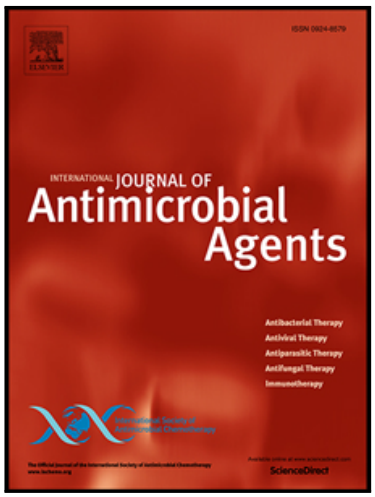

NSafety and Effectiveness of Azithromycin in Patients with COVID-19: an open-label randomized trial

Ehsan Sekhavati , Fatemeh Jafari , SeyedAhmad SeyedAlinaghi , Saeidreza Jamali Moghadam Siahkali , Sara Sadr , Mohammad Tabarestani , Mohammad Pirhayati , Abolfazl Zendehdel , Navid Manafi , Mahboubeh Hajiabdolbaghi , Zahra Ahmadinejad , Hamid Emadi Kouchak , Sirous Jafari , Hosein Khalili , Mohamadreza Salehi , Arash Seifi , Fereshteh Shahmari Golestan , Fereshteh Ghiasvand

PII: S0924-8579(20)30341-1
DOI: https://doi.org/10.1016/j.ijantimicag.2020.106143
Reference: ANTAGE 106143

To appear in: *International Journal of Antimicrobial Agents*

Please cite this article as: Ehsan Sekhavati , Fatemeh Jafari , SeyedAhmad SeyedAlinaghi , Saeidreza Jamali Moghadam Siahkali , Sara Sadr , Mohammad Tabarestani , Mohammad Pirhayati , Abolfazl Zendehdel , Navid Manafi , Mahboubeh Hajiabdolbaghi , Zahra Ahmadinejad , Hamid Emadi Kouchak , Sirous Jafari , Hosein Khalili , Mohamadreza Salehi , Arash Seifi , Fereshteh Shahmari Golestan , Fereshteh Ghiasvand , NSafety and Effectiveness of Azithromycin in Patients with COVID-19: an open-label randomized trial, *International Journal of Antimicrobial Agents* (2020), doi: https://doi.org/10.1016/j.ijantimicag.2020.106143

Highlights:

- **Ventricular arrhythmias can happen in concurrent use of azithromycin and hydroxychloroquine.**
- **Combination therapy with hydroxychloroquine and azithromycin can reduce the length of hospitalization in COVID-19 patients.**
- **Preparatory risk assessment can limit the risk of arrhythmias in patients receiving hydroxychloroquine and azithromycin combination therapy.**

Title: Safety and Effectiveness of Azithromycin in Patients with COVID-19: an open-label randomized trial

Authors:
Ehsan Sekhavati[1], Fatemeh Jafari[2,3], SeyedAhmad SeyedAlinaghi[4], Saeidreza Jamali Moghadam Siahkali[5], Sara Sadr[2], Mohammad Tabarestani[6], Mohammad Pirhayati[3], Abolfazl Zendehdel[7], Navid Manafi[3], Mahboubeh Hajiabdolbaghi[8], Zahra Ahmadinejad[9], Hamid Emadi Kouchak[8], Sirous Jafari[8], Hosein Khalili[10], Mohamadreza Salehi[8], Arash Seifi[8], Fereshteh Shahmari Golestan[11], Fereshteh Ghiasvand[9,*]

1- Assistant Professor of Cardiology, Department of Cardiology, Ziayian Hospital, Tehran University of Medical Sciences, Tehran, Iran

2- Mazandaran University of medical sciences, school of medicine, Sari, Iran

3- Iran University of medical sciences, school of medicine, Tehran, Iran

4- Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran

5- Department of Infectious Diseases, Ziayian Hospital, Tehran University of Medical Sciences, Tehran, Iran

6- Medical Students Research Committee, Mazandaran University of medical sciences, school of medicine, Sari, Iran

7- Associate Professor of Internal Medicine, Geriatric Department, Ziayian Hospital, Tehran University of Medical Sciences, Tehran, Iran

8- Department of Infectious Diseases, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

9- Liver Transplantation Research Center, Department of Infectious Diseases, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

10- Department of pharmacotherapy, faculty of pharmacy, Tehran University of Medical Sciences, Tehran, Iran

11- Nurse Working In Department of Infectious Diseases, Tehran University of Medical Sciences, Tehran, Iran

***Corresponding author**: Fereshteh Ghiasvand, MD.
Liver Transplantation Research Center, Department of Infectious Diseases, Imam Khomeini Hospital Complex, Keshavarz boulevard, Tehran University of Medical Sciences, Tehran, Iran. 14197-33141, I.R. of Iran. Tel: +98 21 61192659, Fax: +98 21 66581657, E-mail: ghiasvand_62@yahoo.com

Abstract

Background: As no specific pharmacologic treatment has been validated for use in COVID-19, we aimed to assess the effectiveness of azithromycin in these patients at a referral center in Iran.

Methods: An open-label, randomized, and controlled trial was conducted on patients with laboratory confirmed COVID-19. The 55 patients of the control group receiving hydroxychloroquine and lopinavir / ritonavir were compared with the 56 patients of the case group who in addition to the same regimen were also receiving azithromycin. Patients with prior cardiac disease were excluded from the study. Furthermore, patients from the case group were assessed for cardiac arrythmia risk based on the American college of cardiology (ACC) risk assessment for use of azithromycin and hydroxychloroquine. The main outcome measures were vital signs, SpO2 levels, duration of hospitalization, need for and length of intensive care unit (ICU) admission, mortality rates, and results of 30-day follow-up after discharge.

Results: Initially, there was no significant difference between the general conditions and vital signs of the two groups. The SpO2 levels at discharge were significantly higher, the respiratory rate was lower, and the duration of admission was shorter in the case group. There was no significant difference in the mortality rate between the two groups.

Conclusion: Patients who received azithromycin in addition to the hydroxychloroquine and Kaletra regimen had a better general condition. The hydroxychloroquine-azithromycin combination may be beneficial for individuals who are known to have a very low underlying risk for cardiac arrhythmias based on the ACC criteria.

Keywords: COVID-19, SARS-CoV-2, Azithromycin, Hydroxychloroquine, lopinavir, ritonavir.

Introduction

In late December 2019, an outbreak of an emerging disease with a remarkably high virulence in Wuhan, China, soon became a global concern. Disease symptoms resemble a viral pneumonia and genetic analysis of lower respiratory tract samples of early infected patients showed an infection caused by a novel coronavirus subsequently named COVID-19, also known as 2019-nCoV. The disease rapidly spread throughout China and infected multiple other countries [1,2]. On March 12th, the world health organization (WHO) declared the epidemic of COVID-19 as a global pandemic. In addition to the primary respiratory involvements, reports show other organ systems including gastrointestinal, neurological, and hematopoetic systems can also be considerably affected by this virus [3,4]. Coronavirus infection in humans are mostly mild, and a meta-analysis of the epidemiologic studies conducted in China showed 12.6 to 23.5% of patients experience a severe form of the disease with an overall mortality rate of 2.0-4.4% [5]. There are no specific pharmacological treatments for the novel coronavirus yet [6]. Repositioning well known medications as antiviral treatment is preferred in circumstances where there is little time for standard randomized control trial (RCT) studies and preliminary laboratory investigations into a new medication. Complete knowledge of the possible side effects and safety profiles of old medications lays the groundwork for better monitoring the treatment effect and outcome [7]. Multiple medications have been used in clinical trial studies against COVID-19. Chloroquine, an immunomodulant drug, is widely used as an antimalarial agent and it was discovered to have broad spectrum antiviral effects in 2006 [8]. Hydroxychloroquine (an analogue of chloroquine) has a better clinical safety profile, and allows for a higher daily dose compared to chloroquine [9,10]. Lopinavir/ritonavir combination has been approved, and used in human immunodeficiency virus (HIV) infection across the world, both substances are protease inhibitors but ritonavir also enhances the pharmacokinetic and pharmacodynamics properties of lopinavir [11]; and these antiviral agents have been used in the treatment of middle east respiratory syndrome (MERS) [12]. Lopinavir has also been proven to have *in vitro* activity against SARS-CoV infection (SARS) in humans [13–15]. Azithromycin, a macrolide antibiotic, has shown efficacy in preventing severe respiratory infections in patients suffering from viral pneumonia [16] and *in vitro* studies have demonstrated that it is active against Zika and Ebola viruses [17] and has a high affinity for the binding interaction site of the SARS-CoV-2 spike and angiotensin converting enzyme II (ACE II) [18]; which is the critical human cell receptor of the COVID-19 and, it is believed that blocking this interaction can potentially cure the infection [19].

The hydroxychloroquine and azithromycin combination has been very well received among physicians and according to an online international survey of 5,500 physicians, fielded over April 13th-15th, these medications are the most commonly used medication in treatment of COVID-19 [20]; but there is a considerable cardiac risks associated with the concomitant use of azithromycin and hydroxychloroquine and cardiac arrhythmias caused by QT interval prolongation can potentially increase the mortality rate in patients who are treated with this combination [21,22].

In this clinical trial we used the scoring system proposed by the American College of Cardiology (ACC) [23] to exclude patients with a moderate to high risk of cardiac arrhythmias from the study and evaluate the potential treatment benefits of this combination in patients with low risk for QT prolongation and arrhythmia.

Material and methods

Participants

Between April 24th and May 8th, 202 patients with compelling clinical symptoms for a diagnosis of COVID-19 were admitted to Ziaeian Hospital, Tehran, Iran. All patients underwent reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing, and a lung CT-Scan. The inclusion criteria were a positive RT-PCR test and significant findings compatible with radiographic imaging of a COVID-19 pulmonary involvement. The exclusion criteria were age less than 18 years old, pregnancy or nursing during the time of admission, past history or concurrent cardiac disease, recent history of antiviral therapy, and contraindications for use of hydroxychloroquine, azithromycin, or lopinavir/ritonavir (kaletra, AbbVie Inc. North Chicago, IL 60064), such as retinopathy or G6PD deficiency, or a history of allergic reactions to these medicines.

Study arms and treatment plans

Patients were randomly divided into two treatment groups of 56 and 55 patients. On the first day of admission, laboratory studies including complete blood count (CBC), and erythrocyte sedimentation rate (ESR) were performed. The first (case) group received daily oral azithromycin 500 mg, twice-daily oral lopinavir/ritonavir 400/100 mg, and daily 400 mg of oral hydroxychloroquine. The second (control) treatment group received twice-daily oral lopinavir/ritonavir 400/100 mg, and oral daily 400 mg of hydroxychloroquine; for both treatment groups, all medications were administered for five days.

On the first day of admission, for the patients assigned to the first treatment group, the risk for ventricular arrhythmia in concurrent treatment with hydroxychloroquine and azithromycin was calculated based on the proposed guideline by the ACC [23], and patients with a score of seven or higher, were excluded from the study.

Patients were assessed by daily measurements of core body temperature, respiratory rate (RR), heart rate (HR), and peripheral capillary oxygen saturations (SpO2). Daily electrocardiogram (ECG) studies were also conducted to monitor possible evolution of QTc (corrected QT) interval prolongation; in which case, treatment with azithromycin and hydroxychloroquine would have been stopped. For correction of QT interval, Bazett formula ($QT_C = QT / \sqrt{RR}$) was used [24]. In case of deterioration in general and/or pulmonary conditions, methyl-prednisolone was prescribed [25]. Patients were discharged when they achieved a stable SpO2 > 92%, had no respiratory distress, and were afebrile for three consecutive days. The primary end points in this trial were decrease in mortality, duration of hospitalization, and need for ICU admission. The secondary endpoints were determined as the improvements in SpO2 and vital signs, and also the general well-being of the patients.

Sample size calculation was performed for non-inferiority tests of difference between two group proportions. We assumed the effectiveness of 65% for the intervention group and effectiveness of 50% for the control group. We also assumed the margin of non-inferiority of at least 10% between two group. With these assumptions, sample size of 48 cases in each group was calculated. After consideration of dropout rate of 10%, the total sample size of 110 cases was calculated. The power of the study was determined as 90% (G*Power, Erdfelder, Faul, & Buchner, 1996).

Ethical considerations

In accordance to the declaration of Helsinki, written informed consent was obtained from all participants before initiation of the study. Patients were assured that declining to participate or leaving the study at any point would not affect the quality of their treatment and that they would thereafter receive standard care. The study protocol was approved by the institutional review board of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.165).

Measurements and statistical analysis

Distribution of age, gender, initial clinical symptoms and vital signs measured on the first day of admission were compared between the two groups. The vital signs including core body

temperature, RR, HR and SpO2 were also compared on the third and last day of treatment between the two groups as an outcome measure. Difference in duration of hospitalization, number of patients whose condition deteriorated and needed ICU admission, length of ICU hospitalization, difference between mortality rates, and results of 30-day follow-up after discharge were also evaluated as outcome measures.

Analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Quantitative variables were reported by mean and standard deviation (SD) and qualitative variables were reported using frequency and percentage. Because of the normal distribution of the data, the independent t-test was used to assess the means differences. Chi-square and Fisher exact tests were used to assess the statistical relationships between categorical variables. The level of significance was set as P value < 0.05 for all analyses. Number needed to treat (NNT) with a confidence interval (CI) of 95% was reported for need for ICU admission, need for intubation, and mortality rate. We also evaluated the effect size based on Hedges' g because of the difference in the number of participants in each group.

Safety

Since a step wise plan was practiced in our study, patients with any prior cardiac disease were excluded from the study. Furthermore, the ACC criteria for risk assessment of simultaneous use of azithromycin and hydroxychloroquine were assessed for each person to make sure no patient has increased risk of ventricular arrythmia. All patients were also monitored closely for any signs of ECG rhythm abnormality or clinical features of cardiac arrhythmia.

Results

Demographic characteristics

Based on the inclusion criteria and after excluding 91 cases, 111 cases were included in the study which were randomized and allocated between two groups of case (56 patients) and control (55 patients). All day required treatment duration-patients completed their five

The ventricular arrhythmia risk score was three in 12 (21.4%) patients, four in 32 (57.1%) patients, and five in 12 (21.4%) patients. The mean age and demographic factors such as gender were not significantly different between the two arms (P value = 0.70 and 0.387, respectively) **(Table 1)**.

Clinical and para-clinical findings

Table 1 illustrates clinical features and laboratory test results of patients in both groups. Fever, dyspnea, chills, cough, production of sputum, hemoptysis, and chest pain were not significantly different between the two groups (P value > 0.05). Myalgia, headache, and vomiting were initially more reported by the control patients (P values = 0.000, 0.005, 0.031, respectively). Weakness was significantly more often found in patients of the case group (P value = 0.042) . The mean SpO_2 levels upon admission and on the third day of admission were not remarkably different between the two groups (P values = 0.920, 0.610 respectively). Laboratory test results did not show a significant difference between two groups (P value > 0.05).

Treatment outcomes

Table 2 shows treatment outcomes in both treatment groups. Core temperature was not significantly different between the case and the control group (36.88 *vs* 36.77°C respectively ,P value= 0.19). At discharge, SpO_2 levels were significantly higher in the case group (93.95% *vs* 92.40%, P value = 0.030) and the RR was significantly lower (15.85 *vs* 17.42 respirations per minute, P value = 0.010) in that group. Duration of hospitalization in the case group was significantly shorter than the control (4.61*vs* 5.96 days, P value = 0.02) (**Figure 4**). The calculated effect size for SpO_2 levels, RR at discharge, and duration of hospitalization were -0.461, 0.721 and, 0.618 (all medium effect sizes) respectively (**Table 2**). Two patients in the case and seven patients in the control groups needed ICU admission which did not show statistical significance (3.5% vs. 12.7% respectively, P value = 0.07). Three patients in the control group were intubated during the course of admission *versus* no patients in the case group; which was statistically insignificant (P value = 0.118) **(Figure3**). The difference between the mean duration of ICU admission was not significant between the groups (5.00 *vs* 4.43 days, P value = 0.157). There was one mortality in the control group and no mortalities in the case group; this difference was insignificant (P value = 0.495). No patient in either group experienced cardiac arrhythmia or QTc prolongation.

Discussion

During the rapid global pandemic of COVID-19, it is important to have an effective and safe treatment plan. There are several reports on the effectiveness of various medications, but none of them have been proven to be significantly effective yet. Recently, a combination

therapy of hydroxychloroquine and azithromycin has become one of the most favored treatment regimens among medical professionals [26–28]. studies have shown the combination of hydroxychloroquine and azithromycin can reinforce the efficacy of hydroxychloroquine [28,29]. Gautret et al conducted a non-randomized open-label clinical trial that has shown promising results for the combination of HCQ and azithromycin. In their study, they reported that the HCQ/azithromycin combination has a significant effect on viral load reduction within only three to six days of treatment in COVID-19 patients [29], but a number of reviews have questioned the randomization technique used in this study and pointed that the small study patient population and other methodological pitfalls question the certainty with which the results of this study are to be received [30–33]. Million et al., published an article which was an extension to the previous study by Gautret et al., in which they conducted a retrospective analysis of 1,061 cases in France and reported that the HCQ/azithromycin combination therapy is beneficial and significantly lowers the mortality rate [34].

In the current study, as an open-label blocked randomized clinical trial, we found that patients who received azithromycin in addition to hydroxychloroquine had a shorter duration of hospitalization in comparison to the control group; with a medium effect size (P value = 0.020, Hedges' g = 0.618). Calvalcanti et al, in their study as a multicenter, randomized, open-label, three-group, controlled trial evaluated the safety and efficacy of hydroxychloroquine and azithromycin in hospitalized patients with suspected or confirmed COVID-19. They reported that the duration of hospital stay was higher in patients who were treated with both hydroxychloroquine and azithromycin compared to those who were only treated with hydroxychloroquine; but this difference was non-significant (10.3 vs 9.6, Odds ratio:0.7, 95% CI: -0.6-1.9) [35].

In our study, there were two patients in the case (3.57%) and seven patients in the control group (12.73%) who needed ICU admission, which does not show statistical significance. Rosenberg et al, in their retrospective multicenter cohort study evaluated 1,438 patients with confirmed diagnosis of COVID-19. They reported a higher frequency of ICU admission in patients receiving hydroxychloroquine and azithromycin (30.7%) or hydroxychloroquine alone (19.2%) compared to those receiving only azithromycin (10.9%) [36].

In our study there was one mortality in the control group and no mortalities in the case group; this difference was insignificant (P value = 0.495); but, Arshad et al, in their multi-center retrospective observational study in hospitalized patients positive for COVID-19 reported that

treatment with azithromycin alone significantly decreased the mortality hazard ratio by 66% and combination therapy with hydroxychloroquine decrease the mortality hazard ratio by 71%. They also performed a multivariate COX regression model and found that combination therapy had no significant effect on mortality rate [37]. Rosenberg et al., reported the probability of death for patients who were under treatment by hydroxychlorquine and azithromycin was 25.7% (CI 95%:22.3%-28.9%). They compared patients who were treated with hydroxychloroquine, azithromycin, and both with patients who received no treatment and reported there was no significant association between treatment with these medications—alone or in combination—and the in-hospital mortality rate [36]. However, the observational design of their study may limit definite interpretations of their findings. Despite the results of other studies which report an effective virucidal potency for the combination of hydroxychloroquine and azithromycin [34,36,38], Molina et al., reported that they didn't find any evidence to support the efficacy of this combination in viral clearance or improvement of clinical status of their patients [33].

Our study also showed that patients in the experimental treatment group who were treated with azithromycin in addition to the main treatment regimen, had significantly higher SpO_2 levels (P value = 0.030) and a lower respiratory rate at the time of discharge (P value = 0.010). The effect sizes showed the differences between two groups in these variables were considerable (Hedges' g = -0.461, Hedges' g = 0.721, respectively). Calvalcanti et al reported that patients receiving hydroxychloroquine and azithromycin compared to patients who received azithromycin alone had a non-significant lower rate of need for oxygenation with high flow nasal cannula or non-invasive ventilation during the treatment (9.3% vs 10.7%, Odds ratio: 0.92, 95% CI: 0.5-1.7) [35].

Possible side effects of a treatment are determining factors in evaluating the suitability of a medication regimen. Chloroquine or hydroxychloroquine as a monotherapy has some common adverse effects such as pruritus, nausea, headache and some uncommon but serious adverse effects such as arrhythmias due to QT interval prolongation, hypoglycemia, idiosyncratic hypersensitivity reactions and neuropsychiatric effects [39]. Prolongation of the QTc interval and *torsade de pointes* (TdP) are the most important side effects of separate, and specially concomitant treatments with HCQ and macrolides such as azithromycin that can negatively affect the survival rate [35,37]. Lane et al evaluated the safety of HCQ alone, and in combination with azithromycin. They studied 323,122 patients who were treated with this combination, and concluded that a short term treatment with HCQ is safe but, a long-term treatment or addition of azithromycin to the treatment—even in short-term—may increase the

risk of heart failure or cardiovascular mortality rate which can be caused by their synergetic effects on the QTc interval, leading to a lethal arrhythmia [40]. Considering the possible side effects of this combination therapy, clinicians should consider having a baseline corrected QT interval and monitoring of QTc intervals, heart-rate and serum electrolytes during administration of these drugs [38]. A scoring system to predict the risk of QT interval prolongation in hospitalized patients has been designed (Table 1); Score of less than 7, 7 to 10, and greater than 11 respectively correlate with a low, medium and high risk of QT interval prolongation in hospitalized patients [23]. In our study, all patients had a risk score of less than 6, all patients were monitored during treatment and none of them experienced QTc interval prolongation, which would have warranted a halt in treatment with hydroxychloroquine and azithromycin.

Limitations

A small sample size and an open label design are the limitations of our study. Because of the shortage in our resources, we could not test the viral loads of the patients in daily intervals.

Conclusion

The patients in the group receiving the experimental treatment regimen which included azithromycin, had a significantly shorter hospital stay and significantly higher SpO_2 and lower respiratory rates at discharge. However, risk scoring system should be utilized before initiating treatment to prevent QTc prolongation, especially for high risk patients.

Declarations

Funding: Supported by the Tehran University of Medical Sciences' research center [grant numbers 47493]

Competing Interests: No

Ethical Approval: The project was approved by Tehran University of medical sciences ethics board (IR.TUMS.VCR.REC.1399.165)

References

[1] Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents 2020:105924.

[2] Wang L, Wang Y, Ye D, Liu Q. A review of the 2019 Novel Coronavirus (COVID-19) based on current evidence. Int J Antimicrob Agents 2020:105948.

[3] Sadr S, SeyedAlinaghi S, Ghiasvand F, Hassan Nezhad M, Javadian N, Hossienzade R, et al. Isolated severe thrombocytopenia in a patient with COVID-19: A case report. IDCases 2020;21:e00820. https://doi.org/10.1016/j.idcr.2020.e00820.

[4] Behzad S, Aghaghazvini L, Radmard AR, Gholamrezanezhad A. Extrapulmonary manifestations of COVID-19: Radiologic and clinical overview. Clin Imaging 2020;66:35–41.

[5] Hu Y, Sun J, Dai Z, Deng H, Li X, Huang Q, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Virol 2020:104371.

[6] Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care 2020;57:279–83. https://doi.org/https://doi.org/10.1016/j.jcrc.2020.03.005.

[7] Colson P, Rolain J-M, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. Int J Antimicrob Agents 2020;55:105923.

[8] Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. Lancet Infect Dis 2006;6:67–9.

[9] Marmor MF, Carr RE, Easterbrook M, Farjo AA, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: a report by the American Academy of Ophthalmology. Ophthalmology 2002;109:1377–82.

[10] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020.

[11] Okubo K, Isono M, Asano T, Sato A. Lopinavir-Ritonavir Combination Induces Endoplasmic Reticulum Stress and Kills Urological Cancer Cells. Anticancer Res 2019;39:5891–901.

[12] Arabi YM, Alothman A, Balkhy HH, Al-Dawood A, AlJohani S, Al Harbi S, et al. Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): study protocol for a randomized

controlled trial. Trials 2018;19:81.

[13] Chen F, Chan KH, Jiang Y, Kao RYT, Lu HT, Fan KW, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 2004;31:69–75.

[14] Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, Chan KS, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59:252–6.

[15] Wu C-Y, Jan J-T, Ma S-H, Kuo C-J, Juan H-F, Cheng Y-SE, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci 2004;101:10012–7.

[16] Bacharier LB, Guilbert TW, Mauger DT, Boehmer S, Beigelman A, Fitzpatrick AM, et al. Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial. Jama 2015;314:2034–44.

[17] Bosseboeuf E, Aubry M, Nhan T, Pina JJ, Rolain JM, Raoult D, et al. Azithromycin Inhibits the Replication of Zika Virus. J Antivir Antiretrovir 2018;10:6–11.

[18] Sandeep S, McGregor K. Energetics Based Modeling of Hydroxychloroquine and Azithromycin Binding to the SARS-CoV-2 Spike (S) Protein-ACE2 Complex 2020.

[19] Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell 2020;181:905-913.e7.

[20] Sermo. Sermo's COVID-19 Real Time Barometer Study 2020. https://public-cdn.sermo.com/covid19/c7/cf1f/1fcad8/cad8234b3d9288a1ed3ae51afc/w4-sermo-covid-19-barometer.pdf (accessed April 15, 2020).

[21] Chorin E, Dai M, Shulman E, Wadhwani L, Bar-Cohen R, Barbhaiya C, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med 2020. https://doi.org/10.1038/s41591-020-0888-2.

[22] Morgan ND, Patel S V, Dvorkina O. Suspected hydroxychloroquine-associated QT-interval prolongation in a patient with systemic lupus erythematosus. JCR J Clin Rheumatol 2013;19:286–8.

[23] Timothy F. Simpson. Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment For COVID-19 2020. https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19 (accessed March 29, 2020).

[24] Rabkin SW. Nomenclature, categorization and usage of formulae to adjust QT interval for heart rate. World J Cardiol 2015;7:315. https://doi.org/10.4330/wjc.v7.i6.315.

[25] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA 2020;323:1824–36. https://doi.org/10.1001/jama.2020.6019.

[26] Choudhary R, Sharma AK. Potential use of hydroxychloroquine, ivermectin and azithromycin drugs in fighting COVID-19: trends, scope and relevance. New Microbes New Infect 2020:100684.

[27] Gautret P, Lagier J-C, Parola P, Meddeb L, Mailhe M, Doudier B, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020:105949.

[28] Jean S-S, Lee P-I, Hsueh P-R. Treatment options for COVID-19: The reality and challenges. J Microbiol Immunol Infect 2020;in press. https://doi.org/https://doi.org/10.1016/j.jmii.2020.03.034.

[29] Fanin A, Calegari J, Beverina A, Tiraboschi S. Hydroxychloroquine and azithromycin as a treatment of COVID-19. Intern Emerg Med 2020;23:105949. https://doi.org/10.1007/s11739-020-02388-y.

[30] Hulme OJ, Wagenmakers E-J, Damkier P, Madelung CF, Siebner HR, Helweg-Larsen J, et al. A Bayesian reanalysis of the effects of hydroxychloroquine and azithromycin on viral carriage in patients with COVID-19. MedRxiv 2020.

[31] Negida A, Bahbah EI. Comments on the Hydroxychloroquine/Azithromycin Study and Lessons for Future Clinical Trials of COVID-19 Treatments 2020.

[32] Dahly D, Gates S, Morris T. Statistical review of hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label nonrandomized clinical trial. Prepr Posted Online 2020;23.

[33] Molina JM, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect 2020;50:384. https://doi.org/10.1016/j.medmal.2020.03.006.

[34] Million M, Lagier J-C, Gautret P, Colson P, Fournier P-E, Amrane S, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis 2020:101738. https://doi.org/https://doi.org/10.1016/j.tmaid.2020.101738.

[35] Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al.

Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med 2020. https://doi.org/10.1056/nejmoa2019014.

[36] Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA 2020;323:102433. https://doi.org/10.1001/jama.2020.8630.

[37] Arshad S, Kilgore P, Chaudhry ZS, Jacobsen G, Wang DD, Huitsing K, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis 2020;97:396–403. https://doi.org/10.1016/j.ijid.2020.06.099.

[38] Mitra RL, Greenstein SA, Epstein LM. An algorithm for managing QT prolongation in coronavirus disease 2019 (COVID-19) patients treated with either chloroquine or hydroxychloroquine in conjunction with azithromycin: Possible benefits of intravenous lidocaine. Hear Case Reports 2020:10.1016/j.hrcr.2020.03.016. https://doi.org/10.1016/j.hrcr.2020.03.016.

[39] Juurlink DN. Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. Can Med Assoc J 2020;192:E450 LP-E453. https://doi.org/10.1503/cmaj.200528.

[40] Lane JCE, Weaver J, Kostka K, Duarte-Salles T, Abrahao MTF, Alghoul H, et al. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. MedRxiv 2020;in press:2020.04.08.20054551. https://doi.org/10.1101/2020.04.08.20054551.

Figure captions:

Figure 1. Randomization and treatment protocols of the patients

Figure 2. Comparison of SpO2 (%) changes between the two groups.

Figure 3. Intensive care unit (ICU) Admission and need for intubation (no. of person %) in azithromycin and control group.

Figure 4. Comparison the mean duration of hospitalization between two groups.

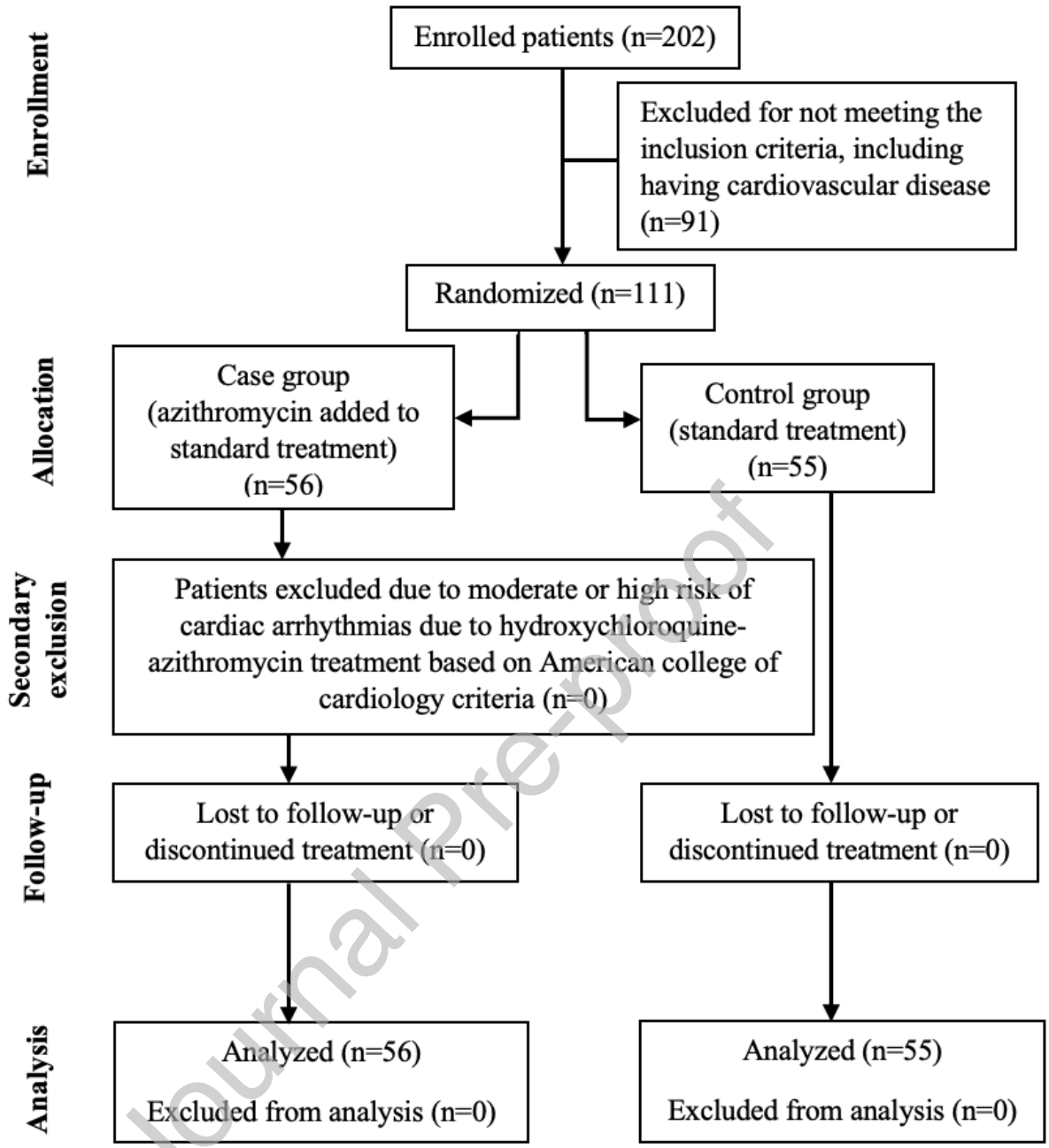

Figure 1.

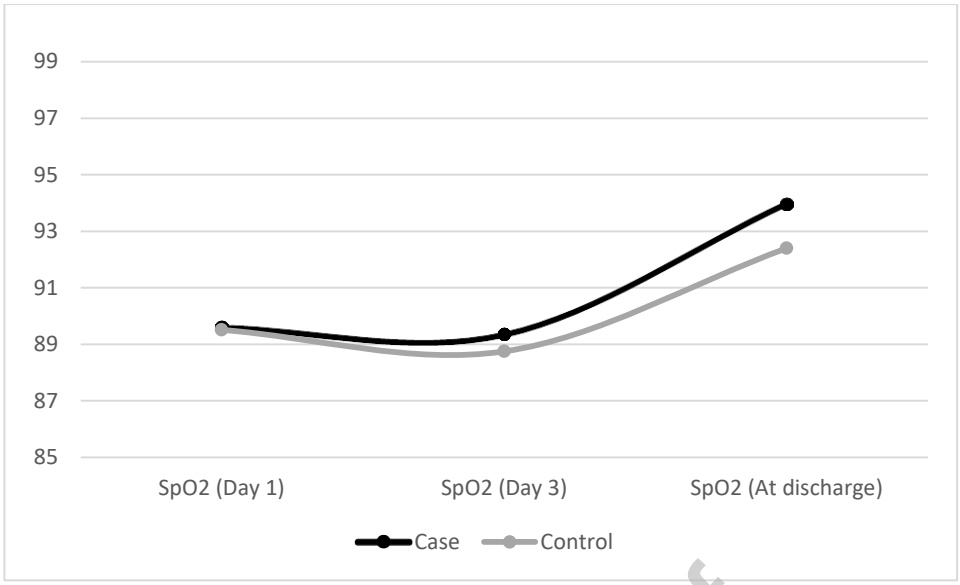

Figure 2.

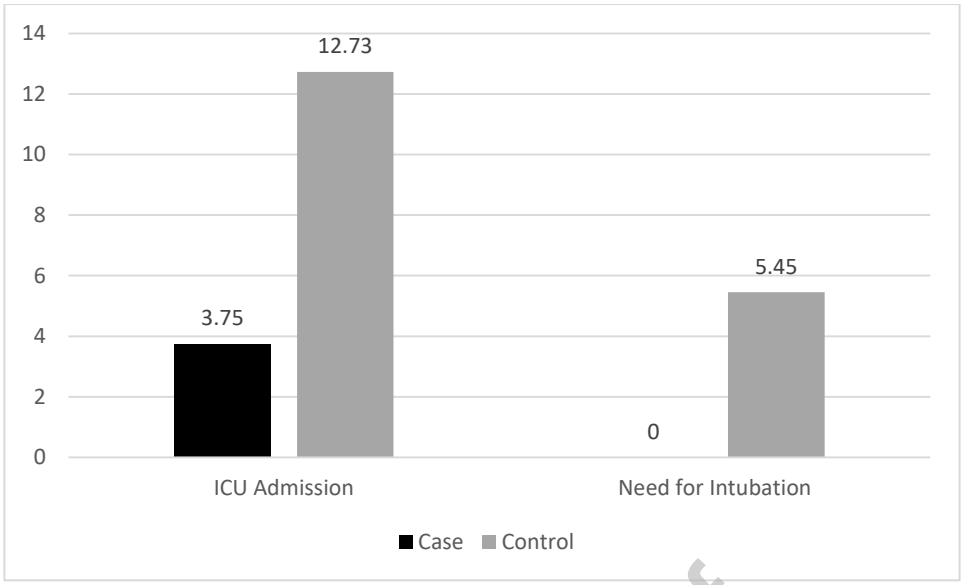

Figure 3.

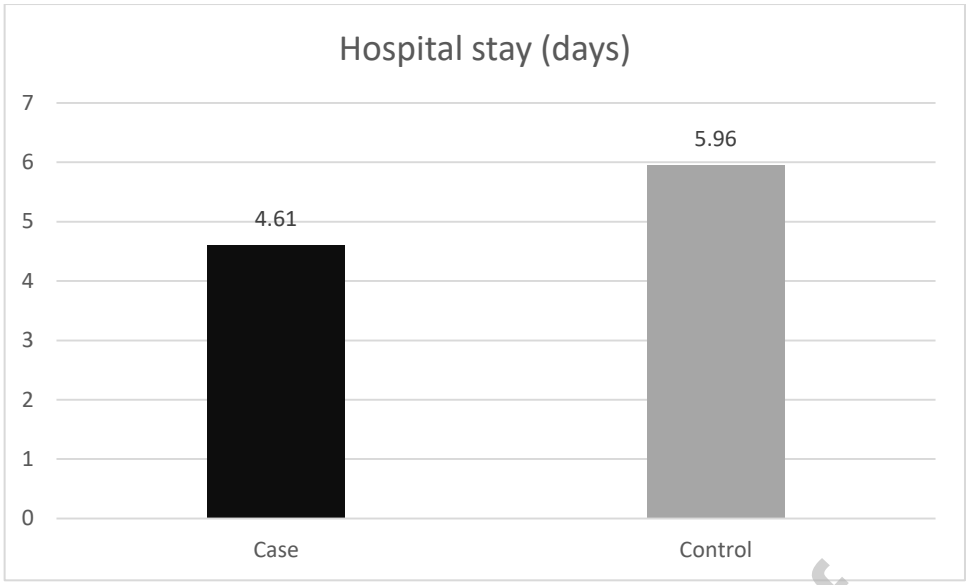

Figure 4.

Table1- Demographic, Clinical and para-clinical findings

VARIABLES		Group		
		Azithromycin	**control**	**P value**
		Mean ±SD / n (%)	**Mean ±SD** / n (%)	
Age (year)		54.38±15.92	59.89±15.55	**0.700**
Body temperature upon admission, (°C)		38.07±0.69	37.72±0.91	**0.020**
White-cell count (×10^9/litter)		6.94±2.65	6.28±2.30	**0.160**
Hemoglobin count (g/dl)		13.65±1.97	12.80±1.94	**0.200**
Platelet count (×10^9/litter)		230.45±111.77	238.46±99.56	**0.690**
ESR		64.86±29.12	70.71±32.05	**0.320**
Respiratory rate upon admission		23.75±5.19	22.62±5.72	**0.280**
SpO_2% upon admission		89.61±2.98	89.51±6.84	**0.920**
Day 3 SpO_2%		89.36 ±4.59	88.75 ±7.67	**0.610**
Sex-no. (%)	Female	28(50.00)	32(58.18)	**0.387**
	Male	28(50.00)	23(41.82)	
Fever		38(67.86)	33(60.00)	**0.389**
Dyspnoea		41(73.21)	43(78.18)	**0.542**
Myalgia		18(32.14)	22(74.55)	**0.000**
Chill		18(32.14)	25(45.45)	**0.150**
Weakness		10(17.86)	3(5.45)	**0.042**
Cough		34(60.71)	41(74.55)	**0.120**
Sputum		3(5.36)	8(14.55)	**0.105**
Haemoptysis		3(5.36)	0(0.00)	**0.243**
Headache		6(10.71)	18(32.7)	**0.005**
Vomiting		7(12.50)	16(29.09)	**0.031**
Chest pain		10(17.86)	12(21.82)	**0.601**
Primary End points	**Hospital stay (days)**	4.61±2.59	5.96±3.21	**0.020**
	Need for ICU admission	2(3.57)	7(12.73)	**0.070**
	Death	0(0.00)	1(1.82)	**0.495**
Secondary End points	**Discharge Body temperature, (°C)**	36.88±0.33	36.77±0.53	**0.190**
	ICU length of stay (days)	5.00 ±0.01	4.43 ± 2.99	**0.157**
	Respiratory rate at discharge	15.85 ±1.99	17.42 ±2.42	**0.010**
	SpO_2 at discharge	93.95±2.14	92.40±4.58	**0.030**
	Need for Intubation	0(0.00)	3(5.45)	**0.118**

Table 2- Outcome of patients in azithromycin and control group

VARIABLES	Hedges' g	CI 95%
SpO_2 at discharge %	-0.461	-0.838 - -0.084
Respiratory rate at discharge	0.721	0.337 - 1.105
Hospital stay (days)	0.618	0.103 - 0.858

Table 3- Calculation of risk score for QTc interval prolongation

Risk factors	Score
Age ≥ 68 years	1
Female sex	1
Loop diuretic	1
Serum K+ ≤ 3.5 mEq/L	2
Admission QTc ≥ 450 ms	2
Acute MI	2
≥ 2 QTc-prolonging drugs	3
Sepsis	3
Heart failure	3
One QTc-prolonging drug	3
Maximum Risk Score	21

K+ = potassium; MI = Myocardial infarction