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## Research Article

### A comparative study on Ivermectin- Doxycycline and Hydroxychloroquine- Azithromycin therapy on COVID19 patients.

Abu Taiub Mohammed Mohiuddin Chowdhury<sup>1</sup>; Mohammad Shahbaz<sup>2</sup>; Md Rezaul Karim<sup>3</sup>;  
Jahirul Islam<sup>4</sup>; Guo Dan<sup>1</sup>; He Shuixiang<sup>1</sup>

<sup>1</sup>Department of Gastroenterology, First affiliated hospital of Xi'an Jiaotong University,  
Xi'an. China

<sup>2</sup>Chakaria Upazilla Health Complex, Cox's Bazar. Bangladesh.

<sup>3</sup>Hubei Key Laboratory of Embryonic Stem Cell Research, Institute of Neuroscience, Hubei  
University of Medicine, Shiyan, China.

<sup>4</sup>Department of Epidemiology and Health Statistics; Xi'an Jiaotong University. China.

Correspondence to:

He shuixiang

Email: [dyyyjxk@xjtu.edu.cn](mailto:dyyyjxk@xjtu.edu.cn)

Professor and Head

Department of Gastroenterology, First Affiliated Hospital of Xi'an Jiaotong University,  
Xi'an, Shaanxi; P.R. China 710061

# A comparative study on Ivermectin- Doxycycline and Hydroxychloroquine- Azithromycin therapy on COVID19 patients.

## **Abstract:**

**Background:** The worldwide COVID-19 pandemic was caused by a newly discovered Coronavirus. The treatment methods for COVID-19 are emerging and rapidly evolving. Existing drugs, including Ivermectin and Hydroxychloroquine, offer the hope of effective treatment in early disease. In this study, we investigated and compared outcomes of Ivermectin-Doxycycline vs. Hydroxychloroquine-Azithromycin combination therapy COVID19 patients with mild to moderate disease.

**Methods:** Patients with mild to moderate COVID-19 disease, tested positive by RT PCR for SARS-CoV-2 infection at Chakoria Upazilla Health Complex, Cox's Bazar, Bangladesh, were included in this study. Patients were divided randomly into two groups: Ivermectin 200µgm/kg single dose + Doxycycline 100mg BID for 10 days in group A, and Hydroxychloroquine 400mg 1<sup>st</sup> day, then 200mg BID for 9 days + Azithromycin 500mg daily for 5 days in group B. PCR for SARS-CoV-2 was repeated in all symptomatic patients on the second day onward without symptoms, or, for those who were asymptomatic (throughout the process), on the 5<sup>th</sup> day after taking medication and repeated every two days onward if the result is positive. Time to negative PCR and time to full symptomatic recovery was measured for each group.

**Results:** All subjects in the Ivermectin-Doxycycline group (group A) reached a negative PCR for SARS-CoV-2, at a mean of 8.93 days, and all reached symptomatic recovery, at a mean of 5.93 days, with 55.10% symptom-free by the 5<sup>th</sup> day. In the Hydroxychloroquine-Azithromycin group (group B), 96.36% reached a negative PCR at a mean of 6.99 days and were symptoms-free at 9.33 days. Group A patients had symptoms that could have been caused by the medication in 31.67% of patients, including lethargy in 14 (23.3%), nausea in 11 (18.3%), and occasional vertigo in 7 (11.66%) of patients. In Group B, 46.43% had symptoms that could have been caused by the medication, including 13 (23.21%) mild blurring of vision and headache; 22 (39.2%) increased lethargy and dizziness, 10 (17.85%) occasional palpitation, and 9 (16.07%) nausea and vomiting.

Conclusion: The Ivermectin-Doxycycline combination showed a trend toward superiority to the Hydroxychloroquine-Azithromycin combination therapy in the case of patients with mild to moderate COVID19 disease, though the difference in time to becoming symptom-free and the difference in time to negative PCR was not statistically significant.

**Keywords:** Ivermectin; Doxycycline; Hydroxychloroquine; Azithromycin; Randomized Controlled Trial (RCT); COVID-19, Bangladesh

### **Background:**

Coronavirus disease 2019 (COVID19) is a WHO declared a global pandemic. Over eight million people have already been infected by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), and billions have been affected by the socioeconomic squeal. As SARS-CoV-2 is a novel virus, there are not yet proven treatment options. Early treatment, before the disease becomes severe, would be optimal. Current considerations for treatment include Lopinavir/ritonavir, favipiravir, and remdesivir, which are all currently in wide use in the case of moderate to severe COVID19 patients. Treatments for patients earlier in disease with mild to moderate symptoms have not been as well established. Chloroquine and Hydroxychloroquine (HCQ) are not helpful in moderate to severe disease but have become the current standard for mild to moderate and early disease. Chloroquine has been shown as a potential suppressor of SARS-CoV-2 in a vitro study. [1] Though many trials have shown a good outcome in mild to moderate cases, unfortunately, chloroquine's toxicity is an important concern. [2] The less toxic derivative, Hydroxychloroquine (HCQ), has also been found to be effective. [3] Very recently, Ivermectin, an anti-parasitic drug, has been described as highly effective in an in-vitro study against SARS-CoV-2. [4] HCQ-Azithromycin combination therapy has also been shown to be a possibly effective combination therapy in the treatment of SARS-CoV-2. [5, 6] These two studies reported 100% and 83% recovery in the 6<sup>th</sup> and 7<sup>th</sup> day with a reduced hospital stay. Very recently, there have been several observational studies in Bangladesh showing encouraging results in a case series of Covid19 patients given a combination of Ivermectin and Doxycycline. There has not yet been a randomized study of Ivermectin in patients with mild to moderate Covid19. Ivermectin is well-tolerated, with less toxicity and fewer adverse effects compared to HCQ. Due to drug complications, and recent discouraging statements by WHO about HCQ treatment, it is important to find an effective, economical alternative to HCQ. Therefore we

decided to investigate the efficacy of Ivermectin-Doxycycline combination therapy and compare it to the standard HCQ-Azithromycin therapy among the mild to moderate cases of COVID19 patients.

### **Methodology:**

All patients who tested positive for SARS-CoV-2 infection by RT PCR at Chakoria Upazilla Health Complex, Cox's Bazar; Bangladesh from May 2<sup>nd</sup> to June 5<sup>th</sup>, 2020 were initially included in this study, including those with and without symptoms. The PCR analysis of the collected sample was done in Cox's Bazar Medical College. All patients received a full evaluation, including a history of current illness, comorbid condition, and associated complaints. Patients with unstable comorbid conditions like bronchial asthma, COPD, ischemic heart disease, uncontrolled diabetes mellitus, advanced renal and hepatic disease, carcinoma, hospitalized, and Immuno-compromised patients were then excluded. Patients were all examined with a pulse oximeter and only those with normal oxygen saturation of 95% or above were included. Patients with respiratory symptoms received chest radiograph and only those with normal or near-normal chest radiograph were included.

Randomization was done using an odd-even methodology applied to registration numbers, in a consecutive fashion in a 1:1 ratio, by the hospital registration office. Treatment was given and final enrolment was done by the attending physician (Investigator). All the patients enrolled in the study were treated as an outpatient.

For the study purpose, the patients were divided into two groups, as follows:

Group A (n=60): Ivermectin 200µgm/kg single dose + Doxycycline 100mg BID for 10days

Group B (n=56): Hydroxychloroquine 400mg 1<sup>st</sup> day then 200mg BID for 9days + Azithromycin 500mg daily for 5Days.

Dosing of Ivermectin was determined by the current standard of care depending on some observational study performed in Bangladesh. HCQ dosing was decided as per "National guideline for COVID19 management 4.0".

All subjects were also provided with symptomatic treatment for fever, headache, cough, myalgia, etc. Drug interactions and contraindications for each individual were considered carefully. The

schedule of medication intake was properly explained to each patient. Instructions for Group A included that the Ivermectin tablet (200µg/kg) single dose was to be taken on an empty stomach one hour before a meal on the first day and that the Doxycycline 100 mg capsule was to be taken twice daily after food for 10 days starting from day one. Instructions for Group B included that the Hydroxychloroquine 400mg (2tablets of 200mg each) was to be taken on the first day then 200mg (one tablet) twice daily after food for 9days, and that the Azithromycin 500mg (one tablet of 500mg) was to be taken once daily after food for 5days starting from day one. Patients were advised to self-isolate, and to take proper nutrition, hydration, and to maintain a sanitary environment.

All subjects underwent repeat nasopharyngeal and throat swab PCR for SARS-CoV2 every other day until their PCR was negative. These repeat PCR tests began on the 5th day after taking the medication for subjects who began the study and remained symptom-free. For subjects who began the study with symptoms or developed symptoms, the PCR repeat testing began on the 2<sup>nd</sup> symptom-free day onward. The investigators had telephone contact with all subjects every 3 days throughout the study, to determine if there were any adverse effects or side effects of the therapy. Endpoints were a negative PCR and resolution of symptoms. The duration from the first day of drug intake to the negative PCR was counted as the Recovery Period to Negative PCR, and the duration from the first day of drug intake to the disappearance of symptoms was counted as the Period to Symptomatic Recovery. "Adverse Effects" were determined by the existence of the pharmacological side effects of the particular drug during treatment. A detailed history of adverse effects (other than the previous disease symptoms) experienced by each participant was collected during the follow-up sample collection. Informed written consent was obtained in every case. An asymptomatic participant was who presented with no symptom of COVID-19 and remain the same until the negative PCR.

Statistical analysis was done by Graph pad Prism software. Column analysis was done to find the mean with the standard deviation in each group. T-test was done to see the significance between the values where needed.

## **Results:**

This study was completed in a pre-determined period from May 2<sup>nd</sup> to June 5<sup>th</sup>, 2020. There were 181 patients who tested positive for SARS-CoV-2 infection in that period. 42 patients had comorbid conditions (some required hospitalization) that might affect the recovery time; 14 patients were unwilling to participate in the study, and 9 patients did not show-up (3 from group A and 6 from group B) for follow-up sample collection, so these were excluded. Following exclusion, 116 patients were included in this study.

Table 1: The total number of patients was 116; male 90 and female 26, age 16 to 80years, mean age 33.94years ( $\pm 14.12$ years). Group-A (Ivermectin + Doxycycline): male 43 (71.67%), female 17 (28.33%), age  $35.72 \pm 15.1$  years; males 37 years and female 32.88 years. Group-B (Hydroxychloroquine + Azithromycin): male 47 (83.93%), female 9(16.07%), age 31.91years; male 31.35, and female 34.5 years.[Figure 1 A &B]

Out of the total, 91 (78.45%) were symptomatic, and 25 (21.55%) were asymptomatic patients with contact history. This is 49(81.67%) and 11(18.33%) in the case of Group A; 42 (75%) and 14 (25%) in the case of Group B.

In Group A recovery to negative PCR rate was 100% (60/60). The mean recovery duration to negative PCR was 8.93days (8 to 13days). 41 (63.3%) patients had no new complaints other than their presenting symptoms. New symptoms that may be attributed to drug adverse effect or progression of COVID-19 disease included lethargy in 14(23.3%), nausea in 11(18.3%), and occasional vertigo in 7(11.66%) of patients. [Figure 1 D]

In Group B, out of 56 patients, two male patients were referred to a tertiary hospital and did not recover to a negative PCR as part of the study. The recovery rate to negative PCR was therefore 96.36% (54/56). The mean duration of recovery to negative PCR was 9.33 days (5 to 15 days). 30 (53.57%) of the patients had no new complaints other than their presenting symptoms. New symptoms that may be attributed to drug adverse effect or progression of COVID-19 disease included 13(23.21%) with mild blurred vision and headache; 22 (39.2%) with increased lethargy and dizziness, 10 (17.85%) with occasional, mild palpitation, and 9 (16.07%) with nausea and vomiting. [Figure 1 E]

The difference between Group A and Group B recovery to negative PCR duration is not statistically significant in unpaired t-test,  $P=0.2314$ . [Figure 1 C] Subgroup analysis of the

recovery duration: Male  $9.18 \pm 1.90$  days and female  $8.92 \pm 1.32$  days,  $P=0.515$ ; in Group-A male  $8.907 \pm 1.342$  days and female  $9 \pm 1.173$  days,  $P=0.44$ , Group-B male  $9.18 \pm 1.90$  days and female  $8.92 \pm 1.32$  days,  $P=0.407$ . The unpaired t-test between the recovery duration of both group male and both group female individually were not significant  $P = 0.18$  and  $0.69$ , respectively.

The mean duration of symptomatic recovery was 5.93days (5 to 10 days) in Group A and 6.99days (4 to 12 days) in Group B. [Figure 1 G] This difference in time to symptomatic recovery between Group A and Group B is not statistically significant in unpaired t-test,  $P=0.071$ . [Figure 1 G]

In Group A, over half of the subjects had become symptom-free by 5 days, 27 (55.10%), with the remaining subjects becoming symptom-free on day6 (16.32%), day7 (12.24%), day8 (8.16%), day9 (4%), and day10 (2.04%). [Figure 1 H] In Group B, recovery was slower with subjects becoming symptoms free on 4<sup>th</sup> day 3(7.14%), 5<sup>th</sup> day 10(23.8%), 6<sup>th</sup> day 9(21.43%), 7<sup>th</sup> day 8(19.04%), 8<sup>th</sup> & 9<sup>th</sup> day 4(9.52% each), 11<sup>th</sup> day 2(4.76%), and 10<sup>th</sup> & 12<sup>th</sup> day (2.38% each). [Figure 1 H]

In the secondary analysis of only those subjects who began the study with symptoms, the mean duration of time to negative PCR was 9.061 days in Group A and 9.738 days in Group B, which is not statistically significant in unpaired t-test,  $P=0.0714$ . The mean duration of time to becoming negative PCR of patients without symptoms was 8.364 days in Group A and 7.917 days in Group B, which is not statistically significant in unpaired t-test,  $P=0.443$ . [Figure 2 B] Further analysis shows the highest recovery was achieved on the 8<sup>th</sup> day among Group A patients in case of both asymptomatic ( $n=11$ ) and symptomatic ( $n=49$ ) patients, 8(72.72%) and 22(44.89%) respectively. [Figure 2 C & D] This recovery was relatively slower in Group B. On the 6<sup>th</sup> day 3(7.5%), 7<sup>th</sup> day 1(2.5%), 8<sup>th</sup> day 9(22.5%), 9<sup>th</sup> & 10<sup>th</sup> day 8(20%) each, 11<sup>th</sup> & 12<sup>th</sup> day 4(10%) each, 13<sup>th</sup> day 1(2.5%), and 14<sup>th</sup> day 2(5%) in case of Group B patients with symptoms ( $n=40$ ). Among asymptomatic patients ( $n=14$ ) this was 1(7.5%) on the 5<sup>th</sup> day, 2(14.2%) individually 6<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 10<sup>th</sup> day, 4(28.57%) 9<sup>th</sup> day, and 1(7.1%) on the 11<sup>th</sup> day. [Figure 2 C & D]

## Discussion:

The COVID-19 pandemic in Bangladesh is part of the Coronavirus worldwide pandemic disease caused by a newly discovered Coronavirus. Initially, it was called the novel Coronavirus and later named severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) due to its similar characteristics with severe acute respiratory syndrome Coronavirus 1 (SARS-CoV-1).[7-9] The treatment methods for COVID-19 are emerging and rapidly evolving because of ongoing research being done worldwide by a record number of investigators. Due to the uniqueness of each medical and research facility, the approach to the care of patients with COVID-19 varies from institution to institution; in Bangladesh, many patients with mild to moderate disease were being treated with Hydroxychloroquine (HCQ) and Azithromycin. New concerns about HCQ has led us to seek alternatives with shorter recovery time and better tolerability. Thus, we have undertaken a comparative therapeutic analysis, comparing these standard drugs with Ivermectin and Doxycycline.

HCQ, a less toxic derivative of chloroquine, is an antimalarial drug and has decades of treatment use as an immunomodulator. [10] At present, it has been the topic of discussion concerning its potential use to treat patients with COVID-19.[11] It is thought that the effect of HCQ on antigen cross-presentation may occur, in which a dendritic cell presents the antigen to CD8<sup>+</sup>Tcells. Thus, improving their priming followed by the activation of CD8<sup>+</sup> T-cells through antigen recognition, this results in the induction of selective killing of the infected cells. Therefore, it may accelerate viral clearance in COVID-19.[13] Some studies show that severe deterioration in some patients with COVID-19 has been closely associated with dysregulated and excessive cytokine release termed "cytokine storm" [14, 15] HCQ was found effective in inhibiting SARS-CoV-2 infection in vitro and can significantly decrease the production of cytokines and especially the pro-inflammatory cytokines.[16]

Azithromycin is in the macrolide group of antibiotic drugs used in the treatment of several bacterial infections, including pneumonia. It is known to reversibly bind to the 50S ribosomal subunit of the 70S ribosome to inhibit the translocation step of protein synthesis, but whether it has an antiviral effect or not is not yet known. It has been studied as part of the possible treatment of COVID-19 in combination with HCQ and has been reported to add benefit. [17, 18] However, a recent report failed to establish whether it has any antiviral activity or any synergistic activity with HCQ in the treatment of COVID-19.[19] Therefore, a further

comparative study can enhance the significance of the combination therapy of HCQ and Azithromycin.

Ivermectin is a relatively safe and well-tolerated anti-parasitic drug for head lice, scabies, onchocerciasis, and strongyloidiasis that acts by inhibiting nuclear transport activity. [20] In-vitro studies have shown its function against human immunodeficiency virus (HIV), dengue, influenza, and most recently, against SARS-CoV-2. This effectiveness against SARS-CoV-2 infection is due to its critical interaction of RNA viruses responsible for integrase protein nuclear import.[21, 22] A recent report suggests that Ivermectin reduces mortality rates in hospitalized patients with COVID-19.[23] However, it is not known if antiviral levels are attainable while using known dosing regimens of Ivermectin therapy in patients with COVID-19.[24, 25] Thus, it is vital to investigate the dose regimens of Ivermectin for COVID-19 treatment or to determine if there is appropriate synergism using combination therapy with another drug.

Doxycycline is in the tetracycline class of antibiotics that acts via the inhibition of bacterial ribosomes. It is a well-tolerated bacteriostatic drug that has a long history of clinical use.[26] The efficacy and tolerability of Ivermectin and Doxycycline were established in combination with an earlier study for the treatment of onchocerciasis.[27] Several recent studies have suggested a therapeutic role of Doxycycline against COVID-19.[28, 29]

In this randomized treatment study, we used two different drug combinations, Ivermectin-Doxycycline (Group A) and Hydroxychloroquine-Azithromycin (Group B), for the outpatient therapy of patients with mild to moderate COVID-19 in Bangladesh. The presenting symptoms of the COVID19 patients were fever, cough, sore throat, weakness, chest discomfort, breathing difficulty, diarrhoea, myalgia, and abdominal pain. To avoid the influence in the recovery duration, we solely selected the cases devoid of any severe comorbidities. Only patients with mild to moderate disease that could be treated as outpatients were included. HCQ dosing was decided as per "National guideline for COVID19 management 4.0".

The difference in recovery to negative PCR duration was not significant ( $P=0.231$ ) among the two groups. Still, the mean duration of recovery is shorter 8.933days in the case of Ivermectin-Doxycycline (Group A) than that of Hydroxychloroquine-Azithromycin (Group B) 9.33 days. [Figure 1 C] Also, the Ivermectin-Doxycycline group had a better outcome ratio of 100% (60/60) recovery to negative PCR compared to that of HCQ 96.36% (54/56).

The difference in recovery to becoming symptom-free was 5.93days (5 to 10 days) in Group A and 6.99days (4 to 12 days) in Group B. This difference was not statistically significant. The Ivermectin group showed a better symptomatic recovery (5.93days) in comparison to the HCQ group (6.99days). [Figure 1 G] In the case of Group-A most of the patients gained symptomatic recovery on the 5<sup>th</sup> (55.50%), 6<sup>th</sup> (16.32% and 7<sup>th</sup> (12.24%) day, this is 23.8%, 21.43% and 19.04% in the Group-B.[Figure 1 H] In the case of symptomatic and asymptomatic patients the Ivermectin-Doxycycline combination expressed an earlier and faster relief of COVID features and viral clearance than that of HCQ-Azithromycin combination. [Figure: 2 A, C & D] Though the mean recovery duration is not statistically significant in an unpaired t-test. [Figure 2: B] This suggests Ivermectin-Doxycycline may have better efficacy in reducing the COVID-19 symptoms than that of HCQ-Azithromycin therapy.

Additional considerations are tolerability and compliance. In our study, the Ivermectin-Doxycycline group had better patient compliance and fewer adverse effects as compared to the HCQ-Azithromycin group, 31.67%, and 46.42% respectively. [Figure 1 D & E] The adverse effects of HCQ in our study are similar to others,[30] with 39.2% of patients complaining of lethargy-dizziness, and with blurred vision and occasional palpitations noted by 23.21% and 17.85% of patients in the HCQ group. In comparison, the adverse effects seen in Group A were also lethargy, nausea, and occasional vertigo but at a lower rate than in Group B, with 23.3% complaining of these adverse effects in Group A.

The sex difference was examined but there were no significant differences in outcome between the males and females in this study. In case of Group A, both male and female had almost the same duration of recovery to negative PCR (8.9 and 9 days) but in Group B (9.45 and 8.78 days), male patients had a longer duration of recovery to negative PCR than the females (9.18 days and 8.92 days).[Figure 1 F]

According to this study, both the Ivermectin-Doxycycline and HCQ-Azithromycin treatment regimens were tolerated and may have been an effective treatment for mild to moderate SARS-CoV-2 infection. With regard to time to becoming symptom-free, Ivermectin-Doxycycline combination is superior to HCQ-Azithromycin therapy for mild to moderate degrees of COVID-19 patients. In addition, the Ivermectin-Doxycycline combination is superior to HCQ-Azithromycin in terms of safety, side-effect profile, and compliance. We strongly believe that increasing the duration of Ivermectin treatment to 3days will offer further benefit in

reducing the recovery period of COVID beyond that which was seen in our study. This will also prevent disease progression and morbidity to COVID-19 patients.

Our study has limitations; these include relatively small sample size, the dose of Ivermectin, case selection, also the outcome may be biased by additional factors like severity of the disease, lack of cooperation of some participants, and unknown comorbidity.

### **Conclusion:**

Researchers have suggested different drug combination therapies for COVID-19. According to our study, the Ivermectin-Doxycycline combination therapy has a better success of symptomatic relief; shortened recovery duration, reduced adverse effects, and superior patient compliance compared to the Hydroxychloroquine-Azithromycin combination. Based on our outcomes, Ivermectin is a better choice for the treatment of patients with mild to moderate COVID-19 disease. This study has limitations; despite this, we tried to select our study group patients without any major or unstable comorbid condition as far as possible to avoid differences in treatment outcomes among the groups. Further study is required on a larger scale with an increase in the duration of Ivermectin treatment.

### **Abbreviations:**

COVID-19: Coronavirus disease 2019

COPD: Chronic Obstructive Pulmonary Airway Disease.

HCQ: Hydroxychloroquine

RT PCR: Real-time Polymerase Chain Reaction

RNA: Ribonucleic acid

SARS-Cov-2: Severe acute respiratory syndrome Coronavirus 2

WHO: World Health Organization

RCT: Randomized Controlled Trial

### **DECLARATIONS:**

**Clinical trial registration:** ClinicalTrials.gov NCT04434144; “A Comparative Study on Ivermectin and Hydroxychloroquine on the COVID19 Patients in Bangladesh”.

**Detail study protocol:** <https://clinicaltrials.gov/ct2/show/NCT04434144>

**Ethics:** The study was approved by the hospital ethics committee of Chakoria Upazilla Health Complex.

**Consent to participate:** The purpose of this research was explained to the participant. Once the verbal consent was understood and agreed upon, written consent was then obtained from the participants. There was no participant in bellow 16 years.

**Consent to publish:** The authors have read the manuscript and gave consent to publish.

**Competing Interests:** None to declare.

**Availability of data and materials:** The datasets used and/or analyzed during the current study are uploaded as supporting documents after anonymization.

**Funding:** Not applicable.

**Authors' contributions:**

ATMMC gave the basic research concept, analyzed & collected the data of COVID19 patients, and wrote the manuscript.

MS was responsible for patient selection, treatment, patient management, follow-ups, patient counseling, and data collection.

MRK partially wrote the discussion part of the article.

GD and JI interpreted the data for analysis.

HS gave the concept of research maintained supervision.

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Table 1: Baseline characteristics of the study group patients.

<b>Parameters</b>	
Number of patients (n)	116
Male	90 (77.58%)
Female	26 (22.41%)
Group A (n)	60
Group A Male (n)	43 (71.67%)
Group A Female (n)	17 (28.33%)
Group B (n)	56
Group B Male (n)	47 (83.93%)
Group A Female (n)	9 (16.07%)
Age (in years)	33.94±14.12 (8 to 80 Years)
Symptomatic	91 (78.45%)
Asymptomatic	25 (21.55%)
Age <b>Group A</b> (in years)	35.72±15.1
Male	37.14±14.72
Female	32.88±16.2
Symptomatic (n)	49 (81.67%)
Asymptomatic (n)	11 (18.33%)
Age <b>Group B</b> (in years)	31.91±12.72
Male	31.35±12.95
Female	34.5±11.74
Symptomatic (n)	42 (75%)
Asymptomatic (n)	14 (25%)

## Figure legends:

Figure 1: (A) Number of patients according to gender among the groups. (B) Gender variation of age among the study groups (data presented as mean  $\pm$  SD). (C) Recover duration of Ivermectin-Doxycycline and HCQ-Azithromycin group; note: the difference between the recovery duration among the groups is not statistically significant  $P=0.231$ . (D) Adverse effect expressed by the patients of Group-A. (E) Adverse effect experienced by the patients of Group-B. (F) Variation of the recovery duration according to the gender; note: males in Group-B and males as gender, in general, have a longer recovery period than the females. (G) Duration of the symptomatic recovery (in days) among the groups. The difference between the duration among groups is not significant  $P=0.071$ . (H) Subgroup analysis of the recovery duration among the groups. Note: Group-A has a higher number of symptomatic recoveries in the early days, this indicates a better efficacy of Ivermectin-Doxycycline therapy.

Figure 2: (A) Comparison between the symptomatic recoveries among the study groups. Note: Group A (Ivermectin-Doxycycline) showed a pick recovery on the 5<sup>th</sup> day. In Group B (HCQ-Azithromycin) the symptomatic recovery started relatively earlier on the 4<sup>th</sup> day but had a slow trend. (B) Mean duration of recovery (beginning of the treatment to the negative PCR) of the patients with and without symptoms among Group A & B was not statistically significant in the subgroup analysis. (C) Subgroup analysis of recovery duration of the symptomatic patients among the study groups. Maximum numbers of negative PCR were achieved on the 8<sup>th</sup> day in both groups. Group A 22(44.89%) and Group B 9(22.5%). The recovery rates are faster in Group A; though relatively earlier but slow in Group B. (D) Subgroup analysis of recovery duration of the asymptomatic patients. Most patients in Group A gained viral clearance on 8<sup>th</sup> day 8(72.72%). Not: first PCR was done on the 5<sup>th</sup> day. In Group B 1(7.1%) was recovered on the 5<sup>th</sup> day and 2(14.2%) on the 6<sup>th</sup> day. The highest recovery was observed on the 9<sup>th</sup> day 4(28.57%)

Figure 3: Flow diagram of randomization and treatment assignment of the participants.