Hydroxychloroquine/ Chloroquine in Patients With COVID-19 in Wuhan, China: A Retrospective Study

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Abstract

Background: We aim to evaluate the treatment value and safety of hydroxychloroquine (HCQ)/ chloroquine (CQ) in COVID-19.

Methods: We retrospectively reviewed the medical charts of patients with COVID-19 admitted to an inpatient ward in Wuhan from 2020. 02. 08 to 2020. 03. 05. Patients with HCQ/ CQ and age, gender, disease severity matched ones without HCQ/ CQ were selected at a 1:2 ratio. The clinical, laboratory and imaging findings were compared between these two groups. The multivariate linear regression analysis was performed to identify the factors that might influence patients' virus shedding periods (VSPs).

Results: A total of 14 patients with HCQ/ CQ and 21 matched were analyzed. The HCQ/CQ treatment lasted for an average of 10.36±3.12 days. The VSPs were a little longer in the HCQ/ CQ treatment group (26.57±10.35 days vs. 19.10±7.80 days, *P*=0.020). There were 3 patients deceased during inpatient period, two patients were with HCQ/ CQ treatment (*P*=0.551). In the multivariate linear regression analysis, disease durations at admission (t=3.643, *P*=0.001) and HCQ/CQ treatment (t=2.637, *P*=0.013) were independent parameters for patients' VSPs prediction. One patient with CQ had recurrent first-degree atrioventricular block (AVB) and obvious QTc elongation, another one complained about dizziness and blurred vision which disappeared after CQ discontinuation. One patient with HCQ had transient AVB.

Conclusions: The HCQ/ CQ administration is not related to neither less mortality cases nor shorter VSPs. HCQ rather than CQ is relative safe and tolerable.

Background

Since December 2019, the outbreak of severe acute respiratory syndrome coronary virus 2 (SARS-Cov-2) infection has swept over the whole world in a few months. By May 5, 2020, more than 3.5 million cases have been confirmed and the death toll raises to over 250 thousand, globally[1]. The manifestation spectrum of SARS-Cov-2 infection is a complex of disease, corona virus disease-2019 (COVID-19), which is composed of not only pneumonia, but also heart/ kidney/ liver injury, and coagulopathy, etc.[2, 3].

Due to lacking of specific anti-virus drugs, the management of COVID-19 is still challenging. The results of two randomized controlled clinical trials of the promising anti-virus agents, i.e. Lopinavir/ Ritonavir and Remdesivir, showed that these drugs were not that effective as we had expected in Chinese patients with COVID-19[4, 5]. Because several inflammatory factors are observed dramatically increasing, overreactive immunopathological mechanisms are surmised to be responsible for multiple organ damage in COVID-19[6]. Some researchers hypothesize that patients with COVID-19 might benefit from some anti-rheumatic drugs, such as hydroxychloroquine (HCQ)/ chloroquine (CQ) and tocilizumab (TCZ),for their effects on immune regulation and suppression[7].

CQ is a traditional anti-malaria drug. As a derivate of CQ, HCQ is less toxic to retina and heart and is the background treatment in systemic lupus erythematosus (SLE)[8]. Yu and colleagues reported that HCQ

treatment could reduce serum interleukin-6 (IL-6) levels in patients with COVID-19[9]. Except for the anti-inflammatory activity, HCQ/ CQ has potential anti-virus effects [10, 11]. Liu *et al* reported that both HCQ and CQ could inhibit SARS-Cov-2 replication and entering into cells in vitro[12]. HCQ/ CQ has already been recommended by the Chinese and the Shanghai management guideline for COVID-19[13, 14]. Furthermore, both the US Food and Drug Administration and the Indian Council for Medical Research have permitted the empiric use of HCQ in COVID-19 patients[15, 16]. With the surging demands for HCQ in COVID-19, some patients under long-term HCQ treatment for autoimmune disease, such as SLE, were threatened by HCQ shortage. Therefore, some rheumatologists campaigned for using HCQ rationally in COVID-19 in which the data and evidence were limited and inconclusive[17]. Unfortunately, the treatment effect of HCQ/CQ in COVID-19 remains equivocal by far.

During the outbreak of COVID-19, a multidisciplinary medical team from Beijing Hospital took in charge of an independent inpatient ward to manage the COVID-19 patients in the Sino-French New City Branch of Tongji Hospital in Wuhan, China. Some of the patients took HCQ/ CQ during their inpatient period. We performed the following retrospective analysis to evaluate the potential treatment value and safety of HCQ/ CQ in COVID-19 management.

Methods

Patients

Medical charts of patients admitted to one inpatient wards in Wuhan from February 08, 2020 to March 05, 2020 were reviewed. Due to the potential while uncertain treatment effects of TCZ on COVID-19, patients receiving TCZ were excluded from the study. Finally, patients with HCQ/ CQ treatment and age, gender and disease severity matched patients without HCQ/CQ treatment were analyzed. The matching process was performed by the SPSS software (version 26.0) and the PS matching package with a 1:2 ratio. The Caliper value was set 0.2 in the matching process.

Methods

The demographic data, clinical manifestations, comorbidities, laboratory findings and image involvement patterns assessed by computed tomography (CT) were carefully and thoroughly collected from medical charts.

The disease severity was classified as mild, general, severe and critically severe according to the Chinese management guideline for COVID-19 (Supplement) [13]. The CURB-65 severity score was calculated according to the standard definition[18]. The estimated glomerular filtration rate (eGFR) was calculated via the CKD-EPI equation [19]. The concurrent respiratory pathogen infections, including type A influenza, type B influenza, mycoplasma pneumoniae, chlamydia pneumoniae, respiratory syncytial virus, adenovirus, parainfluenza virus and legionella pneumophilia infections, were confirmed by the presence of immunoglobulin M to specific pathogens with the enzyme-linked immunosorbent assay.

The nasopharyngeal swabs were taken based on physicians' judgement on clinical purposes. And the ribonucleic acids (RNAs) of SARS-Cov-2 collected by swabs were tested with the polymerase chain reaction (PCR) method[20]. The virus shedding periods (VSPs) were defined as from symptoms onset to the first day of the consecutive negative PCR results before discharging (Supplement). The drugs for treating COVID-19 purposes taken by the patients were recorded and analyzed since the outpatient department. With corticosteroids (GCs) treatment was defined as exposure to systemic GCs. The dosage of GCs was converted to methylprednisolone (MP) (prednisone: methylprednisolone=1.25:1). The new symptoms and complains after HCQ/CQ treatment were carefully recorded.

Statistical Analysis

Statistics analyses were conducted by the SPSS software (version 26.0). Numerical data was expressed as mean ± standard deviation (SD) or quantiles (Q1: first quantile; Q2: second quantile; Q3: third quantile), while categorial data was expressed as numbers. Numerical data was compared with the independent sample *t*-test. Categorical data was compared with the chi-square or the Fisher exact test, as appropriate. The multivariate linear regression analysis was performed to identify the factors that might influence patients' VSPs. Virus shedding period was set as the dependent variable. Continuous or dichotomous independent variables, such as disease duration at admission, with or without HCQ/ CQ treatment, dosage of GCs *et al.* selected according to clinical judgment, were analyzed in the regression formulation with the stepwise method. In the multivariate linear regression analysis, MP dosage in patients without GCs was recorded as zero. All probabilities were 2-sided, and P values< 0.05 were considered to be statistically significant.

Results

From February 8, 2020 to March 5, 2020, a total of 63 COVID-19 patients were admitted to our ward. All the patients were confirmed with SARS-Cov-2 infection via PCR. Except for 5 patients who received TCZ treatment, 58 patients were treated by non-biological drugs. Among the 58 patients, 11 patients and 3 patients were treated by HCQ and CQ, respectively. After age, gender and disease severity matching, 21 patients without HCQ/ CQ treatment were selected and analyzed (Figure 1).

For the 35 patients, the average age was 62.20±11.88 years old and male were dominant. The span from symptoms onset to admission were 13.00±7.24 days. Although fever was common at disease onset (77.14%), fever was observed in only 20% of patients at admission. Twenty-six patients (74.28%) had at least a comorbidity, most of which was hypertension. In the 35 patients, 21 of them suffered from multiple pathogen infections in addition to SARS-Cov-2, and influenza was the most common concomitant infectious disease (57.14%) (Table 1). Procalcitonin elevation was recorded in 9 patients which indicating bacterial infection. Ferritin elevation was observed in 34 out of the 35 patients, while IL-6 elevation in 17 patients. Serum IL-1β, IL-2R, IL-8, IL-10 and tumor necrosis factor-α (TNF-α) levels were tested in 14 patients. As a result, serum IL-1β, IL-2R, IL-8, IL-10 and TNF-α elevation were detected in 1, 8, 2, 0 and 6 patients, respectively.

Twenty-two patients took anti-influenza drugs, i.e. oseltamivir or arbidol or both. Most patients (94.28%) received traditional Chinese medicine (TCM) treatment. And the types of anti-virus agents were similar between these two treatment groups (Table 2). Antibiotics were concomitantly administrated with HCQ/ CQ in 17 patients. And moxifloxacin was the most commonly used antibiotic (13/17). HCQ/ CQ was not administrated in combination with azithromycin in our patients. GCs were administrated in 12 (34.28%) patients. There were more patients taking GCs in the HCQ/ CQ treatment group (57.14% vs. 19.05%, *P*=0.031) (Table 2). The detailed information of GCs was available in 11 patients. Patients took GCs at a median of 14 days after symptoms onset (Q1: 12 days, Q3: 19 days). The GCs treatment lasted for a median of 6 days (Q1: 4 days, Q3: 7 days). And the median cumulated dosage of GCs was 280mg (MP or equivalent, Q1: 160mg, Q3: 480mg).

The dosage of HCQ was either 200mg (n=5) or 400mg (n=6) twice a day. And the dosage of CQ was 500mg (n=3) twice a day (Figure 2). The average disease duration before HCQ/ CQ initiation was 21.00±5.98 days (Q1: 16.50 days; Q2: 22.00 days; Q3: 26.25 days). The HCQ/CQ treatment lasted for an average of 10.36±3.12 days (Q1: 10.75 days; Q2: 11.00 days; Q3: 12.00 days). Only 1 of the 14 patients received HCQ treatment after virus shedding. The SARS-Cov-2 RNAs turned to be undetectable after an average of 7.31±6.05 days (Q1: 3.00 days; Q2: 5.00 days; Q3: 9.50 days) since HCQ/ CQ initiation in the rest 13 patients. The average VSPs were22.09±9.51 days, which was a little longer in the HCQ/ CQ treatment group (26.57±10.35 days vs. 19.10±7.80 days, *P*=0.020). However, the average swab testing intervals didn't differ between patients with and without HCQ/ CQ treatment statistically (5.77±1.36 days vs. 6.34±1.80 days, *P*=0.346) (Table 2).For the patients whose VSPs were longer than 22 days, the differences of average VSPs in patients with and without HCQ/CQ treatment were not statistically different (31.75±9.72 days/n=8 vs. 28.67±3.56 days/n=6, *P*=0.477). In the multivariate linear regression analysis, disease durations at admission (t=3.643, *P*=0.001) and HCQ/CQ treatment (t=2.637, *P*=0.013) were independent parameters for patients' VSPs prediction. The linear regression formulation was listed as following. Meanwhile, neither GCs treatment (t=-0.313, *P*=0.772) nor MP dosage (t=-0.706, *P*=0.766) was related to VSPs statistically. And after treatment, acute exudation lesions were largely absorbed in pulmonary CT (Figure 3). There were 3 patients deceased during inpatient period in our study, and two patients were with HCQ/ CQ treatment (*P*=0.551).

Virus shedding period (days) = 10.039+0.697×disease durations at admission+7.140×with or without HCQ/CQ treatment (0, if without HCQ/CQ treatment; 1, if with HCQ/CQ treatment).

Electrocardiographs (ECGs) were conducted at least once in 12 out of the 14 patients (9 patients with HCQ treatment, and 3 patients with CQ treatment). First-degree atrioventricular block (AVB) was recorded in 2 patients. One patient was in each treatment group. No second or third AVB was noticed. First-degree AVB disappeared after HCQ discontinuation. However, the first-degree AVB disappeared after CQ discontinuation and reoccurred 10 days later. The QTc interval longer than 500 milliseconds was recorded in the identical patient after CQ treatment. Another patient with CQ treatment complained about dizziness and blurred vision. And the symptoms disappeared after CQ being withdrew. No patient complained about new symptoms during HCQ treatment.

Discussion

The conventional anti-malaria drug HCQ/ CQ was regarded as a promising agent once again for its dual function in inflammation modulation and virus inhibition since the beginning of the pandemic. Although lacking of good clinical evidence, HCQ/CQ was recommended by several countries' health administrations for COVID-19 treatment [13, 15, 16]. However, in the present study, we found out that HCQ/CQ was related to neither less mortality cases nor shorter VSPs.

In the several past decades, several researchers have confirmed the anti-virus effects of HCQ/ CQ in vitro and in vivo [8, 10, 11]. HCQ/ CQ could prevent the coronavirus from entering the host cells by interfering with endosomal acidification essential for membrane fusion. However, coronavirus could invade the host cells via the alternative non-endosomal pathway which is not blocked by HCQ/ CQ [21]. CQ could also interfere with virus post translation modification by PH modulation[22]. At the meantime, HCQ/ CQ shows potential treatment value for COVID-19 by acting on host cells directly. HCQ/ CQ could inhibit glycosylation of the cell membrane protein angiotensin converting enzyme-2, to which the SARS-Cov-2 is attaching [23]. HCQ/ CQ could downregulate the toll like receptor (TLR) on activated immune cells and block TLR signal transduction, and prohibit several inflammatory factors secretion, such as IL-6[9, 24].

By far, a few clinical studies have analyzed the effects of HCQ/ CQ in COVID-19 treatment. Gautret and colleagues reported that most of patients with COVID-19 were virologicaly cured 6 days after HCQ initiation, especially those being treated in combination with azithromycin[25]. However, Gautret *et al*'s study had a relatively small sample size and two selection bias. First, the patients in the treatment and control group were not from the same medical center. Second, the virus loads in the HCQ treatment were lower compared to those in the control group without HCQ treatment at inclusion, indicating that the patients in the HCQ treatment group were at a later disease phase and were more likely to get disease selflimitation [26]. In a randomized clinical trial (RCT), Chen and colleagues reported that after being treated by HCQ with a dosage of 400mg per day for 5 days, the clinical and radiological manifestation improve rates were higher in the HCQ treatment group (80.6% vs. 54.8%)[27]. In another randomized study with mild to moderate COVID-19 patients, Tang *et al* noticed that the rates of negative conversion of SARS-Cov-2 were similar in patients with and without HCQ treatment (85.4% vs. 81.3%)[28].In a retrospective study, Mallat and colleagues reported that HCQ treatment was an independent factor for longer VSPs. The median time from confirmed positive to negative nasopharyngeal swab results were 17 days in the HCQ treatment group and 10 days in the control group (P=0.023). It is worth noting that HCQ was administrated at an early stage of the disease course in Mallat's study[29].

In our study, the number of mortality cases were not statistically different between patients with and without HCQ/ CQ treatment. The result might be ascribed to several factors. Firstly, HCQ/ CQ was administrated in a later phase of the disease. In some patients, we used HCQ/ CQ due to persistent SARS-Cov-2 RNA positivity for salvage treatment purposes. It is widely accepted that anti-virus should be taken as early as possible in influenza and corona virus infection [5, 30]. Secondly, the half-life of HCQ/ CQ is as long as 40-60 days due to the large distribution volume in the blood. And it usually takes several weeks

before HCQ/ CQ reaching maximal activity[31]. In COVID-19, HCQ/ CQ treatment only lasted for an average of 10 days. Therefore, HCQ/ CQ might be withdrew before it worked. Thirdly, for ethic factors concern, several kinds of drugs, such as GCs, ribavirin, TCM *et al.*, were administrated empirically and anecdotally at the same time. These concomitantly taken drugs might have covered up the potential treatment values of HCQ/ CQ on COVID-19. Fourthly, due to the small sample, the statistical power was not able to different the mortality rates in different treatment groups. Fifthly, it might be true that HCQ/ CQ didn't have any effect on lowering mortality rates in COVID-19.

The average VSPs were similar to those reported in the previous study[32]. After the multivariate linear regression analysis, we identified that disease durations at admission and HCQ/CQ treatment were independent parameters related to patients' VSPs, indicating patients might get better prognosis if being well treated earlier. Though HCQ/ CQ treatment was an independent parameter for longer VSPs, we should bear in mind that in some cases HCQ/ CQ was administrated for salvage purpose due to persistent SARS-Cov-2 RNA positivity. Furthermore, VSPs were not statistically different between patients with longer VSPs (VSPs>22 days) in these two treatment groups. It was interesting that more patients took GCs with HCQ/ CQ treatment. However, after being adjusted by other confounders, neither GCs treatment nor GCs dosage was an independent parameter for VSPs prediction. Actually, the effect of GCs in COVID-19 remains controversial and disputable. In SARS and Middle East Respiratory Syndrome (MERS), GCs administration is related to delayed virus RNA clearance [33, 34]. However in the SARS or MERS studies were either taking rather high dose of GCs[33] or were critically ill[34]. On the other hand, patients with SARS of influenza might benefit from low-to-moderate GCs[35, 36]. In the present study, our patients took a low-to-moderate dose of GCs during a relative short period of time. As a result, we didn't find correlations between GCs treatment and prolonged VSPs. A team consist of front-line physicians from the Chinese Thoracic Society suggested that after careful benefits and harms evaluation short term use of low-to-moderate dose of GCs could be prudently administrated in patients with COVID-19[37].

One of the major concerns for HCQ/ CQ treatment in COVID-19 is the side effect. HCQ/ CQ related retinopathy always occurs after months even years of HCQ/ CQ administration[31]. Meanwhile, HCQ/ CQ related arrythmia might be lethal. And the risk is rising together with other arrhythmogenic drugs, such as azithromycin[31]. Borba *et al.* reported that high dose of CQ (600mg twice daily) was related to prolonged QTc interval and should not be recommended in critically ill patients[38]. Lane and colleagues reported that HCQ monotherapy was safe in COVID-19. However, HCQ in addition to azithromycin might result in heart failure and cardiovascular mortality [39]. Tang *et al.* found that HCQ was safe in patients with COVID-19, the most common adverse effects were diarrhea and vomiting[28]. Similarly, HCQ was safe and tolerable in our patients. On the contrast, among the three patients with CQ treatment, one patient complained about dizziness and blurred vision and another patient had recurrent first-degree AVB and obvious QTc elongation.

The major limitation of the study was the relatively small sample size. The sample size of the patients without HCQ/ CQ was expected to be 28. However, after age, gender and disease severity matching, only 21 patients without HCQ/ CQ treatment met the matching criteria and were finally selected. Secondly,

some patients were treated with HCQ/ CQ for persistent SARS-Cov-2 RNA positivity. These patients, per se, are refractory. Therefore, selection bias exists in our patients. Thirdly, due to the retrospective nature of the study, although we found out that HCQ/ CQ treatment was related to longer VSPs, we couldn't tell whether HCQ/ CQ prolonged SARS-Cov-2 RNA clearance or not.

Conclusion

In summary, we identify that the HCQ/ CQ administration is not related to neither less mortality cases nor shorter VSPs at later phase of COVID-19. More studies are needed to explore whether HCQ/ CQ treatment would lead to SARS-Cov-2 RNA clearance delay or not. And HCQ rather than CQ is a safe and tolerable drug in COVID-19 patients.

Abbreviations

HCQ: hydroxychloroquine; CQ: chloroquine; SARS-Cov-2: severe acute respiratory syndrome coronary virus 2; COVID-19: corona virus disease-2019; SLE: systemic lupus erythematosus; IL-6: interleukin-6; CT: computed tomography; eGFR: estimated glomerular filtration rate; RNAs: ribonucleic acids; PCR: polymerase chain reaction; VSPs: virus shedding periods; GCs: corticosteroids; MP: methylprednisolone; SD: standard deviation; TNF-α: tumor necrosis factor-α; TCM: traditional Chinese medicine; ECGs: Electrocardiographs; AVB: atrioventricular block; TLR: toll like receptor; RCT: randomized clinical trial; MERS: Middle East Respiratory Syndrome.

Declarations

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Declarations

Not applicable.

Authors contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. YC and CH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AL, YC, XW, XX, MG and CH designed this study initially. ZC, JH and YM were responsible for data acquisition. ZC and AL analyzed and interpreted the data. ZC and AL drafted the main manuscript of the article.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the institutional review board of Beijing Hospital (approval letter number: 2020BJYYEC-084-01). Informed consent has been obtained from all participants.

Consent for publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests to disclose.

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Tables

Table 1. Clinical characteristics, laboratory and imaging findings of the 35 patients at admission.

	Total (n=35)	With HCQ/CQ (n=14)	Without HCQ/CQ (n=21)	*P* value
Age	62.20±11.88	61.00±13.00	63.00±11.33	0.633
Male	23	10	13	0.721
Disease duration (days)	13.00±7.24	13.00±7.14	13.00±7.49	1.000
Clinical manifestation at beginning				
Fever	27	10	17	0.685
Fatigue	25	11	14	0.704
Cough	26	12	14	0.262
Diarrhea	8	3	5	1.000
Myalgia/ arthralgia	10	7	3	0.053
Fever at admission	7	2	5	0.676
Comorbidities				
Hypertension	13	7	6	0.199
Diabetes mellites	5	2	3	1.000
Carcinoma*	5	3	2	0.369
Stroke	1	1	0	0.400
Coronary artery disease	2	1	1	1.000
Lung disease**	6	1	5	0.366
HBV infection	7	3	4	1.000
Disease severity status				
General	19	7	12	0.678
Severe/ Critical	16	7	9	
CURB-65 score				
0	15	6	9	1.000
1-5	20	8	12	
Laboratory results				
WBC ($x10^9$/ L)	6.13±2.45	6.27±2.96	6.05±2.12	0.801
	4.33±2.38	4.68±2.88	4.10±2.01	0.490

Neu (x10^9/ L)				
Lym (x10^9/ L)	1.08±0.52	1.05±0.56	1.09±0.50	0.828
Neu/ Lym	5.27±4.31	6.16±5.13	4.69±3.67	0.329
Hb (g/L)	123.17±18.43	126.14±19.22	121.19±18.08	0.444
PLT (x10^9/ L)	266.37±111.96	283.86±110.58	254.71±114.04	0.459
ALT (U/ L)	33.14±28.69	27.00±21.31	37.24±32.56	0.308
AST (U/ L)	32.11±20.96	27.00±13.72	35.52±24.37	0.244
Alb (g/ L)	33.26±5.60	31.94±6.51	34.14±4.87	0.260
LDH (U/ L)	282.69±126.59	310.00±130.40	264.48±123.78	0.304
eGFR (ml/ min/ 1.73m^2)	89.33±15.88	86.17±12.15	91.43±17.92	0.345
≥90 ml/ min/ 1.73m^2	20	7	13	0.486
≤90 ml/ min/ 1.73m^2	15	7	8	
Fibrinogen (g/L)	5.17±1.59	5.82±1.19	4.74±1.66	***0.045***
	Total (n=35)	With HCQ/CQ (n=14)	Without HCQ/CQ (n=21)	*P* value
(Continued from previous page)				
D-Dimer (ug/ml FEU)	3.63±5.42	4.30±6.65	3.18±4.54	0.556
≥1.0 ug/ml FEU	21	8	13	0.778
≤1.0 ug/ml FEU	14	6	8	
NT-pro-BNP (ug/mL)	253.20±346.51	318.29±520.19	209.81±152.60	0.372
cTnI (pg/mL)	9.11±9.51	8.43±9.38	9.56±9.79	0.736
ESR (mm/h) (n)	47.75±26.74 (32)	58.62±19.90 (13)	40.32±28.70 (19)	0.056
hsCRP (mg/ L)	33.89±38.61	31.47±24.06	35.50±46.39	0.767
Procalcitonin (ng/ mL)	0.17±0.46	0.10±0.08	0.21±0.60	0.507
≥0.1 ng/mL	9	5	4	0.432
≥0.1 ng/mL	26	9	17	
Ferritin (ug/ L) (n)	819.36±628.02 (31)	689.45±494.53 (13)	913.18±707.92 (18)	0.336
IL-6 (ug/ mL) (n)	14.49±15.62	13.28±9.27 (13)	15.37±19.19	0.721

	(31)		(18)	
Other respiratory pathogen infection[#]	21	10	11	0.260
Imaging findings				
GGO	30	14	16	0.069
Consolidation	19	7	12	0.678
Bilateral pulmonary infiltration	34	14	20	1.000
Interstitial changes	17	7	10	0.890
Hydrothorax	7	1	6	0.203

* Including carcinoma in the stomach (n=2), urinary bladder (n=1), bone (n=1) and breast (n=1); ** lung disease refers to chronic obstructive lung disease (n=3), emphysema (n=2), bronchiectasis (n=1), lung fibrosis (n=1) and bullae (n=1); # other concurrent respiratory pathogen infection with a specific serum immunoglobulin M positive confirmed by the enzyme-linked immunosorbent assay includes type A influenza (n=18), type B influenza (n=2), mycoplasma pneumoniae (n=2) and chlamydia pneumoniae (n=1). WBC□white blood cell; Neu: neutrophil; Lym: lymphocyte; Hb: hemoglobulin; PLT: platelet; ALT: alanine transaminase; AST: oxaloacetic transaminase; LDH: lactate dehydrogenase; eGFR: estimated glomerular filter rate; NT-pro-BNP: N-terminal pro-Brain Natriuretic Peptide; cTnI: cardiac troponin I; ESR: erythrocyte sedimentation rate; hsCRP: high sensitivity C reactive protein; IL-6: interleukin-6; GGO: ground glass opacity; HCQ: hydroxychloroquine; CQ: chloroquine.

Table 2. Treatment and outcomings of the 35 patients.

	Total (n=35)	With HCQ/CQ (n=14)	Without HCQ/CQ (n=21)	*P* value
Treatment				
Antivirus agents				
Ribavirin	9	4	5	1.000
Lopinavir/ Ritonavir	4	1	3	0.635
Oseltamivir	18	8	10	0.581
Arbidol	10	6	4	0.151
TCM	33	14	19	0.506
Types of antivirus agents	2.11±0.93	2.36±0.75	1.95±1.02	0.213
Corticosteroids	12	8	4	***0.031***
IVIG	9	4	5	1.000
Antibiotics	22	10	12	0.392
Anticoagulant	8	3	5	1.000
Virus shedding period (days)*	22.09±9.51	26.57±10.35	19.10±7.80	***0.020***
Swab testing times	3.81±2.04	5.15±2.38	2.89±1.10	***0.001***
Consecutive swab testing negative times before discharging	3.03±1.23	3.23±1.42	2.89±1.10	0.457
Swab testing interval (days)	6.10±1.63	5.77±1.36	6.34±1.80	0.346
Outcomings				
Discharged	32	12	20	0.551
Deceased	3	2	1	

TCM: traditional Chinese medicine; IVIG: intravenous immune globulin; HCQ: hydroxychloroquine; CQ: chloroquine.

Figures

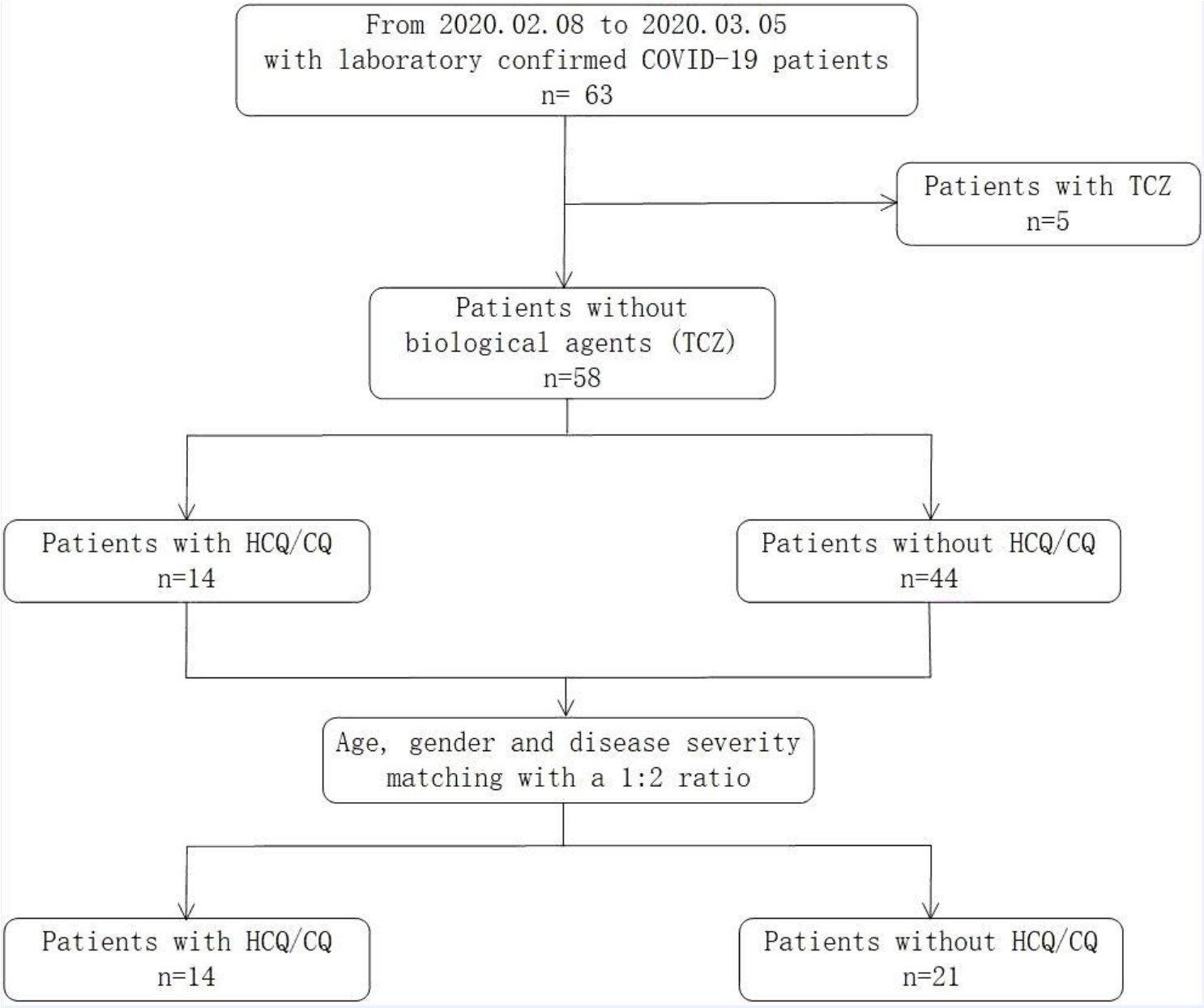

Figure 1

The flow diagram of patient selection in the present study. COVID-19: corona virus disease-2019; TCZ: tocilizumab; HCQ: hydroxychloroquine; CQ: chloroquine.

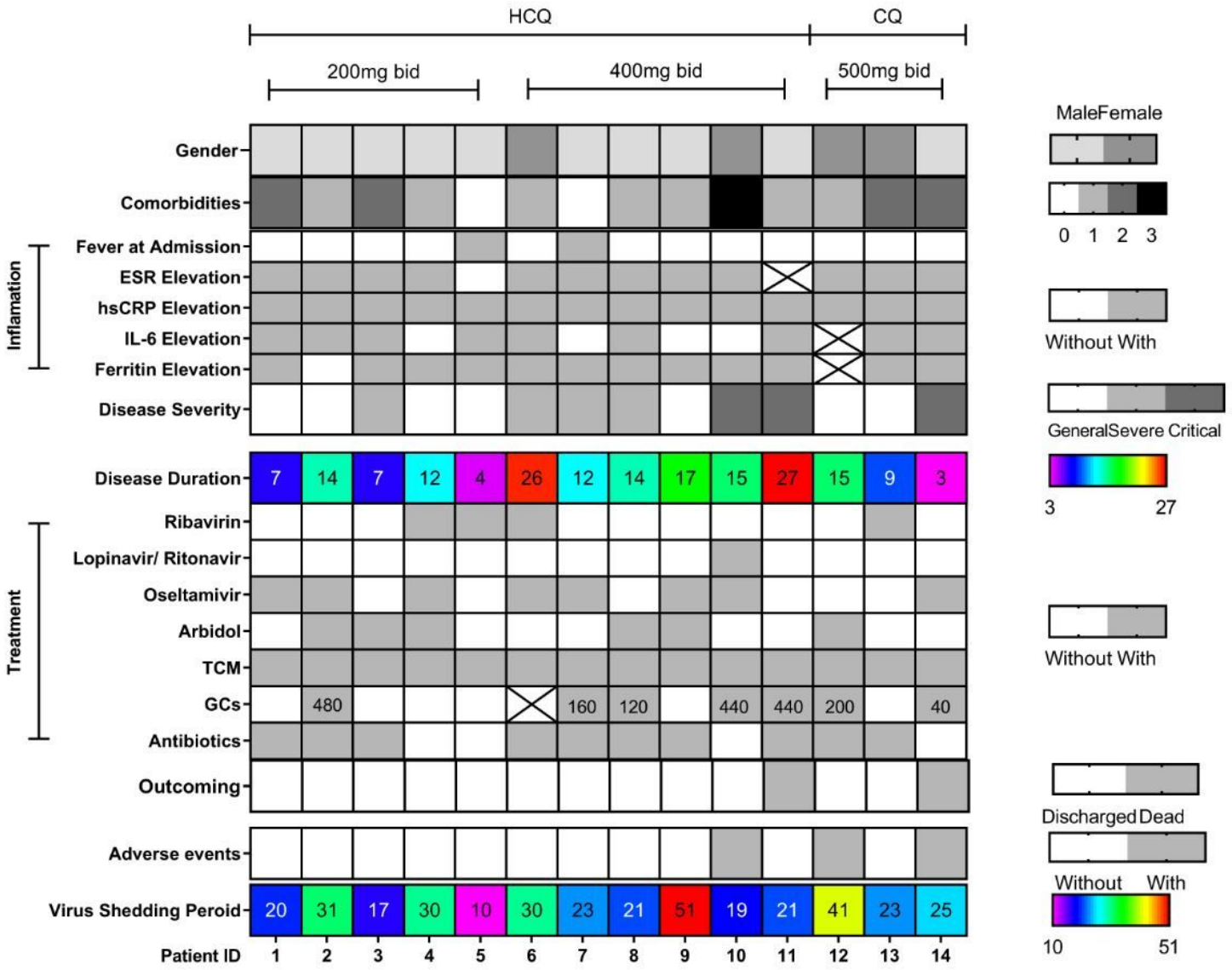

Figure 2

The detailed clinical, treatment and outcoming information of patients with HCQ/ CQ treatment. HCQ: hydroxychloroquine; CQ: chloroquine; ESR: erythrocyte sedimentation rate; hsCRP: high sensitivity C reactive protein; IL-6: interleukin-6; TCM: traditional Chinese Medicine; GCs: glucocorticoids. Comorbidities refers to the types of comorbidities in one single patient. Disease severity was classified according to the Chinese management guideline for COVID-19. Disease duration (days) was calculated from symptom onset to inpatient department admission. GCs were summed as methylprednisolone or equivalent and the total dosages of GCs were recorded in the corresponding square, respectively. Patient No.10 had transient first-degree atrioventricular block (AVB). Patient No.12 complained about dizziness and blurred vision which disappeared after CQ discontinuation. Patient No.14 had recurrent AVB and obvious QTc elongation even after CQ withdrew. The virus shedding period was defined as from symptoms onset to the first day of the consecutive negative PCR results before discharging. The X was put in the square in which the data was not available.

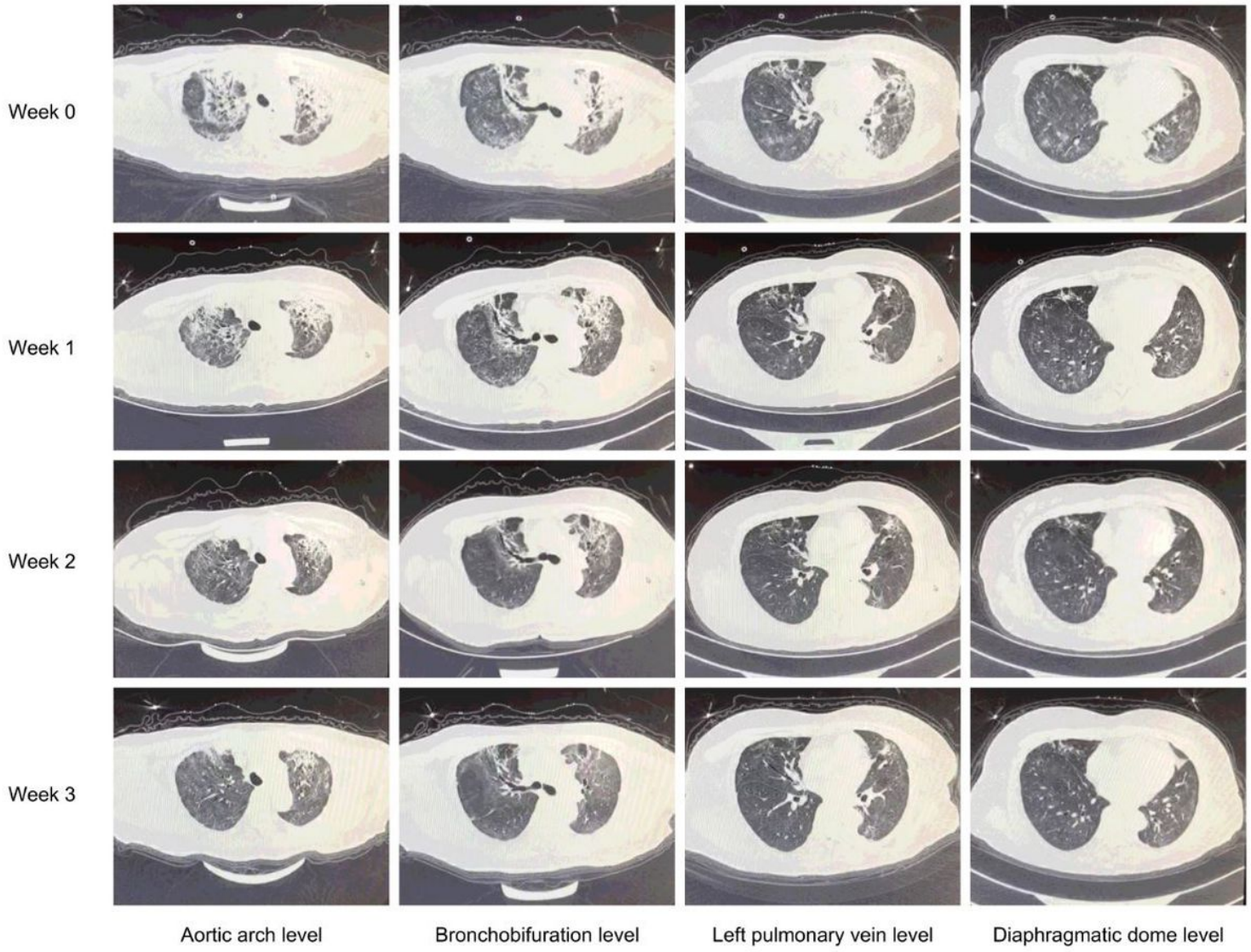

Figure 3

The computed tomography findings of one patient (No.6) before (week 0) and 1, 2, 3 weeks after HCQ administration, respectively. After the comprehensive treatment together with HCQ, the ground-glass opacity lesions were largely absorbed, while some of the fibrosis stripe lesions were left.

Supplementary Files

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