Review Article

A Systematic Review on the Therapeutic Relevance of Hydroxychloroquine/Chloroquine in the Management of COVID-19

Gerard Mccabe[1,2]*, Dhruv Satya Sahni[1,2]*, Srishti Ramsaha[3]

[1]Department of General Surgery, Glasgow Royal Infirmary, [2]Department of General Surgery, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK, [3]Centre of Excellence for Biomedical and Biomaterials Research, University of Mauritius, Reduit, Mauritius
*Equal contribution by the author

Abstract

Background: The coronavirus disease-2019 (COVID-19) pandemic is coming to the fore and has surfaced as a public health emergency of international concern. The lack of vaccines or an effective treatment has led to the global hunt for potential pharmaceuticals in adequately managing this disease. This systematic review highlights the efficacy of chloroquine and its derivative hydroxychloroquine in the treatment of COVID-19 and also explores the safety profile of these drugs. **Methods:** EMBASE, COCHRANE, and PubMed databases were searched for studies on the use of hydroxychloroquine or chloroquine in the treatment of COVID-19. **Results:** Twenty articles were selected including expert opinions, National Guidelines, three small randomized controlled trials, and one prospective study. Both hydroxychloroquine and chloroquine have shown promising results including reduction in hospital length of stay and overall mortality. Moreover, concomitant use with azithromycin seems to reduce viral load to a greater extent. **Conclusions:** Considering the known safety profile of these drugs in the treatment of other diseases, their availability and affordability, chloroquine and hydroxychloroquine are potential antiviral agents in the treatment of COVID-19. However, reported side effects of these drugs when used in conjunction with azithromycin in patients with comorbidities have raised significant safety concerns. High-quality randomized clinical trials are warranted to provide more comprehensive evidence of the safety of these drugs in patients infected with COVID-19.

Keywords: Chloroquine, coronavirus, coronavirus disease 2019, hydroxychloroquine, pneumonia, severe acute respiratory syndrome-CoV-2

INTRODUCTION

In December 2019, the first case of a novel disease was reported in Wuhan, in Hubei province of China. On further investigation, it was discovered that this was a new variant of Severe Acute Respiratory Syndrome (SARS) coronavirus or SARS-CoV. As of August 17, 2020, coronavirus disease 2019 (COVID-19) has spread across 215 countries and territories worldwide, with total cases crossing 21.8 million and a mortality of over 773,000.[1] It was deciphered that its main mode of transmission is from Human-Human via direct contact or droplets.[2,3] However, airborne transmission of SARS-CoV-2 can also occur during medical interventions with aerosol-generating procedures.

Although a vast majority of cases showed mild flu-like symptoms such as fever, malaise, and cough, a significant proportion of these cases progressed to develop acute respiratory distress syndrome, respiratory failure, and multiple organ failure caused by uncontrolled cytokine storms.[3,4] As the pandemic of coronavirus disease (COVID-19) continues to undermine public health in numerous countries, global efforts are being geared toward developing a vaccine against this virus. As of now, there is no known proven specific pharmacological treatment for the disease. Globally, the

Address for correspondence: Dr. Dhruv Satya Sahni,
Department of General Surgery, Lister Building, University of Glasgow,
Glasgow Royal Infirmary, Glasgow, United Kingdom.
E-mail: dhruvsatya2949@gmail.com

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treatment has been focused on symptomatic and respiratory support.[5] Moreover, poor prognosis associated with the use of resuscitation fluids (hypotonic crystalloids, starches, or gelatine) and systemic corticosteroids, calls for the cautious use of positive end-expiratory pressure and intravenous fluids. Hence, significantly limiting the therapeutic options for COVID-19 pneumonia.[6]

In the hunt for an effective treatment to improve remission from COVID-19 infection and reduce mortality, multiple drugs including a range of antivirals and immunomodulators such as chloroquine and hydroxychloroquine are being validated for their efficacy and safety in numerous clinical trials. *In vitro* studies and smaller clinical trials held in China and France have suggested that chloroquine and hydroxychloroquine are effective in reducing viral replication and consequently decreasing viral load in numerous infections including those caused by SARS-associated coronavirus (CoV) and MERS-CoV.[7-9] Chloroquine has been widely used for over half a century for the treatment of malaria in different regions of the world and figures in the World Health Organization (WHO) list of essential medications.

Nonetheless, the efficacy and safety of this drug for treatment of SARS-CoV-2 pneumonia has not been sufficiently studied. Its high availability, low cost, and an established clinical profile makes it a potential candidate for treatment of this public health emergency.[10] In this perspective, this systematic review summarizes all the available evidence till date including opinions, guidelines, preliminary, and prospective studies evaluating the use of chloroquine and hydroxychloroquine in patients with COVID-19 and sheds light on the efficacy and safety profile of these drugs in treating this infection.

METHODS

A systematic search was carried out using EMBASE, COCHRANE, and PubMed databases from the onset of the COVID-19 epidemic to April 01, 2020 to identify articles discussing the use of hydroxychloroquine or chloroquine in the treatment of COVID-19. Two independent reviewers were involved in the identification and screening and extraction of information from these articles. We used the key words "SARS-CoV-2," "2019-nCoV," "COVID-19," "Coronavirus," "Wuhan," and these were searched in conjunction with "Chloroquine," "Hydroxychloroquine," "Treatment," "Therapeutics," and "Therapy." We also searched for any published data ranging from expert opinion to meta-analysis. Database searches were devoid of language restrictions considering that majority of the data and publications coming from China and Italy were in their native language. In addition, we used the snowballing method to review the references of the selected articles for further potential papers. We did not include any papers specifically discussing *in vitro* studies. The search was also expanded to the Chinese Clinical Trial Registry, Clinicatrial.Gov, and the International Clinical Trials Registry Platform (WHO) to retrieve data on ongoing trials and those

planned in the near future. Official National Guidelines were also explored for information regarding drugs used in the management of COVID-19. The review team adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.[11] Any discrepancies or doubts regarding the exclusion criteria were resolved by mutual consensus.

RESULTS

The initial search identified 958 results through the PubMed, EMBASE, and COCHRANE databases and 47 through other sources [Figure 1]. Following screening by title and text and removal of duplicates, we evaluated twenty articles in full text. These selected articles comprising expert opinions, National Guidelines, three small randomized controlled trials, and one prospective study, discussed the use or potential use of chloroquine or hydroxychloroquine in the treatment of COVID-19. The findings from these articles have been summarized in Table 1a-c. To date, 37 clinical trials have been recorded on the trial registries [Table 2a-d].

DISCUSSION

Among the 20 articles analyzed in this systematic review on chloroquine and hydroxychloroquine usage for the treatment of COVID 19, the majority were based on expert opinions and National Guidelines, with only three small randomized control trials and one prospective cohort study. All the National Guidelines recommended the use of these drugs in the treatment regimen of patients testing positive for COVID-19 [Table 1a]. In addition, the ICMR guidelines of India were the first to implement the use of hydroxychloroquine in asymptomatic health-care workers treating suspected or confirmed cases and household contacts of infected patients.[12]

The efficacy of chloroquine against other viral infections in *in vitro* studies was highlighted in an Editorial by French researchers, with the aim of encouraging the inclusion of this drug in clinical trials.[19] They further argued that the favorable risk–benefit balance, the high safety, and the relatively lower cost of this drug justifies its relevance in addressing the current COVID-19 pandemic. The expert consensus published by a multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province recommended the use of chloroquine phosphate in patients with SARS-CoV-2 pneumonia, classified as mild, moderate, or severe, provided there was no evidence of contraindications to this drug.[13]

Based on the apparent efficacy and acceptable safety of chloroquine phosphate in patients with COVID-19 pneumonia in multicenter clinical trials conducted in China, this drug was recommended for treating this infection in a larger population.[5] A letter from the Chinese researchers stated that the State Council of People's Republic of China had included the use of Chloroquine Phosphate in the 6th Edition of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19, for the treatment of novel coronavirus pneumonia.
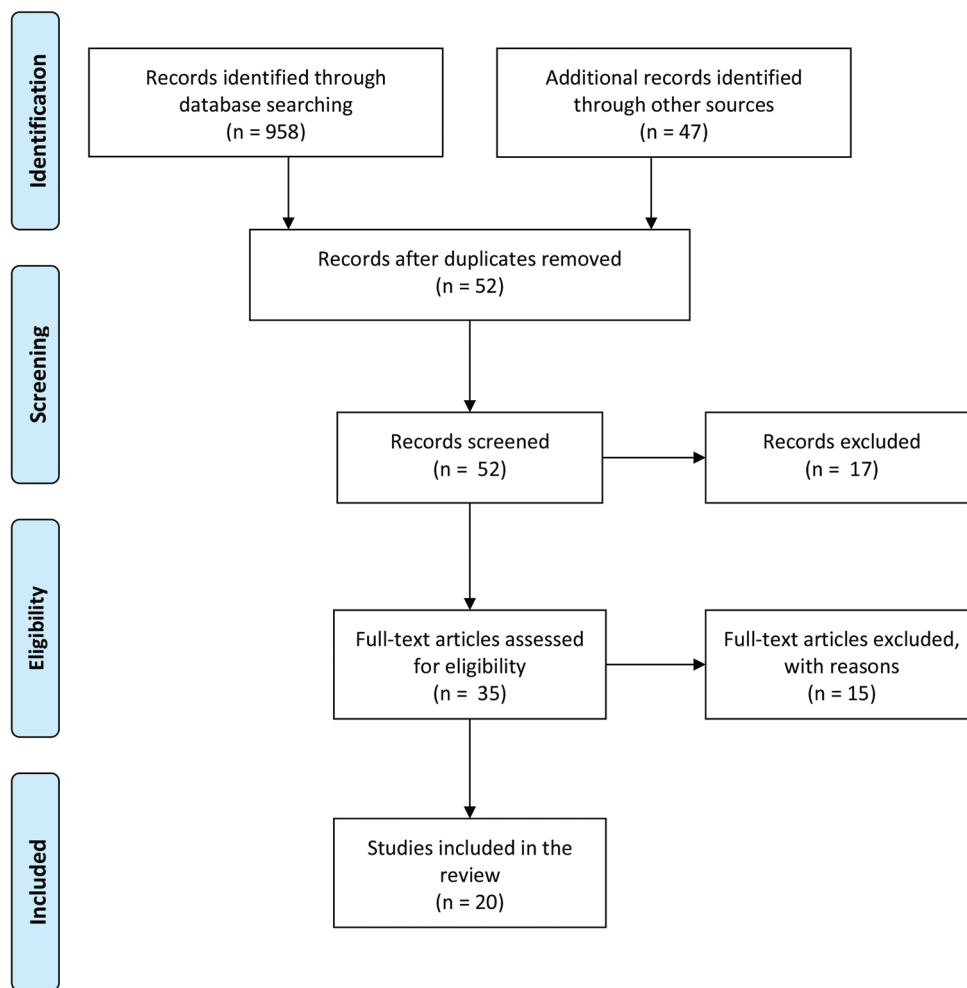
Figure 1: PRISMA flow diagram for search outcome of systematic review on the use of chloroquine/hydroxychloroquine as a treatment option for COVID-19

[5] Using a similar model, chloroquine/hydroxychloroquine was approved for treatment later by the respective control bodies in Italy, India, France, and USA after its trial use lead to patient recovery in multiple centers across these countries.

Nonetheless, recommendations from researchers in China advocate the use of hydroxychloroquine over chloroquine, considering the relatively severe side effects of the latter.[22] They also emphasized that hydroxychloroquine has a similar antiviral activity to chloroquine, while having a safer clinical profile, being more cost effective, and readily available than chloroquine. In addition, a randomized controlled trial conducted in China reported a significant reduction in time taken for clinical recovery and resolution of pneumonia in patients receiving hydroxychloroquine.[26] The expert opinions also suggested that hydroxychloroquine treatment can potentially improve outcomes in terms of decrease in length of stay in hospitals and decline in overall mortality [Table 1b].

An open-label nonrandomized clinical trial documented a remarkable reduction in viral load of SARS-CoV-2, when hydroxychloroquine was concurrently administered with azithromycin [Table 1c].[24] However, one randomized controlled trial in China and a prospective cohort study in France refuted these claims and reported no additional of using hydroxychloroquine over conventional treatment and no evidence of a strong antiviral activity from the combined therapy of hydroxychloroquine and azithromycin, respectively.[25,27] Amidst the reports with promising results from the use of chloroquine and hydroxychloroquine in treatment of COVID-19, many researchers and clinicians have also expressed concern over the safety profile of these drugs, especially when used in conjunction with azithromycin and have cited the possibility of QTc prolongation, particularly in patients with underlying cardiovascular conditions.[29,30]

The National Guidelines from Italy are contradictory in this aspect and suggest the use of chloroquine or hydroxychloroquine in a wide range of patients, ranging from those with mild respiratory symptoms and comorbidities to patients with severe respiratory failure.[14] Some reports also recommend practitioners to exercise caution when prescribing chloroquine/hydroxychloroquine for COVID-19 patients. For instance, a public document released by the Dutch Center of Disease control laid emphasis on the need to discontinue

Table 1a: National guidelines assessing the use of chloroquine and hydroxychloroquine in effectively managing patients with Coronavirus disease 2019 infection

Title	Published Date	Article type	Country	Trial summary
ICMR National COVID-19 task force[12]	March 17, 2020	National guideline	India	Hydroxychloroquine for prophylaxis of SARS-CoV-2 infection is recommended for:
				Asymptomatic healthcare workers involved in the care of suspected or confirmed cases: 400 mg twice a day on day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals
				Asymptomatic household contacts of laboratory confirmed cases: 400 mg twice a day on day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals
Expert consensus on Chloroquine phosphate for the Treatment of novel coronavirus pneumonia (Original Article in Chinese)[13]	March 12, 2020	National guideline	China	Chloroquine phosphate tablet, 500 mg twice/day for 10 days for patients diagnosed as mild, moderate and severe cases of COVID-19 pneumonia without contraindications to chloroquine
Italian Society of Infectious and Tropical disease (Lombardy section) (Original Article in Italian)[14]		National guideline	Italy	Use of chloroquine 500 mg × 2/day or hydroxychloroquine 200 mg/day for 10 days, the treatment duration may vary from 5 to 20 days according to clinical severity
				The suggested target population ranges from patients with mild respiratory symptoms and comorbidities to patients with severe respiratory failure
FDA grants emergency authorisation to Chloroquine for COVID-19[15]	March 31, 2020	National guideline	USA	The chloroquine phosphate may only be used to treat adult and adolescent patients who weigh 50 kg or more and are hospitalized with COVID-19, for whom a clinical trial is not available, or participation is not feasible
				The hydroxychloroquine sulphate may only be used to treat adult and adolescent patients who weigh 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible
Discovering drugs to treat COVID-19[16]	February 29, 2020	Communication	China	Latest version of the guidelines for the prevention, diagnosis, and treatment of novel coronavirus-induced pneumonia issued by the NHC of the People's Republic of China for tentative treatment of COVID-19
				Fifth edition of the guidelines recommends antivirals including IFN-α, lopinavir/ritonavir, and ribavirin for treatment of COVID-19. Chloroquine phosphate and arbidol are included in the sixth edition of the guidelines based on the preliminary outcomes of clinical studies
Dutch Centre for disease control[17]		Public document	Netherlands	The suggested regimen in adults requiring admission to hospital needing oxygen therapy/ICU admission consists of: 600 mg of chloroquine base followed by 300 mg after 12 h on day 1, then 300 mg × 2/day/os on days, 2-5 days
				This document also underlined:
				The need for stopping the treatment at day 5 to reduce the risk of side effects, considering the long half-life of the drug (30 h)
				The need to differentiate between regimens based on chloroquine phosphate and chloroquine base since 500 mg of the first correspond to 300 mg of the second
Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies[5]	February 19, 2020	Recommendation	China	Chloroquine phosphate has been is recommended for inclusion in the next version of the guidelines for the prevention, diagnosis, and treatment of pneumonia caused by COVID-19 issued by the NHC of the People's Republic of China for treatment of COVID-19 infection in larger populations in the future
COVID-19 adult treatment algorithm[18]	April 01, 2020	Hospital guideline	USA	Use of hydroxychloroquine for 5 days as 1st line regimen in confirmed nonsevere COVID-19 patients with comorbidities

ICMR: Indian Council For Medical Research, FDA: Food and Drug Administration, COVID-19: Coronavirus disease 2019, NHC: National Health Commission, IFN-α: Interferon alfa, ICU: Intensive care unit, SARS-CoV-2: Severe acute respiratory syndrome associated coronavirus 2

chloroquine after 5 days of treatment since the drug has a long half-life (30 h) and to minimize the risk of side effects.[17] This document also stated that it is crucial to differentiate between regimens based on chloroquine phosphate and chloroquine base due to the difference in composition of the active compound [Table 1a].

The clinical trials identified from the trial registries comprise numerous randomized controlled trials with larger patient

Table 1b: Editorial, commentary, and opinion pieces assessing the use of chloroquine and hydroxychloroquine in effectively managing patients with coronavirus disease 2019 infection

Title	Published date	Article type	Country	Trial summary
Chloroquine for the 2019 novel coronavirus SARS-CoV-2[19]	February 15, 2020	Editorial	France	The authors underlined the *in vitro* efficacy of chloroquine in other viral infections, especially SARS, to advocate their use in clinical trials. They also discussed the potentially favourable risk-benefit balance, the high safety, and the low expenditure of this drug. Consequently, they suggested its use to fight the against the current COVID-19 outbreak
Of Chloroquine and COVID-19[20]	March 05, 2020	Commentary	France	The use of chloroquine in the treatment of SARS-CoV-2 should be examined, while taking into account the potential detrimental effect of the drug observed in previous attempts to treat acute viral diseases
New insights on the antiviral effects of Chloroquine against coronavirus: What to expect for COVID-19?[10]	March 11, 2020	Opinion piece	France	Similar to the emphasis already made in 2007 in the same journal, the possibility of using chloroquine to fight orphan viral infections was advocated

Could Chloroquine/hydroxychloroquine be harmful in COVID-19 treatment?[21]	March 03, 2020	Opinion piece	Italy	Despite the *in vivo* antiviral activity, no acute virus infection has been successfully treated by chloroquine/hydroxychloroquine in human
				    Chloroquine/hydroxychloroquine did not show any anti SARS-CoV effect on *in vivo* model
				    The pathogenesis of COVID-19 is still unknown; therefore the immune effect provoked by chloroquine/hydroxychloroquine administration in COVID-19 patients is unpredictable

COVID-19: A recommendation to examine the effect of Hydroxychloroquine in preventing infection and progression[22]	March 20, 2020	Opinion piece	China	It was proposed that hydroxychloroquine, which exhibits an antiviral effect highly similar to that of chloroquine, could serve as a better therapeutic approach. It has a safer clinical profile and is suitable for those who are pregnant. It is cheaper and more readily available in China
Aminoquinolines against COVID-19: Chloroquine or hydroxychloroquine[23]	March 16, 2020	Opinion piece	Iran	Although there are more clinical data on the anti-coronaviral activity of chloroquine than that of hydroxychloroquine, both of these agents are theoretically similar in their antiviral activity. Moreover, chloroquine is not as widely available as hydroxychloroquine in some countries. In addition, chloroquine is associated with greater adverse effects than hydroxychloroquine. For example, in patients with COVID-19, prolongation of QTc interval can result from the interaction of chloroquine and lopinavir/ritonavir. Hence, it is important to administer hydroxychloroquine instead of chloroquine

COVID-19: Coronavirus disease 2019, SARS-CoV-2: Severe acute respiratory syndrome associated coronavirus 2

cohorts. The outcomes primarily assessed are mortality, viral load, and time to recovery [Table 2a-d]. Data from these trials are much awaited to provide greater insight into the effectiveness of chloroquine/hydroxychloroquine for treatment of COVID-19. Following completion of the randomized controlled trials underway, an updated systematic review or meta-analysis will enable a more accurate assessment of the risk–benefit balance of administering these drugs in COVID-19 patients. Although other drugs, in particular Remdesivir, Lopinavir-ritonavir have been identified as possible therapeutic options, the widespread availability and affordability of chloroquine/hydroxychloroquine makes them a more desirable candidate for treatment of this global pandemic, subject to proven efficacy and safety in clinical trials. Countries like India already have a high manufacturing capacity and considerable supplies of this widely proclaimed "game-changer" drug. This manufacturing capacity will be of immense aid if and when the off label use of chloroquine might lead to major drug shortage in the fight against Malaria.

CONCLUSIONS

As the number of COVID-19 cases continue to increase exponentially in multiple regions of the world, it is imperative to develop an effective approach to stem this tide. The known clinical profile of chloroquine from its long-standing use, its low cost, and widespread availability has led to extensive research on its potential application in the management of COVID-19. In the light of preliminary data from recent randomized controlled trials suggesting potential improvement in clinical outcomes, both chloroquine and hydroxychloroquine are promising antiviral agents in the treatment of COVID-19 pneumonia. However, the reported side effects of these drugs when used in conjunction with azithromycin in patients with comorbidities have raised significant safety concerns and led to a need for further high-quality randomized clinical trials. Adequately coordinated clinical studies such as pan-continental multicentre trials, which include a larger cohort of patients, would not only provide more comprehensive evidence of the

Table 1c: Clinical trials and review articles assessing the use of chloroquine and hydroxychloroquine in effectively managing patients with coronavirus disease 2019 infection

Title	Published date	Article type	Country	Trial summary
Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label nonrandomized clinical trial[24]	March 20, 2020	Open labelled non randomised RCT	France	Despite its small sample size, the survey shows that hydroxychloroquine treatment is associated with a significant viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin Twenty cases were treated in this study and showed a significant reduction of the viral carriage at day 6 compared to controls, and much lower average disease duration than reported for untreated patients. Combination treatment with azithromycin and hydroxychloroquine proved to be more efficient for virus elimination
A pilot study of hydroxychloroquine in the treatment of patients with COVID-19[25]	February 29, 2020	RCT	China	Use of hydroxychloroquine has no benefit over standard treatment in terms of negative viral RNA test and radiological progression
Efficacy of Hydroxychloroquine in patients with COVID-19: Results of a RCT[26]	April 01, 2020	RCT	China	Use of hydroxychloroquine could significantly shorten TTCR and promote absorption of pneumonia
No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection[27]	March 28, 2020	Prospective cohort study	France	No evidence of a strong antiviral activity or clinical benefit of the combination of hydroxychloroquine and azithromycin for the treatment hospitalized patients with severe COVID-19, was observed
A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19[28]	March 10, 2020	Systematic analysis	Italy	Chloroquine is widely used, safe, cheap, and shown to be effective in viral infections in preclinical studies Specific preclinical evidence and expert opinions suggest potential use against SARS-CoV-2 A search in trial registries shows that 23 clinical trials are on-going in China There is an urgent need of high-quality clinical data from different geographic areas
Chloroquine and Hydroxychloroquine as available weapons to fight COVID-19[8]	March 14, 2020	A review of evidence from *in vitro* studies systematic review and recommendations	France	The antiviral activity of hydroxychloroquine is probably the same as that of chloroquine, due to their similar mechanism of actions. Hydroxychloroquine, can considered as a safer therapeutic option for the treatment of SARS-CoV-2, since it will be prescribed over a longer period of time. For optimal treatment, it may be necessary to administer a loading dose followed by a maintenance dose

RCT: Randomized controlled trial, COVID-19: Coronavirus disease 2019, TTCR: Time to clinical recovery, SARS-CoV-2: Severe acute respiratory syndrome associated coronavirus 2

Table 2a: Characteristics of clinical trials evaluating the efficacy and safety of chloroquine in patients infected with coronavirus disease 2019

ID	Current recruiting status	Study design	Country	Population (with COVID-19 pneumonia)	Intervention group	Comparison group	Primary outcomes
ChiCTR2000029939	Yes	Single blind RCT	China	50	Chloroquine phosphate	According to the guidance of the "Diagnosis and Treatment Scheme of COVID-19" published by the NHC	Length of hospital stay
ChiCTR2000029837	No	Double blind RCT	China	120	Chloroquine	Placebo	NAAT
ChiCTR2000029826	No	Double blind RCT	China	45	Chloroquine	Placebo	Mortality rate
ChiCTR2000031204	Yes	Multicentre single blind RCT	China	300	Oral chloroquine phosphate	Placebo	Clearance time of viral RNA
ChiCTR2000030718	Yes	RCT	China	80	Chloroquine phosphate	None	TTCR

Contd...

Table 2a: contd...

ID	Current recruiting status	Study design	Country	Population (with COVID-19 pneumonia)	Intervention group	Comparison group	Primary outcomes
ChiCTR2000030417	No	RCT	China	30	Chloroquine phosphate aerosol inhalation solution	Water for injection atomization inhalation combined with standard therapy	Temperature returns to normal for >3 days
ChiCTR2000029542	Yes	Prospective cohort	China	20	Chloroquine	Standard	NAAT negative time
ChiCTR2000029988	Yes		China	80	Chloroquine phosphate	None	TTCR
ChiCTR2000029975	No	Single arm RCT	China	10	Chloroquine phosphate	None	TTCR
ChiCTR2000029741	Yes	Parallel RCT	China	112	Chloroquine	Lopinavir/ritonavir	Length of stay
NCT04323527	Yes	RCT	Brazil	440	Chloroquine diphosphate		Mortality

RCT: Randomized controlled trial, COVID-19: Coronavirus disease 2019, NHC: National Health Commission, NAAT: Nucleic-acid amplification test, TTCR: Time to clinical recovery

Table 2b: Characteristics of clinical trials evaluating the efficacy and safety of hydroxychloroquine in patients infected with coronavirus disease 2019

ID	Current recruiting status	Study design	Country	Population (with COVID-19 pneumonia)	Intervention group	Comparison group	Primary outcomes
ChiCTR2000029868	No	Multicentre RCT	China	360	Hydroxychloroquine	Conventional	NAAT
ChiCTR2000029803	No	RCT	China	320	Hydroxychloroquine	Abidol HCl	Dx progression
ChiCTR2000031174	No	Preventive RCT	China	1000	Hydroxychloroquine		NAAT
ChiCTR2000029559	Yes	Double blind RCT	China	300	Hydroxychloroquine	Starch pill	NAAT
NCT04323631	No	Prospective cohort	Israel	1116	Hydroxychloroquine	None	Number of patients having severe infection/death
NCT04315896	No	Double blind RCT	Mexico	500	Hydroxychloroquine	Placebo	Hospital mortality
NCT04318444	No	To study PEP	USA	1600	Hydroxychloroquine	None	Number of patients reporting lab positive COVID-19
NCT04325893	No	Double blind multicentre RCT	France	1300	Hydroxychloroquine	Placebo	Death (within 14 days)
NCT04316377	No	RCT	Norway	203	Hydroxychloroquine sulphate		Decrease in viral load

RCT: Randomised controlled trial, COVID-19: Coronavirus disease 2019, NAAT: Nucleic-acid amplification test, PEP: Postexposure prophylaxis

Table 2c: Characteristics of clinical trials evaluating the efficacy and safety of both chloroquine and hydroxychloroquine in patients infected with coronavirus disease 2019

ID	Current recruiting status	Study design	Country	Population (with COVID-19 pneumonia)	Intervention group	Comparison group	Primary outcomes
ChiCTR2000029899	Yes	RCT parallel	China	100	Hydroxychloroquine Chloroquine		TTCR
ChiCTR2000029898	Yes	RCT parallel	China	100	Hydroxychloroquine Chloroquine		Time to clinical improvement
ChiCTR2000030054	No	RCT	China	120	Hydroxychloroquine sulphate 0.2 g bid for 4 days a day The first dose of chloroquine phosphate was 1 g × 2 days, and the 3rd day was 0.5 g × 12 days	Standard therapy	Clinical recovery time
ChiCTR2000029992	No	RCT	China	100	Chloroquine phosphate 1.0 g for 2 days for the first dose, and 0.5 g for 12 days from the 3rd day Hydroxychloroquine sulphate 0.2 g bid ×14 days	Recommended clinical plan for coronavirus pneumonia	Clinical recovery time

TTCR: Time to clinical recovery, RCT: Randomised controlled trial, COVID-19: Coronavirus disease 2019

Table 2d: Characteristics of clinical trials evaluating the efficacy and safety of combination therapy in patients infected with coronavirus disease 2019

ID	Current recruiting status	Study design	Country	Population (with COVID-19 pneumonia)	Intervention group	Comparison group	Primary outcomes
ChiCTR2000029935	Yes	Single arm clinical trial	China	100	Conventional treatment combined with chloroquine	None	Length of hospital stay
ChiCTR2000030987	Yes	RCT	China	150	Faviparvir plus chloroquine phosphate	Faviparvir Placebo	Improvement or recovery in respiratory symptoms
ChiCTR2000030031	Cancelled		China	120	Chloroquine with standard therapy	Placebo with standard therapy	Time of conversion of viral NAAT
ChiCTR2000029609	Yes	Multicentre RCT	China	205	Oral chloroquine phosphate (mild-moderate) Oral lopnavir/ritonavir (mild-moderate) Chloroquine phosphate plus lopinavir/ritonavir (severe) Oral chloroquine phosphate (severe) Oral lopinavir/ritonavir (severe)	Lopinavir/ritonavir	NAAT
NCT04321993	No	Prospective cohort	Canada	1000	Lopinavir/ritonavir Hydroxychloroquine sulphate Baricitinib (janus kinase inhibitor) Sarilumab (anti-IL-6 receptor)	Standard care	Clinical status on day 15
NCT04307693	Yes	Prospective cohort	South Korea	150	Lopinavir/ritonavir Hydroxychloroquine sulphate		Viral load
NCT04303507	No	PEP double blind RCT	UK	40000	Chloroquine/hydroxychloroquine		Number of people symptomatic Severity of symptoms
NCT04321616	No	Open adaptive RCT	Sweden	700	Hydroxychloroquine Remdesivir		In hospital mortality (3 weeks)
NCT04324463	No		Canada	1500	Azithromycin Chloroquine		Outpatient-hospital admission/death Inpatient mortality
NCT04321278	No		Brazil	440	Azithromycin plus hydroxychloroquine	Hydroxychloroquine	Clinical status
NCT04322396	No	PEP of hospitalised patients	Denmark	226	Azithromycin plus hydroxychloroquine	Placebo	Number of days alive and discharged from hospital within 14 days
NCT04322123	No	RCT	Brazil	630	Hydroxychloroquine Hydroxychloroquine plus azithromycin		Clinical status
ISRCTN50189673 (recovery trial)	Yes	RCT	UK	Not decided	Lopinavir-Ritonavir Interferon-beta-1a Dexamethasone Hydroxychloroquine	No additional treatment	Vital status Hospitalisation Use of ventilation Use of renal dialysis/hemofilteration

RCT: Randomized controlled trial, PEP: Postexposure prophylaxis, NAAT: Nucleic-acid amplification test, IL-6: Interleukin-6, COVID-19: Coronavirus disease 2019

safety of these drugs in patients infected with COVID-19 but also increase the generalisability of the study.

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Conflicts of interest
There are no conflicts of interest.

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