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The impact of hydroxychloroquine and azithromycin on the corrected qt interval in patients with the novel Coronavirus disease 2019

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SUMMARY

OBJECTIVE: With the coronavirus disease 2019 (COVID-19) continuing to spread all over the world, although there is no specific treatment until now, hydroxychloroquine and azithromycin have been reported to be effective in recent studies. Although long-term use of hydroxychloroquine and azithromycin has been reported to cause QT prolongation and malign arrhythmia, there is not enough data about the effect of short-term use on arrhythmia. Therefore, this study aims to assess the effect of hydroxychloroquine alone and hydroxychloroquine + azithromycin on corrected QT (QTc).

METHODS: A baseline electrocardiogram and on-treatment baseline electrocardiogram were retrospectively collected in COVID-19 patients who received hydroxychloroquine and/or azithromycin. The QTc interval was calculated, and the baseline and peak QTc intervals were compared. In addition, the peak QTc intervals of monotherapy and combination therapy were compared.

RESULTS: Of the 155 patients included, 102 (65.8%) patients were using hydroxychloroquine, and 53 (34.2%) patients were using hydroxychloroquine + azithromycin combination. The use of both hydroxychloroquine alone and hydroxychloroquine + azithromycin combined therapy significantly prolonged the QTc, and the QTc interval was significantly longer in patients receiving combination therapy. QTc prolongation caused early termination in both groups, 5 (4.9%) patients in the monotherapy group and 6 (11.3%) patients in the combination therapy group.

CONCLUSION: In this study, patients who received hydroxychloroquine for the treatment of COVID-19 were at high risk of QTc prolongation, and concurrent treatment with azithromycin was associated with greater changes in QTc.

KEYWORDS: Hydroxychloroquine. Azithromycin. Coronavirus Disease-19. Cardiac arrhythmias.

INTRODUCTION

The new coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogen soon spread all over the world[1]. While the first case in Turkey was detected on March 11, 2020, the disease was declared as a pandemic by the World Health Organization (WHO) on March 12, 2020[2], and it continued to spread increasingly; there is no proven treatment for it so far.

In some published studies, it has been reported that the combined use of hydroxychloroquine (HCQ) and azithromycin (AZT) reduces the viral load and may have an effect on mortality and morbidity[3-5]. HCQ, a chloroquine analog thought to be safer than chloroquine (CQ), an antimalarial and immunomodulatory agent, has been shown to have an antiviral effect on SARS-CoV-2[4,6]. AZT, a macrolide group antibiotic, has in vitro antiviral effects, such as viral replication, entry into the host cell,

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and potential immunomodulation[7]. An in vitro study has shown that the combined use of HCQ + AZT had synergistic effects on SARS-CoV-2[8], and this combination therapy is widely used by clinicians in Turkey and in the world. Although, in some studies, both agents have been shown to prolong the QT interval, drug-induced torsades de pointes (TdP), and drug-induced sudden cardiac deaths, independently from each other, there is insufficient data on the effect of monotherapy or combination therapy on QT duration and malign arrhythmia development in COVID-19 patients[9,10]. In this study, we aimed to investigate the effect of HCQ and AZT use alone or in combination on QT duration and arrhythmia in COVID-19 patients.

METHODS

This study was conducted retrospectively in Eskisehir City Hospital between 15 March and 15 August 2020. For inclusion in the study, 350 patients over the age of 18 years, who were proven positive by the polymerase chain reaction method or who were hospitalized (to ward and/or intensive care unit) with a high probability of COVID-19 as a result of thorax computerized tomography (CT), were screened. Of these patients, 155 patients met the inclusion criteria and were chosen for this study. These patients had baseline electrocardiogram (ECG) before starting HCQ or HCQ+AZT treatment and had ECG on a daily basis during the treatment. Patients who did not have a baseline ECG, ECG on a daily basis, difficulty obtaining an ECG, and ECGs that could not be evaluated clearly were not chosen for the study.

The treatment regimen of the patients hospitalized with the diagnosis of COVID-19 in our center was a 2× 400 mg oral loading dose for HCQ followed by 2× 200 mg for five days and a 500 mg loading dose for AZT followed by 250 mg per day for 5 days. The treatment continued for 10 days, for those who had symptoms, a persisted fever for five days, and whose polymerase chain reaction test was not negative. In all patients, the baseline ECG was obtained before starting the treatment, and daily ECGs were obtained during the treatment. All ECGs of the patients were evaluated, and the QRS, PR, and QTc intervals of the ECG obtained before the treatment were taken as basis for the baseline values. Although, for the peak values, the QTc interval was prolonged in daily ECG during treatment, time and day, when it is the longest, were taken into account. The last day of treatment was taken into account for patients whose QTC interval did not prolong. HCQ and/or AZT were not initiated as hospital treatment procedures for the patients with a QRS interval >500 ms on baseline ECG.

All ECGs were evaluated retrospectively by two independent cardiologists; when there was a conflict between them, ECGs were evaluated by a third cardiologist. The QT interval was measured from the onset of the first deflection of QRS complex to the end of T wave. The end of the T wave was determined by the tangent method. QTc durations were calculated manually using the Bazett's formula. D2 lead was used to measure the QT interval. In cases where the T wave in D2 lead could not be clearly identified, V6 lead was used as an alternative. If there was a bundle branch block in the basal, the JT interval was measured and 120 ms was added to obtain the QT interval duration. Severe QTc prolongation was defined as an increase in QTc intervals of more than 60 ms (ΔQTc>60) compared with baseline or as a QTc of 500 ms or greater[11]. The treatment was discontinued for the patients with severe QTc prolongation during treatment. The demographic features, medical histories, medications, laboratory results, and ECG details of the patients were obtained from the hospital data recording system. This study has been approved by the Eskisehir Osmangazi University Ethics Committee and the Ministry of Health of the Republic of Turkey. Due to the retrospective nature of this study, the medical ethical committee waived the requirement for individual informed consent.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 23.0 (Armonk, New York, NY, USA). Continuous data are given as medians (Q1–Q3). Categorical data are given as percentage (%). Shapiro-Wilk's test was used to investigate the suitability of the data for normal distribution. In order to compare the groups that do not conform with the normal distribution, Mann-Whitney U test was used for the situations with two groups. In the analysis of the created cross-tables, Pearson's exact chi-square analysis was used. The Wilcoxon test was used to compare ECG changes during treatment with the patients' baseline ECGs. For statistical significance, $p<0.05$ value was accepted as a criterion.

RESULTS

The mean (SD) age of 155 patients (58.7 male, 41.3% female) included in the study with the diagnosis of COVID-19 was 52.4±20.3. The most common comorbid diseases were hypertension and diabetes mellitus in 63 (40.6%) and 37 (23.9%) patients, respectively. One hundred forty-four (92.9%) patients included in this study were hospitalized in the ward, while 11 (7.1%) patients were admitted to the intensive care unit. Of the 144 patients who were admitted to the ward, 15 (10.4%) patients were transferred to the intensive care unit after their medical condition worsened during their follow-up. Vasopressor treatment was given, and mechanical ventilation was applied to 16 (10.3%) patients. Nineteen (12.3%) patients died. One hundred and two (65.8%) patients were using HCQ, of which 53 (34.2%) patients were using a combination of HCQ+AZT. None of the patients

were using AZT alone. All patients were in sinus rhythm with baseline heart rate (SD) of 83±17.8 beats/min. The median (IQR) baseline QRS, PR, and QTc durations of all patients were 91 (80–103), 145.5 (128.7–16.0), and 407 (385–426) ms, respectively. The demographic information, laboratory results, medical history, and medications of the patients are given in Table 1.

The QRS, PR, and QTc durations on-treatment were significantly longer in both the groups receiving HCQ alone and a combination of HCQ + AZT compared with the baseline (p<0.001) (Table 2).

Comparing HCQ monotherapy and HCQ+AZT combination therapy, there was no significant difference between median (IQR) baseline QRS (92.5 [80.75–105.50] ms *versus* 90.0 [80.0–102.5] ms; p=5), baseline PR (147.0 [135.0–160.0] ms *versus* 144.0 [120.0–160.0] ms; p=0.53), and baseline QTc (408.0 [389.2–427.5] ms *versus* 404.0 [384.0–420.0] ms; p=1).

The median (IQR) maximum QTc duration on-treatment was significantly longer in patients who received combination therapy compared to those who received monotherapy (456.0 [422.0–467.5] ms versus 428.0 [412.75–449.25] ms; p<0.001). At the same time, the median (IQR) change in QTc duration was 46.0 (40.5–54.5) ms in the group receiving HCQ+AZT and 18.0 (11.0–30.0) ms in the group receiving HCQ alone (p=0.001) (Table 3). Of the 11 patients with significant

Table 1. Baseline characteristics of the patients.

Characteristic (n=155)	Median (min–max) or number (%)
Age (years)	52.46±20.307
Female sex	64 (41.3)
Male sex	91 (58.7)
Hypertension	63 (40.6)
Hyperlipidemia	12 (7.7)
Diabetes mellitus	37 (23.9)
Obesity	15 (59.7)
Smoking	45 (29)
Coronary artery disease	25 (16.1)
Chronic obstructive pulmonary disease/asthma	32 (20.6)
Chronic kidney disease ≥ stage III	12 (7.7)
Heart failure	10 (6.5)
Prior Atrial fibrillation/flutter	9 (5.8)
Prior permanent pacemaker/ automated internal cardioverter defibrillator	2 (1.2)
Malignancy	10 (6.5)
Medications, n(%)	
Hydroxychloroquine	101 (65.2)
Azithromycin	0
Hydroxychloroquine/ azithromycin	54 (34.8)
ACEI/ARB	34 (21.9)
Beta blocker/nondihydropyridine calcium channel blocker	21 (13.6)
Digoxin	4 (2.6)
Antiplatelets	13 (8.4)
Oral anticoagulants	8 (5.2)
LMWH	106 (68.4)
Favipiravir	29 (18.7)
Oseltamivir	5 (3.2)
Laboratory results on admission, median (IQR)	
WBC (10^3/μL)	6.90 (5.01–9.68)
Hemoglobin (g/dL)	13.4 (12.10–15.30)
Platelet (10^3/μL)	199.0 (166.0–254.0)
Lymphocyte (10^3/μL)	1.59 (1.15–2.23)
Neutrophil (10^3/μL)	3.75 (2.76–6.37)
Serum potassium (mmol/L)	4.30 (4.00–4.30)
Serum sodium (mmol/L)	138.0 (136.0–140.0)
Calcium (mg/dL)	8.90 (8.40–9.40)
Creatinine (mg/dL)	0.86 (0.76–1.13)
Ferritin	100.0 (56.0–233.0)
D-dimer (μg/mL)	0.60 (0.29–1.71)
CRP (mg/L)	13.60 (2.30–61.90)
Troponin I (pg/mL)	2.80 (0.960–15.10)
LDH (IU/L)	195.0 (160.0–247.0)
Development of new arrhythmias, n(%)	
New AF	3 (1.9)
VT	1 (0.6)
Torsade de pointes	1 (0.6)
VF	1 (0.6)

ACEI: angiotensin converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; CRP: C-reactive protein; LDH: lactate dehydrogenase; LMWH: low molecular weight heparin; WBC: white blood count; VT: ventricular tachycardia; VF: ventricular fibrillation.

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Table 2. Electrocardiographic changes of the study cohort.

Durations, median (IQR) (ms)	Baseline	Peak	p-value
QRS duration with HCQ	92.5 (80.75–105.5)	97.5 (88.0–109.2)	<0.001
QRS duration with HCQ+AZT	90.0 (80.0–102.5)	95.0 (85.5–109.0)	<0.001
PR duration with HCQ	147 (135.0–160.0)	159.0 (141.0–168.5)	<0.001
PR duration with HCQ+AZT	144.0 (120.0–160.0)	156.0 (139.5–171.0)	<0.001
QTc duration with HCQ	408.0 (389.2–427.5)	428.0 (412.7–449.2)	<0.001
QTc duration with HCQ+AZT	404.0 (384.0–420.0)	456.0 (422.0–467.5)	<0.001

AZT: azithromycin; QTc: corrected QT; HCQ: hydroxychloroquine.

Table 3. Comparison of baseline characteristics and ECG findings of patients who received hydroxychloroquine and hydroxychloroquine+azithromycin.

Characteristic	Total (n=155)	Hydroxychloroquine (n=102)	Hydroxychloroquine/ azithromycin (n=53)	p-value
Length of stay at ward, mean±SD	9.54±4.28	9.64±4.31	9.31±4.25	0.88
Length of stay at intensive care unit, mean±SD	7.92±3.76	7.18±3.18	8.46±4.15	0.29
Radiographic findings of pneumonia	118 (76.1)	76 (74.5)	42 (49.2)	0.32
Mechanically ventilation	16 (10.3)	7 (6.9)	9 (17.0)	0.049
In hospital death	19 (12.3)	10 (9.8)	9 (17.0)	0.15
Vasopressor support	16 (10.3)	7 (6.9)	9 (17.0)	0.049
Comorbidities, n (%)				
Hypertension	63 (40.6)	38 (37.3)	25 (47.2)	0.15
Diabetes mellitus	37 (23.9)	26 (25.5)	11 (20.8)	0.32
Heart failure	10 (6.5)	5 (4.9)	5 (9.4)	0.22
Chronic kidney disease≥stage III	12 (7.7)	8 (7.8)	4 (7.5)	0.60
Coronary artery disease	25 (16.1)	16 (15.7)	9 (17.0)	0.5
Chronic obstructive pulmonary disease/asthma	32 (20.6)	21 (20.6)	11 (20.8)	0.56
Malignancy	10 (6.5)	6 (5.9)	4 (7.5)	0.46
Smoking	45 (29)	30 (29.4)	15 (28.3)	0.52
ECG findings median (IQR) (ms)				
Baseline QRS duration	91.0 (80.0–103.0)	92.5 (80.75–105.50)	90.0 (80.0–102.5)	0.5
Post-treatment QRS peak	97.0 (86.0–109.0)	97.5 (88.0–109.25)	95.0 (85.5–109)	0.68
ΔQRS	4.0 (0.0–9.0)	2.0 (0.0–8.25)	5.0 (1.0–9.5)	0.14
Baseline QTc duration	407.0 (385.0–426.0)	408.0 (389.25–427.50)	404.0 (384.0–420.0)	0.1
Post-treatment QTc peak	437.0 (414.0–460.0)	428.0 (412.75–449.25)	456.0 (422.0–467.5)	<0.001
ΔQTc	27.0 (13.0–45.0)	18.0 (11.0–30.0)	46.0 (40.5–54.5)	<0.001
Baseline PR duration	145.50 (128.7–160.0)	147.0 (135.0–160.0)	144.0 (120.0–160.0)	0.53
Post-treatment PR peak	159.0 (140.0–170.0)	159.0 (141.0–168.50)	156.0 (139.5–171.0)	0.97
ΔPR	7.0 (1.0–13.0)	5.0 (0.0–12.25)	10.0 (5.0–15.0)	0.022
QTc peak day	5.0 (4.0–5.0)	5.0 (4.0–6.0)	4.0 (3.0–5.0)	0.022
Drug withdrawal due to QRS prolongation	11 (7.1)	5 (4.9)	6 (11.3)	0.12

ΔPR, PR changes during treatment; ΔQRS, QRS changes during treatment; ΔQTc, QTc changes during treatment. The p-values indicated show that they are statistically significant. SD: standart derivation; ECG: electrocardiography; IQR: interquartile range; QTc: corrected QT.

prolongation in the QTc duration, 5 (4.9%) patients were in the monotherapy group, and 6 (11.3%) patients were in the group receiving combination therapy (p=0.12). The median (IQR) maximum QTc duration was significantly longer in patients who had stopped taking the drug in the combination group compared with the group receiving monotherapy treatment (478 [467.7–499.5] and 413.0 [410.0–444.5] ms; p<0.001). Moreover, it was observed that patients who received combination therapy reached the median (IQR) maximum QTc earlier than those who received monotherapy (4.0 [3.0–5] days *versus* 5.0 [4.0–6.0] days; p=0.02). Besides QTc prolongation, 3 (1.9%) patients developed new atrial fibrillation, and 1 (0.6%) patient developed severe arrhythmias, such as ventricular tachycardia (VT), ventricular fibrillation (VF), and TdP, during cardiopulmonary resuscitation and died. The maximum QTc duration of this patient was 444 ms. None of the patients had VT, VF, or TdP due to drug-induced QTc prolongation.

DISCUSSION

The most important findings of this study are as follows:

1. The use of both HCQ alone and HCQ+AZT combined therapy significantly prolonged the QTc.
2. HCQ alone prolonged the QTc interval by median (IQR) 18.0 (11.0–30.0) ms, while the combined use of HCQ + AZT prolonged it by median (IQR) 46.0 (40.5–54.5) ms.
3. VT, VF, or TdP due to QTc prolongation was not observed in both the groups. One patient developed a malign cardiac arrhythmia, whose maximum median (IQR) QTc duration was 444 ms.

Many treatments were tried for SARS-CoV-2 disease in Wuhan, China, in December 2019, and the disease was declared as a pandemic by the WHO on March 12, 2020. Among these therapies, chloroquine (CQ)/HCQ and/or HCQ+AZT have been shown to be effective by inhibiting virus cell fusion in some studies, so these drugs have become widely used[12,13]. However, until now, there are a limited number of studies showing a positive effect of these two drugs on SARS-CoV-2. In a study of 30 patients, it was reported that CQ did not reduce the viral load or shorten the time taken for fever to decrease and did not stop the progression of the disease[14]. In another study, HCQ and/or HCQ+AZT were shown to be effective on morbidity and mortality[15]. The most feared side effects of these treatments are TdP and sudden cardiac death due to QTc prolongation. QT prolongation and development of TdP due to high-dose or chronic HCQ use are limited to a few case reports, and although QTc prolongation is a predictive for TdP, it is not specific. The relationship between QT prolongation and TdP is not linear because drugs that prolong QT have not been consistently associated with cardiac arrhythmias. Among all QT-prolonging drugs, the TdP incidence of antiarrhythmic drugs was reported as 1–5%, while the TdP incidence of noncardiovascular drugs was reported as 0.001%[16]. Studies have reported that AZT, a macrolide group drug, prolongs the QT interval[10]. Although AZT was shown to cause sudden cardiac death in a study conducted in 2012, there is insufficient evidence regarding QTc prolongation and cardiac death due to TdP[17]. In a recent study, Bakhshaliyev et al. reported no arrhythmia and cardiac death in patients with COVID-19 who were treated with HCQ+AZT[18]. In addition, in many small-scale studies in which HCQ and/or AZT treatment was used in monotherapy or in combination increasingly upon the onset of the COVID-19 epidemic, it was shown that these two drugs did not cause TdP or sudden cardiac death due to QTc prolongation[16,19-22].

In our study, the QTc interval of the patients who received HCQ or HCQ+AZT was significantly longer compared with the baseline (p<0.001). When monotherapy and combination therapy were compared, QTc durations of the group receiving combination therapy were significantly prolonged compared with the group receiving monotherapy. In both groups, treatment of 11 (7.1%) patients was interrupted due to QTc prolongation, but no malign arrhythmia or TdP was observed even in this group. There was a patient who developed VT and VF, in which case such rhythms developed during cardiopulmonary resuscitation. At the same time, the time to reach the maximum QTc duration was shorter in the group receiving combination therapy in this study, compared with the monotherapy group.

The limitations of this study are the absence of a control cohort of patients with COVID-19 infections who were not treated with any of these medications. Although this would have provided a stronger analysis, nearly every hospitalized patient with COVID-19 received one or more of these medications during the course of their admission during this study period. The number of patients with underlying cardiac disease in the study is small, potentially limiting generalizability to that population.

CONCLUSION

In this study, it was shown that QTc interval was prolonged significantly after both monotherapy and combined therapy. QTc prolongation was significantly greater in the combination group. Despite this increase, very few patients had the medications discontinued prematurely due to QT prolongation.

The important point was that this study showed that QTc prolongation was not associated with malignant arrhythmia such as TdP and arrhythmic death in both groups.

AUTHOR CONTRIBUTIONS

BM: Conceptualization. **HA:** Data curation. **MA:** Writing – original draft. **SM:** Writing – review & editing.

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42. https://doi.org/10.1001/jama.2020.2648
2. World Health Organization. Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020. Geneva: World Health Organization; 2020. [cited on March 15, 2020]. Available from: https://www.who.int/dg/speeches/detail/who-director-generals-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020
3. 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
4. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, 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. https://doi.org/10.1016/j.ijantimicag.2020.105949
5. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269-71. https://doi.org/10.1038/s41422-020-0282-0.
6. Tran DH, Sugamata R, Hirose T, Suzuki S, Noguchi Y, Sugawara A, et al. Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A(H1N1) pdm09 virus infection by interfering with virus internalization process. J Antibiot (Tokyo). 2019;72:759-68. https://doi.org/10.1038/s41429-019-0204-x
7. Andreani J, Le Bideau M, Duflot I, Jardot P, Rolland C, Boxberger M, et al. In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect. Microb Pathog. 2020;145:104228. https://doi.org/10.1016/j.micpath.2020.104228
8. Morgan ND, Patel SV, Dvorkina O. Suspected hydroxychloroquine-associated QT-interval prolongation in a patient with systemic lupus erythematosus. J Clin Rheumatol. 2013;19:286-8. https://doi.org/10.1097/RHU.0b013e31829d5e50
9. Kezerashvili A, Khattak H, Barsky A, Nazari R, Fisher JD. Azithromycin as a cause of QT-interval prolongation and torsade de pointes in the absence of other known precipitating factors. J Interv Card Electrophysiol. 2007;18(3):243-6. https://doi.org/10.1007/s10840-007-9124-y
10. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. J Am Coll Cardiol. 2010;55(9):934-47. https://doi.org/10.1016/j.jacc.2010.01.001
11. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2:69. https://doi.org/10.1186/1743-422X-2-69
12. 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;71(15):732-9. https://doi.org/10.1093/cid/ciaa237
13. Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease19 (COVID-19). Zhejiang Da Xue Xue Bao Yi Xue Ban. 2020;49(2):215-9. https://doi.org/10.3785/j.issn.1008-9292.2020.03.03
14. Pellaud C, Grandmaison G, Thien HPPH, Baumberger M, Carrel G, Ksouri H, et al. Characteristics, comorbidities, 30-day outcome and in-hospital mortality of patients hospitalised with COVID-19 in a Swiss area – a retrospective cohort study. Swiss Med Wkly. 2020;150:w20314. https://doi.org/10.4414/smw.2020.20314
15. Saleh M, Gabriels J, Chang D, Soo Kim B, Mansoor A, Mahmood E, 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. https://doi.org/10.1161/CIRCEP.120.008662
16. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012;366(20):1881-90. https://doi.org/10.1056/NEJMoa1003833
17. Bakhshaliyev N, Uluganyan M, Enhos A, Karacop E, Ozdemir R. The effect of 5-day course of hydroxychloroquine and azithromycin combination on QT interval in non-ICU COVID19(+) patients. J Electrocardiol. 2020;62:59-64. https://doi.org/10.1016/j.jelectrocard.2020.08.008
18. Van den Broek MPH, Möhlmann JE, Abeln BGS, Liebregts M, van Dijk VF, van de Garde EMW. Chloroquine-induced QTc prolongation in COVID-19 patients. Neth Heart J. 2020;28(7-8):406-9. https://doi.org/10.1007/s12471-020-01429-7
19. Sinkeler FS, Berger FA, Muntinga HJ, Jansen MMPM. The risk of QTc-interval prolongation in COVID-19 patients treated with chloroquine. Neth Heart J. 2020;28(7-8):418-23. https://doi.org/10.1007/s12471-020-01462-6
20. 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;26(6):808-9. https://doi.org/10.1038/s41591-020-0888-2
21. Hor CP, Hussin N, Nalliah S, Ooi WT, Tang XY, Zachariah S, et al. Experience of short-term hydroxychloroquine and azithromycin in COVID-19 patients and effect on QTc trend. J Infect. 2020;81(2):e117-9. https://doi.org/10.1016/j.jinf.2020.05.058