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The effect of the basal frontal QRS-T angle on disease severity and mortality in Covid-19 patients

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Abstract

This study aimed to determine the relationship between the frontal QRS-T angle, the severity of the disease, and mortality, calculated with the ECG data taken during admission to the hospital. In this retrospective study, patients hospitalized in intensive care units and regular services with Covid-19 disease at Health Sciences University Mehmet Akif Inan Training and Research Hospital between April-September 2020 were included. Patients who were not given Covid-19 medication except for five days of Hydroxychloroquine (HC) and Azithromycin (AZ) with no cardiac disease history and daily taken ECGs were included in the study. A total of 135 patients were included in this study. While 45.9% of the patients received only HC treatment, 54.1% also received additional AZ treatment. It was observed that the frontal QRS-T angle was significantly longer in intensive care patients and intubated patients ($p =<0.001$). ROC curve analysis demonstrated that the best cut-off value for predicting mortality was 101.5º. The in-hospital mortality rate was significantly higher in patients with widened frontal QRS-T angle ($p = 0.008$). QRS widening, QTc prolongation, and QRS-T angle widening were substantially more frequent in intensive care patients ($p=0.001$,$p<0.001$, and $p<0.001$, respectively). Significantly QTc prolongation was observed more frequently in patients hospitalized in intensive care and followed up intubated ($p<0.001$ and $p=0.003$, respectively). The most common QTc prolongation time was on the 4th day of treatment in both groups (43.8% and 46.8%). Multivariate logistic regression analysis showed that frontal QRS-T angle ≥ 101.5º (OR: 7.08, 95%CI: 1.17-42.75, $P = 0.033$) was an independent predictor of mortality. The prolonged frontal QRS-T angle in Covid-19 patients increases the severity of the disease and mortality rates. The frontal QRS-T angle can be used to determine the prognosis of Covid-19 patients due to its advantages, such as easy evaluation and no extra costs.

Keywords: Covid-19 disease; frontal QRS-T angle; QTc prolongation; mortality

1. Introduction

Obviously, Coronavirus Disease 2019 (COVID-19) is the most significant health problem of the 21st century. Almost 35 million people worldwide have been infected with the virus, and one million people have died from this disease as of October 2020, since its origin in December 2019, according to the Johns Hopkins COVID-19 Resource Center (1). It may show a wide range between asymptomatic course and mild upper respiratory tract infection and severe ARDS (2). Myocardial damage is also one of the critical pathogenic features of COVID-19.

With the demonstration that Covid-19 caused cardiac damage, concerns were raised about Hydroxychloroquine (HC) and Azithromycin (AZ) used in the treatment because these drugs were known to prolong QT and correct QT (QTc) (3,4). Thereupon, studies reporting the use of these drugs may increase mortality in COVİD-19 patients have emerged (5). However, since many studies claim that it may increase mortality, some studies claim the opposite, so a definite opinion on this issue could not be concluded (6). The only precise information on the subject is that the cardiac impact of Covid-19 disease is severe.

The frontal QRS-T angle, which has recently become a popular field of study, shows the main direction of electrical cardiac activity (7). The QRS-T angle is defined as the difference between ventricular depolarization (QRS axis) and repolarization (T axis). An increased QRS-T angle is an indicator of abnormal ventricular repolarization. Electrocardiographic (ECG) risk indicators such as QT prolongation and other commonly used traditional cardiovascular risk factors have been recognized as strong and independent risk indicators for cardiac morbidity and mortality (8). Its predictive value and usability in many diseases, such as hypertension and coronary artery diseases, have been investigated and found useful (9-11). Since cardiac damage is common in Covid-19, there are many studies on cardiac biomarkers and QT-QTc prolongation, while there are only a

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few studies on the frontal QRS-T angle. Our study aimed to investigate whether the frontal QRS-T angle is beneficial in predicting in-hospital mortality in hospitalized patients due to Covid-19. We also planned to examine whether AZ and HC potentialize QTc prolongation and the effect of QTc prolongation on mortality.

2. Matherials and Methods

This study was carried out under the Declaration of Helsinki and approved by the Ethics Committee of Harran University (Approval Number E.4192). After obtaining the ethics committee's approval, patients who were hospitalized in intensive care and regular services in Şanlıurfa Health Sciences University Mehmet Akif İnan Training and Research Hospital due to Covid-19 disease between April 2020 and September 2020 were included in the study. Patients with Covid PCR (+) and who received HC with/without AZ in the treatment of Covid-19 were included in the study. Among these patients, those who were hospitalized for at least five days, those whose ECG was taken at the first admission to the hospital, and those whose ECG was taken every day during 5-day HC treatment were included in the study. The patients who are not receiving HC treatment, receiving other treatments other than HC and AZ in the treatment of Covid 19, using other drugs such as antidepressants, antibiotics, antiarrhythmic drugs known to prolong QTc, patients with previously known cardiac disease, patients who did not have a 5-day ECG examination, and the patient's under HC treatment for autoimmune diseases such as lupus were excluded from the study.

The data were obtained from patient files and the hospital data system. The condition of a 12-lead surface ECG was sought from all patients during admission to the hospital and every day during treatment. Demographic and biochemical data were collected, including basal troponin, creatinine, potassium, calcium, and C-reactive protein (CRP). As a result of the evaluations, serum creatinine, potassium, calcium, and CRP values of the day with the highest QTc prolongation were noted as maximum values.

2.1. Surface ECG and Measurements

A 12-lead surface ECG with a paper speed of 25 mm / s and a signal size of 10 mm / mV was provided to all patients during admission to the hospital and every day for five days of treatment.

Frontal QRS-T angle measurement: The ECG device automatically measured the frontal plane QRS angle and T angle. The absolute value of the difference between the QRS angle and the T angle was determined as the frontal QRS-T angle. (frontal QRS-T angle = | QRS axis – T axis |). If this difference was greater than 180 °, the frontal QRS-T angle was calculated again by subtracting 180 ° from this value (Fig. 1) (12). After the measurements, the best cut-off value of the frontal QRS-T angle for predicting mortality was determined with receiver operating characteristic (ROC) curve analysis (13). The best cut-off value of frontal QRS-T angle was found to be 101.5º. Our study population was divided into two groups according to this cut-off value as follows: patients with frontal QRS-T angle < 101.5º (absent QRS-T widening) and patients with frontal QRS-T angle ≥ 101.5º (present QRS-T widening).

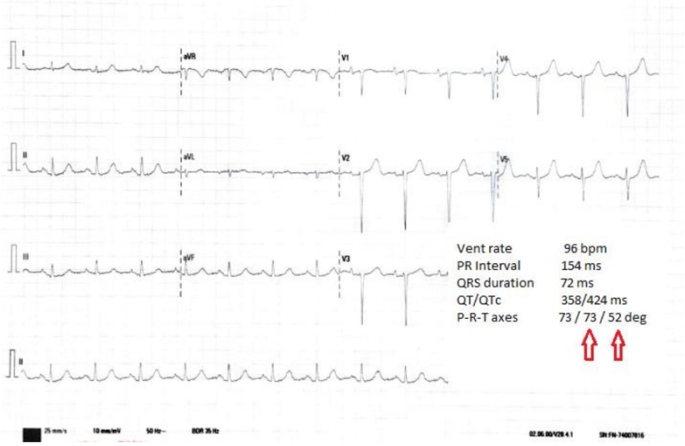

Fig. 1. Frontal QRS-T angle measurement

QTc prolongation: QTc ≥ 440 or 60 units higher than the previous value. It is based on the measurement automatically made by the ECG device.

QRS widening: QRS ≥120. It is based on the measurement automatically made by the ECG device.

2.2. Data Extraction

The patient's age, gender, and comorbid diseases were noted from the patient files. Heart rate, QT and QTc duration, QRS durations, and calculated frontal QRS-T angles were recorded from the ECG data of these patients. Troponin, creatinine, potassium, calcium, and CRP values were recorded from the hospital database. The ECGs taken during five days of treatment were interpreted, and the day with the highest QTc prolongation was determined. Creatinine, potassium, calcium, and CRP values were noted as maximum values on the day of the highest QTc prolongation.

2.3. Statistical Analyses

Statistical analysis was performed using SPSS version 23.0 software (SPSS Inc., Chicago, IL, USA). In descriptive statistics, the One-Sample Kolmogorov Smirnov test determines normal distribution, while categorical variables are expressed in numbers and percentages. Normally distributed variables were expressed as mean ± standard deviation and compared with independent sample t-test, whereas non-normally distributed variables were expressed as median (25-75th interquartile range) and compared with the Mann-Whitney-U test. The Chi-Square test calculates the difference between categorical variables. ROC curve analysis was performed to determine the best frontal QRS-T angle cut-off value for predicting mortality. Multivariate logistic regression analysis with backward elimination was used to determine the independent predictors of mortality. A p-value of <0.05 was considered statistically significant.

3. Results

After obtaining the ethics committee's approval, 302 patients

who were hospitalized for Covid-19, including intensive care units and regular services, were included in the study. One hundred and sixty-seven of 302 patients were excluded from the study according to exclusion criteria; a total of 135 patients were included. The mean age of these patients was 51.2 ± 19.5, and 63% were male. The most common comorbidity among the patients was hypertension (21.5%). While 45.9% of the patients received only HC treatment, 54.1% also received AZ treatment in addition to this treatment. Basal characteristics of the patients are shown in Table 1.

Table 1. Baseline characteristics of study population

	All patient n=135 mean±sd/ n(%)
Age	51,2±19,5
Gender	
Female	50 (%37)
Male	85 (%63)
Chronic diseases	
Diabetes Mellitus	16 (%11,9)
Hypertension	29 (%21,5)
COPD/Asthma	22 (%16,3)
Cancer	7 (%5,2)
Hospitalization	
ICU	48 (%35,6)
Regular service	87 (%64,4)
Intubated patients	19 (%14,1)
Medication	
HC+AZ	73 (%54,1)
HC	62 (%45,9)

AZ: Azytromycin, COPD: Chronic obstructive pulmonary disease, HC:Hydroxychloroquine, ICU: Intensive care unit

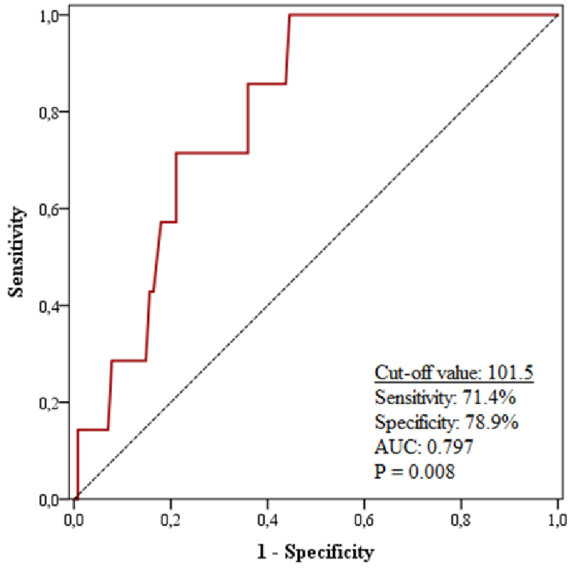

Fig. 2. ROC curve analysis of frontal QRS-T angle for predicting mortality

ROC curve analysis was performed to determine the best frontal QRS-T angle cut-off value for predicting mortality. The best frontal QRS-T angle cut-off value for predicting mortality was 101.5º (Fig. 2). Our study population was divided into two groups: patients with frontal QRS-T angle < 101.5º and patients with frontal QRS-T angle ≥ 101.5º. Basal characteristics of the patients according to the frontal QRS-T angle, laboratory, and ECG data evaluation are shown in Table 2. The mean age was significantly higher in those with increased frontal QRS-T angle (p <0.001). It was observed that the frequency of intubated patients was significantly higher in patients with widened frontal QRS-T angle (p = <0.001). It was observed from laboratory data that troponin (p <0.001) and CRP (p =0.002) values obtained during hospitalization were significantly higher in patients with widened QRS-T angle. In addition, QTc prolongation and QRS widening were significantly more frequent in patients with widened frontal QRS-T angle (p <0,001 and p = 0,001, respectively).

Table 2. Evaluation of baseline characteristics, laboratory and ECG data of the patients according to the frontal QRS-T angle

	QRS-t widening		
	Present (n=32)	Absent (n=103)	
	mean±sd / median (25-75th IQR) / n(%)		*p* value
Age	66,8 ± 14,6	46,4 ± 18,4	**<0,001**
Gender			
Female	13 (%40,6)	37 (%35,9)	0,630
Male	19 (%59,4)	66 (%64,1)	
Hospitalization			
ICU	28 (%87,5)	20 (%19,4)	**<0,001**
Regular service	4 (%12,5)	83 (%80,6)	
Intubated patients	14 (%43,8)	5 (%4,9)	**<0,001**
Chronic diseases			
Diabetes Mellitus	9 (%29)	7 (%6,8)	**0,002**
Hypertension	18 (%40,6)	16 (%10,7)	**0,003**
COPD/Asthma	11 (%34,4)	11 (%10,8)	**0,002**
Cancer	4 (%12,5)	3 (%2,9)	0,054
Labaratory initial			
Troponin-I	63,9 (26,3-117,8)	4 (3-8,5)	**<0,001**
Creatinin	1,13±0,49	0,91±0,27	0,025
K	4,49±0,89	4,25±0,50	0,153
CRP	62,1 (14,4-159,8)	23,0 (3,5-45)	**0,002**
QTc prolongation	26 (%81,3)	45 (%43,7)	**<0,001**
QRS widening	10 (%31,3)	7 (%6,8)	**0,001**
Mortality	5 (15,6)	2 (1,9)	**0,008**

AZ: Azytromycin, COPD: Chronic obstructive pulmonary disease, CRP: C-Reactive protein, HC: Hydroxychloroquine,ICU:Intensive care unit, K: Potasium, QTc: corrected QT

Baseline characteristics, and evaluation of laboratory and ECG data of patients with in-hospital mortality are shown in Table 3. All patients with in-hospital mortality were hospitalized in the intensive care unit (100%). In-hospital mortality was significantly higher in patients with diabetes mellitus and cancer (p = 0.036, and p = 0.003, respectively). The in-hospital mortality rate was significantly higher in patients with widened frontal QRS-T angle (p = 0.008).

Table 3. Evaluation of baseline characteristics, laboratory and ECG data of the patients with in-hospital mortality

	Exitus		
	Present (n=7)	Absent (n=128)	
	mean±sd / n(%)		*p* value
Age	63,9±13	50,5±19,6)	0,389
Gender			
Female	2 (%28,6)	48 (%37,5)	1
Male	5 (%71,4)	80 (%62,5)	
Hospitalization			
ICU	7 (%100)	41 (%32)	**0,001**
Regular service	-	87 (%68)	
Chronic diseases			
Diabetes Mellitus	3 (%42,9)	13 (%10,2)	**0,036**
Hypertension	1 (%14,3)	28 (%21,9)	1
COPD/Asthma	2 (%28,6)	20 (%15,6)	0,319
Cancer	3 (%42,9)	4 (%3,1)	**0,003**
Labaratory initial			
Troponin-I	41,5(23,4-87,5)	5 (3-23,6)	**0,008**
Creatinin	1,14±0,41	0,95±0,34	0,418
K	4,14±0,41	4,29±0,74	0,289
CRP	63 (29,8-172)	24,6(3,7-57,7)	**0,043**
Labaratory Max			
Creatinin	1,5±0,97	0,85±0,34	0,756
K	4,44±0,87	4,2±0,58	0,450
CRP	46 (22-238)	12 (2-51,3)	**0,018**
Medication			
HC+AZ	5 (%71,4)	68 (%53,1)	0,452
HC	2 (%28,6)	60 (%46,9)	
QRS max	102,7±10,3	97,3±33,8	0,565
QRS widening	1 (%14,3)	16 (%12,5)	1
QTc max	458,7±15	430,1±44,1	0,658
QTc prolongation	6 (%85,7)	65 (%50,8)	0,119
QRS-T	108,7±47,5	57,9±50	**0,010**
QRS-T widening	5 (%71,4)	27 (%21,1)	**0,008**

AZ: Azytromycin, COPD: Chronic obstructive pulmonary disease, CRP: C-Reactive protein, HC: Hydroxychloroquine, ICU:Intensive care unit, K: Potasium, QTc: corrected QT

Baseline characteristics, laboratory and ECG data evaluation of patients hospitalized in intensive care, and regular services are shown in Table 4. While the mean age of patients in the intensive care unit was higher (p <0.001), there was no significant difference in terms of gender. All chronic diseases were observed more frequently in intensive care patients. Considering the ECG data, QRS widening, QTc prolongation and widened frontal QRS-T angle were significantly more frequent in intensive care patients (p = 0,001, p <0,001, and <0,001, respectively).

Table 4. Evaluation of baseline characteristics, laboratory and ECG data of the patients staying in intensive care unit and regular service

	Intensive care unit stay		
	ICU	Regular	*p* value
	mean±sd / n(%)		
Age	66,3±14,7	42,9±16,7	**<0,001**
Gender			
Female	21 (42%)	29 (58%)	0,230
Male	27 (31,8%)	58 (68,2%)	
Chronic diseases			
Diabetes Mellitus	10 (62,5%)	6 (37,5%)	**0,016**
Hypertension	22 (75,9%)	7 (24,1%)	**<0,001**
COPD/Asthma	18 (81,8%)	4 (18,2%)	**<0,001**
Cancer	6 (85,7%)	1 (14,3%)	**0,008**
Medication			
HC+AZ	27 (37%)	46 (63%)	0,706
HC	21 (33,9%)	41 (66,1%)	
QRS widening	12 (70,6%)	5 (29,4%)	**0,001**
Max QRS	116±51	99±11	**0,011**
QTc prolongation	41 (57,7%)	30 (42,3%)	**<0,001**
Max QTc	459±33	433±22	**<0,001**
QRS-t widening	28 (58,3%)	4 (4,6%)	**<0,001**
QRS-t	104,4±45,3	36,4±35,7	**<0,001**

AZ: Azytromycin, Ca: Calsium, COPD: Chronic obstructive pulmonary disease, CRP: C- Reactive protein, HC: Hydroxychloroquine, ICU:Intensive care unit, K: Potasium, QTc: corrected QT

The evaluation of patients according to QTc prolongation is shown in Table 5. The mean age was significantly higher in those with QTc prolongation (p <0.001). Significantly, QTc prolongation was observed more frequently in patients hospitalized in intensive care, in patients who were followed up intubated, and in hypertensive patients (p <0.001, p = 0.003 and p = 0.016, respectively). It was observed that the troponin (p < 0.001) and maximum CRP levels (p =0.001) were significantly higher in the group with QTc prolongation.

Table 5. Evaluation of baseline characteristics, laboratory and ECG data of the patients with QTc prolongation

	QTc prolongation		
	Present (n=71)	Absent (n=64)	*p* value
	mean±sd / n(%)		
Age	57,3±19,3	44,5±17,6	**<0,001**
Gender			0,335
Female	50 (%37)	29 (%40,8)	
Male	85 (%63)	42 (%59,2)	
Hospitalization			**<0,001**
ICU	41 (%57,7)	7 (%10,9)	
Regular service	30 (%42,3)	57 (%89,1)	
Intubated patients	16 (%22,5)	3 (%4,7)	**0,003**
Chronic diseases			
Diabetes Mellitus	16 (%11,9)	11 (%15,5)	0,168
Hypertension	29 (%21,5)	21 (%29,6)	**0,016**

COPD/Asthma	22 (%16,3)	15 (%21,1)	0,109
Cancer	7 (%5,2)	6 (%8,5)	0,119
Labaratory initial			
Troponin-I	12 (3,9-50)	3,05 (3-7)	**<0,001**
Creatinin	1,02±0,39	0,91±0,28	0,072
K	4,31±0,89	4,25±0,47	0,509
CRP	29,8(5,4-92,4)	23,8(2,8-45)	0,075
Labaratory Max			
Creatinin	0,92±0,44	0,85±0,37	0,361
K	4,14±0,68	4,29±0,47	0,235
CRP	25,9(6,7-130)	9,4 (1,0-25,9)	**0,001**
Medication			
HC+AZ	73 (%54,1)	36 (%50,7)	0,408
HC	62 (%45,9)	35 (%49,3)	

AZ: Azytromycin, COPD: Chronic obstructive pulmonary disease, CRP: C-Reactive protein, HC: Hydroxychloroquine, ICU:Intensive care unit, K: Potasium, QTc: corrected QT

Elongation days of QTc in patients with QTc prolongation are shown in Figure 3. QTc prolongation was observed in 71 (52.6%) of the patients. There was no significant difference between those who only received HC and those who received HC+AZ in treatment (p = 0.408). In both groups, QTc prolongation was the most common on the 4th day of treatment (43.8% versus 46.8%).

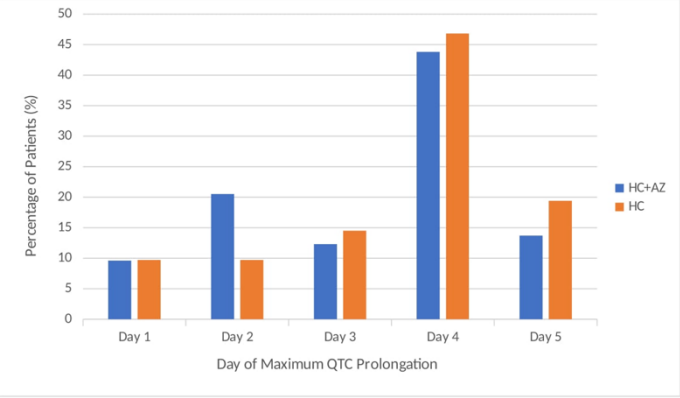

Fig. 3. Elongation days of QTc in patients with QTc prolongation

The independent predictors of mortality were determined by multivariate logistic regression analysis. It was found that frontal QRS-T angle ≥ 101.5 (OR: 7.08, 95%CI: 1.17-42.75, P = 0.033) and cancer (OR: 15.19, 95% CI: 2.17-106.40, P = 0.006) were the independent predictors of mortality (Table 6).

Table 6. Multivariate logistic regression analysis for demonstrating the independent predictors of mortality

	Odds Ratio	95% Confidence Interval	P
Frontal QRS-T angle ≥ 101.5º	7.08	1.17-42.75	**0.033**
Cancer	15.19	2.17-106.40	**0.006**

Entered variables: age, gender, QRS widening, QTc prolongation, frontal QRS-T angle ≥ 101.5º, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, cancer, initial troponin, creatinine and c-reactive protein, and maximum c-reactive protein

4. Discussion

In this study, we investigated the relationship between the severity of the disease and in-hospital mortality with the basal frontal QRS-T angle in the ECGs of Covid-19 patients during admission to the hospital. In addition, we examined whether the QTc prolongation was caused by AZ and HC, which are the drugs used in the treatment of Covid-19 disease, has a significant effect on mortality.

The rate of cardiac damage was around 20% in Covid-19 patients (14). Many studies investigating myocardial damage have shown that cardiac biomarkers, especially cardiac troponin I and T, increase in infected patients (15). However, there has not been a study based on ECG data to determine this cardiac damage at the time of admission to the hospital. This study was planned because it is thought that with the early detection of this cardiac damage, relevant measures can be taken earlier.

Although the spatial QRS-T angle is a better prognostic marker for cardiac risk estimation, in this study, we used the frontal planar QRS-T angle instead of the spatial QRS-T angle because special software is required for spatial QRS-T measurement, and the more complex special knowledge is required for this measurement (16). As non-cardiologist intensive care professionals, we found it appropriate to use the frontal QRS-T angle in our study because it has a more practical measurement and does not require special knowledge. Previous studies have shown that frontal QRS-T measurement is an appropriate clinical substitute for spatial QRS-T measurement in risk estimation (17). Previous studies have shown that the frontal QRS-T angle is useful in determining repolarization abnormalities before significant ECG changes occur (7). Damaged or inhomogeneous areas of the myocardium due to ischemia cause abnormal ventricular repolarization, and an increased QRS-T angle emerges (18). In recent years, many studies have shown that cardiac damage can be determined by widened frontal QRS-T angle. The clinical benefit of frontal QRS-T widening has been established in anterior myocardial infarction (19,20), hypertrophic cardiomyopathy (21), ischemic cardiomyopathy(22), and myocarditis (23). In our study, increased basal frontal QRS-T angle, QTc prolongation, and QRS widening were significantly common in intensive care patients. In addition, when we included all electrocardiographic parameters in the multivariate analysis, we found that only widened frontal QRS-T angle was the independent predictor of mortality. Therefore, it can be concluded that there is a significant difference between the prolongation of the basal frontal QRS-T angle at the time of admission to the hospital and the severity of the disease and in-hospital mortality.

Since the use of HC in autoimmune diseases is very old, it has been known for a long time that it can prolong QTc [3]. In addition, AZ is an antibiotic known to prolong QTc, and these

two drugs are often used in combination in Covid-19 patients. Studies have reported that the QTc prolongation effect of these drugs is more common in patients with known cardiac disease (4,24). It has also been shown that the use of these drugs together with other drugs known to prolong QTc (such as antiarrhythmics, antidepressants, and antibiotics) has been shown to potentialize QTc prolongation (25). We, therefore, did not include patients with known heart disease and those who normally use drugs known to cause QTc prolongation in this study, as we wanted to investigate whether adding AZ to the treatment in our study potentializes QTc prolongation, as the effect of HC administration. In addition, in order to understand which day of the treatment will QTc prolongation is common, we included patients whose ECG was recorded for five days of HC treatment in our study. In this way, we thought that in patients who are not monitored, such as intensive care, we could at least have an idea on which days ECGs should be taken. In correlation with previous studies (18), we found that QTc prolongation was more common in the ECG on our study's 4th day of treatment. In addition, we found that concomitant AZ use did not potentialize QTc prolongation in patients using HC. This finding was inconsistent with some previous studies (24,25). However, in none of these studies, patients with cardiac disease and those using drugs such as antiarrhythmic and antidepressants are known to prolong QTc were not excluded from the study. The different study results may be due to the different study designs.

As we wanted to examine the effects of drugs on QTc prolongation, it was important to have 5-day ECGs of the patients. Since there are reservations in terms of transmission of Covid-19 disease, having ECG from patients every day may increase the risk of disease transmission. By using methods such as telemetry, reservations such as the transmission of the disease can be removed, and ECGs of the patients can be accessed safely (26). However, in centres where such methods are not available, we believe that ECGs of the patients should be taken at least on the 4th day of the treatment to check whether there is QTc prolongation. It is important to determine if there is QTc prolongation in patients before home discharge and if necessary, it should be consulted with the cardiologist.

Our study has many limitations. The most important is the retrospective design of our research. In addition, patients who did not have a baseline ECG and did not have 5-day ECGs during treatment were not included in the study. This fact may present a bias. Our study was single-centred, and the limited number of patients was also an important limitation.

At the time this study was designed, hydroxychloroquine was routinely given to covid 19 patients in TÜRKİYE. Azithromycin could be added to the patient's treatment according to the clinician's preference. Other treatment methods (antiviral treatments, plasma therapy, etc.) were unavailable in our country at the time this study was designed. It is important to evaluate the study from this perspective.

As a result, the increased Frontal QRS-T angle in Covid-19 patients increases the severity of the disease and mortality rates. The frontal QRS-T angle seems to be a standard parameter that can be used in the follow-up of Covid-19 patients due to its advantages, such as not needing any extra knowledge about its evaluation, being easily calculated by anyone with standard ECG data, and not causing additional costs such as blood tests.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Authors' contributions

Concept: G.P., B.C., Design: G.P., B.C., Data Collection or Processing: G.P., M.T., Analysis or Interpretation: G.P., M.T., T. B.T., F.T.B., Literature Search: G.P., B.C., T.B.T., F.T.B., Writing: G.P., B.C., M.T., T.B.T., F.T.B

Ethical Statement

Approval was obtained from Harran University Clinical Research Ethics Committee, the study started. The ethics committee decision date is 15/06/2020 and the number of ethical committee decisions is HRU/20.11.18.

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