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SYSTEMATIC REVIEW

Efficacy and Safety Data of Treatments for Novel Coronavirus Pneumonia (SARS-Cov-2): A Systematic Review and Network Meta-Analysis of Randomized Trials

Alhassane Diallo, MD, PhD[1*], Marie Traoré, MD[2], Miguel Carlos-Bolumbu, MD[3], Mamadou Hassimiou Diallo, MSc[4] and Boubacar Djelo Diallo, MD[5]

[1]*INSERM, U1137, CIC-EC 1425, Department of Epidemiology, Biostatistics, Clinical Research, AP-HP Hospital Bichat, University Paris Diderot, Paris, France*

[2]*Service de Rhumatologie, APHP Henry Mondor, Paris, France*

[3]*Urgences Réanimation Centre Hospitalier Sud Essonnes CHSE, Paris, France*

[4]*AP-HP, Hôpitaux Universitaires Pitié Salpêtrière - Charles Foix, Unité de Recherche Clinique Salpêtrière - Charles Foix, Paris, France*

[5]*Faculté des Sciences et Techniques de la Santé, Université Gamal Abdel Nasser de Conakry, Service de Pneumo-Phtisiologie, CHU Conakry, Hôpital National Ignace Deen de Conakry, Guinea*

***Corresponding author:** *Dr. Alhassane Diallo, MD, PhD, INSERM, U1137, CIC-EC 1425, Department of Epidemiology, Biostatistics, Clinical Research, AP-HP Hospital Bichat, University Paris Diderot, Paris, France, Tel: +33140256256*

Abstract

To date, there is no definite effective treatment for the novel coronavirus (SARS-CoV-2) pandemic. To compare and rank SARS-Cov-2 treatment according to their efficacy and safety. Using the terms *Covid-19 or SARS-CoV-2 and treatment*, a literature search was performed from MEDLINE, GOOGLE, and CENTRAL databases until July 01, 2020. Randomized clinical trials (RCTs) against SARS-CoV-2 disease were included. The studies excluded were those with nonrandomized design or those with a lack of information on outcomes. To evaluate studies methods, the Cochrane Risk of Bias Tools was used. Efficacy and adverse reaction number were extracted. A frequentist network meta-analysis using random-effect model was conducted. The risk ratio (RR) and 95% CI were calculated for clinical improvement, all-cause mortality, and any adverse event 28-days after randomization. The study protocol is registered with PROSPERO, number CRD42020176977. A total of 14 RCTs, which assessed 11 different treatments and 2,898 participants (range of mean age; 44.7 to 70 years; 1,731 [59.7%] men) were included in the analysis. The overall quality of evidence was rated as high to moderate. 1,658 (57.2%) patients had a clinical improvement, and 5-day of remdesivir was ranked as the better treatment (P-score 0.86). RR compared with standard of care was 1.39 (95% CI 1.00-1.93). 246 (8.5%) patients died within a 28-days after randomization. None difference between treatments in terms of reducing mortality was found. Among the 1,166 (40.2%) reported adverse events (AEs), 467 (40%) were severe. Arbidol (RR, 0.22, [0.07-0.74]), 450 mg of HCQ (0.31, [0.12-0.84]), remdesivir for both 5-day (0.35, [0.16-0.78]) and 10-day (0.36, [0.18-0.72]), and standard of care (0.38, [0.21-0.70]) were associated with low risk of any AEs relative to colchicine. In this study, different treatments were associated with similar effects in reducing deaths, remdesivir for 5-day was associated with more clinical improvement, and colchicine and hydroxychloroquine had more safety concern. Data from ongoing clinical trials are need to drive more precise conclusions on efficacy and safety.

Keywords

SARS-CoV-2, Network meta-analysis, Treatment

Abbreviations

RCT: Randomized Controlled Trials; RR: Risk Ratio; RDVs: Remdesivir for 5-day; RDV: Remdesivir more than 5-day; FPV: Favipiravir; LPVRTV: Lopinavir/Ritonavir; LPVRTVRBV: Lopinavir/Ritonavir and Ribavirin; ARB: Arbidol (Umifenovir); Plasma: convalescent plasma; StdCare: Standard of care; AZT: azithromycin; HCQ low: Low Dose of Hydroxychloroquine (450 mg); HCQ: Hydroxychloroquine; HCQAZT: Association Hydroxychloroquine and Azithromycin

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Background

The ongoing pandemic responsible for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) commonly designated Covid-19 is by far the worst and deadliest worldwide infection in the past 20-year. To date, more than 10.7 million cases and 512,331 deaths had been globally reported [1]. The emergency of this situation accelerated the randomized trials of many repurposed drugs which efficacy had been highlighted *in vitro* or the therapeutic experience from the SARS-CoV-1, and Middle East respiratory syndrome (MERS)-CoV infection [2].

Of 14 published randomized trials in SARS-CoV-2 virus to date, only three has been shown a clinical benefit for compared to the standard of care. Chen Z, et al. [3] conclude that 400 mg/d of hydroxychloroquine (HCQ) for 5-day improve pneumonia in 80.6% of patients; Deftereos, et al. [4] indicate that patients who received colchicine (1.5 mg loading dose followed by 0.5 mg after 1 h and maintenance doses of 0.5 mg twice daily) had significantly improved time to clinical deterioration, and remdesivir was found to be superior to placebo to shortening the time to recovery [5]. Although these previous studies included a small sample, trials involving thousands of patients are ongoing especially RECOVERY (NCT04381936), DISCOVERY (NCT04315948), and SOLIDARITY (NCT04330690).

Furthermore, while the question of HCQ efficacy for SARS-CoV-2 virus has raised many debates, literatures data are conflicting. Data from Million, et al. [6], Lagier, et al. [7], and Arshad, et al. [8] indicated the effective of HCQ to reduce mortality in COVID-19 disease, while those from Singh, et al. [9] completely showed the opposite sense with 2.17-fold increase in mortality for patients treated by HCQ, and those from four observational comparative studies [10-13] concluded to the ineffective of HCQ.

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 our knowledge, no network meta-analysis has been conducted to summarize publish and unpublished data on promising treatments against Covid-19 infection. In this study, we reported a preliminary result of a network meta-analysis (NMA) of randomized trials to compare and rank the efficacy and safety of tested treatments in patients with SARS-CoV-2 virus.

Methods

Search strategy and selection criteria

We searched through MEDLINE, GOOGLE, and Cochrane library (CENTRAL) for randomized controlled trials (RCTs) that investigated the efficacy and safety of treatments against the SARS-CoV-2 virus. The search was restricted to randomized trials conducted in human, and published in any language before July 01, 2020. Trials in which participant were non-randomly allocated to receive SARS-CoV-2 virus treatment were excluded. Using the search terms listed in the Supplementary (eMethod), AD and MT identified all relevant studies, then independently reviewed their full texts, and in case of disagreement, differences were resolved through the arbitration of another author (MCB). Extracted data included: First author name and year of publication, country, RCTs design, study follow-up, age (mean), proportion of men 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 medication which was tested to evaluate their efficacy and safety in patients infected by the SARS-CoV-2 virus. Globally, 11 different treatments were compared and ranked (Table 1). 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 of care for the trial site.

Primary and secondary outcomes

The primary outcome was clinical improvement within a 28-day after randomization. Clinical improvement was defined as patient discharge or a reduction of 2 points on a 6-point disease severity scale which 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. Secondary outcomes were all-cause mortality and any Adverse Events (AEs) during treatment course. Because the variability of the endpoint assessment for efficacy and safety outcomes, we considered the lasted evaluation.

Data analysis

Original clinical trials were described using study characteristic summary table and forest plot. The Cochrane risk of bias tools [14] and Revman version 5.4 were used to assess the risk of bias and to generate its figure respectively. We opted for a frequentist approach to compare efficacy and safety between tested treatments 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, RRs > 1 correspond to beneficial treatment effects of the first treatment com-

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Table 1: Characteristics of included randomized trials investigating the efficacy and safety of SARS-Cov-2 virus.

Study	Location	Design	Age (mean, years)	Follow-up (days)	Proportion of men participants	Dosing Information, number of participants randomized in each treatment group	Main primary endpoints	Sponsorship
Chen Jun, et al. [17]	China	Open-label, RCT	46.7-50.5	15	70%	400 mg Hydroxychloroquine (HCQ) orally for times daily for 5 days (n = 15); Standard of care (bed rest, oxygen inhalation, antiviral drugs as lopinavir/ritonavir, and antibacterial drugs if necessary; n = 15)	Negative conversion rate of SARS-CoV-2 nucleic acid in respiratory pharyngeal swab on days 7 after randomization.	NR
Li Ling, et al. [20]	China	Open-label, RCT	70	28	58.3%	4 to 13 ml/kg Convalescent plasma transfusion (n = 51); Standard of care (antiviral, antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines; n = 51)	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].	CIFMS
Cao, et al. [24]	China	Open-label, RCT	58[b]	28	60.3%	400 mg and 100 mg of the oral combination Lopinavir/Ritonavir respectively twice a day for 14 days (n = 99); Standard of care (supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and ECMO; n = 100)	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
Wang, et al. [22]	China	RCT, double-blind	65[b]	28	59.1%	200 mg on day 1 and 100 mg on days 2 to 10 in single daily infusions of Remdesivir (n = 158); placebo (n = 79)	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, NKRDPC, and BSTP

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Borba Silva, et al. [23]	Brazil	RCT, phase IIb, double-blind	51.1	28	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; n = 41); 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; n = 40)	Lethality by at least 50% in the high-dose group compared with the low-dose group at day 28.	Government of the Amazonas State
Goldman, et al. [21]	US, Italy, Spain, Germany, Hong Kong, Singapore, South Korea Taiwan	Open-label, RCT	62[b]	28	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 (n = 200) and 10-day group (n = 197).	Clinical status on day 14, assessed on a 7-point ordinal scale[a].	Gilead Sciences
Li Yueping, et al. [19]	China	Exploratory RCT, double-blind	49.4	21	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)
Chen Zhaowei, et al. [3]	China	RCT, double-blind	44.7	6	46.8%	400 mg Hydroxychloroquine (HCQ) per day orally between days 1 and 5 (n = 31); Standard of care (oxygen therapy, antiviral agents, antibiotic agents, and immunoglobulin, with or without corticosteroids; n = 31)	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)
Tang, et al. [26]	China	Open-label, RCT	46	28	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; n = 75); Standard of care (n = 75)	Negative conversion of SARS-CoV-2 by 28 days.	Emergent Projects of National Science and technology (2020YFCO844500)

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Chen Chang, et al. [18]	China	Open-label, RCT	29.7[c]	7	46.6%	1600 mg of Favipiravir twice first day followed by 600 mg, twice daily, for the following days (n = 120); 200 mg of Arbidol, three times daily plus Standard of care (n = 120)	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	NKRDPC (2020YFC0844400)
Hung, et al. [25]	Hong Kong	Open-label phase 2, RCT	52[b]	14	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 (n = 86); 400 mg of Lopinavir and 100 mg of Ritonavir every 12 h for 14 days (41)	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 Sanming Project of Medicine
Deftereos [4]	Greece	Open-label, RCT	64[b]	21	58.1%	1.5 mg of Colchicine followed by 0.5 mg 60 min later and maintenance doses of 0.5 mg twice daily (n = 56); 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; n = 54)	Time from baseline to-clinical deterioration, defined as a grade increase on an ordinal clinical scale[a]	ELPEN, Acarpia, and Karian Pharmaceuticals companies
Huang [16]	China	RCT, phase 2, double-blind		14	59.1%	500 mg of Chloroquine orally twice daily for 10 days (n = 10); 400 mg of Lopinavir and 100 mg of Ritonavir orally twice daily for 10 days (n = 12);	Viral negative-transforming time and the negative conversion rate of SARS-CoV-2 RT-PCR at day 10, 14.	NR
Beigel [5]	US, UK, Denmark, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore	RCT, double-blind		25	64.3%	200 mg on day 1, followed 100 mg daily for up to 9 additional days in single daily infusions of Remdesivir (n = 538); placebo (n = 521)	Time-to-recovery, defined as the first day, during the 28 days after enrollment, on which a patient satisfied categories 1, 2, or 3 on the eight-category scale[a]	National Institute of Allergy and Infectious Disease

RCT: Randomized controlled trials; [a]Disease 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; [b]Median age; [c]Proportion of patients aged 65 years or older; CIFMS: 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; BSTP: 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.

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pared to the second, while for the secondary outcomes, it was the reverse. To display the relative efficacy and safety outcomes of all available pairwise comparisons between treatments, a league tables were used. To choose the preferred regimen, the P-score which ranging from 0 (worse treatment) to 1 (best treatment) was computed for each treatment, then treatment with a higher P-score was selected as the better than the competing each treatment. Heterogeneity and inconsistency were quantified using the global Q test proposed by Rucker [15]. 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 [15]. 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. Because the small number of included trials that reported all-cause mortality at 28 days and safety, we performed two sensitivity analyses by adding nonrandomized comparative studies in meta-analysis to compare and rank mortality and any adverse event between pharmacological drugs. In these observational comparative studies, patients who were exposed to treatment were those receiving intervention or control at study baseline or received it during the follow-up period before the assessment of efficacy and safety outcomes. None subgroup analysis was performed. All analyses were performed using R package '*netmet*' [15]; *P-values* < 0.05 was considered significant for the difference between treatments.

Results

Included studies

The initial search through all database identified 1,007 citations, of which 469 were screened by title and abstract after removing duplicates. Of the 27 full-text citations reviewed, 14 RCTs [3-5,16-26] that met the in-

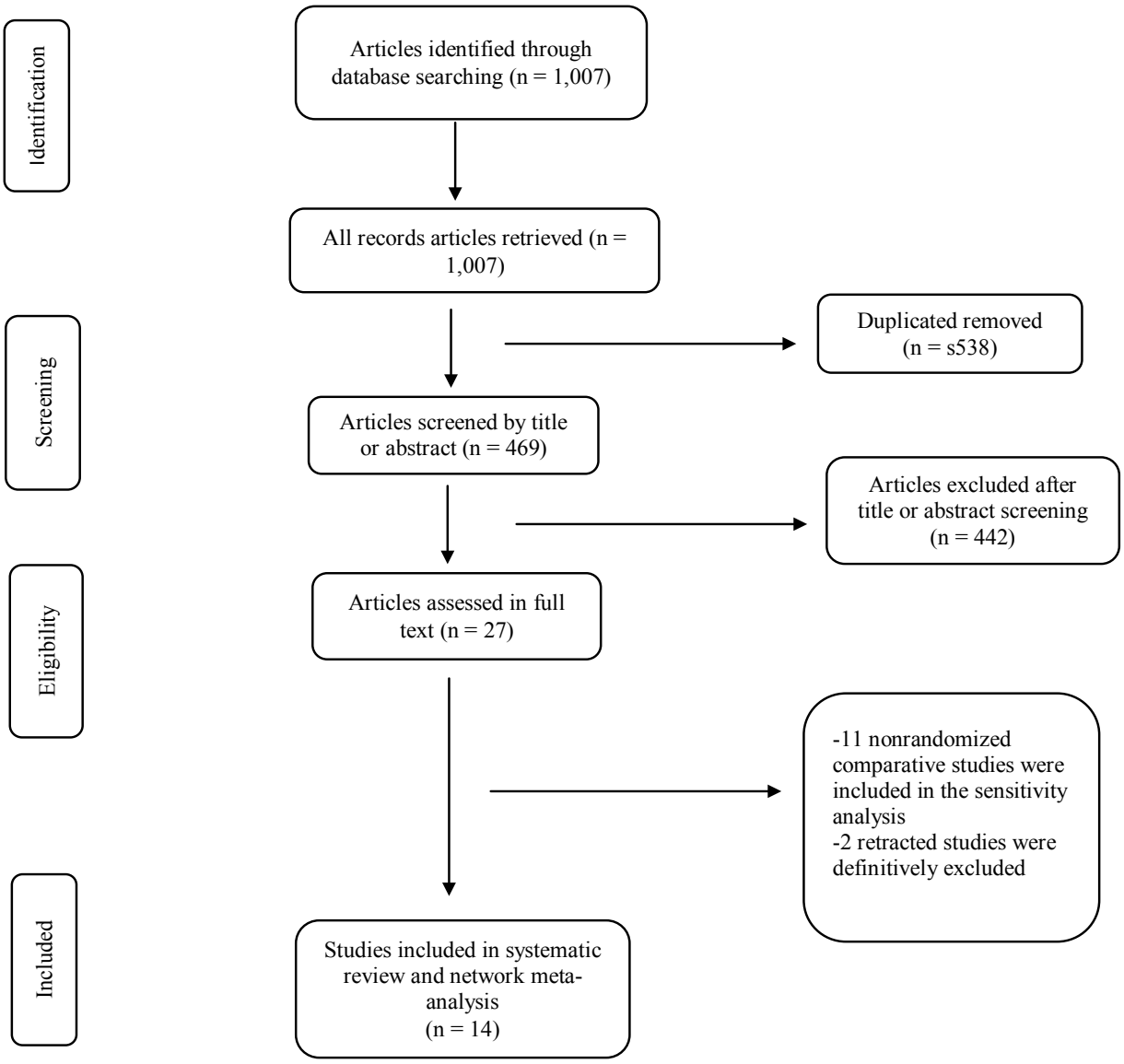

Figure 1: PRISMA Flowchart of studies selected for meta-analysis of RCT SARS-CoV-2 treatments. RCT: Randomized clinical trial.

clusion criteria were finally included in the quantitative network meta-analysis (Figure 1). These 14 RCTs (two phase 2 and five blinded) included together 2,898 patients infected by the SARS-CoV-2 virus with mean age between 44.7 and 70 years, and 1,731 [59.7%] were men, and followed from 6 to 28 days. 1,656 (57.1%) patients had comorbidity with the most common were hypertension (1,029; 35.5%) and diabetes (627; 21.6%).

The methodological quality of included RCTs is shown in Figure 2. Overall, the risk of bias was low in two RCTs, moderate in three RCTs, and high in the rest

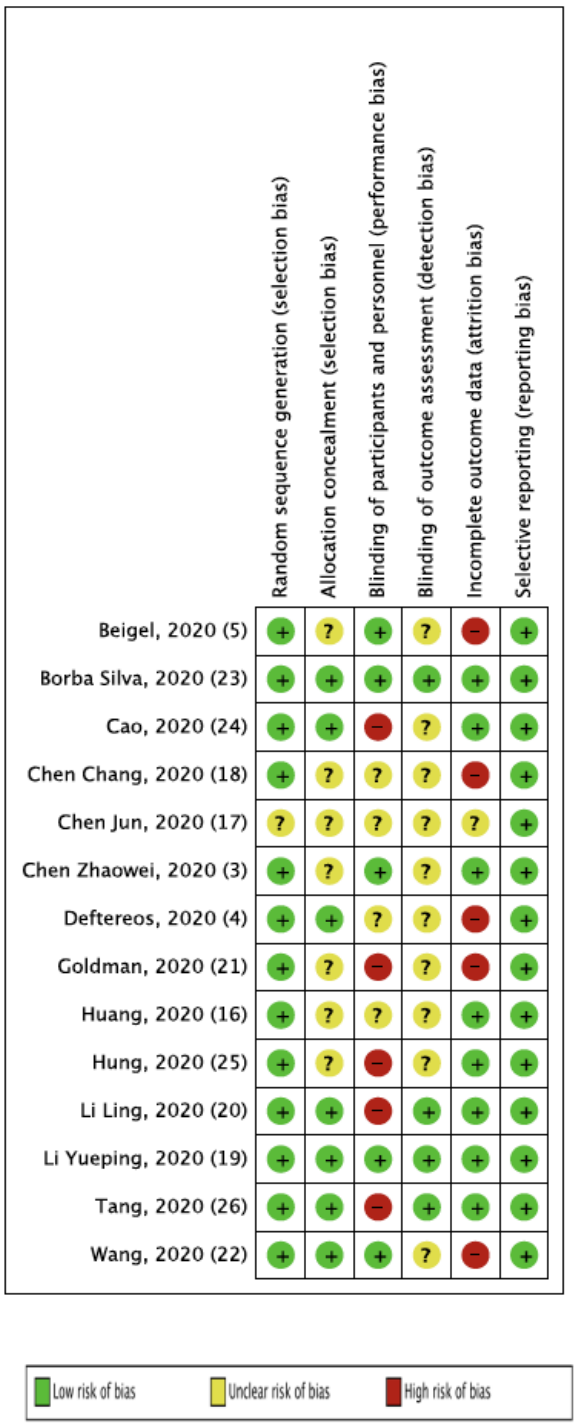

Figure 2: Summary of risk bias assessment for RCTs SARS-CoV-2 treatments comparisons.
Number in parenthesis are references.

(Supplementary Figure 1 and Supplementary Table 1). A higher risk of attrition bias (incomplete outcome data), and performance bias (blinding participants and personnel) occurred in five and five of 14 RCTs respectively.

Clinical improvements

Data for primary efficacy outcome (clinical improvement) were performed in 12 of the 14 RCTs yielding nine treatments and 14 comparisons [3-5,16-21,22,26]. Of the 2,898 participants, 1,658 (57.2%) had clinical improvement 28 days after randomization. Figure 3 shows the network for clinical improvement captured by the SARS-CoV-2 virus treatment, and the corresponding pairwise comparisons are summarized in Supplementary Table 2. 100 mg of Remdesivir once daily on 5 days was ranked with a higher probability to achieve clinical improvement at 28 days (P-score 0.86). Except between remdesivir and standard of care, no significance difference between treatments was found from the pairwise comparisons (Supplementary Table 2). Risk ratio (RR) for 100 mg of remdesivir once daily on 5 days compared with Standard care was 1.39 (95% CI 1.00-1.93). Likewise, no significant differences between direct and indirect treatment estimates comparisons or evidence of publication bias according to the comparison-adjusted funnel plot were found (Supplementary Figure 2).

All-cause mortality within a 28-day

Data for all-cause mortality were reported in seven trials [4,5,20-24] yielding six treatments and six comparisons. A total of 246 (8.5%) patients died within a 28-days post-randomization, and colchicine (1.5 mg loading dose followed by 0.5 mg after 1 h and maintenance doses of 0.5 mg twice daily) was ranked as the best option with a probability of 83% (P-score 0.83) to be associated with a lower risk of death. No significant difference was observed between treatments (Figure 4 and Supplementary Table 3), RR for colchicine compared to the Standard care was 0.91 (0.45-1.83).

Safety

For the safety outcome, the network meta-analysis was performed in all 14 RCTs, yielding 11 treatments and 16 comparisons. A total of 1,166 (40.2%) adverse events were reported at the treatment end, either 28-day after randomization. Arbidol (200 mg daily twice three times for 14 days) was ranked as the best option with a probability of 86% (P-score 0.86) to be associated with a lower risk of any AEs. Compared to colchicine, we found that arbidol, low dose of HCQ (450 mg), remdesivir for both 5 and 10-day, association lopinavir/ritonavir, and standard of care were significantly associated with low risk of any AEs (Figure 2). The corresponding risk reductions were 78% (0.22, 0.07-0.74) for arbidol, 69% (0.31, 0.12-0.84) for low dose of HCQ, 65% (0.35, 0.16-0.78) for 5-day of remdesivir, 64% (0.36, 0.18-0.72) for 10-day of remdesivir, 62% (0.38, 0.21-0.70) for standard of care,

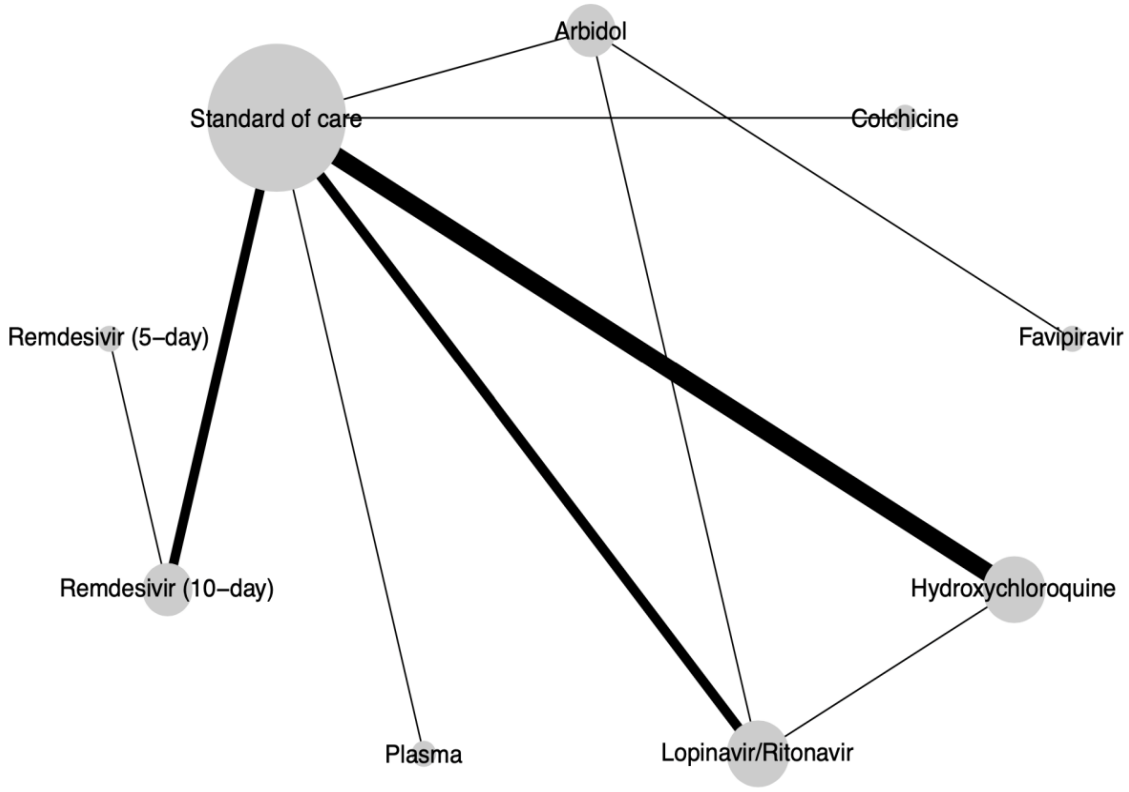

Figure 3: Network graph of eligible SARS-CoV-2 treatments comparisons for clinical improvement.

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.

and 53% (0.47, 0.23-1.00) for lopinavir/ritonavir. In addition, we found that a low dose of HCQ reduced the risk of any AEs by 50% (0.50, 0.27-0.90) when compared to high dose of HCQ (Supplementary Table 4).

Among the 1,166 reported adverse events (AEs), 467 (40%) were severe. The most common severe adverse events were acute respiratory failure or acute respiratory distress syndrome (ARDS) reported in 226 patients (117 in remdesivir, 97 in standard of care, and 12 in lopinavir/ritonavir), followed by the secondary infection in 17 cases (13 in standard of care and four in remdesivir), septic shock in 25 patients (14 in remdesivir, three in lopinavir/ritonavir, and eight in standard of care), and pneumothorax in 12 patients (seven in remdesivir and five in standard of care). For any severe AEs, network meta-analysis was performed in six RCTs involving six comparisons of six different treatments. A combination of lopinavir/ritonavir and ribavirin was associated with a risk reduction for any severe AEs with a probability 90% (P-score 0.90). Compared to standard of care, remdesivir for both 5 and 10 days and lopinavir/ritonavir reduced the risk of any severe AEs by 53% (0.47, 0.32-0.69), 23% (0.77, 0.63-0.94), and 40% (0.60, 0.37-0.98) respectively (Figure 2). Moreover, we found that the short exposition of remdesivir (5 days) reduced the risk of any severe AEs by 39% (0.61, 0.44-0.85) compared to the long exposition (10 days) (Supplementary Table 5).

Sensitivity, heterogeneity, and consistency

In sensitivity analysis, after adding the 11 nonrandomized comparative studies of treatments against SARS-CoV-2 virus, colchicine (P-score 0.83) and arbidol (P-score 0.79) remained the best options to reduce all-cause mortality and any AEs 28 days after randomization respectively (Supplementary Table 6 and Supplementary Table 7). For mortality outcome, sensitivity analysis involved 36 comparisons of 10 different treatments in 17 studies including 17,251 patients in whom 2,669 (15.5%) died. We not found any difference between treatments in terms of risk reduction of death (Supplementary Table 2). For any AEs, sensitivity analysis involved 30 comparisons of 13 different treatments in 18 studies including 8,637 patients who reported 2,219 (25.7%) AEs. Compared to HCQ, azithromycin, remdesivir for 10-day, and standard of care were associated with 47% to 55% relative risk reductions of any AEs (Supplementary Table 7). The specific relative reductions were as follow: For azithromycin, 55% reduction (0.45, 0.24-0.84); for 10-day remdesivir, 49% reduction (0.51, 0.26-0.99); and for standard of care, 47% reduction (0.53, 0.36-0.80). When compared to colchicine, azithromycin, and standard of care were associated with 62% to 67% relative risk reductions. The specific relative reductions were as follow: for azithromycin, 67% reduction (0.33, 0.11-0.95) and for standard

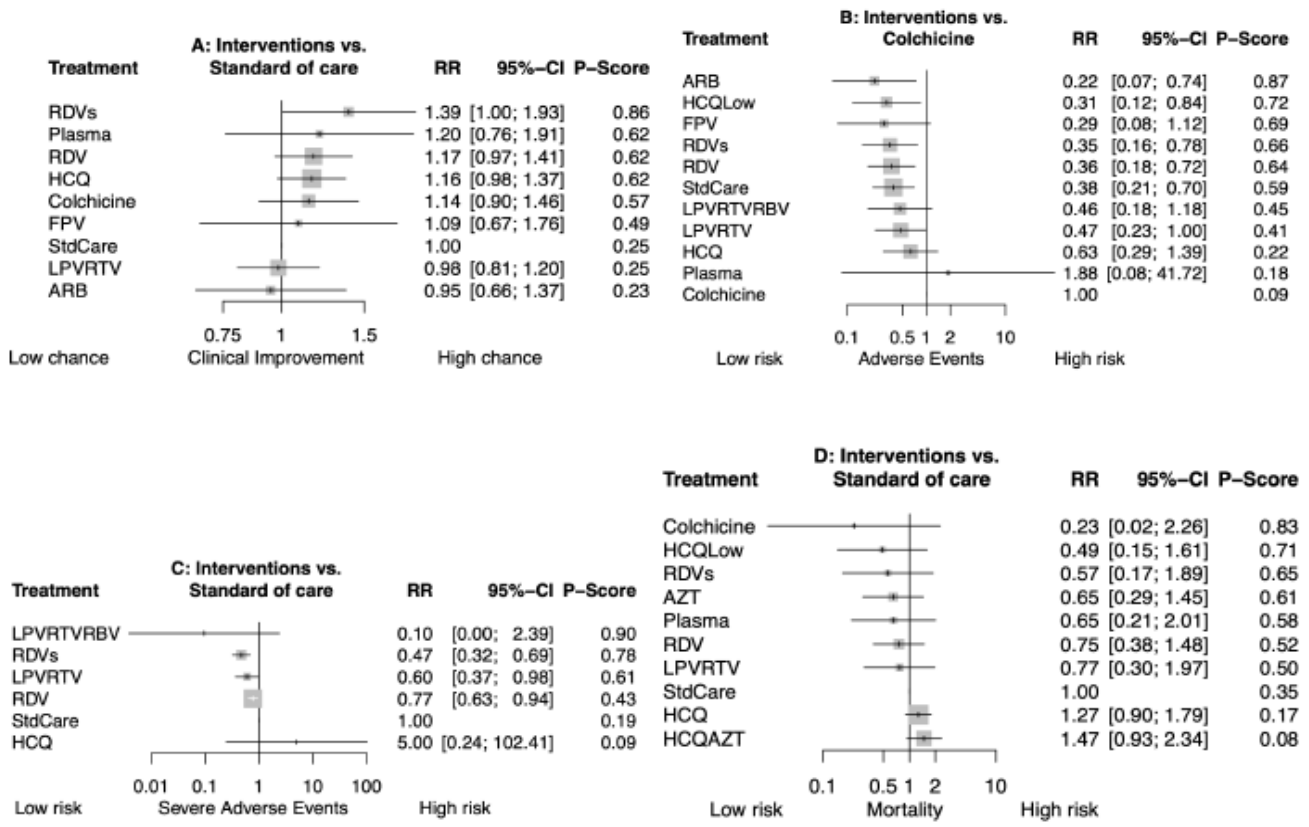

Figure 4: Network meta-analysis comparing single treatment with standard of care (A, C, and D) or colchicine (B) of SARS-CoV-2 outcomes.

A) Clinical improvement; B) Any adverse event; C) Any severe adverse event; D) All-cause mortality; Treatment 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), while RRs > 1 is favor for control (any AEs or serious AEs and mortality). RDVs: Remdesivir for 5-day; RDV: Remdesivir more than 5-day; FPV: Favipiravir; LPVRTV: Lopinavir/ritonavir; LPVRTVRBV: 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; HCQAZT: Association hydroxychloroquine and azithromycin.

of care, 62% reduction (0.38, 0.16-0.91). Furthermore, in direct comparisons, we found that azithromycin was associated with 58% to 50% relative risk reduction when compared to azithromycin plus HCQ (0.42, 0.22-0.82) and HCQ alone (0.50, 0.26-0.97). Likewise, standard of care was associated with 54% to 48% relative risk reduction when compared to azithromycin plus HCQ (0.46, 0.24-0.89) and HCQ alone (0.52, 0.34-0.80).

Global heterogeneity was low for clinical improvement (Cochran's Q 9.01; p = 0.11; $\tau^2 = 0.010$; $I^2 = 44.5\%$ [0%-78%]). For adverse event and mortality after including nonrandomized studies, global heterogeneity was significant (47.0; p < 0.0001; $\tau^2 = 0.141$; $I^2 = 76.6\%$ [59.2%-86.6%] and 117.82; p < 0.0001; $\tau^2 = 0.233$; $I^2 = 86.4\%$ [79.7%-90.9%] respectively), mainly due to significant between-design heterogeneity (AEs) and between-design as well as within-design heterogeneity (mortality). These finding were supported by the heat plot displayed in the Supplementary (Supplementary Figure 3, Supplementary Figure 4, Supplementary Figure 5 and Supplementary Figure 6).

Discussion

In this study, we conducted the first network meta-analysis, based on 14 RCTs including 2,898 patients randomly assigned to 11 different treatments against the SARS-CoV-2 virus. Pooled results suggest that a 5-day course of remdesivir was superior to standard of care in terms of clinical improvement and to reduce adverse event, but with a comparable effectiveness to other pharmacological drugs. Moreover, our findings suggest that arbidol, low dose of HCQ (450 mg), favipiravir, lopinavir/ritonavir, and standard of care were superior to colchicine in risk reduction of any AEs.

None difference between treatments in all-cause mortality reduction was found. Relative risk reduction of all-cause mortality within a 28-day for standard of care compared to HCQ was 0.80, 0.54-1.19 which supported the evidence indicating the absence of the efficacy of HCQ to reduce mortality in COVID-19 disease. These findings were conflicting with those reported previously [6,7]. While, Million, et al. [6] shows that patients who received HCQ had a risk reduction of death of 68% (0.32, 0.19-0.52) compared to those treated

without HCQ, Singh, et al. [7] completely indicates the opposite sense with 2.17-fold increase in mortality for patients treated by HCQ. Moreover, we found that HCQ was associated with more adverse events than azithromycin, remdesivir for 10-day, and standard of care (Supplementary Table 6).

Although, our study provides the most current evidence to date on the comparative efficacy and safety of available treatments against the SARS-CoV-2 virus, these findings should be interpreted with caution. We are aware that all pharmacological drugs classified as the best options for clinical improvement, all-cause mortality or safety concerns have only tested once. More data is needed to replicate these results. However, after the addition of nonrandomized comparatives studies, the results remained stable for mortality and safety, suggesting a robustness of the data.

To date several trials registered in ClinicalTrials.gov databases are ongoing, and results are expected in the coming months. Recently, the RECOVERY trial investigators had communicated on possible superiority of dexamethasone to manage mortality in hospitalized SARCoV-2 patients with severe condition [27]. According to their results, 6 mg of dexamethasone once per day for ten days would reduce deaths by 35% (0.65, 0.48-0.88) in ventilated patients and by 20% (0.80, 0.67-0.96) and by 20% (0.80, 0.67-0.96) in other patients receiving oxygen only. However, the efficacy of dexamethasone against lower respiratory tract infection is not revolutionary, and has been proved in several clinical studies [28]. 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 the SAR-CoV-2 virus.

Despite our efforts to minimize publication bias by including unpublished studies like those posted in preprint database, this preliminary study had some 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, or risk of bias). Second, the different endpoint used for the assessment of efficacy and safety outcomes which may influence the results.

Conclusion

In this study, remdesivir for 5-day was reported to be more effective than standard of care to achieve clinical improvement, different treatments were associated with a similar risk reduction of death, and colchicine and HCQ had more safety concern compared to arbidol, favipiravir, low dose of HCQ (450 mg), remdesivir for both 5 and 10 days, and standard of care. However, data from ongoing clinical trials are need to drive more precise conclusions on efficacy and safety.

Declarations

Ethical approval and consent to participate

No applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data are available upon request (alhassane.diallo@inserm.fr).

Competing interests

We declare no competing interests in relation to this work.

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Author Contributions

AD conceived the study design, analyzed the data, and drafted the manuscript, MCB supervision of data collection, and critical revision of the manuscript, AD and MT collected data, MHD analyzed the data, BDD, and MT interpreted and substantially revised the manuscript. All authors approved the final version of the manuscript.

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