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Statistical review of *Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial*

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The following review has been prepared in collaboration with members of the MRC-NIHR Trials Methodology Research Partnership [1]. The reviewers named above, and other, unnamed discussants of the paper, are all qualified statisticians with experience in clinical trials. Our objective is to provide a rapid review of publications, preprints and protocols from clinical trials of COVID-19 treatments, independent of journal specific review processes. We aim to provide timely, constructive, focused, clear advice aimed at improving both the research outputs under review, as well as future studies. Given our collective expertise (clinical trial statistics) our reviews focus on the designs of the trials and other statistical content (methods, presentation and accuracy of results, inferences). This review reflects the expert opinions of the named authors, and does not imply endorsement by the MRC-NIHR Trials Methodology Research Partnership, its wider membership, or any other organization.

Here we review *Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial*, by Tang *et al*. A preprint of the trial was posted to medrxiv.org on April 14th (https://www.medrxiv.org/content/10.1101/2020.04.10.20060558v1).

Our review, detailed below, identified issues with how the decision was made to stop the trial early, the randomization and allocation concealment procedures, and the methods for estimating subgroup specific effects. We also felt that the authors overstated the case for efficacy. Due to these issues, we recommend that it would be more appropriate to interpret the study as an inconclusive finding.

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Study Summary

The paper reports a two-arm parallel randomized controlled trial planned in 360 patients hospitalized with rt-PCT confirmed COVID-19. The study was conducted in 16 Chinese COVID-19 treatment centers in February, 2020. Patients were randomized using a 1:1 allocation ratio to receive either standard-of-care, or standard-of-care plus hydroxychloroquine (1200 mg daily for three days, then 800 mg daily for up to 2 weeks in patients with mild/moderate illness, or up to 3 weeks in patients with severe illness). The primary outcome was the time to a negative SARS-CoV-2 rt-PCR, up to 28 days post-randomization. Secondary outcomes included the time to improvement of clinical symptoms (normalization of fever, SpO2, and respiratory symptoms), time to normalization of elevated CRP, and time to recovery of lymphopenia, all up to 28 days post-randomization.

According to the paper, there was a planned interim analysis once 150 patients were treated for at least 7 days. At this point, based on the results we present below, the decision was made to stop the trial. In the intention-to-treat analysis (n = 75 in each arm), the hazard ratio (HR) for time to a negative rt-PCR was 0.85 (95%CI 0.58 to 1.23) favoring the hydroxychloroquine arm. The HR for time to resolution of symptoms was 1.01 (0.59 to 1.74; n = 119), though in a subgroup of these patients who weren't prescribed any other anti-SARS-CoV-2 medicines during the trial (n = 28), the HR for time to resolution of symptoms was 8.8 (1.1 to 71.2) favoring the hydroxychloroquine arm. The HR for time to normalization of elevated CRP was 1.31 (0.64 to 2.71; n = 48) and the HR for recovery of lymphopenia was 1.16 (0.44 to 3.04; n = 38), both favoring the hydroxychloroquine arm. Finally, the reduction of CRP from baseline to day 28 was greater in the hydroxychloroquine arm (difference in means of 4.27, p = 0.045, n = 137).

Based on these findings, the authors concluded that administration of hydroxychloroquine led to greater alleviation of clinical symptoms, possibly "through anti-inflammatory properties" and clinicians should consider its use in "symptomatic patients with elevated CRP...particularly in patients at higher risk."

We sincerely thank the authors for their contribution to our collective understanding of COVID-19, for their commitment to the timely dissemination of research results.

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Major comments

The methodological basis for stopping early was unsound.

As noted in the summary above, the reported analysis was of data from 150 patients, while the study planned to recruit 360. The authors reported that this was a planned interim analysis and that they would employ an alpha-spending approach to maintain strict type 1 error control. When applied properly, an alpha-spending approach means that earlier looks are “penalized” in that you would require a smaller p-value than your nominal type 1 error rate (e.g. 0.05) to declare a “statistically significant” result. However, there is no evidence of using this approach in the reported analysis - all of the results are interpreted in light of their nominal p-values, with no such penalty. Further, there was no detail provided on how the data safety and monitoring board (DSMB) considered this information when they concluded there was “good efficacy of HCQ in symptom alleviation and anti-inflammation reported from the interim analysis”.

Interestingly, the discussion seems to imply that the early stopping was at least partly driven to the decline in cases in mid March. If the decision to stop early was in fact due to poor enrollment, with no consideration of the interim results, then our concerns about early stopping are somewhat alleviated, as it is a very different situation compared to having the *option* to stop or continue. However, it is still confusing to say you are using a methodologically sound approach to early stopping, and then completely ignore it when analysing and interpreting the study data.

Recommendations:
For future studies

- It is often a good idea to consider including a methodologically sound method for early stopping for treatment futility and/or efficacy, though investigators often don’t. There are multiple approaches available under both frequentist and Bayesian frameworks for statistical inference. However, once the decision has been made to use such an approach, you need to follow through on the analysis and interpretation.

For the reader

- Lack of clarity around the reasons for stopping early, and failure to implement their planned approach to the interim analysis, mean that the results should be interpreted cautiously.

The interpretation of subgroups was done incorrectly.

It is common to estimate treatment effects in patient subgroups. Generally, the appropriate way to do this is to use a multivariable model that includes a treatment-by-subgroup interaction term.

The authors unfortunately did not describe exactly how they estimated their reported subgroup estimates, and only reported the 95% CIs of these effects within subgroups. This matters because a large estimated effect on a secondary outcome in one subgroup seemingly played an important role in their conclusion that hydroxychloroquine was efficacious (HR 8.8 [95%CI 1.1 to 71.2] for time to resolution of symptoms in 28 patients who weren't prescribed any other anti-SARS-CoV-2 medicines during the trial). This conclusion is apparently based on the observation that the subgroup specific CI didn't include the null HR of 1, without consideration of the interaction term that would more directly indicate whether the effect in this group is different than that in its complement (patients who *did* receive another nti-SARS-CoV-2 medicines during the trial).

Finally, the evaluation of so many subgroups raises concerns about multiplicity. As the number of subgroups tested increases, so does the probability of seeing a "significant" result by chance. Thus basing the conclusion of the trial on a single such subgroup result (out of many tested subgroup effects) is problematic.

For future studies

- If you are interested in estimating subgroups-specific treatment effects, the subgroups should be pre-registered in the protocol's statistical analysis plan; then tested using the appropriate treatment by subgroup interaction term; and cautiously interpreted in a manner that considers multiplicity.

For this study

- Report interaction terms from multivariable models that test for subgroup specific treatment effects, and interpret the results in light of any resulting multiplicity.

For the reader

- Lack of clarity around how subgroup effects were estimated, incorrect statsitical inference based on subgroup specific CIs, and testing many subgroups with no consideration of multiplicity, should warrant increased caution when interpretating the results.

Important details regarding the randomization and allocation concealment were unclear or missing.

The randomisation was 1:1 and apparently stratified by mild/moderate or severe COVID19. However, there was no mention of blocking or any other means of restricting the randomization within strata, and the analyses of the data did not adjust for the stratification; and without blocking, it would be unusual to land exactly on a 75:75 allocation by chance alone (about 6%). It is also not clear if there was stratification by centre (which would be typical in a multi-centre trial), and there are no details on how the allocations were distributed to centres or how allocation concealment was maintained. This is particularly concerning for an unblinded study.

For future studies

- Please refer to CONSORT [3] when designing and reporting your trial. There is excellent guidance there on randomization and allocation concealment procedures.

For this study

- Clarify the reporting of the randomization and allocation concealment, following CONSORT.

For the reader

- The lack of clarity around randomization and allocation concealment warrant increased caution when interpreting the results.

The overall conclusions are questionable.

While the authors acknowledged there was no apparent difference in study arms on the primary outcome, a negative rt-PCR by day-28 post-randomization, they concluded that doctors should consider its use in "symptomatic patients with elevated CRP … particularly in patients at higher risk" due to greater alleviation of clinical symptoms, possibly "through anti-inflammatory properties". However, this is based on a questionable subgroup effect for symptom alleviation (described above) but no apparent alleviation of symptoms in the entire sample, and a greater reduction of CRP (which was not an outcome listed in the trial registry) in the hydroxychloroquine arm. Further, even when the data hinted that hydroxychloroquine might lead to beneficial outcomes more quickly, it didn't translate to differences in these outcomes at the end of the study period. Thus even without the issues described earlier in the review (and other minor points raised below), we suspect most experts would view this as a null or inconclusive finding.

For the reader

- This study should be interpreted as a null or inconclusive result, not as evidence for the efficacy of hydroxychloroquine.

Minor points

- The subgroup analysis that played such an important role in the authors' interpretation of the study data was based on a post-randomization factor that could have been influenced by treatment and prognosis. This is especially problematic since the trial was not blinded.

- They reported that the interim analysis took place when they had 150 patients completing at least 7 days of treatment, but it isn't clear how many of those patients completed their treatment regimen, or how many were followed up the full 28 days post-randomization (there were no deaths).

- It's unclear how "symptom alleviation" was calculated. Did participants have to meet all three criteria (normalization of fever, SpO2, and respiratory symptoms)? Further, it's not possible to tell how the individual criteria were assessed, which is important since the trial was unblinded and the subjectivity of this outcome is clearly important as it contributed to the authors' conclusion that hydroxychloroquine was efficacious.

- Adjustment for prognostic covariates using multivariable models would have likely improved the precision of effect estimates. Similarly, CRP and blood lymphocytes were analysed as changes from baseline, whereas a baseline-adjusted model would have been a more efficient use of the data.

- The overall description of methods and presentation of results were chaotic and confusing. Some examples include:

> The % of events in figure 2 (70.7% vs74.7%) differs from the text (85.4% vs 81.3%). The same happens for symptom alleviation figures reported in the text and in figure 3.
>
> There was inconsistency between outcome designations in the text and figures. For example, figure 3 reads "cumulative improvement rate", but in the results section the outcome is called "symptom alleviation".
>
> The analysis sets vary across outcomes, with no clear explanation of why. Authors described their analysis as "intention-to-treat", but this seems to be the case for the primary outcome only. Other outcomes, such as improvement, exclude asymptomatic participants, and the analysis of normalization of elevated CRP excludes those with normal CRP.
>
> Outcomes mentioned in the methods were not reported in the results.

Open Data

No.

Anonymized datasets can be made available on reasonable request after approval from the trial management committee and after signing a data access agreement. Proposals should be directed to the corresponding author.

Open Analysis Code

No.

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Pre-registered study design

No.

PubPeer

There may be comments on the PubPeer page for the published version of this paper.
https://pubpeer.com/publications/C4637CE5485BC9935137B01EDC87E6

References

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CONSORT CHECKLIST

To support the review, we completed the CONSORT checklist [10] below. Material taken directly from the paper (or trial registry) is in *italics.* Our additional comments are in **bold**.

Title and abstract

1a Identification as a randomised trial in the title

Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial

1b Structured summary of trial design, methods, results, and conclusions.

Title: Identification of the study as randomised	Yes
Authors: Contact details for the corresponding author	Yes
Trial design: Description of the trial design (eg, parallel, cluster, non-inferiority)	Yes
Methods	
Participants: Eligibility criteria for participants and the settings where the data were collected	No
Interventions: Interventions intended for each group	Yes
Objective: Specific objective or hypothesis	Yes
Outcome: Clearly defined primary outcome for this report	Yes
Randomisation: How participants were allocated to interventions	No
Blinding (masking): Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	No
Results	
Numbers randomised: Number of participants randomised to each group	Yes
Recruitment: Trial status	No
Numbers analysed: Number of participants analysed in each group	No
Outcome: For the primary outcome, a result for each group and the estimated effect size and its precision	Yes
Harms: Important adverse events or side-effects	Yes
Conclusions: General interpretation of the results	Yes
Trial registration: Registration number and name of trial register	Yes
Funding: Source of funding	No

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Introduction

Background and objectives

2a Scientific background and explanation of rationale

See introduction.

2b Specific objectives or hypotheses

To assess the efficacy and safety of hydroxychloroquine (HCQ) plus standard-of-care (SOC) compared with SOC alone in adult patients with COVID-19. [**abstract**]

Having encountered numerous challenges, we conducted a multicenter, open-label, randomized, controlled trial to assess the efficacy and safety of HCQ sulfate in adult patients with COVID-19. [**introduction**]

Evaluate the efficacy and safety of high dose Hydroxychloroquine Sulfate Tablets in treatment of mild/normal/severe type novel coronavirus pneumonia. [**registry**]

Methods

Trial design

3a Description of trial design (such as parallel, factorial) including allocation ratio

Having encountered numerous challenges, we conducted a multicenter, open-label, andomized, controlled trial to assess the efficacy and safety of HCQ sulfate in adult patients with COVID-19. [**introduction**]

Multicenter, open-label, randomized controlled trial. [**abstract**]

This study was a multicenter, randomized, parallel, open-label, trial of oral HCQ in hospitalized patients with COVID-19 [**methods**]

1:1 allocation ratio implied by: *150 patients hospitalized with COVID-19. 75 patients were assigned to HCQ plus SOC and 75 were assigned to SOC alone (control group).* [**abstract**]

3b Important changes to methods after trial commencement (such as eligibility criteria), with reasons

No apparent changes.

All authors vouch for the veracity of the data, analyses, and trial protocol and vouch that the trial was conducted and reported consistently with the protocol, which together with the statistical analysis plan, is available in the appendix.

Participants

4a Eligibility criteria for participants

Eligible patients were at least 18 years of age, had ongoing SARS-CoV-2 infection confirmed with real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR). Patients who were willing to participate in this trial had to consent not to be enrolled by other clinical trials during the study period. A chest computed tomography examination result is needed for determining disease severity before randomization. Patients had to receive HCQ orally. Patients with known allergy to HCQ or existing conditions that could lead to severe adverse events during the trial period were excluded, particularly those with severe liver or renal diseases that could impair the ability to metabolize high doses of HCQ. Those unable to co-operate with investigators due to cognitive impairments or poor mental status were considered inappropriate for this trial. Female patients who were pregnant or during lactation period were excluded. Full eligibility criteria are provided in the protocol (appendix). [**paper**]

Inclusion criteria1. Aged 18 years old and above; 2. Meet the novel coronavirus pneumonia (COVID-19) diagnostic criteria. The upper and lower respiratory tract RT-PCR confirmed that 2019-nCoV nucleic acid positive, chest CT imaging examination could be used in conjunction; 3. SaO2/SpO2≤94% under indoor air, or PaO2/FiO2<300mgHg (for severe type patients); 4. Sign informed consent; 5. Do not participate in the clinical study of other study drugs within 28 days. Exclusion criteria：1. Aged less than 18 years old; 2. Other serious medical diseases such as malignant tumor, heart, liver and kidney disease, uncontrollable metabolic disease, etc; 3. Not suitable for gastrointestinal administration; 4. Pregnant or lactating women; 5. Those who are allergic to the ingredients of this product; 6. Mental state can not cooperate with the observer or cognitive impairment; 7. Severe liver disease (such as child Pugh score >=C, AST > 5 times ULN); 8. Patients with known severe renal impairment (creatinine clearance rate <=30 ml/min) or continuous renal replacement therapy, hemodialysis, peritoneal dialysis. [**registry**]

4b Settings and locations where the data were collected

Patients were enrolled at 16 government-designated COVID-19 treatment centers from three provinces in China (Hubei, Henan and Anhui province) between February 11, 2020 and February 29, 2020.

19 locations listed in the registry.

Interventions

5 The interventions for each group with sufficient details to allow replication, including how and when they were actually administered

Treatment group: standard treatment according to the guideline recommendation combined with: Day 1 to day 3: oral hydroxychloroquine sulfate tablets (100mg / tablet, 200mg / tablet), 400mg each time, 3 times a day; Day 4 to day 14/21: oral hydroxychloroquine sulfate tablets (100mg / tablet, 200mg / tablet), 400mg each time, 2 times a day. Control group: standard treatment according to the guideline recommendation. Treatment period: 14 days for mild/normal type, 21 days for severe type. [**registry**]

The patients were treated with SOC aligning with the indications from the updating National clinical practice guidelines for COVID-19 in China. Treatment of HCQ was begun within 24 hours after randomization and was administrated with a loading dose of 1, 200 mg daily for three days followed by a maintained dose of 800 mg daily for remaining days (total treatment duration: 2 weeks or 3 weeks for mild/moderate or severe patients, respectively). Dose for HCQ will be adjusted when adverse events are related to HCQ as judged by investigators.

6a Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed

The primary endpoint for this trial was the negative conversion of SARS-CoV-2 within 28-day.

Key secondary endpoints included the alleviation of clinical symptoms, laboratory parameters, and chest radiology within 28-day. Definition for the alleviation of clinical symptoms was 1) resolving from fever to an axillary temperature of ≤36.6 and; 2) normalization of SpO2 (>94% on room air) and; 3) disappearance of respiratory symptoms including nasal congestion, cough, sore throat, sputum production and shortness of breath. Normalization of laboratory parameters were focused on CRP, ESR, IL-6 and TNF-α level.

Other secondary outcomes for severe cases included all-cause mortality, clinical status as assessed with the six-category ordinal scale on days 7, 14, 21 and 28, days of mechanical ventilation, extracorporeal membrane oxygenation, supplemental oxygenation, and hospital stay for severe cases. Disease progression was assessed in mild/moderate cases.

Safety outcomes included adverse events that occurred during the study period. Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities coding dictionary and will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events.

6b Any changes to trial outcomes after the trial commenced, with reasons

Sample size

7a How sample size was determined

The trial was designed to enroll approximately 360 subjects (180 per group) to assure a power of 80% and the family-wise type-I error ≤0.05. The sample size was calculated based on the alternative hypothesis of a 30% increase in the speed of virus nucleic acid negativity, therefore, a total of 248 events is needed with a Log-Rank test.

7b When applicable, explanation of any interim analyses and stopping guidelines

An interim analysis was planned when around 150 patients were treated for at least 7 days. O'Brien-Fleming cumulative α-spending function by Lan-DeMets algorithm（Lan-Demets, 1983) was applied to control family-wise type-I error.

Randomisation

Sequence generation

8a Method used to generate the random allocation sequence

8b Type of randomisation; details of any restriction (such as blocking and block size)

Patients meeting eligibility criteria were stratified according to the disease severity (mild/moderate or severe) and were then randomly assigned (in a 1:1 ratio) to receive either SOC or SOC plus HCQ. Patients were enrolled by the site investigator. The statistician performed the randomization

Allocation concealment mechanism

9 Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned

...equal numbers of cards with each group assignment number randomly generated by computer were placed in sequentially numbered envelopes that were opened as the patients were enrolled.

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Implementation

10 Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions

No additional information.

Blinding

11a If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how

No placebo was used and drugs were not masked.

Neither patients, nor investigators, nor statisticians were masked to treatment assignment.

11b If relevant, description of the similarity of interventions

Statistical methods

12a Statistical methods used to compare groups for primary and secondary outcomes

The overall negative conversion rate was estimated and compared by analyzing time to virus nucleic acid negativity using the Kaplan-Meier method on intention-to-treat population. The hazard ratio was estimated by the Cox model, which is the higher, the more rapid the conversion is. The same approach was applied to analyze other key secondary endpoints. Forest plot was used to display hazard ratios generated for each subgroup.

Absolute changes from baseline of CRP and blood lymphocyte count by last assessment were compared between actual treatment groups using the Two-Sample T-test. Significance was claimed for other analyses than primary analysis if p-value <0.05.

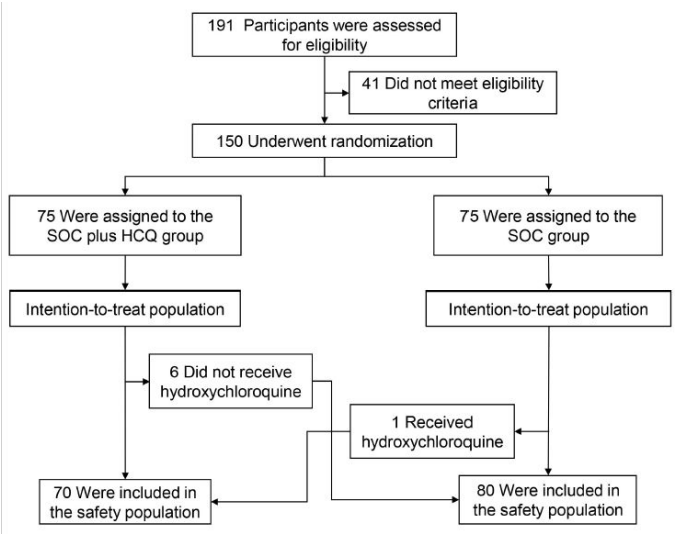
Data analyses were conducted on SAS version 9.4.

12b Methods for additional analyses, such as subgroup analyses and adjusted analyses

Results

Participant flow (a diagram is strongly recommended)

13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome



13b For each group, losses and exclusions after randomisation, together with reasons

A total of 191 patients admitted with COVID-19 from February 11, 2020 to February, 29 2020, were assessed for eligibility, of which 41 did not meet eligibility criteria. The remaining 150 patients underwent randomization; Among them, 75 patients were assigned to SOC and 75 patients to SOC plus HCQ group (Figure 1).

Recruitment

14a Dates defining the periods of recruitment and follow-up

2020-02-06To 2020-06-30; Recruitment status: Completed [**registry**]

14b Why the trial ended or was stopped

Baseline data

15 A table showing baseline demographic and clinical characteristics for each group

The mean age of the patients was 46 years and 55% were male. The mean day from disease onset to randomization was 16.6 and 89% of the patients had concomitant medication before randomization. The majority of the patients had mild to moderate COVID-19 (99%) and only 2 patients (1%) were severe upon screening. Baseline demographic, epidemiological and clinical characteristics of the patients between the two groups are shown in Table 1. By 14 March 2020 (the cutoff date for data analysis) The median duration of follow-up was 21 days (range, 2 to 33) in the SOC group and 20 days (range, 3 to 31) in the SOC plus HCQ group. Of the 75 patients assigned to receive SOC plus HCQ, 6 patients did not receive any dose of HCQ; of them, 3 patients withdrew consent and 3 patients refuse to be administrated HCQ.

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Table 1. Baseline Demographic and Clinical Characteristics of the Patients in the Intention-to-Treat Population.

Characteristics*	SOC plus HCQ (N=75)	SOC (N=75)	Total (N=150)
Age — yr	48.0±14.1	44.1±15.0	46.1±14.7
Male sex — no. (%)	42 (56.0)	40 (53.3)	82 (54.7)
Body-mass index (% with missing data)†	23.9±3.24 (1.3)	23.2±3.0 (5.3)	23.5±3.2 (3.3)
Days from disease onset to randomization (% with missing data)	16.0±9.9 (2.7)	17.1±11.1 (1.3)	16.6±10.5 (2.0)
Exposure history — no./total no. (%)			
Hubei province exposure	50/72 (69.4)	53/71 (74.6)	103/143 (72)
Contact with confirmed COVID-19 patient (s)	39/72 (54.2)	32/71 (45.1)	71/143 (49.7)
Others	1/72 (1.4)	1/71 (1.4)	2/143 (1.4)
No exposure	2/72 (2.8)	9/71 (12.7)	11/143 (7.7)
Unknown	5/72 (6.9)	5/71 (7)	10/143 (7)
Medication prior to randomization — no. (%)	47 (62.7)	43 (57.3)	90 (60.0)
Disease severity — no. (%)			
Mild	15 (20.0)	7 (9.3)	22 (14.7)
Moderate	59 (78.7)	67 (89.3)	126 (84.0)
Severe	1 (1.3)	1 (1.3)	2 (1.3)
Coexisting conditions — no./total no. (%)	28 (37.3)	17 (22.7)	45 (30.0)
Diabetes	12 (16.0)	9 (12.0)	21 (14.0)
Hypertension	6 (8.0)	3 (4.0)	9 (6.0)
Others	21 (28.0)	10 (13.3)	31 (20.7)
Vital Signs (%with missing data)			
Body temperature — °C	36.9±0.47 (4)	36.8±0.48 (0.0)	36.8±0.5 (2.0)
Pulse — beats/min	82.75±8.0 (2.7)	82.5±9.4 (5.3)	82.6±8.7 (4.0)
Respiratory rate — breaths/min	19.6±1.3 (2.7)	19.7±1.7 (6.7)	19.6±1.5 (4.7)
Systolic blood pressure — mm Hg	126.3±13.2 (6.7)	123.5±11.2 (8.0)	124.9±12.3 (7.3)
Diastolic blood pressure — mm Hg	79.1±8.5 (6.7)	76.8±8.0 (8.0)	77.9±8.3 (7.3)
Pulse oximetry — %	97.4±1.6 (0)	97.3±1.6 (2.7)	97.4±1.6 (1.3)
Symptoms — no./total no. (%)			
Fever	43/72 (59.7)	40/75 (53.3)	83/157 (52.9)
Cough	35/68 (51.5)	26/68 (38.2)	61/136 (44.9)
Sputum production	11/68 (16.2)	4/68 (5.9)	15/136 (11)
Shortness of breath	15/68 (22.1)	4/68 (5.9)	19/136 (14)
Nasal congestion	0 (0)	0 (0)	0 (0)

Numbers analysed

16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

Outcomes and estimation

17a For each primary and secondary outcome, results for each group, and the

estimated effect size and its precision (such as 95% confidence interval)

17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended

Primary:

Overall, the negative conversion rate of SARS-CoV-2 among patients who were assigned to receive SOC plus HCQ was 85.4% (95% confidence interval [CI], 73.8%, 93.8%), similar to that of the SOC group 81.3% (95%CI, 71.2% to 89.6%) within 28-day.

Negative conversion rate at specific time-point, 4-, 7-, 10-, 14- or 21-day was also similar between the two groups.

The negative conversion time did not differ between SOC plus HCQ and SOC group (median, 8 days vs. 7 days; hazard ratio, 0.846; 95%CI, 0.580 to 1.234; P=0.341) (Figure 2_panel A).

Secondary:

The overall rate of symptoms alleviation within 28-day was not different between patients with SOC with (59.9%, 95%CI, 45.0% to 75.3%) and without HCQ (66.6%, 95%CI, 39.5% to 90.9%).

The median time to alleviation of clinical symptoms was similar in the SOC plus HCQ group than that in the SOC group (19 days versus 21 days).

More rapid alleviation of clinical symptoms with SOC plus HCQ than with SOC alone was observed during the second week since randomization (Figure 3_panel A).

Comparing to SOC alone, the addition of HCQ on SOC led to more rapid normalization of elevated baseline CRP and recovery of baseline lymphocytopenia, although the overall improvement rate become similar within the 28-day (Figure 4_panel A, B).

The declined value of CRP from baseline by last assessment was significantly greater in SOC plus HCQ group than in the SOC group (absolute change, 6.986 versus 2.723 milligram/liter, P=0.045) (Figure 5).

Similarly, the elevation of blood lymphocyte count at last assessment from baseline was greater in SOC plus HCQ group than that in the SOC group (absolute change, 0.062 versus 0.008 ×109/liter, P=0.547) (Figure 5).

Comprehensive analysis for other prespecified secondary outcomes including the reduction of erythrocyte sedimentation rate, IL-6 or TNF-α was not available due to very limited data of these parameters on pre-specified visiting date.

Ancillary analyses

18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory

Post hoc analyses were performed in subgroups to explore any decrease of negative conversion time by the addition of HCQ upon SOC. No such effects were observed in the analyzed subgroups according to age (≥45 years versus <45 years), BMI value (≥24 kg/m2 versus <24 kg/m2), presence or absence of existing conditions, days between disease onset and randomization (≥7 days versus <7 days), baseline CRP value (≥upper limit of normal versus <upper limit of normal), baseline lymphocyte count (<lower limit of normal versus ≥lower limit of normal) and with or without contaminant use of potential anti-viral agents for treating COVID-19 during the study period (Figure 2_panel B).

The efficacy of HCQ on the alleviation of symptoms (Hazard ratio, 8.83, 95%CI, 1.09 to 71.3) was more evident when the confounding effects of other anti-viral agents were removed in the post-hoc subgroup analysis (Figure 3_panel B). No significant difference between SOC plus HCQ group and SOC group on symptoms improvement was observed in other subgroup analyses (Figure 3_panel B)

Harms

19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms42)

Six patients assigned to the SOC plus HCQ group but did not receive HCQ treatment were classified as HCQ non-recipient in the safety population. One patient in the SOC group wrongly received 14-day of HCQ treatment with an accumulative dose of 11, 600 mg. This patient was classified as HCQ recipient in the safety population (Figure 1). Safety endpoints were compared between HCQ recipient and non-recipient (Table 2). In HCQ recipients, the median duration of HCQ treatment was 14 days (range, 1 to 22). Between randomization and final visit, a total of 21 patients (30%) in the SOC plus HCQ group reported adverse events, significantly (P=0.001) higher than those (7 patients, 8.8%) reported in the SOC group (Table 2). No patients reported serious adverse events in the SOC group whereas 2 patients reported serious adverse events due to disease progression and upper respiratory infection. The case with upper respiratory infection had finished the 14-day treatment of HCQ and developed throat-drying and pharyngalgia without evidence of pneumonia on chest computed tomography during the extended follow-up period. The most common adverse events in the SOC plus HCQ group were

diarrhea, which was more frequent than that in the SOC group (10% versus 0%, P=0.004). HCQ was discontinued in one patient due to blurred vision and was adjusted to give a lower dose in one patient who reported thirst. These two adverse events were both transient with a period of 1-2 day

Discussion

Limitations

20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses

Generalisability

21 Generalisability (external validity, applicability) of the trial findings

Interpretation

22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

Other information

Registration

23 Registration number and name of trial registry

ChiCTR2000029868
http://www.chictr.org.cn/showprojen.aspx?proj=49524

Protocol

24 Where the full trial protocol can be accessed, if available

The pre-print says there is a protocol, but we have not been able to find it.

Funding

25 Sources of funding and other support (such as supply of drugs), role of funders

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