European Journal of Therapeutics

DOI: 10.5152/eurjther.2021.21022

Original Article

Evaluation of Corrected QT Intervals of 74 COVID-19 Patients Treated with Hydroxychloroquine in Combination with or without Azithromycin and/or Favipiravir

Oğuz Abdullah Uyaroğlu[1], Yusuf Ziya Şener[2], Murat Özdede[1], Nursel Çalık Başaran[1], Lale Özışık[1], Taha Koray Şahin[3], Uğur Canpolat[2], Ahmet Çağkan İnkaya[4], Hikmet Yorgun[2], Gülay Sain Güven[1], Kudret Aytemir[2]

[1]Division of General Internal Medicine, Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[2]Department of Cardiology, Hacettepe University, Faculty of Medicine, Ankara, Turkey

[3]Department of Internal Medicine, Hacettepe University, Faculty of Medicine, Ankara, Turkey

[4]Department of Clinical Microbiology and Infectious Disease, Hacettepe University, Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objective: We aimed to evaluate the degree of QTc prolongation and associated factors in patients with COVID-19 in association with their usage of hydroxychloroquine (HCQ) with or without the combination of azithromycin (AZ) and/or favipiravir (FAV).

Methods: This single-center, retrospective study was conducted in a tertiary care university hospital. We retrospectively examined the pre- and post-treatment electrocardiogram (ECG) records of 74 patients.

Results: The median age was 44 (interquartile range [IQR] 27), and 34 (45.5%) of them were women. All these 74 patients were treated with HCQ. Sixty-three of them (83.2%) were treated with AZ, and eight patients (10.8%) also were treated with plus favipiravir. All ECGs were in sinus rhythm, and arrhythmia was not developed in any patients. The median (IQR) baseline QTc of 74 patients was 400 (375-421) milliseconds, the median (IQR) post-treatment QTc was 418 milliseconds (391-432), and the change was statistically significant ($P < .001$). There was no statistically significant difference in QTc prolongation between treatment groups. In the linear regression model, moderate disease activity, higher Modified Early Warning Score (MEWS) score ($\geq$2), and heart rate were independent predictors. QTc prolongation of more than 60 milliseconds was observed in five patients (6.7%). Post-treatment QTc value of over 500 milliseconds was observed in three patients (4%), and the drugs were discontinued.

Conclusions: This is the first study that demonstrates that MEWS score and disease severity are related to higher QTc prolongation values. HCQ, AZ, and FAV should be safely used in patients with lower MEWS score and without the severe disease, in conjunction with QTc follow-up.

Keywords: COVID-19, corrected QT, hydroxychloroquine, azithromycin, favipiravir

INTRODUCTION

Coronavirus disease-2019 (COVID-19), first reported in Wuhan, China, on December 8, 2019 and declared a pandemic by the World Health Organization (WHO) on March 11, 2020, has infected over 110 million people globally to date.[1]

There is still no valid treatment known for COVID-19 patients. In the beginning of pandemic, hydroxychloroquine (HCQ), often in combination with azithromycin (AZ), is being widely used for the treatment of COVID-19.[2–4] HCQ is an antimalarial drug, which has also been used in the treatment of systemic lupus erythematosus, rheumatoid arthritis, and other connective tissue disorders.[5] AZ is a macrolide antibiotic used to treat a wide variety of bacterial infections and also has antiviral activity. AZ also has immunomodulatory effects by inhibiting proinflammatory interleukins (IL)-5, IL-6, IL-8, IL-1β, and IL-10 and producing IL-13 and tumor necrosis factor alpha.[6] Favipiravir

How to cite: Uyaroğlu OA, Şener YZ, Özdede M, et al. Evaluation of Corrected QT Intervals of 74 COVID-19 Patients Treated with Hydroxychloroquine in Combination with or without Azithromycin and/or Favipiravir. *Eur J Ther* 2021; 27(4): 311–317.

ORCID iDs of the authors: O.A.U. 0000-0003-0440-2026; Y.Z.Ş. 0000-0001-5151-5133; M.Ö. 0000-0002-6981-1210; N.Ç.B. 0000-0002-1290-6905; L.Ö. 0000-0002-3494-8997; T.K.Ş. 0000-0002-3590-0426; U.C. 0000-0002-4250-1706; A.Ç.İ. 0000-0001-7943-8715; H.Y. 0000-0001-7673-229X; G.S.G. 0000-0001-8176-9767; K.A. 0000-0001-9279-8424.

Corresponding Author: Oğuz Abdullah Uyaroğlu **E-mail:** oguzuyaroglu@hotmail.com

Received: February 28, 2021 • **Accepted:** March 23, 2021

(FAV), an RNA-dependent RNA polymerase inhibitor, is an another antiviral used in the treatment of COVID-19.[7]

Although HCQ and AZ are frequently used in clinical practice and generally well tolerated before the COVID-19 pandemic, their cardiotoxic effects are known in advance. Concerns have been reported about QT prolongation, torsade de Pointes (TdP), and the risk of sudden cardiac death induction after extensive use of these drugs.[8,9] Prolonged QT interval due to FAV, which is now being used for the treatment of COVID-19 in some regions, has also been reported.[10] Although WHO discontinued HCQ treatment arms,[11] many countries, especially Asians, still use HCQ for COVID-19.[12]

In this study, we aimed to evaluate the degree of QT prolongation and associated factors in patients with COVID-19 in association with their usage of HCQ with or without combination AZ and/or FAV.

METHODS

Study Design and Population

This single-center, retrospective study was conducted in a tertiary care university hospital. We retrospectively examined the electrocardiogram (ECG) records of 223 probable or confirmed COVID-19 adult patients (≥18 years old) hospitalized to COVID-19 wards between March 20, 2020, the first case admitted to our center, and May 20, 2020.

The "confirmed case" was a patient with positive SARS-CoV-2 RT-polymerase chain reaction (PCR) from nasopharyngeal swab or a positive SARS-CoV-2 antibody test. The "probable case" was further divided into "clinically suspected" and "radiologically diagnosed" categories. A "clinically suspected case" was defined as a patient with sudden onset of fever, cough, or dyspnea, who had acute respiratory symptoms that cannot be explained with any other cause and who tested negative for SARS-CoV-2 RT-PCR plus a negative pulmonary imaging test.[13] The "radiologically diagnosed" patient was a clinically suspected case who also had chest imaging findings compatible with COVID-19. In this study, all patients were treated.

Main Points

- Although hydroxychloroquine and azithromycin are frequently used in clinical practice and generally well tolerated before COVID-19 pandemic, their cardiotoxic effects are known in advance.
- A statistical difference was found in terms of QTc prolongation in ECGs taken before and after treatment in patients using azithromycin and/or favipravir in addition to hydroxychloroquine. However, there was no statistically significant difference in QTc prolongation between treatment groups.
- Predictors of QTc prolongation were pretreatment heart rate, disease severity, and Modified Early Warning Score (MEWS) score.
- Hydroxychloroquine, azithromycin, and favipravir should be safely used in patients with lower MEWS score and without severe disease, in conjunction with QTc follow-up.
- This is the first study that demonstrates that MEWS score and disease severity are related to higher QTc prolongation values.

We further classified patients in three categories based on the severity of the clinical presentation according to WHO classification: mild, moderate, and severe.[14] Severe patients with sepsis and/or acute respiratory distress syndrome requiring intensive care unit (ICU) at the time of admission or those who were transferred to the ICU during the hospital stay or those who were transferred from the ICU to the COVID-19 wards were excluded considering that critically ill patients with COVID-19 might have different effects on ECG. So, we analyzed mild or moderate patients ECGs.

Hospitalization, treatment, and discharge decisions of the cases were held by the Infectious Diseases Department or consultant physicians (A.Ç.İ.) of the wards according to the guidelines composed and regularly updated by the Scientific Board of the Ministry of Health of the Republic of Turkey.[13] The standard regimen of HCQ was 400 mg twice on the first day, and then 400 mg day^{-1} for 4 days, and AZ was 500 mg on the first day, and then 250 mg day^{-1} for 4 days. The standard regimen of FAV was 1,600 mg twice (2 × 1,600) on the first day, and then 1,200 mg day^{-1} (2 × 600 mg) for 4 days.

We routinely took the initial ECG from all patients on the admission day before any treatments. The ECGs taken were automatically transferred to the hospital computer system. However, 47 patients' ECGs were not recorded in the hospital computer system. We reached the control ECGs of only 74 of the remaining 176 patients after treatment was initiated. Unfortunately, ECGs were not routinely taken at certain hours (e.g., 72 hours later) after treatment was initiated. In the evaluation phase, we calculated the median withdrawal time of 74 control ECGs taken after treatment was initiated. The comparison of the control ECGs of the patients at the beginning and after the initiation of treatment was made. ECGs were manually evaluated by cardiologists (Y.Z.Ş., U.P., and H.Y.) to calculate QTc intervals using the Bazett formula and so-called excess correction method for QRS values greater than 120 milliseconds.

Local ethical committee approval (approval number: GO 20/353, date: March 31, 2020) and permission of the Health Ministry of Turkish Republic were obtained.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25 (IBM SPSS Corp.; Armonk, NY, USA). In descriptive statistics, number and percentage were used for categorical variables. For continuous variables with normal distribution, mean and standard deviation were used, and for continuous variables that do not show normal distribution, median, interquartile range (IQR), and percentiles (25-75) were preferred. The suitability of variables to normal distribution was examined using visual and analytical methods. Non-normally distributed numerical data were analyzed using the Mann–Whitney U test and Wilcoxon test. The

Table 1. Demographic Characteristics of the Patients

	Total: 74 n (%)	QTc Differences, Median (IQR)	*P*
Age, Median (IQR), Year	44 (27)		
<60 years		13.5 (49)	.900
≥60 years		13 (30)	
Sex, n (%)			
Female	34 (45.9)	12.0 (29.25)	.770
Male	40 (54.1)	15.0 (36)	
Underlying Medical Illnesses, n (%)			
Diabetes mellitus	14 (18.9)	1.0 (28.75)	**.052**
Hypertension	17 (23)	18.0 (33.5)	.923
Coronary artery disease	7 (9.5)	18.0 (55.0)	.971
Chronic heart failure	4 (5.4)	33.0 (50.25)	.300
Obstructive pulmonary disease	9 (12.2)	4.0 (28.5)	.120
Malignancy	5 (6.8)	23.0 (41.0)	.211
Chronic kidney disease	6 (8.1)	8.5 (52.75)	.507
Hypo/hyperthyoidism	5 (6.8)	18 (28)	.643
Smoking	17 (23)	22.0 (35.0)	.115
Alcohol	8 (10.8)	8.5 (28.0)	.297
Drugs, n (%)			
ACEI/ARB	7 (9.5)	16.0 (35)	.664
Metformin	14 (18.9)	1.0 (28.75)	**.052**
Acetylsalicylic acid	3 (4.1)	13.6 (40.2)	.603
Beta blockers	6 (8.1)	26.5 (51)	.342
Calcium channel blockers	3 (4.1)	28.6 (21.8)	.275
Steroid	5 (6.8)	16 (73)	.917

ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

parameters affecting ΔQTc were investigated using the Spearman correlation test. A multiple linear regression model was used to identify independent predictors. The model fit was assessed using appropriate residual and goodness-of-fit statistics. For all comparisons, *P*-values less than .05 were considered as statistically significant.

RESULTS

Demographic Characteristics

Seventy-four patients were diagnosed with probable/confirmed COVID-19. Fifty-one cases (68.9%) were confirmed by PCR, and the remaining part were diagnosed clinically and radiologically.

The median age was 44 (IQR 27), and 34 (45.5%) of them were woman.

The most common comorbidities were hypertension (n = 17, 23%) and diabetes mellitus (n = 14, 19%).

There were only mild (n = 13, 17.6%) and moderate (n = 61, 82.4%) COVID-19 pneumonia cases since severe cases were admitted to ICU, exclusively.

See Tables 1–3 for demographic characteristics, symptoms, signs, diagnostic criteria, and treatments of patients on admission.

ECG Evaluation of ECGs

The median duration between baseline and post-treatment ECGs was 62 (IQR = 20) hours. All baseline and post-treatment ECGs were in sinus rhythm. The median (IQR) baseline QTc of 74 patients was 400 (375-421) milliseconds, the median (IQR) post-treatment QTc was 418 milliseconds (391-432), and the change was statistically significant ($P < .001$) (see Table 4).

All these 74 patients were treated with HCQ that QTc was significantly increased. Sixty-three of them (83.2%) were treated plus with AZ, and eight patients (10.8%) also were treated with plus FAV to HCQ plus AZ. There was no statistically significant difference in QTc prolongation between treatment groups (see Table 3).

Six patients had (8.1%) longer baseline QTc than 450 ms, and nine patients (12.2%) had longer post-treatment QTc than 450 ms. Arrhythmia was not developed in any patients. QTc prolongation more than 60 milliseconds was observed in five patients (6.7%). The biggest ΔQTc was 80 milliseconds. Post-treatment QTc value of over 500 milliseconds was observed in three patients (4%), and the drugs were discontinued. One of the three patients was using only HCQ, one was using HCQ plus AZ, and the other was using HCQ plus AZ plus FAV. AZ was seen to prolong the ΔQTc; however, there was no statistically difference ($P = .5$).

Diabetes mellitus, metformin use, myalgia, heart rate, higher Modified Early Warning Score (MEWS) score (≥2), and

Table 2. Symptoms, Signs, and Diagnostic Criteria of Patients on Admission

	Total: 74 n (%)	QTc Differences Median (IQR)	*P*
Symptoms, n (%)			
Fever	41 (55.4)	13.0 (28.5)	.663
Fatigue	51 (68.9)	14.0 (29.0)	.944
Cough	53 (71.6)	12.0 (29.0)	.666
Myalgia	40 (54.1)	10.0 (24.75)	.099
Dyspnea	18 (24.3)	9.5 (26.75)	.364
Sore throat	21 (28.4)	14.0 (39.0	.569
Heart rate, mean (SD)	88 (19)		
Heart rate, n (%)			
60-100	56 (75.7)	18.5 (27)	**.003**
>100	18 (24.3)	0.5 (70)	
Respiratory rate, median (IQR)			
Respiratory rate, n (%)	20 (2)		
<24 min^{-1}	65 (87.8)	12.0 (31.5)	.811
24-30 min^{-1}	7 (9.4)	18.0 (11)	
>30 min^{-1}	2 (2.7)	22.5 (40.3)	
Saturation, mean (SD)	96 (3)		
Oxygen support, n (%)			
Not required	65 (87.8)	12.0 (31)	.325
Nasal oxygen	9 (12.2)	18.0 (30)	
MEWS, n (%)			**.016**
0-1 points	60 (81.1)	10.5 (30.25)	
>2 points	14 (18.9)	25.5 (33.25)	
Disease severity, n (%)			**.003**
Mild	13 (17.6)	-2.0 (26.5)	
Moderate	61 (82.4)	18.0 (24)	
Diagnosis, n (%)			.559
PCR positivity	51 (68.9)	12.0 (32)	
Radiologic (PCR negative)	14 (18.9)	17.0 (34.5)	
Clinical (negative PCR normal CT)	9 (12.2)	27.0 (36.5)	

MEWS, Modified Early Warning Score; PCR, polymerase chain reaction; CT, computed tomography.

Table 3. Treatments of Patients

	Total: 74 n (%)	QTc Differences Median (IQR)	*P*
Treatments, n (%)			.174
Hydroxychloroquine (HCQ)	11 (14.9)	5.0 (36)	.224
HCQ + azithromycin (AZT)	55 (74.3)	16.0 (30)	.490
HCQ + AZT + favipiravir (combination/sequential)	8 (10.8)	16 (53.75)	.123
Oseltamivir	46 (62.2)	12 (25)	.36
Enoxaparin Treatment			
No	19 (25.6)	13.0 (30)	.901
Yes	55 (74.4)	14.0 (30)	

Table 4. Characteristics of ECGs

	Baseline ECG	Post–Treatment ECG	Δ(Delta)	*P*
Heart rate, mean (SD), pulse/minutes	89.6 (14)	80.2 (8)	–8 (13.75)*	**<.001**
PR, median (milliseconds) (IQR)	140 (21.5)	140 (33.5)	2 (16)	.143
QRS, median (milliseconds) (IQR)	80 (11.75)	82 (14)	4 (9.5)	**.002**
QTc, median (milliseconds) (IQR)	400 (25–85) (45)	418 (25–75) (41)	13.5 (29.75)	**<.001**

Δ(Delta); post-treatment—baseline.
*Median (IQR).

Table 5. Linear Regression Model for QTc Prolongation

	Unstandardized Coefficients		Standardized Coefficients		
	B	SE	β	*t*	*P*
Heart rate	–.314	0.180	–0.188	–1.74	.086
MEWS score (≥2 score)	17.350	6.421	0.292	2.702	.009
Moderate disease activity	18.530	6.554	0.303	2.827	.006

R^2: 0.230, ANOVA F = 6.989, $P < .001$.

moderate disease activity seemed to influence ΔQTc (see Tables 1 and 2). However, in the linear regression model, only moderate disease activity, higher MEWS score (≥2), and heart rate were independent predictors (see Table 5).

We also performed statistical analysis in terms of laboratory values that would affect disease activity and ECG changes (hemoglobin, white blood cell count, neutrophil, lymphocyte, platelet count, C-reactive protein, sedimentation, procalcitonin, ferritin, creatine cinase, lactate dehydrogenase, d-dimer, troponin, creatine kinase myocardial band (CK-MB), myoglobin, sodium, potassium, corrected calcium, phosphorus, low-density lipoprotein, and triglycerides), but we could not find any statistically significant result.

DISCUSSION

The main findings of this study are as follows: a statistical difference was found in terms of QTc prolongation in ECGs taken before and after treatment in patients using AZ and/or FAV in addition to HCQ. However, there was no statistically significant difference in QTc prolongation between treatment groups. Predictors of QTc prolongation were pretreatment heart rate, disease severity, and MEWS score. No arrhythmic episodes were developed, and drug cessation due to severe QTc prolongation was required in only three patients (4%) as consistent with literature.

Treatment strategies against COVID-19 include combination of several drugs that have synergistic effects. Chloroquine/HCQ, AZ, protease inhibitors (like lopinavir-ritonavir or darunavir-cobicistat), remdesivir, and FAV are used "off-label" despite the lack of definitive evidence on their efficacy.[15,16] Major concern with these drugs (especially with chloroquine/HCQ and AZ) is QTc prolongation and development of TdP/sudden cardiac death, despite it is a rare manifestation of the treatment.[17] There are several known risk factors for QTc prolongation such as electrolyte disorders (hypokalemia, hypocalcemia, hypomagnasemia, etc.), co-administration of QTc prolonging drugs (antihistaminic drugs, antipsychotic drugs, antiarrhythmic drugs, etc.), use of diuretics, bradycardia, structural heart disease, and channelopathies causing congenital long QT syndromes.[18] It is reported that concomittantly use of diuretics or AZ and higher baseline QTc values (>450 milliseconds) are associated with more QTc prolongation in COVID-19 patients treated with HCQ.[18] In another study, the presence of atrial fibrillation, heart failure, and chronic kidney disease was found to be related to more QTc prolongation in HCQ-treated patients with COVID-19.[19] In our study, we found that baseline heart rate, disease severity, and MEWS score were predictors of QTc prolongation. Patient population in this study is younger than other trials and has lower burden of chronic diseases due to severe patients treated in ICU were excluded. Therefore, significant electrolyte disorders and frequency of chronic diseases were rare as compared with general population. However, this situation provides the advantage of the assessment effects of COVID-19 disease-related physiologic changes and disease severity on QTc prolongation.

In previous studies, it is reported that severe QTc prolongation (>500 milliseconds) was observed in 9-11% of the cases,

leading drug discontinuation in 2.5-3.5% of the patients.[20] Hooks et al.[21] reported that QTc prolongation more than >15% or QTc >500 ms after treatment was occurred in 3.9% of the COVID-19 patients treated with HCQ. In another study including 201 COVID-19 patients treated with HCQ or AZT, drug discontinuation due to QTc prolongation was established in 3.5% of the cases, and arrhythmia-related death did not occur in any patients.[22] In the present study, severe QTc prolongation (>500 milliseconds) was developed in three (4%) patients and the drugs. The lower rates might due to exclusion of severe patients in our study.

Baseline heart rate was found to be negatively correlated with ΔQTc in our study. Despite this finding is statistically significant, it may not have clinical significance due to the possible correction mistakes of Bazett formula in patients with abnormal heart rates. There are several formulas including Bazett, Frederica, Framingham, and Hodges formulas for QT correction according to heart rate, and Bazett formula is the most common used formula even it has disadvantages in patients with heart rates <60 bpm and >100 bpm. Bazett and Fridericia are logarithmic corrections, whereas Hodges and Framingham are linear correction formulas. Bazett formula overcorrects QT interval in patients with heart rates higher than 100 bpm.[23,24] As pretreatment heart rates are significantly higher than the heart rates during or after treatment, pretreatment QTc values should have been overcorrected in our study resulting in underestimated ΔQTc.

MEWS includes parameters of heart rate, respiratory rate, body temperature, systolic blood pressure, and level of consciousness, and it can be obtained within minutes after the patient is admitted, providing a rapid evaluation for clinicians to enable timely treatment to high risk patients.[25] Wang et al.[26] reported that MEWS is an efficient tool for rapid assessment of elderly COVID-19 patients, and it predicts in-hospital mortality. In our study, higher MEWS scores were related to higher ΔQTc values.

Severity of COVID-19 pneumonia is classified by WHO into three categories, and severe disease is associated with increased mortality rates and increased need of ICU admissions.[14] In this study, we demonstrated that moderate disease severity is associated with higher ΔQTc than mild disease severity. Despite our study population includes patients without severe disease and younger patients with lower burden of comorbidities, association between ΔQTc and both MEWS score and disease severity indicates that COVID-19 disease-related physiologic changes are predictors of QTc prolongation even absence of other risk factors for QT prolongation.

First limitation of this study is the exclusion of severe cases from the study. Therefore, effects of MEWS score and diseases severity on ΔQTc could not be generalized into general population. However, this condition provided advantage to evaluate the pure effects of COVID-19-related physiologic alterations on QTc prolongation by excluding confounding factors such as chronic diseases, used medications, and electrolyte disorders. Second limitation is the heterogenous time duration between the baseline ECG and second ECG due to the retrospective nature of the study. Finally, Bazett formula has disadvantages on QT correction in patients with heart rates more than 100 bpm and lower than 60 bpm. However, all of the QT correction formulas have similar disadvantages in different heart rates.

CONCLUSION

Although it is rare, drugs used for COVID-19 treatment may lead to QT prolongation and development of arrhythmias. HCQ, AZ, and FAV should be safely used in patients with lower MEWS score and without severe disease, in conjunction with QTc follow-up. This is the first study that demonstrates that MEWS score and disease severity are related to higher QTc prolongation values. Future large-scale studies are needed to evaluate the role of MEWS score to predict QTc prolongation in COVID-19 patients.

Ethics Committee Approval: Ethical committee approval was received from the Hacettepe University (approval number: GO 20/353, date: March 31, 2020).

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - O.A.U., M.Ö., N.Ç.B., L.Ö., T.K.Ş., U.C., A.Ç.İ., H.Y., G.S.G., K.A.; Design - O.A.U., M.Ö., N.Ç.B., L.Ö., T.K.Ş.; Supervision - O.A.U., N.Ç.B., L.Ö., U.C., A.Ç.İ., H.Y., G.S.G., K.A.; Resources - O.A.U., A.Ç.İ., H.Y., G.S.G., K.A.; Materials - O.A.U., Y.Z.Ş., M.Ö., T.K.Ş., A.Ç.İ.; Data Collection and/or Processing - O.A.U., Y.Z.Ş., H.Y., G.S.G.; Analysis and/or Interpretation - O.A.U., M.Ö., T.K.Ş., H.Y.; Literature Search - O.A.U., Y.Z.Ş., L.Ö., U.C., A.Ç.İ., H.Y., G.S.G.; Writing Manuscript - O.A.U., N.Ç.B.; Critical Review - O.A.U., Y.Z.Ş., M.Ö., N.Ç.B., L.Ö., T.K.Ş., U.C., A.Ç.İ., H.Y., G.S.G., K.A.

Acknowledgement: Thanks to Sevilay Karahan for contributions in terms of statistical analysis.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. World Health Organization. Coronavirus Disease (COVID-19) Dashboard. Data last updated: 2021/02/27, 3:09 pm CET. Available at https://covid19.who.int.
2. Gautret P, Lagier JC, Parola P, 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;56(1):105949. [CrossRef]
3. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: Open label, randomised controlled trial. *BMJ*. 2020;369:M1849. [CrossRef]
4. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med*. 2020;382(25):2411-2418. [CrossRef]
5. Wallace DJ, Tse K, Hanrahan L, Davies R, Petri MA. Hydroxychloroquine usage in US patients, their experiences of tolerability and adherence, and implications for treatment: Survey results from 3127 patients with SLE conducted by the Lupus Foundation of America. *Lupus Sci Med*. 2019;6(1):E000317. [CrossRef]
6. Taylor SP, Sellers E, Taylor BT. Azithromycin for the prevention of COPD exacerbations: The good, bad, and ugly. *Am J Med*. 2015;128(12):1362.e1-1362.e26. [CrossRef]
7. Joshi S, Parkar J, Ansari A, et al. Role of favipiravir in the treatment of COVID-19. *Int J Infect Dis*. 2021;102:501-508. [CrossRef]
8. Chorin E, Wadhwani L, Magnani S, et al. QT interval prolongation and torsade de pointes in patients with COVID-19 treated with

hydroxychloroquine/azithromycin. *Heart Rhythm*. 2020;17(9):1425-1433. [CrossRef]
9. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(9):1036-1041. *Erratum in: JAMA Cardiol*. 2020;5(9):1071. [CrossRef]
10. Chinello P, Petrosillo N, Pittalis S, et al. QTc interval prolongation during favipiravir therapy in an ebolavirus-infected patient. *PLoS Negl Trop Dis*. 2017;11(12):E0006034. [CrossRef]
11. WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19. 2020. Available at https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19.
12. Lin C. Why do Asian countries use hydroxychloroquine for Covid-19 despite Western rejection? ISPSW strategy series: Focus on defense and international security. Available at https://www.ispsw.com/wp-content/uploads/2020/08/711_Lin.pdf.
13. Republic of Turkey Ministry of Health Directorate General of Public Health. COVID-19 (SARS-CoV-2 Infection) Guide (in Turkish). 2020. Available at https://hsgm.saglik.gov.tr/depo/birimler/goc_sagligi/covid19/rehber/COVID-19_Rehberi20200414_eng_v4_002_14.05.2020.pdf.
14. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 diseases is suspected. Interim Guidance, March 13, 2020.
15. Agrawal U, Raju R, Udwadia ZF. Favipiravir: A new and emerging antiviral option in COVID-19. *Med J Armed Forces India*. 2020;76(4):370-376. [CrossRef]
16. The European Society for Cardiology. ESC guidance for the diagnosis and management of CV disease during the COVID-19 pandemic. Available at https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance.
17. Haeusler IL, Chan XHS, Guérin PJ, et al. The arrhythmogenic cardiotoxicity of the quinoline and structurally related antimalarial drugs: A systematic review. *BMC Med*. 2018;16(1):200. [CrossRef]
18. Vandael E, Vandenberk B, Vandenberghe J, Willems R, Foulon V. Risk factors for QTc-prolongation: Systematic review of the evidence. *Int J Clin Pharm*. 2017;39(1):16-25. [CrossRef]
19. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(9):1036-1041. [CrossRef]
20. Crotti L, Arbelo E. COVID-19 treatments, QT interval, and arrhythmic risk: The need for an international registry on arrhythmias. *Heart Rhythm*. 2020;17(9):1423-1424. [CrossRef]
21. Hooks M, Bart B, Vardeny O, et al. Effects of hydroxychloroquine treatment on QT interval. *Heart Rhythm*. 2020;17(11):1930-1935. [CrossRef]
22. Saleh M, Gabriels J, Chang D, et al. Effect of chloroquine, hydroxychloroquine, and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. *Circ Arrhythm Electrophysiol*. 2020;13(6):e008662. [CrossRef]
23. Viskin S. The QT interval: Too long, too short or just right. *Heart Rhythm*. 2009;6(5):711-715. [CrossRef]
24. Charbit B, Samain E, Merckx P, Funck-Brentano C. QT interval measurement: Evaluation of automatic QTc measurement and new simple method to calculate and interpret corrected QT interval. *Anesthesiology*. 2006;104(2):255-260. [CrossRef]
25. Churpek MM, Carey KA, Merced ND, Prister J, Brofman J, Edelson DP. Validation of early warning scores at two long-term acute care hospitals. *Critical Care Med*. 2019;47(12):e962-e965. [CrossRef]
26. Wang L, Lv Q, Zhang X, et al. The utility of MEWS for predicting the mortality in the elderly adults with COVID-19: A retrospective cohort study with comparison to other predictive clinical scores. *Peer J*. 2020;8:e10018. [CrossRef]