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# COVİD-19 Tanısı ile Yatırılan Hastalarda Hidroksiklorokin ve/veya Azitromisin Tedavisinin T tepe-T bitiş Süresi Üzerine Olan Etkisi

## The Impact of Hydroxychloroquine with or without Azithromycin Treatment on T-peak to T-end Time in Patients Hospitalized with Coronavirus Disease (COVID-19)

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### *ÖZ*

***GİRİŞ ve AMAÇ:*** *Çalışmamızın amacı COVİD-19 hastalarında hidroksiklorokin (HQC) ve azitromisin (AZR) tedavisinin, sadece hidroksiklorokin (HCQ) alan hastalara göre T tepe-T bitiş (TpTe) süresi üzerine etkilerini araştırmaktır.*

***YÖNTEM ve GEREÇLER:*** *Çalışmamıza 6 Nisan-30 Nisan 2020 tarihleri arasında COVİD-19 tanısı ile yatırılan ardışık 205 hasta alındı. Hastalar, yalnız HQC verilen ve HQC+AZR kombinasyonu verilenler diye iki gruba ayrıldı. İki grup demografik özellikleri, başvuru ve 3.gün laboratuar parametreleri ve 3.gün elektrokardiografi (EKG) bulgularına göre karşılaştırıldı. Ayrıca tüm hastaların başvuru ve 3.gün EKG'leri karşılaştırıldı.*

***BULGULAR:*** *Tüm hastaların median yaş ortalaması 44 (31-59) olup, % 53'ü erkek hastalardı. Hastaların başvuru EKG'sine göre 3.gün EKG' lerinde; QRS süresi, QT süresi, QTc süresi, QT dispersiyonu, QTc dispersiyonu, TpTe süresi ve TpTe/QTc oranı anlamlı olarak daha fazlaydı. HQC grubunda HQC+AZR grubuna göre, başvuru EKG'lerinde QT dispersiyonu ve QTc dispersiyonu anlamlı olarak daha fazlaydı. İki grubun 3. gün EKG parametreleri ise benzerdi. Lineer regresyon analizi yöntemini kullanarak 3.gün EKG'lerindeki TpTe değerleri için bazı prediktörler tespit ettik. Bunlar; HCQ+AZR kombinasyonunun kullanılması [regressioncoefficient (RE) 0.097 and 95% CI 0.960, 4.109, p = 0.040], kadın cinsiyet (RE -0.119 and 95% CI -4.552, -0.440, p = 0.018) ve başvuru EKG'sindeki TpTe süresi (RE 0.741 and 95% CI 0.637, 0.840, p < 0.001) idi.*

***TARTIŞMA ve SONUÇ:*** *Çalışmamız sonucunda, HQC+AZR kombinasyon tedavisinin HQC grubuna karşı TpTe süresinin uzamasında bağımsız bir prediktör olduğu görülmüştür.*

***Anahtar Kelimeler:*** *COVİD-19, hidroksiklorokin, azitromisin, TpTe süresi*

### *ABSTRACT*

***INTRODUCTION:*** *The aim of our study is to investigate the effects of hydroxychloroquine (HCQ) with azithromycin (AZR) treatment versus HCQ alone on T-endto T-peak (TpTe) time in COVID-19 patients.*

***METHODS:*** *Two hundred-five consecutive patients hospitalized with the diagnosis of COVID-19 were included in our study. Patients were divided into two groups according to the HCQ alone and HCQ+AZR combination treatments administered. These two groups were compared according to the demographic features, admission and follow-up laboratory parameters, admission and 3rd day electrocardiographic (ECG) parameters.*

***RESULTS:*** *The median age of all patients was 44 (31-59) and 53% of them were male. QRS interval, QT interval, QTc interval, QT dispersion, QTc dispersion,TpTe time and TpTe/QTc ratio were significantly higher in the 3rd day ECGs than admission ECGs. In the HCQ group, QT dispersion and QTc dispersion at admission ECG were significantly higher than in the HCQ + AZR group. On the 3rd day ECG parameters of the two groups were similar. We determined the predicting factors of theTpTe time on the 3rd day 's ECG using linear regression analysis. These were the HCQ+ AZR combination treatment [regression coefficient (RE) 0.097 and 95% CI 0.960, 4.109, p = 0.040], female gender (RE -0.119 and 95% CI -4.552, -0.440, p = 0.018), and TpTe time at admission ECG (RE 0.741 and 95% CI 0.637, 0.840, p < 0.001).*

***DISCUSSION AND CONCLUSION:*** *HCQ + AZR combination treatment was found to be an independent predictor in the prolongation of theTpTe time, compared to the HCQ alone treatment.*

***Keywords:*** *COVID-19, hydroxychloroquine, azithromycin, TpTe time*

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## INTRODUCTION

A pneumonia epidemic, which is thought to be caused by a new coronavirus, was detected in the Wuhan city of Hubei province of the People's Republic of China in December 2019, and could not be taken under control and has spread in a short time to entire China and the whole world and particularly to the European continent, resulting in a pandemic (1). The causative virus was first named as the novel coranavirus-2019 (2019-nCoV), and was then renamed as the "Serious Acute Respiratory Syndrome-Coronavirus-2" (SARS-CoV-2) by the World Health Organization (WHO), whereas the disease caused by the virus has been named as the COVID-19 (Coronavirus Disease 2019) (2,3). After the virus was officially detected in our country on March 11th, 2020, the number of cases increased rapidly and was isolated in 150 thousand patients within a period of 2.5 months.
Hydroxychloroquine (HCQ), which has been routinely administered within the scope of the treatment of the COVID-19 disease, is an antimalarial drug and has also been used for many years in the treatment of lupus and rheumatoid arthritis. In addition to being a conventional immunomodulating drug, in-vitro studies have shown that chloroquine reduces viral replication in other infections (including SARS-related corona) (4). Azithromycin (AZR) is a macrolide group antibiotic, and is used in COVID-19 patients to prevent secondary bacterial pneumonia. It has been found that hydroxychloroquine can be effective in the treatment of COVID-19 when administered both alone or in combination with azithromycin (HCQ + AZR). However, the fact that HCQ + AZR prolong the QT interval and the risk of arrhythmia brought to mind the risk of death due to arrhythmia (5). The purpose of our study is thus to investigate the effects of HCQ alone and HCQ + AZR treatments on the TpTe time, which is known to be a predictor of ventricular arrhythmia.

## MATERIALS AND METHODS

### *Study Population*

Our study was designed as a monocentric, retrospective and observational study. Within the scope of our study, data obtained from 264 COVID-19 patients who have been tested positive (+) for COVID-19 on the basis of the PCR (polymerase chain reaction) test and/or thorax computed tomography (CT) at the Diyarbakır GaziYaşargil Training and Research Hospital between the dates of April 6th-April 30th, 2020, were reviewed. Thirty eight of these patients were not included in the study, as they were not hospitalized and received outpatient treatment instead. On the other hand, 21 patients were also excluded from the study, since their 3rd day electrocardiograms (ECG) of hospitalization were not available. 12-lead ECG (admission and 3rd day), radiological imaging (thorax CT), laboratory, and PCR results of the remaining 205 patients were obtained from the hospital registry system. The patients were divided into 2 groups according to the type of the treatment patients received; the group, where only HCQ treatment is given and the group, where HCQ + AZR treatments were given in combination. These two groups were compared according to the demographic features of the patients, laboratory parameters of the patients measured during their admission to the hospital and on the 3rd day of their hospitalization, and their ECGs. Hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, heart failure, chronic kidney failure, malignancy, atrial fibrillation and smoking histories of these patients were querried. Our application to register our study as a Ministry of Health Scientific Research was approved, which was followed by the approval of the ethics committee of our hospital. Our study protocol conforms to the Helsinki Declaration (6).

### *Electrocardiographic Assessment*

ECGs were taken via 12-lead electrocardiography devices with a 25-millimeter/second speed and 10-millimeter/millivolt calibration (Schiller, Germany-Bavaria and Nihon Kohden, Japan-Tokyo), and these ECGs were transferred to the computer environment using a scanner. Both the ECGs taken during the admission of the patients to the hospital and on the 3rd day of their hospitalization were reviewed independently by two cardiologists. ECGs obtained were magnified 300% and the QRS, QT, corrected QT (QTc), and TpTe time as well as QT and QTc dispersions were calculated individually and manually in milliseconds (ms). The QT dispersion

was obtained by calculating the difference between the longest QT interval and the shortest QT interval. V2 chest derivation was used to measure the TpTe time. The time from the peak of the T wave (Tp) to the point where it ends (Te) was measured (7). QTc was calculated according to the Bazett formula (QTc = QT / √RR interval).

***Statistical Analysis***

The analysis of the data was carried out using SPSS (Statistical Package for Social Science for Windows)-24 packaged software. Median value and interquantile range (IQR) were used in the distribution of parametric variables. In comparison of parametric variables, Student-T and Paired-T tests were used for independent and dependent variables that exhibit normal distribution, respectively; whereas for independent and dependent variables that do not exhibit normal distribution, Mann-Whitney-U and Wilcoxon tests were used, respectively. Chi-square and Fischer Exact tests were used in comparison of the categorical variables. The linear regression model was used for the prediction of TpTe prolongation predictors, by applying logarithmic transformation to continuous variables that could not be shown to have had a linear relationship. The statistical significance level of the obtained data was interpreted with the "p" value. Values of $p < 0.05$ were considered to be statistically significant.

**RESULTS**

The median age of all patients was 44 (31-59) and 53% of them were male. The median duration of hospitalization was 6 days (5-8). The number of patients that were smokers was 54 (26.3%). Thirty three patients (16.1%) had hypertension, 31 patients (15.1%) had diabetes mellitus, 11 patients (5.4%) had coronary artery disease, 9 patients (4.4%) had chronic obstructive pulmonary disease, and 6 patients (3%) had atrial fibrillation (Table 1). ECGs of all patients their at admission to the hospital and on the 3rd day were compared. QRS interval [92 (81-104) msvs 94 (88-103) ms, $p < 0.001$], QT interval [355 (338-380) msvs 378 (360-408) ms, $p < 0.001$], QTc interval [431 (410-451) msvs 440 (410-460) ms, $p < 0.001$], QT dispersion [32 (28-40) msvs 37 (30-44) ms, $p < 0.001$], QTc dispersion [40 (34-48) msvs 43 (36-51) ms, $p < 0.001$], TpTe time [88 (80-95) msvs 93 (85-101) ms, $p < 0.001$] and TpTe/QTc ratio [0.20 (0.18-0.22) vs 0.21 (0.19-0.22), $p = 0.001$] were significantly higher on the 3rd day ECGs compared to the ECGs at admission to the hospital. On the other hand, TpTe/QT ratio [0.25 (0.22-0.26) vs 0.24 (0.21-0.26), $p = 0.003$] and heart rate [87 (76-95)/min vs 79 (72-90)/min, $p < 0.001$] were significantly higher at admission ECGs compared to the 3rd day ECGs.(Table 2).

The patients were analyzed in two groups as those who received HCQ treatment and those who received HCQ + AZR combination treatment. The number of patients who received only HCQ treatment was 77 (38%), whereas the number of patients who received HCQ + AZR treatment was 128 (62%). The demographic data, median ages, clinical features, and comorbidities of both groups were comparable. There was no difference between the two groups in terms of antiarrhytmic drug use (e.g beta blocker, amiodarone, digoxin). From among the laboratory parameters measured, alanine aminotransferase (ALT) level was found to be higher in the HCQ + AZR group compared to the HCQ group [19 (15-31) IU/L vs 17 (11-27) IU/L, $p = 0.020$], whereas the white blood cell (WBC) count, potassium level on the 3rd day of hospitalization, and the neutrophil count were found to be higher in HCQ group compared to the HCQ + AZR group [7.73 (5.93-10.0) vs 6.34 (4.50- 8.76), $p = 0.005$, 4.34 (4.05-4.70) vs 4.17 (3.90-4.50), $p = 0.001$ and 5.03 (3.60-7.65) vs 3.66 (2.80-6.52), $p = 0.011$, respectively]. ECGs of the patients of both groups taken at their admission to the hospital and on the 3rd day of their hospitalization were reviewed individually and no difference was found in terms of heart rate, QRS interval, QT and QTc intervals, TpTe time, and TpTe/QT and TpTe/QTc ratios between the ECGs. QT dispersion and QTc dispersion were found to be significantly higher in the ECGs taken the admission of the patients to the hospital, in the HCQ group compared to the HCQ + AZR group, whereas the difference between the QT veQTc dispersions measured on the ECGs of both groups taken on the 3rd day of the hospitalization was not significant (Table 3).

| Table 1. Clinical, demographic characteristics and laboratory parameters of patients | | | | |
|---|---|---|---|---|
| **Variables** | **AllPatients(n=205)** | **HCQ(n=77)** | **HCQ + AZR(n=128)** | **pvalue** |
| Age (years) | 44 (31-59) | 45 (25-66) | 43 (33-56) | 0.930 |
| Gender (male, %) | 108 (52.7) | 39 (50.6) | 69 (53.9) | 0.650 |
| Systolic BP(mmHg) | 110 (100-120) | 110 (100-120) | 110 (100-120) | 0.740 |
| Daistolic BP | 70 (60-80) | 70 (60-80) | 70 (60-80) | 0.900 |
| Heart rate(beats/min) | 88 (80-96) | 88 (80-95) | 89 (80-97) | 0.780 |
| Fever, degree °C | 37.0 (36.7-37.6) | 37.0 (36.8-37.4) | 37.0 (36.7-37.6) | 0.420 |
| Hospitalizationduration (day) | 6.0 (5.0-8.0) | 6.0 (5.0-8.5) | 6.0 (5.0-8.0) | 0.880 |
| HT, n,% | 33 (16.1) | 14 (18.2) | 19 (14.8) | 0.520 |
| DM, n,% | 31 (15.1) | 12 (15.6) | 19 (14.8) | 0.880 |
| Smoking, n,% | 54 (26.3) | 18 (23.4) | 36 (28.1) | 0.430 |
| CAD, n,% | 11 (5.4) | 5 (6.5) | 6 (4.7) | 0.570 |
| CHF, n, % | 6 (2.9) | 2 (2.6) | 4 (3.1) | 0.820 |
| COPD, n, % | 9 (4.4) | 5 (6.5) | 4 (3.1) | 0.250 |
| AF, n, % | 6 (3) | 4 (5) | 2 (2) | 0.197 |
| BB, n,% | 24 (12) | 8 (10) | 16 (13) | 0.672 |
| Amiodarone, n% | 4 (2) | 1 (1) | 3 (2) | 0.608 |
| Digoxin, n % | 6 (3) | 3 (4) | 3 (2) | 0.513 |
| Glucose, mg/dL | 103 (93-121) | 101 (89-118) | 104 (96-127) | 0.054 |
| GFR, ml/min/1.73m$^2$ | 90 (83-98) | 90 (81-95) | 90 (85-98) | 0.390 |
| Creatinine, mg/dL | 0.78 (0.68-0.90) | 0.78 (0.67-0.95) | 0.79 (0.68-0.89) | 0.990 |
| Sodium, meq/L | 138 (136-139) | 138 (137-139) | 138 (136-139) | 0.056 |
| Potassium, meq/L | 4.00 (3.75-4.40) | 3.99 (3.80-4.45) | 4.00 (3.73-4.39) | 0.780 |
| Potassium 3$^{rd}$day, meq/L | 4.2(3.97-4.50) | 4.34(4.05-4.70) | 4.17(3.90-4.50) | **0.021** |
| Calcium, meq/L | 8.8 (8.4-9.1) | 8.9 (8.4-9.1) | 8.7 (8.4-9.0) | 0.090 |
| Calcium, 3$^{rd}$day, meq/L | 8.4(8.1-8.7) | 8.38(8.1-8.7) | 8.36(8.1-8.7) | 0.860 |
| Albumin, gr/dL | 4.3 (4.0-4.5) | 4.3 (4.0-4.6) | 4.3 (4.0-4.5) | 0.430 |
| AST, IU/L | 23 (16-30) | 19 (16-27) | 24 (16-32) | 0.060 |
| ALT, IU/L | 18 (13-29.5) | 17 (11-27) | 19 (15-31) | **0.020** |
| LDH, IU/L | 230 (194-284) | 223 (189-275) | 233 (190-291) | 0.170 |
| CRP, mg/dL | 15.2 (2.0-55.7) | 6.4 (2.0-50.7) | 18.8 (2.6-56.3) | 0.055 |
| D-dimer, ng/ml | 189 (110-163) | 185 (103-428) | 189 (109-319) | 0.770 |
| Troponin I, ng/ml | 0.1 (0.1-0.1) | 0.1 (0.1-0.1) | 0.1 (0.1-0.1) | 0.740 |
| WBC, $10^9$/ L | 6.88 (4.79-9.90) | 7.73 (5.93-10.0) | 6.34 (4.50-8.76) | **0.005** |
| Neu, $10^9$/ L | 4.29 (3.04-7.40) | 5.03 (3.60-7.65) | 3.66 (2.80-6.52) | **0.011** |
| Lym, $10^9$/ L | 1.51 (1.11-2.08) | 1.51 (1.22-2.08) | 1.51 (1.10-2.09) | 0.670 |
| NLR | 2.75 (1.83-5.10) | 3.38 (1.96-5.88) | 2.69 (1.75-4.47) | 0.100 |
| Platelet, $10^9$/ L | 232 (186-276) | 240 (202-284) | 225 (184-2.72) | 0.110 |
| Ex, n,% | 14 (6.8) | 5 (6.4) | 9(7) | 0.900 |

*Note: Data areexpressed as medianinterquantilerangeandcount(percentage)*
*Abbreviations: AF: Atrialfibrillation, ALT: Alaninetransaminase, AST: Aspartattransaminase, AZR: Azithromycin, BB: Beta blocker, BP: Blood pressure, CAD: Coronaryarterydisease, CHF: Chronicheartfailure, COPD: Chronicobstructivepulmonerdisease, CRP: C-reactive protein, DM: Diabetesmellitus, GFR: Glomerularfiltration rate, HCQ: Hydroxychloroquine, HT: Hypertension, LDH: lactatdehydrogenase, Leu: Lymphocyte, Neu: Neuthrophil, NLR:Neuthrophil/lymphocyteratio WBC: White bloodcell*

| Table 2.Comparsion of all patients admission and 3rd day ECGs | | | |
|---|---|---|---|
| **Variables** | **Admission ECG(n=205)** | **3$^{rd}$day ECG(n=205)** | **pvalue** |
| Heart rate, beats/min | 87 (76-95) | 79 (72-90) | <0.001 |
| QRS, ms | 92 (81-104) | 94 (88-103) | <0.001 |
| QT, ms | 355 (338-380) | 378 (360-408) | <0.001 |
| QTc, ms | 431 (410-451) | 440 (410-460) | <0.001 |
| QT dispersion, ms | 32 (28-40) | 37 (30-44) | <0.001 |
| QTcdispersion, ms | 40 (34-48) | 43 (36-51) | <0.001 |
| TpTe, ms | 88 (80-95) | 93 (85-101) | <0.001 |
| TpTe/QT | 0.24 (0.22-0.26) | 0.24 (0.21-0.26) | 0.003 |
| TpTe/QTc | 0.20 (0.18-0.22) | 0.21 (0.19-0.22) | 0.001 |

*Note: Data areexpressed as medianinterquantilerangeandcount(percentage)*
*Abbreviations:ECG: Electrocardiography, QTc: Corrected QT, TpTe: T-peakto T-end time*

| Table 3.Comparsion of HCQ alone and HCQ + AZR group admission and 3rd day ECGs. | | | |
|---|---|---|---|
| | **HCQ(n=77)** | **HCQ + AZR(n=128)** | **pvalue** |
| ***Admission ECG*** | | | |
| Heart rate, beats/min | 85 (73-100) | 89 (70-99) | 0.340 |
| QRS, ms | 93 (86-103) | 92 (84-100) | 0.200 |
| QT, ms | 360 (335-385) | 350 (338-370) | 0.420 |
| QTc, ms | 432 (413-450) | 430 (408-452) | 0.700 |
| QT dispersion, ms | 35 (30-42) | 30 (27-40) | **0.006** |
| QTcdispersion, ms | 44 (35-50) | 37 (33-46) | **0.014** |
| TpTe, ms | 90 (84-96) | 88 (80-95) | 0.090 |
| TpTe/QT | 0.24 (0.22-0.27) | 0.24 (0.22-0.26) | 0.350 |
| TpTe/QTc | 0.20 (0.19-0.22) | 0.20 (0.18-0.22) | 0.270 |
| ***3rd day ECG*** | | | |
| Heart rate, beats/min | 80 (72-87) | 79 (72-90) | 0.910 |
| QRS, ms | 96 (87-104) | 94 (88-102) | 0.900 |
| QT, ms | 380 (361-402) | 376 (360-402) | 0.550 |
| QTc, ms | 437 (419-467) | 441 (412-458) | 0.760 |
| QT dispersion, ms | 40 (30-46) | 36 (30-41) | 0.100 |
| QTcdispersion, ms | 46 (37-56) | 42 (36-49) | 0.090 |
| TpTe, ms | 94 (84-100) | 92 (85-100) | 0.380 |
| TpTe/QT | 0.24 (0.22-0.27) | 0.24 (0.21-0.26) | 0.320 |
| TpTe/QTc | 0.21 (0.19-0.23) | 0.20 (0.19-0.22) | 0.370 |

*Note: Data areexpressed as medianinterquantilerangeandcount(percentage)*
*Abbreviations: AZR: Azithromycin, ECG: Electrocardiography, HCQ: Hydroxychloroquine, QTc: Corrected QT, TpTe: T-peakto T-end time*

| Table 4. Adjusted regression coefficient and SE for individual predictors | | |
|---|---|---|
| | **Regressioncoefficient, 95% CI** | **pvalue** |
| Drugusing( HCQ + AZR) | 0.097 (0.960, 4.109) | **0.040** |
| Age(years) | 0.013 (-0.054, 0.068) | 0.814 |
| Gender(femalevsmale) | -0.119 (- 4.552, - 0.440) | **0.018** |
| HT(yes/no) | -0.029 (-4.530, 2.769) | 0.634 |
| DM(yes/no) | -0.088 (-5.383, 0.292) | 0.078 |
| 3rddaycalcium, meq/L | -0.005 (-2.281, 2.072) | 0.925 |
| 3rddaypotassium, meq/L | 0.005 (-0.029, 0.032) | 0.906 |
| Neu, $10^9$/ L | 0.108 (0.010, 0.543) | 0.420 |
| Admission ECG QRS, ms | 0.086 (-0.010, 0.147) | 0.085 |
| Admission ECG QTc, ms | 0.022 (-0.028, 0.044) | 0.659 |
| Admission ECG TpTe, ms | 0.741 (0.637, 0.840) | **<0.001** |
| Heart rate, beats/min | 0.004 (-0.076, 0.083) | 0.933 |

The QTc dispersions obtained from the ECGs taken on the 3rd day of the hospitalization of patients were found to be higher than 60 ms in a total of 21 patients, 12 (57%) of whom were from the HCQ group and 9 (43%) of whom were from the HCQ + AZR group. QTc duration was higher than 500 ms in 1 patient in HCQ group and 2 patients in HCQ + AZR group. Treatment of these patients was stopped. Treatment-related ventricular arrhythmia or cardiac death were not observed in any of these patients. During the follow-ups, mortality was observed in 14 (6.8%) of the patients, 5 (6.4%) of whom were from the HCQ group and 9 (7.0%) of whom were from the HCQ + AZR group. The mortality rates of two groups were similar (p = 0.90). It was determined that all mortalities were due to noncardiacetiology. Linear regression model was used for the prediction of 3rd day TpTe predictors based on the parameters of patients clinical features, 3rd day laboratory parameters and admission ECGs parameters. R2, which is the performance criterion of the model used, was determined as 0.65. It was revealed through this regression model that the HCQ + AZR combination treatment is associated with prolonged TpTe time compared to the treatment, where only HCQ is given. It was also revealed that the female gender was a negative predictor in the prolongation of TpTe time (Table 4).

**DISCUSSION**

Hydroxychloroquine (HCQ) and Azithromycin (AZR) treatments that are administered to patients within medical treatment during the COVID-19 pandemic are known to prolong the QT and QTcintervals, however there are no data or any studies on the effects of these medications on the TpTe time. It was found as a result of our study on the basis of the patients' 3 rd day ECGs that the HCQ + AZR combination treatment was associated with TpTe prolongation in COVID-19 patients. To the best of our knowledge, our study is the first study to date conducted on the effect of these medications on the TpTe time in COVID-19 patients. COVID-19 disease can present a wide range of clinical manifestations, from a simple upper respiratory infection to a fatal acute respiratory failure. In addition to the clinical manifestations and travel and contact history, polymerase chain reaction (PCR) and/or thorax computer tomography (CT) are very important for diagnosis of COVID-19. Today, there is no specific antiviral treatment the safety and effectiveness of which has been proven. Medications such as hydroxychloroquine, azithromycin, oseltamivir, and favipiravir have been recommended by the World Health Organization in the fight against COVID-19, and these medications are still used in COVID-19 treatment in many centers around the world (8).

Hydroxychloroquine has been used for many years as an antimalarial and immunomodulatory medication. It prolongs the ventricular repolarization and the duration of the action potential through the inhibition of the rapidly activated delayed rectifier potassium channel (Kir) and inhibition of the inwardly rectifying potassium current (İK1). This may increase the risk of ventricular arrhythmia, such as torsade de pointes, causing sudden cardiac death [9]. On the other hand, azithromycin is a macrolide group antibiotic, and, just like chloroquine, can lead to ventricular arrhythmia by prolonging the QT. The mechanism of the prolongation of the QT by azithromycin is not clearly known. It is thought that it prolongs QT through the inhibition of Kir (9).

In vitro and preliminary clinical studies revealed that treatments that include either solely HCQ or a combination of HCQ with AZR can be effective in the treatment of COVID-19. However, the fact that HCQ and AZR prolong the QT interval and the risk of associated ventricular arrhythmia have brought to mind the risk of death due to arrhythmia. Research data in respect of the safety of the treatments that include the HCQ + AZR combination are limited, and it was demonstrated in in-vivo studies that HCQ + AZR or AZR have no synergistic arrhythmic effects (10). As a matter of fact, we have not found an additional risk of ventricular arrhythmia associated with the HCQ + AZR combination. In a study conducted on healthy volunteers, who were given 600 mg chloroquine, QTc was found to prolong by 6.1 ms. Maximum change in QTc compared to the basal QTc was seen in the first 24 hours after the intake of the medication (11). In another study, it was observed that QTc prolonged by 16 ms after 4-5 hours from the intake of the medication in healthy volunteers, who were also given 600 mg of chloroquine (12). In our study, first the ECGs of the patients diagnosed with COVID-19 were taken, then their medical treatments were initiated, and their follow-up ECGs were taken on the 3rd day of their hospitalization. In a study conducted by Nicholas J. Mercuro et al., the COVID-19 patient group that received the HCQ treatment and the COVID-19 patient group that received the HCQ + AZR combination treatment were compared. Following the treatments, QTc was found to be significantly higher in the HCQ group compared to the HCQ + AZR group, whereas the change in QTc was found to be significantly higher in the HCQ + AZR group compared to the HCQ group (13). On the other hand, in our study, we have not found any significant difference in terms of QT and QTc intervals in both groups. However, we have found that the QT dispersion ($p = 0.006$) and QTc dispersion ($p = 0.014$) were significantly higher in the HCQ group compared to the HCQ + AZR group. The QT dispersion indicates the heterogeneity of ventricular repolarization. Increased QT dispersion and QTc dispersion have been found to be associated with ventricular arrhythmia. It is very difficult to distinguish between normal and abnormal values of QT dispersion in an absolute manner, since the normal values of QT dispersion can be within a wide range ($28.7 \pm 9.2$ to $71.7 \pm 7$ ms). It was suggested in a

study that a QT dispersion of 50 ms can be accepted as the upper limit of normal (14). QTc dispersion is assessed in almost every QT dispersion study, but it is also pointed out that the Bazett formula have its limitations in the event of heart rates that are far from the mean values (below 50/min and above 80/min) (15). In our study, we have found a significant difference between ECGs in terms of QT and QTc dispersions in favor of the ECGs taken on the 3rd day of the hospitalization of the patients, whereas among the HCQ alone and HCQ + AZR groups, the QT dispersion and QTc dispersion times were found to be significantly higher in the HCQ group.

A study by Panikkath R. et al. showed that sudden cardiac death may occur in some patients even when QTc is normal. In cases where QTc times are normal or where QTc times cannot be measured accurately (e.g., intraventricular conduction delay or block), TpTe time have been significantly associated with sudden cardiac death. It has been stated that prolongation of TpTe time makes the heart sensitive to reentrant ventricular arrhythmias (16). In some studies, it has been shown that the TpTe time is used as a ventricular repolarization parameter and as a predictor of ventricular arrhythmia. Prolongation of TpTetime has been associated with increased mortality in patients with Brugada syndrome, long QT syndrome, hypertrophic cardiomyopathy and myocardial infarction subjected to primary percutaneous coronary intervention (17, 18). In the study conducted by Gupta P. et al., TpTetime, QT interval as well as the TpTe/QT ratio were demonstrated to be current markers in increased ventricular repolarization distribution and in predicting the ventricular arrhythmias (19). In our study, TpTe time and TpTe/QTc ratio were found to be significantly higher on the ECGs produced on the 3rd day of the hospitalization of the patients compared to the ECGs produced during their admission to the hospital.

The peak time of the T wave (Tp) overlaps with the end of the repolarization of epicardial cells, whereas the end point of the T wave (Te) overlaps with the end of the repolarization of the endocardial cells (19). The TpTe time is a period in which the epicardium is repolarized and fully inducible, and corresponds to the transmural dispersion of repolarization in the ventricular myocardium. That is, there is a good association between the TpTe time and the transmural dispersion of ventricular repolarization (20,21). There are 3 different types of cells that can be identified electrophysiologically in the ventricular myocardium, which are; endocardial cells, subendocardial M (Masonic midmyocardial Moe cells) cells and epicardial cells. Although these cells are histologically similar, their electrophysiological properties are different. Differences in terms of the responses produced by these three types of cells to pharmacological agents and/or pathophysiological conditions often lead to increased electrical heterogeneity, which serve as a trigger mechanism for reentrant arrhythmias. Unlike other types of cells, M cells can disproportionately prolong the action potential. The prolonged action potential of M cells during bradycardia or in a condition that prolongs ventricular repolarization is much more sensitive than the other two types of cells (22). This is probably due to the larger late-sodium and sodium/calcium exchange currents and a weaker in M cells because of slow activation of the delayed rectifier current (23). The prolongation of the repolarization process and of the action potentials in M cells leaves the M cells vulnerable to the emergence of early afterdepolarizations (16,24). If conditions are favorable, this early afterdepolarizations can lead to reentry, subsequently resulting in polymorphic ventricular tachycardia or ventricular fibrillation. Thus, it is probable that prolonged TpTe time corresponds to a prolonged sensitivity. Given the duration and conditions, the risk of ventricular arrhythmogenesis increases (25-27).

Although it is not known how hydroxychloroquine and azithromycin increase TpTe time, it can be concluded as a result of our study that the HCQ + AZR combination treatment increases electrical heterogeneity by prolonging repolarization and action potential of the M cells in ventricular myocardium. Increased electrical heterogeneity may prolong the TpTe time by increasing the ventricular transmural dispersion. It was observed as a result of our study that both the HCQ alone and HCQ + AZR combination

treatments have prolonged the TpTe time, and it was also found as a result of the regression analysis that the HCQ + AZR combination treatment is an independent predictor in prolongation of the TpTe time.

## CONCLUSION

Although hydroxychloroquine and/or azithromycin treatment was often used worldwide at the beginning of the COVID-19 pandemic, these drugs are no longer used as much as before today. These treatments are known to increase the risk of venticular arrhythmia by prolonging the QT and QTc intervals. It was found as a result of our study that the HCQ + AZR combination treatment is an independent predictor in prolonging the TpTe time. For this reason, reviewing the TpTe time alongside the the parameters of QT and QTc intervals can help clinicians to predict a ventricular arrhythmia that may develop during the treatment process. In addition, it can also be said as a result of our study that these medications can be administered more reliably by monitoring the patients closely and performing their ECG follow-ups.

*Limitations*

The fact that our study was a retrospective study constitutes its most important limitation. The relatively low number of the patients included in our study may also be considered as another limitation of our study. Another limitation of our study was that the ECG parameters were calculated manually.

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None
*Conflict of Interest*
None

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