) was computed for each treatment, then the treatment with a higher P-score was selected as better than the competing treatment. Heterogeneity and inconsistency were quantified using the global Q test proposed by Rucker.⁹ The Q statistic is the sum of statistic for heterogeneity, which represent the proportion of total variation in study estimates (within-designs), and a statistic for inconsistency (between-designs), which represents the variability of treatment effect between direct and indirect comparisons at the meta-analytic level. To visualize and identify the nodes of single-design inconsistency, we used a network heat plot. Consistency between direct and indirect comparisons was checked using the so-called node-splitting. To confirm or deny the effect of any corticosteroid on 28-day all-cause mortality reported in the WHO prospective meta-analysis,⁶ we performed one non-prespecified sensitivity analysis by considering any routine corticosteroid as a single treatment (combining dexamethasone, hydrocortisone and methylprednisolone). All analyses were performed using R package 'netmeta';⁹ P-values <0.05 were considered significant for the difference between treatments.

Results

Included studies

The initial search through all database identified 1,042 citations, of which 402 were screened by title and abstract after removing duplicates. Of 38 full-text citations reviewed, 25 RCTs^{6,10-31} that met the inclusion criteria were finally included in the quantitative network meta-analysis (Figure 1). These 25 RCTs (two phase 2 and five blinded) included a total of 11,597 patients infect-

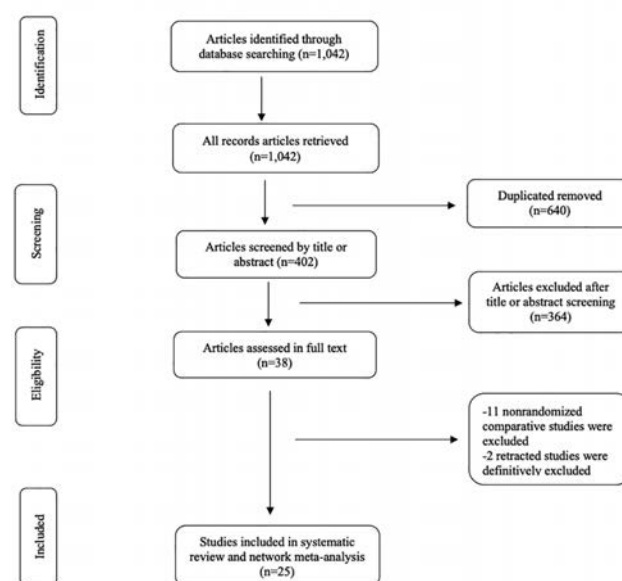


Figure 1. PRISMA flowchart of studies selected for meta-analysis of RCT SARS-CoV-2 treatments. RCT, randomized clinical trial.

ed by the SARS-CoV-2 with mean ages ranging from 29.7 to 70 years; 7,363 (62.3%) were men; they were followed for 6 to 28 days (Table 1). Comorbidities were present in 4,579 (39.0%) patients, the most common being diabetes (2,818; 24.0%) and hypertension (1,761; 15.0%).

The methodological quality of included RCTs is shown in Supplementary Figures 1 and 2. Overall, the risk of bias was low in nine RCTs, moderate in four, and high in the remaining RCT. A higher risk of attrition bias (incomplete outcome data), performance bias (blinding participants and personnel), and selection bias (allocation concealment) occurred in 6, 6, and 1 of the 25 RCTs, respectively.

All-cause mortality within 28 day

All-cause mortality data were reported in 18 trials involving 14 treatments and 22 comparisons. A total of 2,228/10,880 (20.4%) patients died within 28 days of randomization, and ruxolitinib (5 mg twice a day) was ranked as the best option with an 83% probability (P-score 0.83) to be associated with a lower risk of death. Compared to standard care, remdesivir for 10 day reduced the risk of death by 31% (risk ratio (RR) 0.69, [0.48-0.99]). In addition, a low dose of HCQ reduced by 62% (0.38, [0.17-0.89]) the risk of death compared with a high dose of HCQ. No significant difference was observed between the other comparisons (Figure 3; Supplementary Table 1). Likewise, no significant differences were found between direct and indirect comparisons of treatment estimates or evidence of publication bias according to the comparison-adjusted funnel plot (Supplementary Figures 3 and 4).

Clinical improvement

Clinical improvement data were reported in 17 trials involving 13 treatments and 23 comparisons. Among the 4,317 participants in whom clinical status was evaluated, 2,766 (64.1%) experienced clinical improvement within 28 days after randomization.

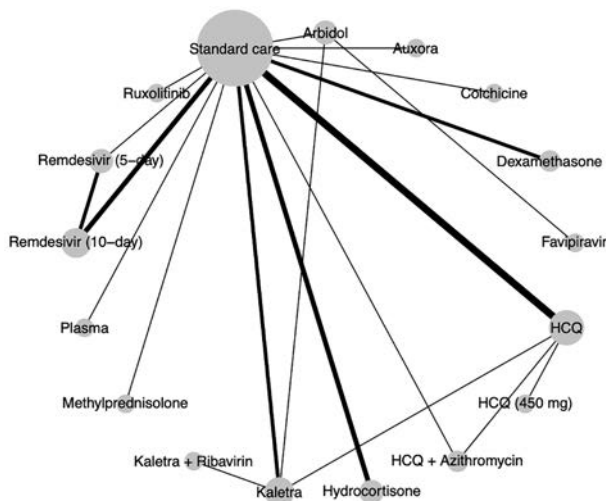


Figure 2. Network graph of eligible SARS-CoV-2 treatments comparisons for any adverse event. Line width is proportional to the number of trials comparing every pair of treatment. The size of the circle is proportional to the number of participants assigned to receive the treatment; Remdesivir (5-day), remdesivir for 5-day; remdesivir (10-day), remdesivir for 10-day; Plasma, convalescent plasma; HCQ, hydroxychloroquine; Kaletra, lopinavir/ritonavir.

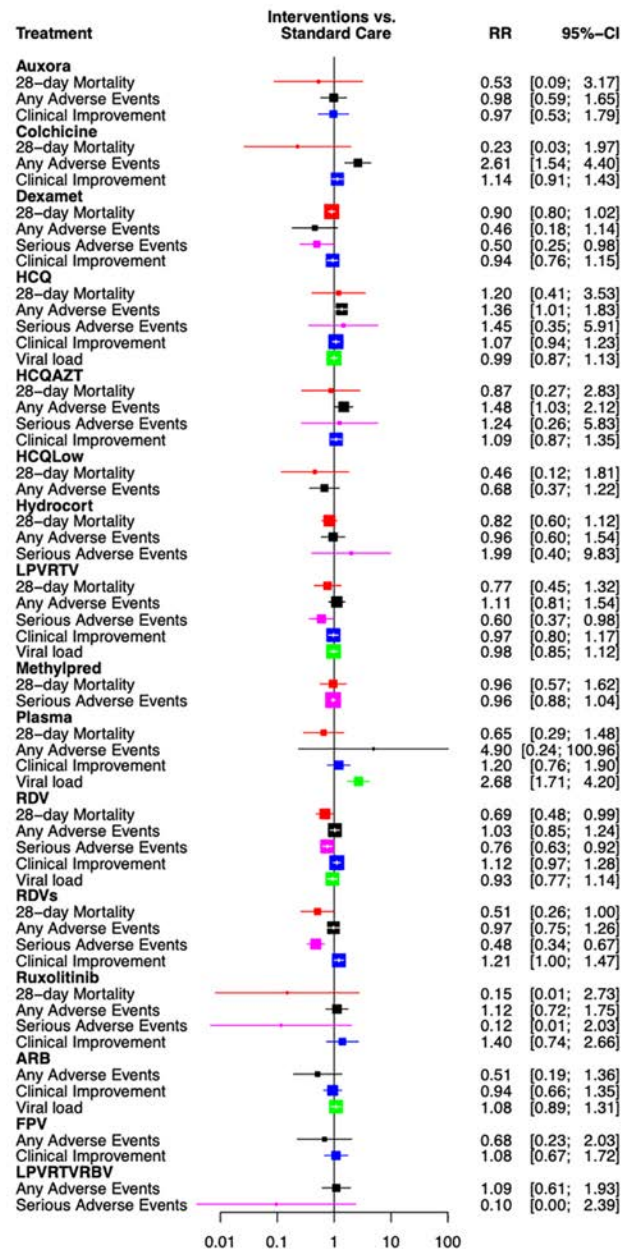


Figure 3. Network meta-analysis comparing single treatment with standard of care of SARS-CoV-2 outcomes. Blue, clinical improvement; black, any adverse event; magenta, any serious adverse event; red, all-cause mortality; green, viral clearance rate. Treatments are ordered in the rank of their chance of being the best option. Treatment estimates are provided as risk ratios (RR) with 95% CIs. RRs >1 indicates a beneficial treatment effects compared to standard care (clinical improvement and viral clearance lead), while RRs >1 is favor for standard care (any AEs or serious AEs and mortality); RDVs, remdesivir for 5-day; RDV, remdesivir more than 5-day; FPV, favipiravir; LPVRTV, lopinavir/ritonavir; LPVRTV + RBV, lopinavir/ritonavir and ribavirin; ARB, arbidol (umafenovir). Plasma, convalescent plasma; StdCare, standard of care; AZT, azithromycin; HCQlow, low dose of hydroxychloroquine (450 mg); HCQ, hydroxychloroquine; HCOAZT, association hydroxychloroquine and azithromycin; Hydrocort, hydrocortisone; Dexamet, dexamethasone; Methypred, methylprednisolone.

Table 1. Characteristics of 25 included trials investigating efficacy and safety of SARS-Cov-2 disease.

Study	Location	Design	Age (mean, years)	Follow-up (days)	Total participants (proportion of men)	Randomized treatments in each group, dosing information	Main primary endpoints	Sponsorship	Risk of bias (Rob2)
Chen Jun <i>et al.</i> ¹¹	China	Open-label, RCT	46.7 – 50.5	15	30 (70%)	400 mg hydroxychloroquine (HCQ) orally for times daily for 5 days; Standard of care (bed rest, oxygen inhalation, antiviral drugs as lopinavir/ritonavir, and antibacterial drugs if necessary)	Negative conversion rate of SARS-CoV-2 nucleic acid in respiratory pharyngeal swab on days 7 after randomization.	NR	Some concerns
Li Ling <i>et al.</i> ¹⁵	China	Open-label, RCT	70	28	102 (58.3%)	4 to 13 ml/kg Convalescent plasma transfusion; Standard of care (antiviral, antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines)	Time-to-clinical improvement within a 28-day period; clinical improvement was defined as patient discharge or a reduction of 2 points on a 6-point disease severity scale. ^a	CFMS	High risk of bias
Cao <i>et al.</i> ¹⁸	China	Open-label, RCT	58 ^b	28	199 (60.3%)	400 mg and 100 mg of the oral combination lopinavir/ritonavir respectively twice a day for 14 days; Standard of care (supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and ECMO)	Time-to-clinical improvement within a 28-day period, defined as time from randomization to either an improvement of two points on a seven-category ordinal scale, ^a or discharge from the hospital, whichever came first.	Major Projects of national Science and Technology on NDCD	High risk of bias
Wang <i>et al.</i> ¹⁹	China	RCT, double-blind	65 ^b	28	237 (59.1%)	200 mg on day 1 and 100 mg on days 2 to 10 in single daily infusions of Remdesivir, placebo	Time-to-clinical improvement within a 28-day period, defined as time from randomization to either an improvement of two points on a seven-category ordinal scale, ^a or discharge from the hospital, whichever came first.	CAMSEP of Covid-19, NKRDP, and BSTP	High risk of bias
Borba Silva <i>et al.</i> ²⁰	Brazil	RCT, phase IIb, double-blind	51.1	28	81 (75.3%)	600 mg hydroxychloroquine (HCQ) or high-dose orally or via nasogastric tube (4×150 mg tablets twice daily for 10 days; total dose 12 g); 450 mg HCQ or low-dose (3×150 mg tablets and 1 placebo tablet twice daily on day 0, 3×150 mg tablets and 1 placebo tablet once a day followed by 4 placebo tablets from day 1 to day 4, then 4 placebo tablets twice daily from day 5 to day 9; total dose 2.7 g)	Lethality by at least 50% in the high-dose group compared with the low-dose group at day 28.	Government of the Amazonas State	Low risk of bias
Goldman <i>et al.</i> ¹⁶	US, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, Taiwan	Open-label, RCT	62 ^b	28	397 (63.7%)	200 mg of remdesivir on day 1 followed by 100 mg of remdesivir once daily for subsequent 4 or 9 days. All group receive a standard of care therapy according to the local guidelines. 5-day group and 10-day group.	Clinical status on day 14, assessed on a 7-point ordinal scale. ^a	Gilead Sciences	High risk of bias
Li Yueping <i>et al.</i> ¹⁴	China	Exploratory RCT, double-blind	49.4	21	86 (46.5%)	200 mg of lopinavir boosted by 50 mg of ritonavir (orally administered, twice daily 500 mg each time for 7-14 days; n=34); 100 mg of arbidol (orally administered, twice daily 200 mg three times for 7-14 days; n=35); Control group (n=17)	Time of positive-to-negative conversion of SARS-CoV-2 nucleic acid from the initiation of treatment to day 21.	IDSG; High-level Clinical Key Specialty (2019-2021)	Low risk of bias
Chen <i>et al.</i> ¹²	China	RCT, 44.7 double-blind	6	62 (46.8%)		400 mg hydroxychloroquine (HCQ) per day orally between days 1 and 5; Standard of care (oxygen therapy, antiviral agents, antibiotic agents, and immunoglobulin, with or without corticosteroids)	Time-to-clinical recovery (TTCR) at 5 days, defined as the return of body temperature and cough relief maintained for more than 72 h.	Science and Technology Department of Hubei Province (2020FCA005)	Some concerns

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Table 1. Continued from previous page.

Study	Location	Design	Age (mean, years)	Follow-up (days)	Total participants (proportion of men)	Randomized treatments in each group, dosing information	Main primary endpoints	Sponsorship	Risk of bias (Rob2)
Tang <i>et al.</i> ¹⁷	China	Open-label, RCT	46	28	150 (55%)	1200 mg hydroxychloroquine (HCQ) daily for three days followed by a maintenance dose of 800 mg daily for the remaining days (two weeks for patients with mild to moderate disease and three weeks for those with severe disease); Standard of care	Negative conversion of SARS-CoV-2 by 28 days.	Emergent Projects of National Science and technology (2020YFC0844500)	High risk of bias
Chen <i>et al.</i> ¹³	China	Open-label, RCT	29.7 ^c	7	240 (46.6%)	1600 mg of favipiravir twice first day followed by 600 mg, twice daily, for the following days; 200 mg of arbidol, three times daily plus Standard of care	Clinical recovery rate at 7 days from beginning of treatment, defined as continuous (>72 h) recovery of body temperature, respiratory rate, oxygen saturation and cough relief after treatment, with following quantitative criteria: axillary temperature 36.6°C, respiratory frequency 24 times/min, oxygen saturation 98% without oxygen inhalation; mild or no cough.	NKRDPCC (2020YFC0844400)	High risk of bias
Hung <i>et al.</i> ²¹	Hong Kong	Open-label phase 2, RCT	52 ^b	14	127 (54%)	400 mg of lopinavir and 100 mg of ritonavir every 12 h, 400 mg of ribavirin every 12 h, 8 million international units of interferon beta-1b on alternate days for 14 days; 400 mg of lopinavir and 100 mg of ritonavir every 12 h for 14 days	Time to providing a nasopharyngeal swab negative for SARS-CoV-2 by 7 days.	Shaw-Foundation, Richard and Carol Yu, May Tam Mark Mei Yin, and Samming Project of Medicine	High risk of bias
Deftereos <i>et al.</i> ³¹	Greece	Open-label, RCT	64 ^b	21	110 (58.1%)	1.5 mg of colchicine followed by 0.5 mg 60 min later and maintenance doses of 0.5 mg twice daily; Standard of care (optimal medical treatment according to local protocols, as established by the National Public Health Organization and following the guideline of the European Centre for Disease Prevention and Control)	Time from baseline to-clinical deterioration, defined as a grade increase on an ordinal clinical scale. ^a	ELPEN, Acarpia, and Karian Pharmaceuticals companies	High risk of bias
Huang <i>et al.</i> ¹⁰	China	RCT, phase 2, double-blind	44	14	22 (59.1%)	500 mg of chloroquine orally twice daily for 10 days; 400 mg of lopinavir and 100 mg of ritonavir orally twice daily for 10 days;	Viral negative-transforming time and the negative conversion rate of SARS-CoV-2 RT-PCR at day 10, 14.	NR	Some concerns
Beigel <i>et al.</i> ²⁴	US, UK, Denmark, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore	RCT, double-blind	58.9	25	1,059 (64.3%)	200 mg on day 1, followed 100 mg daily for up to 9 additional days in single daily infusions of remdesivir; Placebo	Time-to-recovery, defined as the first day, during the 28 days after enrollment, on which a patient satisfied category 1, 2, or 3 on the eight-category scale. ^a	National Institute of Allergy and Infectious Disease	High risk of bias
Cavalcanti <i>et al.</i> ²²	Brazil	Open-label, RCT	50.3	15	665 (58.3%)	400 mg of HCQ twice daily for 7 days (n=221); 400 mg of HCQ twice daily for 7 days plus azithromycin at dose of 500 mg once a day for 7 days (n=217); Standard of care (n=227)	Clinical status at 15 days using the seven-level ordinal scale.	Coalition COVID-19 Brazil and EMS Pharma	High risk of bias
Spinner <i>et al.</i> ²⁵	US	Open-label, RCT	57	28	596 (61.1%)	200 mg of remdesivir intravenously on day 1, followed by 100 mg of remdesivir for 5-day; 200 mg of remdesivir intravenously on day 1, followed by 100 mg of remdesivir for 10-day; Standard of care	The distribution of clinical status assessed on the 7-point ordinal scale on study day 11.	Gilead Sciences	High risk of bias
Cao <i>et al.</i> ²³	Wuhan, China	RCT, phase 2, single-blind	63	21	41 (58.5%)	5 mg of ruxolitinib orally twice a day; Standard of care	Time-to-improvement defined as the time from randomization to an improvement of 2 points on a 7-category ordinal scale or live discharge from the hospital at 14-day.	NR	Low risk of bias

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Treatment with Ruxolitinib 5 mg twice daily was ranked with a high probability of clinical improvement at 28 days (P-score 0.78) to be the best one. Except between remdesivir and standard care, no significance differences between treatments were found from pairwise comparisons (Figure 3 and Supplementary Table 2). RR for remdesivir 100 mg once daily for 5 days compared with standard care was 1.21 (95% CI 1.00-1.47).

Viral clearance rate (negative conversion rate)

Viral clearance rate was assessed in 7^{10,11,14,15,17-19} RCTs involving 6 treatments and 9 comparisons. The use of convalescent plasma was associated with higher viral clearance rate (P-score 1.00) compared to arbidol, standard care, HCQ, lopinavir/ritonavir, and 10-day remdesivir. The corresponding increasing viral clearance rate for convalescent plasma was 2.49 (1.53-4.05) compared to arbidol, 2.68 (1.71-4.20) compared to standard care (Figure 3), 2.70 (1.69-4.30) compared to HCQ, 2.74 (1.72-4.39) compared to lopinavir/ritonavir, and 2.87 (1.76-4.68) compared to 10-day of remdesivir. The remaining comparisons were similar between treatments (Supplementary Table 3).

Any adverse events

Concerning safety outcomes, the network meta-analysis was performed in 21 RCTs, involving 17 treatments and 27 comparisons. Figure 2 shows the network for adverse event captured by the SARS-CoV-2 treatment, and the corresponding pairwise comparisons are summarized in Supplementary Table 4. A total of 1,828/5,077 (36.0%) adverse events were reported at the end of treatment. Dexamethasone was ranked as the best option with a probability of 90% (P-score 0.90) of being associated with a lower risk of any AEs. Except the use of convalescent plasma and the association HCQ plus azithromycin (HCQ+AZT), the remaining treatments were significantly associated with a lower risk of any AEs as compared to colchicine (Supplementary Table 4). The corresponding risk reductions ranged from 48% to 82%. In addition, we found that dexamethasone, arbidol, low dose of HCQ (400 mg), and standard care (Figure 3) reduced the risk of any AEs by 66% (0.34, 0.13-0.88), 62% (0.38, 0.14-1.00), 50% (0.30, 0.14-0.83), and 27% (0.73, 0.55-0.99) when compared with HCQ. The corresponding reduction rate of any AEs when compared with HCQ plus azithromycin (HCQ+AZT) was 69% (0.31, 0.12- 0.83) for

Table 1. Continued from previous page.

Study	Location	Design	Age (mean, years)	Follow-up (days)	Total participants (proportion of men)	Randomized treatments in each group, dosing information	Main primary endpoints	Sponsorship	Risk of bias (Rob2)
Miller <i>et al.</i> ²⁶	US	Open-label, RCT phase 2	60	28	26 (46.2%)	250 mg of auxora at 24 h and subsequent doses of 200 mg at 48 h; Standard of care	Safety and tolerability of auxora at 28-day.	CalciMedica	Some concerns
RECOVERY ²⁸	UK	RCT	59	28	6,425 (71.9%)	Dexamethasone 6mg/d orally or intravenously; Standard care	28-d mortality.	UK Government	Low risk of bias
CAPE COVID ²⁹	France	RCT	62.2	21	149 (69.8%)	Continuous intravenous infusion of hydrocortisone 200 mg for 7 days and decrease to 100 mg for 4 days and 50 mg for 3 days; Placebo	Treatment failure on day 21 (death or persistence dependence of mechanical ventilation or high-flow oxygen therapy).	French Ministry of Health	Low risk of bias
CoDex ²⁷	Brazil	Open-label, RCT	62	28	256 (63.3%)	Dexamethasone 20 mg/d intravenously x 5 d and then 10 mg/d intravenously x 5 d; Standard care	Ventilator free days	Hospital Sirio-libanes	Low risk of bias
REMAP-CAP ⁶	Australia, Canada, European Union, New Zealand, UK, US	Open-label, RCT	59	28	197 (71.4%)	Hydrocortisone 50 mg every 6 h x 7 d; Standard care	Composite of hospital mortality and ICU organ support-free days to 21 d.	MJM Bonten UMC Utrecht	Low risk of bias
DEXA-COVID-19 ⁶	Spain	Open-label, RCT	62	28	19 (57.1%)	Dexamethasone 20 mg/d intravenously x 5 d and then 10mg/d intravenously x 5d; Standard care	60-d mortality.	Dr. Negrin University Hospital	Low risk of bias
Covid Steroid ⁶	Denmark	Blinded, RCT	60.5	28	29 (79.05%)	Hydrocortisone 200mg/d intravenously x 7 d [continuous or bolus dosing (50 mg) every 6h]; Standard care	Days alive without live support at 28 d.	Department of Intensive Care Rigshospitalet Denmark	Low risk of bias
Steroids-SARI ⁶	China	RCT	64.5	30	47 (74.5%)	Methylprednisolone 40mg intravenously every 12h x 5 d; Standard care	Lower lung injury score at 7 d and 14 d.	Pekin Union Medical College Hospital	High risk of bias

^aDisease severity scale was defined as follow: 6-point, death; 5 points, hospitalization plus extracorporeal membrane oxygenation (ECMO) or invasive mechanical ventilation; 4 points, hospitalization plus noninvasive ventilation or high-flow supplemental oxygen; 3 points, hospitalization plus supplemental oxygen (not high-flow or noninvasive ventilation); 2 points, hospitalization plus supplemental oxygen; 1 point, hospital discharge; ^bmedian age; ^cproportion of patients aged 65 years or older; RCT: randomized controlled trials; CFMS: Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences; NDCD: new drug creation and development; CAMSEP: Chinese academy of Medical Sciences Emergency Project of Covid-19; NKRDPC: national key research and development program of China; BSTD: the Beijing science and technology project; IDSG: infectious disease specialty of Guangzhou; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; NR: not reported; RT-PCR: real-time reverse-transcriptase polymerase-chain-reaction.

dexamethasone, 65% (0.35, 0.13-0.96) for arbidol, 54% (0.46, 0.24-0.86) for a low dose of HCQ (450 mg), and 32% (0.68, 0.47-0.97) for standard care (Supplementary Table 4).

Serious adverse events

A total of 598 serious adverse events were recorded from 15 RCTs involving 19 comparisons of 11 different treatments. A combination of lopinavir/ritonavir and ribavirin was associated with a risk reduction for any severe AEs with a probability 86% (P-score 0.86). Compared to standard care, remdesivir for both 5 and 10 days, lopinavir/ritonavir, and dexamethasone reduced the risk of any severe AEs by 52% (0.48, 0.34-0.67), 24% (0.77, 0.63-0.92), 40% (0.60, 0.37-0.98), and 50% (0.50, 0.25-0.98) respectively (Figure 3). Moreover, we found that the short exposition of remdesivir (5 days) reduced the risk of any severe AEs by 37% (0.63, 0.46-0.85) compared with the long exposition (10 days), and by 50% (0.50, 0.35-0.71) compared to methylprednisolone (Supplementary Table 5).

Sensitivity, heterogeneity, and consistency

In sensitivity analysis, after considering any systematic corticosteroids as a single treatment, ruxolitinib (P-score 0.82) remained the best option to reduce all-cause mortality 28 days after randomization (Supplementary Table 6). Compared with standard care, both 5-day and 10-day courses of remdesivir and routine corticosteroids were associated with lower 28-day all-cause mortality. The specific relative reductions were as follows: for 5-day remdesivir, 52% reduction (0.48, 0.23-0.98); for 10-day remdesivir, 34% reduction (0.66, 0.45-0.96); and for routine corticosteroids, 15% reduction (0.85, 0.76-0.95). In addition, a low dose of HCQ reduced by 72% (0.28, 0.09-0.80) the risk of death compared with a high dose of HCQ.

No global heterogeneity was found for mortality (Cochran's Q 7.72; $p=0.36$; $t^2=0.0$; $I^2=9.4\%$ [0%-70.6%]). For adverse event and clinical improvement, global heterogeneity was significant (17.4; $p=0.043$; $t^2=0.02$; $I^2=48.2\%$ [0.0%-75.0%] and 17.2; $p=0.028$; $t^2=0.010$; $I^2=53.4\%$ [1.0%-78.1%] respectively), mainly due to significant between-design heterogeneity (AEs and clinical improvement). These findings were supported by the heat plot displayed in the Supplementary Figures 5 to 9).

Discussion

One month after our previously published report,⁷ we performed an update network meta-analysis of 25 RCTs that included 11,597 patients randomly assigned to 17 different treatments against SARS-CoV-2. Compared to standard care, the administration of a 10-day course of remdesivir was associated with a lower all-cause mortality and serious adverse event at 28 day, and a higher rate of clinical improvement. In addition, we found that compared to high dose, low dose of HCQ was associated with a lower 28-day mortality. Convalescent plasma was associated with a high rate of viral clearance, and dexamethasone and lopinavir/ritonavir were associated with a low risk of serious adverse event.

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group⁶ reported the benefit of administration of systemic corticosteroids to reduce 28-day mortality by 34% in COVID-19 patients compared to standard care. However, when corticosteroid types were considered, a benefit was only observed in patients receiving dexamethasone (0.64, 0.50-0.82). These findings were based on a fixed effect-model, while those on the random-effect model were not significant. After considering all avail-

able option for COVID-19 management, there was no evidence of a benefit of dexamethasone or hydrocortisone or methylprednisolone in reducing 28-day all-cause mortality (Supplementary Table 6). However, all corticosteroids were considered as a single treatment, we found that administration of systematic corticosteroids reduced 28-day mortality by 15%. This is similar in magnitude to the data reported in the RECOVERY trial²⁸ in which dexamethasone reduced by 17% (0.83, 0.75-0.93) 28-day mortality compared to standard care.

Most of the treatments being compared were tested in hospitalized patient with severe condition. At the time these trials were designed, little was known about the physiopathology of COVID-19. To date, we believed that the optimal management of COVID-19 could take in to account the stage of the disease. First, we found that the use of convalescent plasma increases viral clearance, suggesting that convalescent plasma may be beneficial for the early phase of the disease. Second, given the results of a 10-day course of remdesivir on 28-day all-cause mortality and clinical improvement rate, in the absence of contraindication, its use could benefit patient before the onset of a respiratory failure. Finally, as proposed by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, in the absence of compelling contraindication, a corticosteroid regimen should be a component of standard care for critically ill patients with COVID-19.

The place of hydroxychloroquine in the therapeutic panel in patients with COVID-19 is unclear. We found that low dose of hydroxychloroquine (400 mg/d for 5 days) was associated with lower 28-day all-cause mortality and serious adverse event as compared to high dose, but with no benefit compared to usual care. These findings are in line with a recent systematic review of 32 studies (29,192 participants) on the efficacy and safety of chloroquine/hydroxychloroquine for COVID-19. The authors concluded that the available evidence from biased, moderate-risk studies did not suggest any benefit of CQ/HCQ in terms of mortality in hospitalized patients with COVID-19 compared to standard care.³⁷ Nevertheless, available data on the efficacy of HCQ are conflicting.³²⁻³⁶ While Million *et al.*³ shows that patients who received HCQ had a 68% (0.32, 0.19-0.52) reduction in the risk of death compared to those without HCQ, Singh⁴ and Fiolet⁵ indicate the complete opposite with an increase in mortality for patients treated by HCQ. Furthermore, the Canadian trial on the prophylactic role of HCQ shows that hydroxychloroquine did not prevent illness compatible with COVID-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure to COVID-19.³⁸

Although our study provides the most recent evidence to date on the comparative efficacy and safety of available treatments against SARS-CoV-2, these findings should be interpreted with caution. We are aware that the majority of pharmacological drugs classified as the best options for clinical improvement, all-cause mortality or safety concerns have only been tested once, and further data are needed to replicate these results. To date several trials registered in ClinicalTrials.gov databases are ongoing, and results are expected in the coming months. When all ongoing trials are published, an update of this work will be necessary to draw definitive conclusions about the efficacy and safety of the treatments tested against SAR-CoV-2.

Limitations

This study has several limitations. First, the small number of RCTs included in the network meta-analysis negating the possibility of performing subgroup analyzes according to studies characteristics (design, follow-up, sample size, endpoint assessment, patient characteristics, or risk of bias). Second, the different end-

points used to assess of efficacy and safety outcomes may potentially influence the results. Third, we did not find RCT about asymptomatic or pauci-symptomatic patients with positive SARS-CoV-2 test, in whom the standard of care is observation and quarantine.³⁸ In addition, the majority of RCT included a large number of patients who have satisfactory clinical parameters, like SOFA 1, oxygen saturation 97.7%,¹) or those not needing oxygen supplementation.²⁸

Conclusion

In this network meta-analysis of 25 randomized trials against COVID-19 disease, the administration of a 10-day course of remdesivir was associated with lower 28-day all-cause mortality and serious adverse event, and higher clinical improvement rate compared to standard care. Colchicine and high dose of HCQ raised more safety concerns compared to dexamethasone, arbidol, favipiravir, low dose of HCQ (400 mg), remdesivir for both 5 and 10 days, and standard of care. As the pandemic is still ongoing, definitive conclusion will be drawn taking into account the results of ongoing and future studies. Nevertheless, these findings have implications for the design and management of future COVID-19 clinical trials.

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