Evaluation of the Effect of Favipiravir on QT Intervals in COVID-19 Patients with and without Diabetes Mellitus

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ABSTRACT

Objective: To evaluate the effect of favipiravir administered to diabetic and non-diabetic COVID-19 patients on the QT/QTc interval.

Study Design: Analytical study.

Place and Duration of the Study: Republic of Turkey, Ministry of Health, State Hospital, Corlu, Tekirdag, Turkiye, from March to September 2021.

Methodology: Electrocardiogram (ECG) analysis was performed on all participants (n=180) divided into four groups. Group 1 included only healthy volunteers. Group 2 included only cases diagnosed with T2DM. Group 3 included only severe acute respiratory syndrome coronavirus-2 (*SARS-Cov-2*) cases. Group 4 included cases diagnosed with both SARS and T2DM. Favipiravir was administered only to the cases in Group 3 and Group 4. In the cases that were administered favipiravir, the QT/QTc interval was calculated and recorded at different time intervals on the first and fifth days of the therapy. The difference between groups was determined by Tukeye's test after ANOVA. Pearson's correlation test was used to determine whether there was a linear relationship between two numericals. The alpha significance value was determined to be <0.05 in all statistical analyses.

Results: When all groups were compared, it was seen that both QT and QTc values increased in Groups 3 and 4, which were administered favipiravir ($p < 0.05$). Favipiravir may cause an increased risk of ventricular and atrial arrhythmias.

Conclusion: Favipiravir may cause QT interval prolongation, particularly in *SARS-Cov-2* patients diagnosed with T2DM.

Key Words: *COVID-19, Drug-induced long QT syndrome, Intra-infarct haemorrhage; Favipiravir, Type 2 diabetes mellitus.*

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INTRODUCTION

Cardiovascular diseases are among the leading causes of mortality and morbidity in Type 2 diabetes mellitus (T2DM) cases. Concerns about the cardiotoxicity of some pharmaceuticals used in the treatment of severe acute respiratory syndrome coronavirus 2 (*SARS-Cov-2*) patients have been reported.[1] Therefore, the COVID-19 pandemic was an issue with immediate implications for the patients with T2DM, a common metabolic disease.

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The time interval from the beginning of the Q wave to the end of the T wave is called a QT interval. This interval reflects the total time elapsed for the depolarisation and repolarisation of ventricles. The beginning of the R wave is taken as the beginning of the QT interval when there is no Q wave. Standard electrocardiogram (ECG) recording (10 mm/mV calibration and 25 mm/s shift rate) is generally sufficient for QT interval measurement. There are different opinions on the length of a normal QT interval. Generally, the normal QT interval is 350-440 ms and is longer in women than in men.[2] It is well known that prolongation of the QT interval due to medicines may be associated with fatal arrhythmias, such as *torsade de pointes* (TdP).[3] The length of a QT interval is controlled by delayed ventricular potassium flow, the rapid component of which is blocked by some drugs. The results may be fatal when the TdP form of polymorphic ventricular tachycardia occurs due to this blockage.[4] It has congenital and acquired forms and requires urgent intervention.

According to the American Heart Association, chloroquine and hydroxychloroquine, antimalarial and antirheumatic agents used in the treatment of *SARS-Cov-2*, may be directly myocardiotoxic and augment any pre-existing myocardial dysfunction.[5] However, the effect of antiviral drugs, such as lopinavir/ritonavir, favipiravir, and interleukin-6 inhibitor, and monoclonal antibody drugs, such as tocilizumab and sarilumab, on the QT interval has rarely been discussed. Favipiravir was approved as a new flu treatment in China on 15 February 2020, but clinical trials for COVID-19 treatment continue. Favipiravir is an RNA-dependent RNA polymerase inhibitor. Although favipiravir has proven to have only a mild clinical benefit in the management of COVID-19, antiviral agents such as favipiravir continue to be used in the clinical management of *SARS-Cov-2* until more effective anti-*SARS-Cov-2* agents are discovered.

A treatment protocol was prepared by the Science Committee of the Ministry of Health to manage the patients with *SARS-CoV2* in Corlu State Hospital, Turkiye. In accordance with the treatment protocol, the patients are administered a loading dose of 2x1600 mg (200 mg tablet) of favipiravir on the first day followed by 600 mg orally, twice daily for four days. In addition to favipiravir, the patients are administered enoxaparin sodium 4000 IU and dexamethasone (6 mg).

The number of studies examining the QT/QTc interval change that may be developed due to the use of favipiravir in diabetic COVID-19 patients is very few. This study aimed to evaluate the effect of favipiravir on the QT interval used in the treatment of diabetic and non-diabetic patients with *SARS-Cov-2*.

METHODOLOGY

This descriptive study was conducted at the Republic of Turkey, Ministry of Health, State Hospital, Corlu, Tekirdag, Turkiye, from March to September 2021. The sample size was determined using G*Power (3.1.9.4 version). Estimated power was 0.80, alpha (margin of error) was 0.05, effect size was 0.4. This prospective randomised study was conducted with the permission of the General Directorate of Health Services (numbered 2020-12-04T11_20_06). Permission to use the data of the participants in this study was obtained from hospital management (numbered 13441514-929-3960). Also, ethics committee approval was obtained from the Tekirdag Namik Kemal University School of Medicine (Dated: 28/09/2021 and ERC no. 2021.225.09.11).

Voluntary consent and approval for the use of data were obtained from the participants included in the study and/or their relatives. This study respected the life, health, honour, integrity, right to make decisions, privacy, and confidentiality of personal information of the participants involved in this research in accordance with the Declaration of Helsinki.

Patients diagnosed with Type 1 diabetes mellitus, cardiovascular or cerebrovascular disease, liver or renal failure, malignancy, autoimmune diseases, acute or chronic infection, a history of trauma or surgical intervention, or pregnancy were also excluded from the study.

The medical archive histories of the patients diagnosed with T2DM included whether a patient had blood glucose level above 200 mg/dl randomly, fasting glucose level above 126 mg/dl at least two times or, and blood glucose level above 200 mg/dl at two hours in the oral glucose tolerance test and whether they were being treated for T2DM.

Healthy volunteers and patients in all groups were assigned a number before ECG analysis in order to mask which medicine(s) were used in which group. In this way, the researchers did not know which patients were in which group or which medicines were used by which patient, with the exception of the coordinator. In addition, ECG analyses were performed by a cardiologist not associated with the research. ECG results obtained from patients were numbered and coded. Both the researcher who performed the QT interval evaluation by assessing the ECG results and the researcher who performed the statistical evaluation were blinded to the research data.

Age and gender-matched volunteers who visited the hospital for a check-up were assigned to the control group (Group 1). The patients in Group 2 and Group 4 were using metformin and/or insulin aspart and insulin glargine. The patients in Group 3 only used drugs belonging to the routine *SARS-Cov-2* treatment protocol.

Oral favipiravir and paracetamol, intravenous moxifloxacin and dexamethasone, and subcutaneous enoxaparin were administered to Group 3, which included the patients diagnosed only with *SARS-Cov-2*, and to Group 4, which included diabetic patients diagnosed with *SARS-Cov-2*.

On the first day, only tablets of favipiravir (Favira tablet®, Abdi Ibrahim, Istanbul, Turkiye) were administered to patients. For the remaining four days, in addition to favipiravir, Moxifloxacin (Moxacin®, Vem Pharmaceutical Industry, Istanbul, Turkiye), Enoxaparin (Clexane®, Sanofi, Le Trait, France), dexamethasone (Dexoject®, Tum-Ekip-Ilac, Istanbul, Turkiye) and paracetamol (Parol®, Atabay Kimya, Istanbul, Turkiye) were administered to patients in Group 3 and 4. The naming of groups, diagnosis, administration time, and total dosage are given in Table I.

As it can be seen from Table I, to prevent from drug-drug interaction as much as possible, other drugs were administered at different times, other than the half-life hours of favipiravir.

Standard 12-lead ECGs of the participants in all groups were obtained using a Cardiovit AT-102 plus device at 25 mm/s and 10 mm/mV calibration, and the images were transferred to a computer *via* a scanner. The ECG measurement performed in each time period was repeated at least three times in each case to minimise the error. ECG data for the participants in all groups were recorded.

Initial oral loading required adequate blood levels, as favipiravir is both metabolised and inhibited by aldehyde oxidase. The plasma half-life is approximately four hours.[6] The QT interval was recorded 15 min before favipiravir treatment and at 2 h and 4 h after favipiravir administration in patients in Group 3 and

Group 4, who received favipiravir on the first day. The last ECG measurements were taken 4 h after drug administration on the fifth day, after which favipiravir treatment was discontinued and the data were recorded. Thus, a total of four ECG and QT interval analyses were performed for each patient.

Corrected QT interval (QTc) analysis was performed using beats per minute (BPM), rhythm, QT interval, and Bazett's formula in all patients and was statistically analysed.[7] QT and RR intervals were measured manually using Cardio Calipers version 3.3 (Iconico, Inc), electronic measurement software on digital 12-lead ECG recordings. The duration of the QT interval was determined as the time elapsed from the beginning of the QRS wave to the end of the T wave on ECG, and an average of 3-5 beats in the measured derivation was used in the calculation.

The intersection point of the descending arm of the T wave with the isoelectric line was considered as the endpoint of the T wave when the endpoint of the T wave was not clear.ECG analysis was performed by an independent cardiologist who was blinded to study data and groups. Bazett's formula, QTc = QT√ (R-R), was used to determine the interval.

However, it is more difficult to correct estimation in the presence of repolarisation abnormalities, arrhythmias, early atrial/ventricular contractions, or bundle-branch blocks (BBB). A simple formula which has been developed in the presence of left or right BBB was used to calculate the QT interval. The QT interval measured during BBB was corrected using the Bogossian formula. In this formula, the modified QT interval is calculated by subtracting 50% of the length of the BBB-QRS from the measured QT interval (QTm = QTBBB-50% QRSBBB).[8]

The QT interval was prolonged when the QTc was >440 msn in males or >460 msn in females. The QTc more than 500 msn is considered to be associated with an increased risk of TdP. A QTc less than 350 msn is considered as short QT interval.The drug-induced QTc interval prolongation (DQTc) calculated according to previous literature.[9]

Minitab (version 22) was used to evaluate the data. The analyses were performed with a 95% confidence interval. The results are presented as mean absolute deviation (MAD), percentage (%), minimum (min), maximum (max), or mean ± standard deviation (Mean ± SD) in descriptive statistics.

A one-way analysis of variance (ANOVA) test was used to evaluate how multiple independent variables and groups were included, how these independent variables interacted with each other, and the effects of these interactions on the dependent variable. F values, which compared the amount of systematic variance in the data with non-systematic variances, were also calculated in this way. Tukey's honestly significant difference (HSD) test was used in the comparison between groups after the ANOVA when the sample numbers and variances were equal.

Pearson's correlation test was used to determine whether there was a linear relationship between two numerical measurements and, if so, the direction and severity of this relationship. The results were presented with the correlation coefficient (r). The alpha significance value was determined to be <0.05 in all statistical analyses.

RESULTS

There were 45 people in each group. The total number of females was 89 (49.44%) and the number of males was 91 (50.56%). The mean age was 57.58 ± 12.68 years in Group 1 (consisting of healthy volunteers) and 65.29 ± 8.47 years in Group 2 (consisting only of patients diagnosed with T2DM). The mean age in Group 3 (consisting of patients diagnosed only with *SARS-Cov-2*) and Group 4 (consisting of patients diagnosed with T2DM and *SARS-Cov-2*) was 61.24 ± 14.35 years and 67.78 ± 9.82 years, respectively. The mean duration of diabetes in Group 2 and Group 4 was 4.89 ± 3.87 years and 5.07 ± 3.84 years, respectively.

All of these patients in Groups 3 and 4 had high fever. Additionally, the oxygen saturations of the cases in this group were below 90%. However, invasive mechanical ventilation was not needed in these cases. It was understood that the findings of COVID-19 pneumonia were of moderate severity in these patients.

On the first day, 15 minutes before favipiravir administration ($F = 21.44$; $p < 0.001$), QT2: The second hour after favipiravir administration ($F = 18.47$; $p < 0.001$), QT3: The fourth hour after favipiravir administration ($F = 19.66$; $p < 0.001$), QT4: Represents the data of the last ECG evaluation performed on the fifth day of favipiravir administration and at the fourth hour after administration ($F = 26.12$; $p < 0.001$), and QTc represents the corrected QT in the same time frames. QTc1 ($F = 41.22$; $p < 0.001$), QTc2 ($F = 40.10$; $p < 0.001$), QTc3 ($F = 47.38$; $p < 0.001$), and QTc4 ($F = 44.25$; <0.001) values were found to be statistically significant in the comparison of ECG values between the groups ($p < 0.05$). BPM ($F = 36.41$; $p < 0.001$) averages were also found to be statistically significant ($p < 0.05$, Figure 1 and Table II).

Fifteen minutes before favipiravir administration on the first day of treatment, it is noteworthy that the QT1 value was highest in Group 2. The QT2 values were increased 30 minutes after favipiravir administration, only in Group 3. In the fourth hour after favipiravir administration, the QT3 value was reported to be higher only in Group 3.

On the fifth day of favipiravir treatment, in the ECG measurement at the fourth hour after favipiravir administration, the highest results occurred in the group including COVID-19 patients. The next highest results were from the group that included patients with both T2DM and COVID-19. When compared with healthy volunteers and T2DM patients who were not diagnosed with COVID-19, QTC values also increased in the groups with *SARS-Cov-2* in which favipiravir was administered. MAD increase in QTc interval value was found to be 30.86 ms for Group 3 and 32.74 ms for Group 4.

Table I: The naming of groups, diagnosis, administration time and total dosage of favipiravir, moxifloxacin, enoxaparin, dexamethasone, and paracetamol.

Groups	T2DM	*SARS-Cov-2*	Day 1		Day 2-5									
			Favipiravir		Favipiravir		Moxifloxacin		Enoxaparin		Dexamethasone		Paracetamol	
			Time	Total dosage	Time	Total dosage	Time	Total dosage	Time	Total dosage	Time	Total dosage	Time	Total dosage
Group 1 (n = 45)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Group 2 (n = 45)	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Group 3 (n = 45)	-	+	08:00 20:00	3200 mg	08:00 20:00	1200 mg	12:00	400 mg/ 250 ml	16:00	4000 anti-Xa UI/0.4 ml	17:00	8 mg/2 ml	07:00 13:00 23:00	1500 mg
Group 4 (n = 45)	+	+	08:00 20:00	3200 mg	08:00 20:00	1200 mg	12:00	400 mg/ 250 ml	16:00	4000 anti-Xa UI/0.4 ml	17:00	8 mg/2 ml	07:00 13:00 23:00	1500 mg

Table II: Evaluation of ECG parameters with a 95% confidence interval and Tukiye's HSD test after variant analysis.

Variable	Groups	Mean ± SD	Tukiye pairwise comparisons	p-value
QT1	Group 1	356.00 ± 0.00	C	p^a <0.05
	Group 2	405.80 ± 31.85	A	
	Group 3	379.69 ± 38.61	B	
	Group 4	392.27 ± 35.47	A B	
QT2	Group 1	356.00 ± 0.00	C	p^b <0.05
	Group 2	405.80 ± 31.85	A	
	Group 3	379.78 ± 36.73	B	
	Group 4	386.02 ± 41.71	B	
QT3	Group 1	356.00 ± 0.00	C	p^c <0.05
	Group 2	405.80 ± 31.85	A	
	Group 3	384.82 ± 38.22	B	
	Group 4	382.62 ± 36.61	B	
QT4	Group 1	356.00 ± 0.00	C	p^d <0.05
	Group 2	405.80 ± 31.85	A	
	Group 3	397.00 ± 41.61	A	
	Group 4	373.22 ± 28.17	B	
QTC1	Group 1	371.00 ± 0.00	B	p^a <0.05
	Group 2	433.13 ± 39.43	A	
	Group 3	441.18 ± 37.79	A	
	Group 4	439.09 ± 44.04	A	
QTC2	Group 1	371.00 ± 0.00	B	p^b <0.05
	Group 2	433.13 ± 39.43	A	
	Group 3	436.02 ± 47.44	A	
	Group 4	442.40±34.32	A	
QTC3	Group 1	371.00 ± 0.00	B	p^c <0.05
	Group 2	433.13 ± 39.43	A	
	Group 3	439.33 ± 36.42	A	
	Group 4	438.87 ± 36.06	A	
QTC4	Group 1	371.00 ± 0.00	B	p^d <0.05
	Group 2	433.13 ± 39.43	A	
	Group 3	442.96 ± 35.43	A	
	Group 4	438.56 ± 43.02	A	
Heart rate	Group 1	65.733 ± 1.116	B	<0.05
	Group 2	68.689 ± 1.505	B	<0.05
	Group 3	80.60 ± 11.29	A	<0.05
	Group 4	77.78 ± 10.92	A	<0.05

Group 1: Healthy Control; Group 2: Only T2DM; Group 3: Only *SARS-Cov-2*; Group 4: T2DM + *SARS-Cov-2*. P^a symbolises QT1/QTc1, P^b: QT2/QTc2, P^a: QT3/QTc3, and P^d: QT4/QTc4. P^a *vs.* P^c and P^b *vs.* P^d there is statistical significance between p-values (p <0.05).

The mean DQT was 38.32 ± 32.79 ms in Group 3, which consisted only of patients with a diagnosis of *SARS-Cov-2*. In Group 4, which consisted of patients with T2DM and a *SARS--Cov-2* diagnosis, the mean DQT was found to be 22.67 ± 15.20 ms. The mean DQTc was calculated as 28.96 ± 28.88 ms in Group 3, while this mean value was 43.44 ± 29.80 ms in Group 4. DQT/DQTc results were found to be statistically significant (p <0.05).

After evaluating the binary Pearson correlation results of the data of patients in the groups receiving multiple-drug therapy with favipiravir; positive close relationships were found between QT1, QT2, QT3, and QT4 (respectively, r = 0.804; r = 0.734; r = 0.545). Similarly, close positive relationships were found between QTc1, QTc2, QTc3, and QTc4 (respectively, r = 0.769; r = 0.823; r = 0.776). Positive and strong relationships were found between QT1-QTc1, QT2-QTc2, QT3-QTc3, and QT4-QTc4. It is clear that directly measured QT values can represent corrected QTc values. A moderate relationship was found between BPM and QTc1 (r = 0.360), QTc2 (r = 0.367), QTc3 (r = 0.403), and QTc4 (r = 0.420) values.

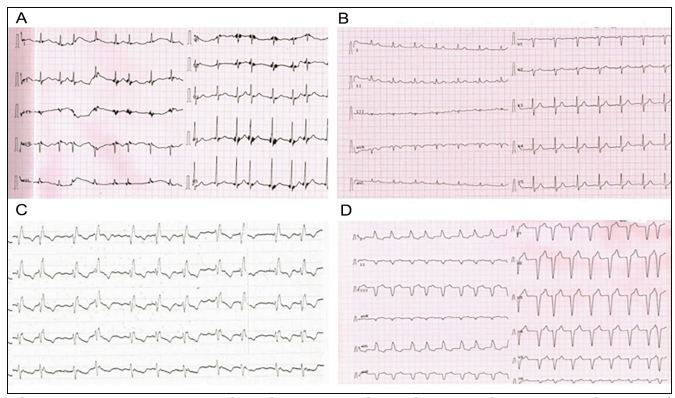

Figure 1: Demonstrative images of patients whose QTc interval changed after the evaluation of ECG data. (A) Sinus tachycardia, atrial premature complex. (B) Normal sinus rhythm. (C) Sinus rhythm and atrial premature complex with right bundle branch block (RBBB). ECG with panel C showing five anterior chest leads (V1–V5). ECG of a patient with a QTc value of 401 before drug administration, reaching a QTc value of 418 2 h after favipiravir administration, and with a QTC value of 444 at 4 h after drug intake. (D) ECG image of the patient whose QTc value increased to 483 at 4h on the fifth day after drug administration. It shows a left bundle branch block (LBBB). ECG in panel C and D; QT is corrected for QRS prolongation in left bundle branch block (LBBB) or right bundle branch block (RBBB) morphology, such that QT = [QT − (QRS − 100)]. Duration of QRS in panel D: 130 msn. ECG in panel C and D; QT is corrected for QRS prolongation in left bundle branch block (LBBB) or right bundle branch block (RBBB) morphology, such that QT = [QT_{LBBB} − (50%*QRS_{LBBB})]. Duration of QRS in panel D: 130 msn.

DISCUSSION

Drugs are a common cause of acquired long QT interval syndrome and TdP. Many drugs have been added to side effect profile lists and continue to be added, as they prolong the QT interval. Antimalarial drugs such as quinine and hydroxychloroquine, HIV antiretrovirals such as lopinavir and ritonavir, fluoroquinolone group drugs such as levofloxacin and moxifloxacin, and anti-infectious macrolide drugs such as azithromycin, erythromycin, and clarithromycin are also known to prolong the QT interval.[10]

The frequent administration of pharmacological agents causing QT prolongation at high doses and/or high concentration intervals may be even riskier in the presence of other concomitant cardiac risks in patients. However, it is difficult to determine the absolute and comparative risk of many drugs associated with QT prolongation because most of the available data comes from the case reports or small observation series. In addition, the incidence of QT prolongation without TdP is probably much higher than the incidence of TdP.

In addition to these pharmacological agents listed above and used in the treatment of *SARS-Cov-2*, T2DM by itself can also cause cardiovascular problems. Therefore, this study aimed to evaluate the effect of favipiravir used in the treatment of COVID-19 patients diagnosed with T2DM on the QT/QTc interval.

In the multicentre studies of Haghjoo *et al*., 2,403 patients were prospectively evaluated.[10] In the research, they evaluated cases treated with chloroquine, hydroxychloroquine, lopinavir/ritonavir, atazanavir/ritonavir, oseltamivir, favipiravir, and remdesivir each alone or in combination with azithromycin.[10] They have reported that patients showed significant QTc prolongation with all the COVID-19 drugs studied, but TdP rarely caused life-threatening arrhythmia.[10]

In their study, Hooks *et al*. mentioned that hydroxychloroquine was considered for the potential treatment of *SARS Cov-2*, but there were many concerns about its safety.[11] The authors retrospectively evaluated the QTc interval with the help of Bazett's formula in the ECGs of 819 patients using hydroxychloroquine for them during rheumatological treatment in the last 20 years. They emphasised that the QT interval was prolonged, and the risk of long QT syndrome increased in patients receiving hydroxychloroquine.[11]

Bun *et al*. analysed the effects of azithromycin and hydroxychloroquine, the torsadogenic effects of which are known, on the QT interval in *SARS-Cov-2* cases using Bazett's and Fridericia's correction formulas.[12] The results were as follows: The baseline average automated QTc was 415 ± 29 ms and was lengthened to 438 ± 40 ms after 48 h of combined therapy. The treatment had to be stopped because of significant QTc prolongation in two out of 71 patients (2.8%). No medicine-induced life-threatening arrhythmia or death was observed. Only in less than 6% of the cases, HCQ/AZT could not be initiated or had to be interrupted.[12]

Zhu *et al*. stated that the lopinavir/ritonavir used in the treatment of two patients diagnosed with COVID-19 may have contributed to the induction of QTc prolongation.[13] Hernandez *et al.* systematically evaluated hydroxychloroquine and chloroquine drugs known to have *in vitro* antiviral activity against *SARS-Cov-2*.[14] They reported that there were increases in the QTc interval of 500 ms or more and that hydroxychloroquine increased the QTc interval by an average of 60 ms compared to the baseline. In addition, they reported that it increased the risk of ventricular tachycardia in patients receiving chloroquine compared to the control group not using chloroquine.[14]

Ayela Mega *et al*. searched electronic databases and systematically evaluated cases, diagnosed with COVID-19 who were in intensive care units between 30-December-2019 and 2020, and who used only hydroxychloroquine or hydroxychloroquine combined with azithromycin.[15] Interestingly, they reported there was no statistically significant difference between the QT interval of patients using only hydroxychloroquine and the QT interval of patients using hydroxychloroquine combined with azithromycin.[15]

However, Sertbas *et al*. recently showed that patients with COVID-19 taking favipiravir and moxifloxacin together had increased QT interval prolongation.[16] All patients received favipiravir in this study. In a case report, the patient using 2 grams of favipiravir twice a day after 6 grams of loading dose for *Ebola virus* treatment had QT and QTc prolongation.[17] It was reported that ECG changes could be due to the use of high-dose favipiravir. Previous studies have shown the effect of favipiravir with other medicines used for COVID-19 on QT interval. Yenercag *et al*. showed that the treatment with hydroxychloroquine, azithromycin, and favipiravir caused ventricular tachycardia episodes in two COVID-19 patients during their hospitalisation in the intensive care unit.[18] In another review analysis of Naksuk *et al*., it was emphasised that the drugs used for the treatment of COVID-19 such as favipiravir and lopinavir/ritonavir can prolong QT interval and cause TdP.[19]

On the other hand, Cap *et al.* showed a significant prolongation in the QTc interval with hydroxychloroquine, but there was no significant change with favipiravir in COVID-19 patients.[20] In this study, with a single-centre retrospective design, clinical, laboratory, and electrocardiographic findings of 189 cases were evaluated.[20] Those using hydroxychloroquine (Group 1, n = 66), hydroxychloroquine plus favipiravir (Group 2, n = 66), and only favipiravir (Group 3, n = 57) were included in the study. Measurements of the QTc interval were made before treatment and 48 hours after the initiation of treatment, and the authors reported that they observed the QTc change as −3ms in Group 3 when only favipiravir was administered and that this result was not statistically significant.[20]

Metformin has been reported to increase QT interval dispersion (QTd) due to the inhomogeneity of ventricular repolarisation when administered at high doses to diabetic rats.[21] However, different results may occur, and the data obtained from animal tissues may be misleading as animal and human tissues are, of course, different.

The QT interval duration and QTd were evaluated in a study comparing the ECGs of 50 patients with T2DM treated with sulfonylureas alone or in combination with metformin, and 40 patients with T2DM treated with insulin alone or in combination with metformin. It was reported that QTd was not different in diabetic acute coronary syndrome patients previously treated with sulfonylureas or insulin compared to the control group.[22]

Changes in cardiac electrophysiology in the form of QT prolongation were observed after exposure to moxifloxacin in both pre-clinical studies and studies on humans.[23] The orally administered moxifloxacin significantly prolonged QTc in a study including 24 healthy Chinese volunteers.[24] This change has not been reported to be significant, even though corticosteroids such as dexamethasone have a risk of affecting the QT interval.

It has been stated that decreased insulin sensitivity in T2DM patients is associated with an increase in the QTc interval, and a case has been reported of cardiac arrest due to hypoglycemia caused by insulin aspart injection.[25] However, no studies with high evidentiary value have been found that evaluate whether insulin aspart/insulin glargine injections affect or do not affect the QT interval in the patients diagnosed with T2DM.

The cumulative urinary excretion rates of unchanged favipiravir and the hydroxylated form were reported to be 0.8% and 53.1%, respectively, for 48 h after the last administration in an oral 7 day multiple-dose study with seven healthy adults (1200 mg + 400 mg daily, then 400 mg twice daily on the second and sixth days, then 400 mg once daily on the seventh day).

Therefore, ECG measurements were performed on the first day of oral administration of favipiravir and on the fifth day after oral administration in this study. QT and QTc values changed after ECG and the differences were statistically significant.

In conclusion, in the present study the average changes in both the QT interval ($F = 78.39$; $p = 0$) and QTc ($F = 174.34$; $p = 0$) values due to the use of multiple medicines, including favipiravir, were statistically significant all groups that were compared by a Tukiye's HSD after an ANOVA ($p < 0.05$).

Prolongation of the QTc interval might be a predictor surrogate marker for the ability of a medicine to cause TdP. In this research, MAD increase in QTc interval value was found to be 30.86 ms for Group 3 and 32.74 ms for Group 4.

DQTc is a main surrogate for proarrhythmic risk assessment. Therefore, DQT/DQTc values were also calculated in this study. It was understood that the averages of both DQT and DQTc increased in Group 3 and Group 4 and that these results were statistically significant ($p < 0.05$).

Based on the ethical rules, it was not possible to administer favipiravir alone, without any other medicine, in treating the patients diagnosed only with *SARS-Cov-2* (Group 3) and patients diagnosed with T2DM and *SARS-Cov-2* (Group 4). Efforts were made to minimise drug–drug interaction by adjusting the time when other drugs were administered based on a 4-h period, which is the half-life of favipiravir. No other routine medications involved in the treatment of the patients were administered until ECG measurements were taken within 4 h of administering favipiravir. However, it cannot be said that the ECG changes in this study were absolutely related to favipiravir.

In this study, Group 3 and 4 including COVID-19 patients received favipiravir and moxifloxacin. Considering the plasma half-life of favipiravir, ECG analysis was observed on the pre-treatment, second hour, fourth hour, and fifth day of favipiravir taken. The authors suggest that favipiravir may have had an effect on QT interval and caused QT prolongation in COVID-19 patients. It is difficult to make definite conclusions regarding the sample size of the study population, the combined use of other pro-arrhythmic agents in COVID-19, drug-drug interactions, and having no longer follow-up data, however, it may be speculated that the use of higher doses of favipiravir may lead to QT prolongation so it may be important to monitories COVID-19 patients in particular at higher risk for malignant arrhythmias and cardiac outcomes such as T2DM.

There are several limitations of this study. First, this was a single-centric, one-time study, therefore it has a relatively small sample size. Second, it was compelling to make a comment on the cause-effect relationship of the favipiravir with QT interval prolongation due the confounding factors such as multiple drugs used for COVID-19 infection. Third, there was no follow-up data to predict whether recovering from the COVID-19 infection and discontinuation of the medicines and favipiravir have had a correction on the QT interval prolongation or torsadogenic effect. Prospective multicentre studies with a larger study population are needed to provide more evidence.

CONCLUSION

Drugs affecting the QT interval might be administered together in patients diagnosed with *SARS-Cov-2* and T2DM simultaneously, and drugs interfering with the metabolism of these medicines must be carefully considered. It must be kept in mind that the active substance in favipiravir may be torsadogenic. It is important to carefully analyse QT and QTc values in the ECG results of patients with T2DM treated with favipiravir and to consider the high risk of arrhythmia.

ETHICAL APPROVAL:

Ethics committee approval was received from Tekirdag Namik Kemal University School of Medicine, dated 28/09/2021 and numbered 2021.225.09.11. In order for the data to be used in this research, permission was received from the Republic of Turkey Ministry of Health, Corlu State Hospital management (number 13441514-929-3960).

PATIENT'S CONSENT:
Voluntary consent and approval for the use of data were obtained from the participants included in the study and/or their relatives.

COMPETING INTEREST:
The authors declare that they have no competing interest.

AUTHORS' CONTRIBUTION:
MD, DB, IY, BEB: Concept, literature search, ethical approval, conduct of the study, data analysis, manuscript writing, and editing.
MD, IY, BB: Literature search, ethical approval, conduct of the study, and manuscript editing.
MD, DB, FBHK, BEB: Examining and evaluating the clinical and laboratory values of the cases.
IY: Conducted statistical evaluations of the data obtained. All authors approved the final version of the manuscript to be published.
All authors approved the final version of the manuscript to be published.

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