Hydroxychloroquine treatment in COVID-19: A descriptive observational analysis of 30 cases from a single center in Wuhan, China

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Abstract
Hydroxychloroquine (HCQ) garnered scientific attention in early February following publication of reports showing in vitro activity of chloroquine (CQ) against coronavirus disease 2019 (COVID-19). While studies are mixed on this topic, the therapeutic effect of HCQ or CQ still need more valid clinical evidence. In this descriptive observational study, we aimed to discuss the treatment response of HCQ in COVID-19 infected patients and 30 cases were included. The demographic, treatment, laboratory parameters of C-reactive protein (CRP) and interleukin-6 (IL-6) before and after HCQ therapy and clinical outcome in the 30 patients with COVID-19 were assessed. To evaluate the effect of mediation time point, we also divided these cases into two groups, patients began administrated with HCQ within 7 days hospital (defined as early delivery group) and 7 days after hospital (defined as later delivery group). We found that, the elevated IL-6, a risk factor in severe patients were reduced to normal level after HCQ treatment. More importantly, patients treated with HCQ at the time of early hospital recovered faster than those who treated later or taken as second line choose for their obvious shorter hospitalization time. In summary, early use of HCQ was better than later use and the effect of IL-6 and CRP level cannot be ruled out.

Keywords
ACE2, COVID-19, cytokine storms, hydroxychloroquine, SARS-CoV-2

1 | INTRODUCTION

In March 2020, WHO declared that the epidemic of new coronavirus pneumonia (coronavirus disease 2019 [COVID-19]) as a pandemic. Until the middle of April, the COVID-19 caused more than 170,000 death all around the word and the data is continuing to rise. However, there is no clear, effective and proven pharmacological treatment. In China of 6th versions of treatment guideline, chloroquine (CQ) was first introduced. In vitro studies have suggested that CQ, an immunomodulant drug traditionally used to treat malaria, is effective in reducing viral replication in other infections, including the severe acute respiratory syndrome (SARS)-associated coronavirus (CoV) and Middle East respiratory syndrome-coronavirus. As with the similar chemical structure and mechanism to CQ, hydroxychloroquine (HCQ) is suggested to be prefer for COVID-19 treatment due to its safer clinical profile.

Clinical investigation found that high concentration of inflammatory cytokines were detected in the plasma of severe and critically ill patients, suggesting that cytokine storm was associated with disease severity. Other than its direct antiviral activity, HCQ is a safe and successful anti-inflammatory agent that has been used extensively in autoimmune diseases and can significantly decrease the production of cytokines and, in particular, proinflammatory factors.
Interestingly, during the analyze of medical records of patients who treated with HCQ in our hospital, we found that patients treated with HCQ at the time of early admission seems to recover faster than those who treated later or taken as second line choose. In this descriptive observational study, we sought to analyze the clinical significance of HCQ medication point and evaluate its relationship with the disease progression in the patients with COVID-19 and to some extent, provide guidance for the clinical use.

2 | METHODS

For this descriptive observational, single-center analysis, we included patients discharged from 30 February to 30 March 2020, at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China). The medication duration of HCQ less than 5 days and the detection index cannot be counted were excluded. COVID-19 was diagnosed based on criteria issued by the National Health Commission of China. During hospitalization, patients with one of respiratory rate >30 breaths/min, SpO2 < 93% on room air, or PaO2/FiO2 < 300mm Hg, were classified as severe cases. Once respiratory failure occurs and mechanical ventilation is required, they were classified as critically ill cases and the others were classified as mild cases. All patients were anonymous. Patient records including clinical and laboratory data were extracted and used for analysis. The study was approved by the ethical committee of Huazhong University of Science and Technology.

In this analysis, patients were divided into two groups, patients began administrated with HCQ within 7 days admission and 7 days after admission.

3 | STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS, version 23.0. Continuous data were expressed as mean and standard deviation. For the continuous variables, the t test was employed to analyze the difference. Data are presented as median (min-max) or as the number and percentage, as appropriate. A two-sided P < .05 was considered statistically significant.

4 | RESULTS

Thirty patients identified as having COVID-19 and treated with HCQ more than 5 days were included in this study. The PRISMA chart for the included studies is showed in Figure 1. The dose of HCQ used in patients was 200 mg bid. As shown in Table 1, For all patients, the average age was 64.3 (33-86) years old, 53.3% (16 of 30) were male and 46.7% (14 of 30) were female. There were 11 (55.0%) male patients and nine (45.0%) female patients in later delivery group, mean age 64.5 ± 13 years (range, 33-86 years). Early delivery group included five (50%) male patients and five (50%) female patients, mean age 64.0 ± 13 years (range, 34-80 years). There was no significant difference in sex and age between the two groups.

In summary, most initial symptom of these patient include fever (22, 73.3%), cough (19, 63.3%), fatigue (7, 23.3%), distress/dyspnea (14, 46.7%), and diarrhea (6, 20%). Separately, there were similar ratio for symptom of fever (7, 70.0% vs 15, 75%), cough (7, 70.0% vs 12, 60.0%), fatigue (2, 20.0% vs 5, 25%), and distress/dyspnea (4, 40.0% vs 10, 50%) in early delivery group and later delivery group. For diarrhea, the later delivery group (6, 30%) is more than the early delivery group (0). For combined disease, most of these patients (19, 63.3%) were combined with diabetes, hypertension or others. There was no significant difference in symptom and coexisting conditions between the two groups.

Of them, 18 (60.0%) patients were moderately ill, 11 (36.7%) patients were severely ill and one (3.3%) patients were critically ill. Notably, a total of nine moderately ill patients progressed to severe illness, seven of which occurred in the later delivery group. For the mean duration from onset to admission, it should be noted that patients in later delivery group (12 days) were relatively shorter than

![FIGURE 1 Flow chart of the included studies. COVID-19, coronavirus disease 2019; CRP, C-reactive protein; HCQ, hydroxychloroquine](image-url)
the others in early delivery group (20 days). More importantly, the median length of hospitalization in early delivery group was 17 days, while the later delivery group was 28.5 days. There was significance between the time.

To further explore the effect of HCQ mediation point on pneumonia, we compared and analyzed the laboratory examination index of patients during different phase of hospitalization (Table 2). Comparing to later delivery group, patients with early delivery HCQ led to more rapid normalization of elevated interleukin-6 (IL-6). In early delivery group, IL-6 declined from 31.0 to 14.52 to 4.48 by 53.2% and 85.5% reduction rate in 7 and 14 days after mediation of HCQ. However, in later delivery group, the reduction rate in 7 and 14 days was 32.3% and 20.05% from 15.11 to 10.24 and 12.08, with a lower initial value. Differently, C-reactive protein (CRP), a nonspecific inflammatory marker in clinic, in later delivery group were declined faster than early delivery group, from 19.27 to 5.93 to 4.58 in later delivery group and from 33.0 to 18.12 to 9.67 in early delivery group. Importantly, the CRP in every patients in early delivery group tend to be a significant downtrend through the 14 days after HCQ treatment while still two patients rise again in later delivery group. For tumor necrosis factor α (TNF-α), there were no significant difference before and after HCQ treatment in both groups.

### TABLE 1  Characteristics of patients in this trial

| Characteristics             | All patients (N = 30) | Early delivery group (N = 10) | Later delivery group (N = 20) | P value |
|-----------------------------|-----------------------|------------------------------|-------------------------------|---------|
| Age, y                      | 64.3 ± 13             | 64.0 ± 13                    | 64.5 ± 13                    | .932    |
| Male, no. (%)               | 16 (53.3)             | 5 (50.0)                     | 11 (55.0)                    | .804    |
| Symptoms, no. (%)           |                      |                              |                              |         |
| Fever                       | 22 (73.3)             | 7 (70.0)                     | 15 (75.0)                    | .770    |
| Cough                       | 19 (63.3)             | 7 (70.0)                     | 12 (60.0)                    | .592    |
| Fatigue                     | 7 (23.3)              | 2 (20.0)                     | 5 (25.0)                     | .760    |
| Distress/dyspnea            | 14 (46.7)             | 4 (40.0)                     | 10 (50.0)                    | .605    |
| Diarrhea                    | 6 (20.0)              | 0 (0)                        | 6 (30.0)                     | .053    |
| Disease severity, no. (%)   |                      |                              |                              |         |
| Moderate                    | 18 (60.0)             | 6 (20.0)                     | 12 (30.0)                    | 1.00    |
| Severe                      | 11 (36.7)             | 4 (80.0)                     | 7 (65.0)                     | .789    |
| Critically ill              | 1 (3.3)               | 0                             | 1 (5)                        | .489    |
| Coexisting conditions, no. (%) | 19 (63.3)             | 7 (70.0)                     | 12 (60.0)                    | .607    |
| Diabetes                    | 3 (10.0)              | 1 (10.0)                     | 2 (10.0)                     | 1.00    |
| Hypertension                | 15 (50.0)             | 5 (50.0)                     | 10 (50.0)                    | 1.00    |
| Others                      | 8 (26.7)              | 4 (40.0)                     | 4 (20.0)                     | .243    |
| Medication time of HCQ      | 9.3 ± 2.8             | 9.4 ± 3.3                    | 9.2 ± 3.2                    | .850    |
| Duration from onset to admission | 15 ± 11.9             | 20 ± 14.5                    | 12 ± 9.5                     | .121    |
| Progressed to severe illness| 9                     | 2                             | 7                             | .490    |
| Median length of hospitalization | 24.5                 | 17                            | 28.5                          | .002    |

Note: Early delivery group, patients treated with HCQ within 7 d of admission; Early delivery group, patients treated with HCQ after 7 d of admission.
Abbreviation: HCQ, hydroxychloroquine.

### TABLE 2  Inflammatory factor change during different time of HCQ treatment

| IL-6, d       | All patients (N = 30) | Early delivery group (N = 10) | Later delivery group (N = 20) | P value |
|---------------|-----------------------|------------------------------|-------------------------------|---------|
| −7-0          | 21.41 ± 30.43         | 31.10 ± 44.64                | 15.11 ± 15.60                 | .03     |
| 0-7           | 10.38 ± 11.71         | 14.52 ± 16.97                | 10.24 ± 7.28                  | .97     |
| 7-14          | 6.81 ± 4.84           | 4.48 ± 2.37                  | 12.08 ± 4.94                  |         |
| P value       | .03                   | .97                          | .97                           |         |

| TNF-α, d      | All patients (N = 30) | Early delivery group (N = 10) | Later delivery group (N = 20) | P value |
|---------------|-----------------------|------------------------------|-------------------------------|---------|
| −7-0          | 10.25 ± 4.19          | 11.86 ± 6.42                 | 9.58 ± 2.89                   |         |
| 0-7           | 9.77 ± 4.48           | 10.27 ± 5.80                 | 9.65 ± 4.25                   | P value |
| 7-14          | 9.96 ± 3.65           | 9.81 ± 5.02                  | 10.88 ± 1.89                  | .97     |
| P value       | .97                   | .97                          | .97                           |         |

| CRP           | All patients (N = 30) | Early delivery group (N = 10) | Later delivery group (N = 20) | P value |
|---------------|-----------------------|------------------------------|-------------------------------|---------|
| −7-0          | 23.75 ± 31.57         | 33.0 ± 45.2                  | 19.27 ± 22.41                 | .03     |
| 0-7           | 8.98 ± 18.33          | 18.12 ± 31.84                | 5.93 ± 8.41                   |         |
| 7-14          | 6.10 ± 11.43          | 9.67 ± 17.37                 | 4.58 ± 5.80                   | P value |
| P value       | .03                   | .03                          | .03                           |         |

Abbreviations: CRP, C-reactive protein; HCQ, hydroxychloroquine; TNF-α, tumor necrosis factor α.
In early delivery group, two (20%) patients were detected with lymphocytopenia in admission and all of them recover to normal lever in 6 days, while the average recover time in later delivery group was 16.5 days and two patients remained lower than normal lever on discharge. Similarly, the alanine transaminase (ALT) (2, 20%) and aspartate aminotransferase (AST) (1, 10%) elevation, makers of hepatocellular damage recovered to normal level for 5 and 17 days in early delivery group. With 9 (45%) elevated ALT and 3 (15%) patients with AST, the average recover time was 15.7 and 8.5 days (Table 3).

5 | DISCUSSION

COVID-19, the novel coronavirus also named SARS-CoV-2, shares about 80% of the genetic sequence with SARS-CoV.6, 7 Additionally, COVID-19 shares the same cell entry receptor, angiotensin-converting enzyme 2 (ACE2), with SARS-CoV.8 HCQ and CQ inhibit receptor binding and membrane fusion, two key steps that are required for cell entry by coronaviruses. CQ has been shown to exert an antiviral effect during preinfection and postinfection conditions by interfering with the glycosylation of ACE2 (the cellular receptor of SARS-CoV) and blocking virus fusion with the host cell.9, 10 On 31st March, medRxiv.org published data of the first completed randomized clinical trial in Wuhan investigating the efficacy of HCQ in patients with COVID-19. The clinical research included 62 patients, and reported significant difference in time to clinical recovery and radiologic findings between the groups. Despite this, the evidence regarding its effect remains limited.10 A retrospective analysis of 1061 cases reported that administration of the HCQ + AZ combination before COVID-19 complications occur is safe and associated with a very low fatality rate in patients.11 However, another retrospective study of 1317 cases reported that no significant difference was found in terms of rates of usage of HCQ or CQ between those who were found positive for SARS-CoV-2 and those who were found negative.12 On the whole, the exact effect is highly controversial.

In this study, we evaluated the effect of HCQ therapy in patients with COVID-19 in real life. Our study showed that the early use of HCQ can effectively shorten the hospitalization time than those patients treated later or taken as second line choose. Furthermore, the proportion from severe converted to critically ill were also lower than later used ones. It’s noting that, patients in later delivery group also taken other antiviral drugs such as abidor or lopinavir/ritonavir before HCQ treatment. Lymphocytopenia count reduction, one of the most typical characteristics of COVID-19 also tend to behaved stronger recovery ability in early used patients. This phenomenon also reflected on the recover of liver damage, which may own to the antiviral effect of HCQ that delayed the attack of coronavirus on liver.

To be different from other antiviral drugs, HCQ possess a good ability of regulating inflammatory cytokines including IL-1, IL-6, and TNF.5, 13 Evidence suggests that patients developed into critical illness also accompanied by a sharp increase of the cytokine especially IL-6.14, 15 So early monitoring and intervention of cytokine turned to be particularly important. And our study results excluded those patients in combined use of corticosteroids. In consistent our study, HCQ can effectively decrease the elevated IL-6 and CRP level in all 30 patients, and the early treatment group tend to be decreased more efficiently.

Based on our preliminary research, the potential of HCQ in the treatment of COVID-19 has been partially confirmed. We speculate that HCQ is a promising practice for COVID-19 on account of no better choice. And the antiviral effect may be partly depends on it’s ability to regulate inflammatory cytokines. More importantly, patients may benefit more from early use of HCQ.

However, due to our small number of cases and observation with sufficient number of patients with COVID-19, basic research is still needed to clarify its specific mechanism and to continuously optimize the treatment plan.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

JL and DL were responsible for the design of the study and revised the final manuscript. YL contributed to the acquisition, analysis and interpretation of data. HX is responsible for summarizing all data and wrote the draft. All data were checked by PL, XL, and LQ.

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### TABLE 3  Change of main feature makers before and after treatment

|                         | Early delivery group (N = 10) | Later delivery group (N = 20) |
|-------------------------|-------------------------------|-------------------------------|
|                         | On admission, no. (%)         | Average time to recovery, d   | On admission, no. (%)         | Average time to recovery, d   |
| Lymphocyte count reduced| 2 (20%)                       | 6 ± 1                         | 8 (40%)                       | 16.5 ± 9                      |
| ALT elevated            | 2 (20%)                       | 5 ± 0                         | 9 (45%)                       | 15.7 ± 9                      |
| AST elevated            | 1 (10%)                       | 17 ± 0                        | 3 (15%)                       | 8.5 ± 1.8                     |

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase.
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