Assessment of COVID-19 Treatment containing both Hydroxychloroquine and Azithromycin: A Natural Clinical Trial

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Abstract

The goal of this study was to assess the clinical effectiveness and safety profile of the COVID-19 treatment protocol (containing both hydroxychloroquine (HCQ) and azithromycin) in an Iraqi specialized hospital. Methods: This prospective study used a pre- and post-intervention design without a comparison group. The intervention was routine Ministry of Health (MOH) approved management of COVID-19 for all patients. The study was conducted in a public healthcare setting in Baghdad, Iraq from March 1st to May 25, 2020. The study outcome measures included the changes in clinical and biochemical parameters during the hospitalization period. Paired t-test and Chi-square test were used to compare the measures of vital signs, lab tests and symptoms before and after treatment. Results: The study included 161 patients who were admitted with positive RT-PCR and clinical symptoms of COVID-19. In terms of severity, 53 (32.9%) patients had mild condition, 47 (29.2%) had moderate condition, 35 (21.7%) had severe condition, and 26 (16.1%) had critical condition. Most patients (84.5%) recovered and were discharged without symptoms after testing negative with RT-PCR, while 11 (6.8%) patients died during the study period. The signs and symptoms of COVID-19 were reduced significantly in response to therapy regimen containing HCQ and azithromycin. The most common reported side effects were stomach pain, hypoglycemia, dizziness, itching, skin rash, QT prolongation, arrhythmia, and conjunctivitis. Conclusions: This natural trial showed that COVID-19 regimen containing both HCQ and azithromycin can be helpful to promote recovery of most patients and reduced their signs and symptoms significantly. It also shows some manageable side effects mostly those related to heart rhythm. In the absence of FDA-approved medications to treat COVID-19, the repurposing of HCQ and azithromycin to control the disease signs and symptoms can be useful.

What is already known about this topic?

There is a controversy about using hydroxychloroquine and azithromycin to treat COVID-19 due to uncertainly of their effectiveness and safety.

What does this article add?

- The experience with Iraqi protocol to treat COVID-19 can help to answer some questions about the effectiveness and safety of this therapy combination which can offer some support to the international community in facing such vicious pandemic.
- This natural trial showed that COVID-19 regimen containing both HCQ and azithromycin can be helpful to promote recovery of most patients and reduced their signs and symptoms significantly.

The trial was not registered because it is a natural trial (quasi experiment) which was conducted according the Iraqi Ministry of Health protocol by a regular healthcare team who is planning to share its experience with the international scientific community.

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus that was first recognized in Wuhan, China, in December 2019 [1]. Genetic sequencing of the virus suggests that it is a beta-corona virus closely linked to the SARS virus [2]. While most people with COVID-19 develop only mild or uncomplicated illness, approximately 14% develop severe disease that requires hospitalization and oxygen support, and 5% require admission to an intensive care unit [3]. In severe cases, COVID-19 can be complicated by acute respiratory distress syndrome (ARDS), sepsis and septic shock, multiorgan failure, including acute kidney injury and cardiac injury [3]. Older age and co-existing diseases have been reported as risk factors for death[4]. On March 12, the WHO officially declared the COVID-19 outbreak a pandemic [5]. As of June 24, 2020, COVID-19 was confirmed in 188 countries with a total confirmed cases of 9,295,365 and more than 478,289 deaths [6]. Iraq had 36,702 confirmed cases, 16,814 recovered cases and 1,330 deaths associated with COVID-19 pandemic as of June 24, 2020[6].

The pandemic of COVID-19 is caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and presents a challenge in regard to identifying effective drugs for prevention and treatment. Up to the time of writing this manuscript, there were no medications approved by the U.S. Food and Drug Administration (FDA) to treat COVID-19[7]. However, the FDA recently created a new emergency program, the Coronavirus Treatment Acceleration Program (CTAP), aimed at speeding up research for the development of COVID-19 treatments[8],[9]. As of May 11, 2020, more than 144 clinical trials had been launched to test COVID-19 treatments, including some drug repurposing or repositioning [8](9). Researchers are also testing medications typically used to treat other conditions to see if they are also effective in treating COVID-19. For example, hydroxychloroquine (HCQ) and chloroquine are two medications that have been used for many decades to treat malaria and autoimmune conditions like rheumatoid arthritis and lupus [10], and azithromycin is an antibiotic commonly used to treat bacterial infections such as bronchitis and pneumonia. They have been shown to have some in vitro activity against viruses like influenza A and Zika[11].

We are ethically committed to share the experience of Iraqi healthcare providers with COVID-19 treatment with the scientific community to help answer some questions about the effectiveness and safety of HCQ and azithromycin containing regimen. The Iraqi Scientific Committee at the Ministry of Health (MOH) adopted a treatment protocol on March 1st, 2020 several days after the detection of the first COVID-19 case in Iraq on February 24, 2020 (Table 1) [12]. The goal of this study was to assess the clinical effectiveness and safety profile of the current COVID-19 treatment protocol (containing both HCQ and azithromycin) in an Iraqi specialized hospital.

Methods

Study Designs, duration and setting

This prospective study used a pre- and post-intervention design. The intervention was the routine MOH approved management of COVID-19 for all patients. In other words, this was a natural clinical trial (quasi experiment) with no comparison group. The study was conducted in a public healthcare center, Al-Shifaa Center for COVID-19 pandemic treatment, Medical City, Baghdad, Iraq. The study included all adult patients with a confirmed COVID-19 infection that were admitted to this hospital over 85 days (from March 1st to May 25, 2020). They were defined as confirmed cases of coronavirus COVID-19 after the result of nasopharyngeal sample using Reverse transcription- polymerase chain reaction (RT-PCR) comes positive.

Exclusion criteria included known allergy to hydroxychloroquine (HCQ) or chloroquine, any contraindications to HCQ or chloroquine and azithromycin including retinopathy and prolonged QT, patients with severely reduced in left ventricular (LV) function, severely reduced in renal function and G6PD deficiency in addition to pregnant and lactating women.

Follow-up protocol and measures

The research team (clinical pharmacist and three specialist physicians) was part of the medical team in the center. They prospectively collected patient medical information from patients, patient records and attending physicians. The information included demographics, disease and treatment characteristics and clinical outcome. Patient's clinical conditions and routine biochemical tests were assessed at baseline and then every day to evaluate the effect of therapy protocol.

Study outcomes:

The study outcome measures were assessed at baseline (at admission) and daily after hospitalization (post-intervention) until discharge of the recovered patient or death. The study outcome measures included the changes in clinical and biochemical parameters during hospitalization period such as disappearance of clinical symptoms, virologic clearance and occurrence of side effects. The routine assessment of vital signs was conducted three times daily. Virologic clearance was measured using real time PCR which was retested at day 6 post hospitalization. Complete recovery was defined as two negative RT-PCR tests (which were usually done on days 6^{th} and 7^{th} of hospitalization). Fourteen days after hospital discharge, recovered patients were retested in outpatient clinics using RT-PCR.

Other outcome measures included the time to clinical recovery (TTCR) and final clinical prognosis (recovery vs death). The TTCR is defined as the time to disappearance of clinical symptoms (e.g. cough and shortness of breath, SOB) and a normal body temperature and respiratory rate for more than 72 hours.

Study patients

Study participants with confirmed cases of COVID-19 were transferred to the study specialized center after having a positive RT-PCR test at one of Medical City Hospitals. After admission, COVID-19 patients were classified according to clinical evaluation to mild cases (no pneumonia on a CT scan), moderate cases (pneumonia on a CT scan), severe cases (respiratory rate [?] 30 breaths /min, oxygen saturation [?] 93% or patients with pneumonia on a CT scan) and critical cases (respiratory failure/need mechanical ventilation). All patients were treated according to the MOH treatment protocol which relies on patient severity status (Table 1).

To assess radiological changes, a chest CT scan was conducted before starting the treatment (day 0) and after 5 days of treatment (day 6). Pulmonary status was classified into three levels: Exacerbated, unchanged, and improved. Medication safety was also assessed by monitoring adverse drug reactions (ADRs), vital signs and lab tests. Routine lab tests during treatment period included liver function tests, renal function tests and fasting blood sugar. Liver function tests included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin. Renal function was assessed using serum urea and creatinine (s.cr). The WHO-UPPSALA causality assessment criteria was used to determine the causality of adverse drug reactions (ADRs) of hydroxychloroquine and azithromycin[13].

All data were recorded in the patient medical record. Consent was obtained from the patients before giving the therapy regimen. The researchers de-identified patient names and addresses to keep patient confidentiality. The study was approved by the Higher Ethical Committee at Medical City Hospitals.

Statistical Analysis:

Statistical Package for the Social Sciences 22 (SPSS, Chicago, IL, USA) was used to analyze the data. For descriptive analysis, categorical variables were presented as frequencies and percentages, while continuous variables were described using mean and standard deviation. A paired t-test was used to compare the means of vital signs and lab tests before and after treatment. The Chi-square test was used to compare categorical variables (presence of fever and cough) before and treatment. A p-value < 0.05 was considered to be statistically significant.

Results

The study included 161 patients [52 (32.3%) women, 109 (67.7%) men] who were admitted with positive RT-PCR and clinical symptoms of COVID-19 (Table 2). The participants' mean age was 44.3 (±17.0) years and average bodyweight was 81.3 (±9.6). The disease was prevalent among the middle age group (41-50 years). One-fifth of patients (19.3%) acquired the infection when they were visiting Iran. Approximately two-thirds (63.4%) of patients were infected by contact with a family member while 17 (10.6%) patients obtained COVID-19 from an unknown person. Some patients were healthcare providers/staff (6.8%) who were infected due to their work in hospitals. In terms of severity, 53 (32.9%) patients had mild condition, 47 (29.2%) had moderate condition, 35 (21.7%) had severe condition, and 26 (16.1%) had critical condition. Approximately, one-quarter (23.6%) of the patients were admitted to the respiratory care unit (RCU) (Table 2). All the 11 deceased patients were admitted in critical condition and had co-existing diseases.

The most common symptoms of COVID-19 patients at admission were cough (64.6%), headache (56.5%), shortness of breath (SOB) (47.2%), sore throat (41.0%), diarrhea (36.6%), exertional dyspnea (32.9%), abdominal pain (31.1%), tiredness (31.1%), loss of appetite (29.8%), vomiting (23.6%), chest tightness (15.5%) (Table 3).

Most patients (84.5%) recovered and were discharged without symptoms after testing negative RT-PCR. However, 14 (8.7%) patients were discharged with mild symptoms (mild cough and/or exertional dyspnea). All recovered patients were required to be retested with RT-PCR 14 days after their hospital discharge.

On the other hand, 11 (6.8%) patients died during the study period. Eight of them died before completing the five-day treatment course (six died within the first 24 hours and two died after 24 hours), while three died after one week of treatment in the intensive care unit (ICU) (Table 4). The deceased patients were admitted to the hospital in critical condition.

The average period of patient hospitalization was 12.9 (±5.5) days. However, the duration of treatment was up to 14 days (for patients with pneumonia). The standard COVID-19 regimen which included hydroxychloroquine (HCQ) and azithromycin had a significant positive effect (P-value < 0.05) on patient body temperature, cough, SOB, respiratory rate (RR), pulse rate (PR), and fasting blood sugar (Table 5). In other words, those signs and symptoms of COVID-19 patients were reduced significantly after using therapy regimen containing HCQ and azithromycin. However, there were non-significant effects of treatment (P-value [?]0.05) on systolic blood pressure (SBP), diastolic blood pressure (DBP), AST, ALT, ALP, total bilirubin, serum urea, and serum creatinine (Figures 1 & 2).

In terms of adverse drug reactions (ADRs), the most common reported ones were stomach pain/cramps, hypoglycemia, headaches, mood changes, dizziness, itching, diarrhea, muscle weakness, nausea, skin rash, vomiting, QT prolongation, arrhythmia, and conjunctivitis (Figure 3). Most ADRs were possible to be caused by HCQ and/or azithromycin. It means they also can be caused by the disease (COVID-19). On the other hand, three ADRs including arrhythmia, QT prolongation and conjunctivitis were probably caused by the two medications (Table 6). In other words, they unlikely to be attributed to COVID-19 disease. The electrocardiograph (ECG) of six (3.7%) patients recorded QTc prolongation, but not more than 450ms. Additionally, arrhythmia was reported in three (1.9%) other patients (Table 6). The medical team stopped the HCQ and azithromycin treatment for three patients who experienced arrhythmia. Then electrolyte levels (calcium and potassium) were measured and corrected to treat the arrhythmia. However, this treatment stoppage occurred after completing the first five days of the therapy course.

Discussion:

The pandemic of coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 presents a challenge in terms of identifying effective drugs for prevention and treatment [14]. HCQ has a long history as safe and inexpensive drug for malaria and autoimmune diseases despite some eye and cardiac side effects [15].

During the study period (from March 1 to May 25, 2020) and before the exponential increase in COVID-19 cases in Iraq (>1000 cases/day) which started on June 5, 2020, admission to one of the MOH quarantine facilities was required by law for confirmed cases. Thus, all patients who tested positive were treated in

government COVID-19 specialized facilities. The study center was one of 22 specialized COVID-19 centers across the country. The number of participants in this study represents 3.5% of the total Iraqi COVID-19 cases during the study period. The therapy regimen was the same across all 22 specialized COVID-19 in Iraq as it was implemented by the MOH. According to the MOH therapy protocol, HCQ and azithromycin should be given for all COVID-19 cases and other anti-viral agents/antibiotics can be added for severe and critical cases [12]. During the study period, the use of convalescent plasma to treat COVID-19 had not been started in the study setting.

In this study, the treatment regimen (containing both HCQ and azithromycin) appeared to help promote recovery in 150 COVID-19 patients (83.2%) in the study center. Although 16% of patients were admitted in critical condition and 26% were admitted to the RCU, the mortality rate was only 6.8%. It is worth mentioning that most deceased patients were admitted in critical condition and died before receiving full course of treatment. The same MOH therapy regimen facilitate recovery in 2,811 cases out of 4,632 COVID-19 patients in Iraq during the study period, and only 163 deaths (3.52%) were reported [6]. This high recovery rate was probably due to the effectiveness of the treatment protocol and close disease monitoring by healthcare providers. They work hard despite several challenges facing Iraqi healthcare system including a shortage in number of quarantine facilities, a shortage in personal protective equipment (PPE) and limited RT-PCR testing[16].

The average of hospitalization period was 12.9 (+-5.5 days) given there was small number of admissions per day during the study period and no high demand for hospital beds. This duration may reflect the fact that about two-third of admitted patients developed pneumonia and needed time to recover. On the other hand, all those who tested negative with RT-PCR on days 6 and 7 after admission were discharged on day 8. The results of our study were comparable to a French clinical trial to evaluate the role of HCQ and Azithromycin on respiratory viral loads in patients with confirmed COVID-19 [17]. The study found a significant reduction of the viral carriage in HCQ/azithromycin group compared to control group at day 6 post-inclusion. The study reported 100% viral clearance in nasopharyngeal swabs with combination of HCQ and azithromycin compared to 57.1% in HCQ alone group and 12.5% in patients who did not receive HCQ ($p< 0.001$)[17]. Chloroquine and HCQ appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification [1819]. These agents also have immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activities in host cells [19],[20]. HCQ has in-vitro activity against SARS-CoV-2 with half-maximal effective concentration (EC50) of 6.14 μM which is lower than that of chloroquine (EC50 = 23.90 μM) after 24 hours of growth[18].

On the other hands, some manageable side effects of HCQ were reported during treatment period. These side effects may disappear during treatment as the body adjusts to the medicine [21]. The reported side effects included stomach pain/cramps, hypoglycemia, headaches, mood changes, dizziness, itching, diarrhea, muscle weakness, nausea, skin rash, and vomiting. Those are common HCQ side effects and appear to be dose-dependent and most often occur with loading doses of 800 mg or higher [22]. In this study, we used an HCQ maintenance dose of 400 mag daily for short-term course which is relatively safe since the recommended daily dose was not exceeded. The most severe and life-threatening complications from use of hydroxychloroquine include QT interval prolongation and the resultant risk of ventricular arrhythmias [23]. In our study, the electrocardiogram (ECG) monitoring showed that six patients developed QT interval prolongation, but not more than 450ms which did not require medical intervention. In contrast, three patients developed arrhythmia and needed medical intervention which consisted of stopping the treatment and normalizing the blood electrolytes (potassium and calcium). The incidence of QT interval prolongation with using chloroquine and hydroxychloroquine is highly dependent on baseline ECG findings, with risk exacerbated using concomitant QT-interval prolonging medications [24]. The combination of azithromycin with HCQ frequently prolongs the QT interval in a clinically significant manner, increasing over time and requiring additional monitoring [25].

Chinese Centre for Disease Control and Prevention includes chloroquine in the treatment guideline for COVID-19 patients which gave high recovery rate (94.5%)[26]. A recent study relying on a multinational

registry analysis which was published on May 22, 2020 found no evidence of hydroxychloroquine effectiveness to treat COVID-19[27]. However, this study was retracted after some expressed concerns about its findings. On March 28, 2020, the U.S. FDA issued Emergency Use Authorizations (EUA) that allowed the use of hydroxychloroquine to treat COVID-19. On June 15, 2020, the FDA revoked this EUA due to the absence of scientific evidence [28]. This controversy about using hydroxychloroquine to treat COVID-19 is due to the absence of findings based on well-designed randomized controlled trials (RCTs). Although there is a debate about the effectiveness and safety of using hydroxychloroquine, the new Iraqi guideline (on June 1, 2020) still includes HCQ to treat mild and moderate cases of COVID-19 since it has been showing promising results and due to the absence of superior alternatives, in addition to its affordability and availability.

This study had some limitations. It was conducted in a single center without a comparison group. Single center findings may not be generalizable. However, a universal therapy regimen has been implemented by the health top authority across all country healthcare settings. Lack of a comparison group can limit the determination of causality between the therapy and the cure or good prognosis. Additionally, some disease-induced symptoms overlap with ADRs during treatment period.

Conclusions

This natural trial showed that COVID-19 regimen containing both HCQ and azithromycin is helpful in treating the majority of patients and reduced their signs and symptoms significantly. It also causes some manageable side effects mostly those related to heart rhythm. In the absence of FDA-approved medications to treat COVID-19, the repurposing of HCQ and azithromycin to control the disease signs and symptoms is potentially useful. The study showed that using this therapy combination (HCQ and azithromycin) is promising and can fill the gap until more effective treatments are found. Future randomized controlled trial can give more definite answers about the effectiveness and safety of such therapy protocol.

Table 1: Iraqi COVID-19 treatment protocol (13)

Therapy regimen	**Case Severity**
Hydroxychloroquine PO (400mg BID first day then 200 mg BID for 5 days), Azithromycin PO (500mg in the first day, then 250 mg daily for 5 days)	Covid-19 patients without pneumonia
Hydroxychloroquine PO (400mg BID first day then 200 mg BID for 14 days), Azithromycin PO (500mg in the first day, then 250 mg daily for 14 days), Tamiflu 75 mg PO BID for 5 days	Covid-19 patients with pneumonia in the ward
Hydroxychloroquine PO (400mg BID first day then 200 mg BID for 14 days), Azithromycin PO (500mg in the first day, then 250 mg daily for 14 days), Tamiflu 75 mg PO BID for 5 days, Kaletra (Lopinavir 200 mg /ritonavir 50 mg) BID for 5 days and antibiotic(s) accordingly	Covid-19 patients with pneumonia in the ICU

"PO" means the medication is taken by mouth. ICU=intensive care unit.

BID=twice a day.

Table 2: Demographic and disease characteristics for patients

Characteristics	Characteristics	Characteristics	N (%)
Age (years)	Age (years)	18-30	35 (21.73)
		31-40	30 (18.63)
		41-50	41 (25.46)

Characteristics	Characteristics	Characteristics	N (%)
		51-60	31 (19.25)
		61-80	24 (14.90)
		Total	161 (100)
Gender	Female	Female	52 (32.3)
	Male	Male	109 (67.7)
Exposure and transmission	Exposure and transmission	Exposure and transmission	Exposure and transmission
Travelers returning from affected areas	Travelers returning from affected areas	Travelers returning from affected areas	32 (19.9)
Exposure direct contact with patient (most of them same family)	Exposure direct contact with patient (most of them same family)	Exposure direct contact with patient (most of them same family)	102 (63.35)
Contact with unknown person	Contact with unknown person	Contact with unknown person	17 (10.55)
Healthcare provider/ staff	Healthcare provider/ staff	Healthcare provider/ staff	11(6.83)
Co-existing diseases	Co-existing diseases	Co-existing diseases	Co-existing diseases
Hypertension	Hypertension	Hypertension	38 (23.60)
Diabetes with A1c > 7.6%	Diabetes with A1c > 7.6%	Diabetes with A1c > 7.6%	37 (22.98)
Ischemic heart diseases	Ischemic heart diseases	Ischemic heart diseases	8 (4.96)
Chronic kidney diseases	Chronic kidney diseases	Chronic kidney diseases	4 (2.48)
Asthma	Asthma	Asthma	8 (4.96)
History of transplant or other Immunosuppression	History of transplant or other Immunosuppression	History of transplant or other Immunosuppression	2 (1.24)
Hepatitis B, C	Hepatitis B, C	Hepatitis B, C	2 (1.24)
Systemic lupus erythematosus (SLE)	Systemic lupus erythematosus (SLE)	Systemic lupus erythematosus (SLE)	1 (0.62)
Pulmonary hypertension	Pulmonary hypertension	Pulmonary hypertension	1 (0.62)
Lymphocytopenia at admission	Lymphocytopenia at admission	Lymphocytopenia at admission	30 (18.63)
Condition severity	Mild	Mild	53 (32.91)
	Moderate	Moderate	47 (29.19)
	Sever	Sever	35 (21.73)
	Critical	Critical	26 (16.14)
Needed respiratory care unit (RCU)	Needed respiratory care unit (RCU)	Needed respiratory care unit (RCU)	38 (23.60)
Needed oxygen therapy	Needed oxygen therapy	Needed oxygen therapy	61 (37.88)
Characteristic	Characteristic	Characteristic	Mean (ST Dev)
Age (years)	Age (years)	Age (years)	44.60±16.44
Body weight (kg)	Body weight (kg)	Body weight (kg)	81.79±9.64
Duration of starting symptoms before admission (days)	Duration of starting symptoms before admission (days)	Duration of starting symptoms before admission (days)	5.24 ± 2.57

Table 3: COVID-19 patient symptoms at admission

Symptom	Frequency (N)	Percent (%)
Cough	104	64.6
Headache	91	56.5
Shortness of breath (SOB)	76	47.2
Sore throat	66	41.0
Diarrhea	59	36.6
Exertional dyspnea	53	32.9
Abdominal pain	50	31.1
Tiredness	50	31.1
Loss of appetite	48	29.8
Vomiting	38	23.6
Chest tightness	25	15.5
Sneezing	7	4.3
Runny nose	2	1.2
Loss of taste/smell	1	0.6
Total	161	100.0

Table 4. The clinical outcomes of COVID-19 patients

Patient category	Patient category	N (%)
Total number of admitted patients	Total number of admitted patients	161 (100
Recovered patients	Recovered patients	136 (84.
Discharged (recovered) patients with mild symptoms	Negative RT-PCR with mild cough or exertional dyspnea	14 (8.69
Death	Within 24 hours	6 (3.72%
	After 24 hours	2 (1.24%
	During the treatment	3 (1.86%
	Total death	11 (6.83
Hospitalization days for recovered patients	Mean ± SD	12.88 ±

SOB=shortness of breath

Table 5: The effect of treatment on clinical condition and biochemical parameters of patients with COVID -19

Parameters	Before treatment	After treatment	P value
Symptoms	N (%)	N (%)	
Cough	104 (64.60%)	14 (8.70%)	.0000*
SOB	76 (47.21%)	11 (6.83%)	.0000*
Fever	38.25 ± 0.64	36.53 ± 0.39	.0000*
Vital signs	Mean ± SD	Mean ± SD	
RR	23.43 ± 5.55	19.66 ± 2.32	.0000*
SBP	129.27± 16.68	126.57 ± 14.88	.1260
DBP	83.77 ± 10.64	84.76 ± 10.46	.4015
PR	96.36 ± 8.31	78.21 ± 3.05	.0000*
Lab tests			
FBS mmol/L	9.61 ± 5.65	6.95 ± 1.72	.0000*
WBCs $*10^3$	11.20 ± 3.33	6.67 ± 1.97	.0000*
Hg g\dl	12.74 ± 1.75	12.70 ± 1.54	.7969

Parameters	Before treatment	After treatment	P value
S.Cr	1.00 ± 0.94	0.95 ± 0.69	.6451
Urea	26.04 ± 34.77	25.61 ± 33.85	.9112
AST	25.32 ± 13.16	27.20 ± 9.34	.1387
ALT	33.63 ± 28.36	34.80 ± 20.15	.6925
ALP	106.47 ± 71.16	107.27 ± 47.38	.9054
Bilirubin	0.73 ± 0.70	0.75 ± 0.57	.7391

*Significant p-value [?] 0.05 according to paired T-test or Chi-square. SOB=shortness of breath, RR=respiratory rate, SBP=systolic blood pressure, DBP=diastolic blood pressure, PR=pulse rate, FBS=fasting blood sugar, WBCs=white blood cells, S.Cr=serum creatinine, AST=aspartate aminotransferase, ALT=alanine aminotransferase, ALP=alkaline phosphatase.

Table 6: The reported adverse reactions of HCQ & azithromycin containing treatment on patients with COVID -19

Side effects	N (%)	Causality term
Stomach pain or cramps	65 (40.37%)	possible
Hypoglycemia	60 (42.86%)	possible
Headaches	57 (35.40%)	possible
Mood changes	55 (34.16)	unlikely
Dizziness	50 (31.06%	possible
Itching	47 (29.19%)	possible
Diarrhea	45 (27.95%)	possible
Muscle weakness	41 (25.47%)	possible
Nausea	40 (24.84%)	possible
Skin rash	35 (21.74%)	possible
Vomiting	30 (18.63%)	possible
QT prolongation	6 (3.73%)	probable
Conjunctivitis	4 (2.48%)	probable
Arrhythmia	3 (1.86%)	probable

Probable=Unlikely to be attributed to disease or other drugs. Possible=Could also be explained by disease or other drugs. Unlikely=Disease or other drugs provide plausible explanations[13].

Figure 1: The effect of treatment on patient clinical condition (signs and symptoms)

Before therapy was measured at baseline (at admission). Vital sign measurements after therapy equal the average of the last three-day measurements. Frequency of patients with symptoms (cough/SOB) after therapy was measured on last day before discharge. SOB=shortness of breath, RR=respiratory rate, SBP=systolic blood pressure, DBP=diastolic blood pressure, PR=pulse rate.

Figure 2: The effect of treatment on FBS, WBCs, and Hg levels

FBS=fasting blood sugar; WBCs=white blood cells; Hg=hemoglobin.

Figure 3-The reported adverse reactions of treatment on patients with COVID -19

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