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Drug-induced QTc interval prolongation in PCR-positive non-ICU COVID-19 patients with diverse findings on chest computed tomography

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Abstract

Background: Some of the drugs used for the treatment of coronavirus disease (COVID-19) can increase the risk of corrected QT (QTc) interval prolongation, which may trigger arrhythmia or even death. Due to the low sensitivity of the reverse transcriptase-polymerase chain reaction (RT-PCR) test, chest computed tomography (CT) imaging is being used for COVID-19 diagnostic correlation and to evaluate whether there is pneumonic involvement in the lung.

Objective: In this study, we aimed to investigate the correlation between lung changes on CT and QTc interval changes on ECG in non-ICU patients with COVID-19 who have a positive PCR test when using drugs that can prolong the QTc interval.

Methods: This was a single-centre retrospective cohort study of hospitalized non-ICU patients. The study included 344 patients (56.1% men) with a mean age of 46.34 ± 17.68 years. The patients were divided into four groups according to their chest CT results: those having typical, atypical, indeterminate, or no pneumonic involvement. The mean QTc intervals and heart rates calculated from electrocardiograms (ECG) during admission to the hospital and after the treatment were compared.

Results: No significant differences were found between the groups' age, gender, and body mass index (BMI). In addition, no significant differences were found between the groups' mean QTc interval values at admission (*P*:.127) or after the treatment (*P*:.205). The groups' heart rate values were also similar, with no significant differences in the mean heart rate on admission (*P*:.648) and post-treatment (*P*:.229) ECGs.

Conclusion: This study has demonstrated findings of COVID-19 infection based on chest CT does not correlate with QT interval prolongation in non-ICU COVID-19 patients. There is a need for additional larger studies investigating the effect of chest CT findings on QT interval prolongation and bradycardia in COVID-19 patients.

1 | INTRODUCTION

In December 2019, several unidentified cases of viral pneumonia were reported in Wuhan City, Hubei Province, China[1]; an RNA virus from the coronavirus family was identified in the samples taken from these patients' respiratory tract. The International Virus Taxonomy Committee named this virus, which caused a pneumonia epidemic in China, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) defined the disease caused by this virus as the coronavirus disease 2019 (COVID-19) on February 11, 2020[2] and declared it as a pandemic on March 11, 2020. Since then, more than 100 million cases and 2 million related deaths have been recorded.

Since the emergence of the disease in China, reverse transcriptase-polymerase chain reaction (RT-PCR) has been used to diagnose the disease in line with the diagnostic criteria based on WHO guidelines. The data on RT-PCR published during the first stages of the epidemic indicated the sensitivity of the test to be between 30% and 60%.[3,4] This low sensitivity was attributed to the sampling method and the quality of the test kits. Many centres used chest computed tomography (CT) together with the RT-PCR testing due to its high sensitivity in detecting COVID-19 even without the clinical signs of pneumonia during the early stages of the epidemic.[4] Although, in March 2020, the American College of Radiology suggested that chest CT should not be used as the first step for the diagnosis of COVID-19,[5] it is still extensively used to provide earlier treatment and isolation in suspected COVID-19 cases due to the low sensitivity of the RT-PCR test and because results can be obtained faster.

Many medications have been used to treat COVID-19 since the outbreak started; however, no effective treatment has been found yet. At the beginning, hydroxychloroquine (HCQ), a drug used as an antimalarial and antirheumatic, was used in the treatment and prevention of COVID-19.[6] Azithromycin, an antibiotic from the macrolide group with immunomodulatory and anti-inflammatory effects, has also been used for treatment.[7] For the cases where atypical pneumonia could not be distinguished and secondary infections are seen, moxifloxacin, an antibiotic from the fluoroquinolone group, was included in the 'Republic of Turkey Ministry of Health (TR MoH) COVID-19 Treatment Guide'. Favipiravir, an RNA polymerase inhibitor shown to be effective in the treatment of other RNA viruses, especially influenza and Ebola, is also used for treatment. However, the use of these drugs may lead to cardiac side effects due to prolongation of the QT interval.

During prolongation of the QTc interval, the prolongation of the action potential may lead to the development of arrhythmia by causing early depolarization. Arrhythmias and other cardiac complications may be observed in patients with COVID-19. The drugs such as HCQ, azithromycin, and moxifloxacin may also increase the risk of arrhythmia. In addition, cardiac arrhythmias are observed more frequently in patients with more severe COVID-19.[8]

It has been shown that clinical condition severity and the use of more than one drug are significantly related to QT interval prolongation.[9] In COVID-19 patients, a significant relationship between lung involvement and disease prognosis based on chest CT results has also been identified.[10] Therefore, in this study, we aimed to investigate the relationship between lung involvement determined on chest CT and QT interval prolongation in PCR-positive, non-ICU COVID-19 patients administered drugs that can prolong the QT interval.

What's known

- QTc interval prolongation can be observed more frequently in patients with critical disease or those being followed-up in the ICU as they typically have a high number of risk factors (female gender, a history of acute myocardial infarction, presence of hypokalaemia, presence of heart failure, use of two or more drugs to prolong QTc, presence of sepsis, advanced age [>68], a QTc interval ≥450 milliseconds on baseline ECG, and use of loop diuretics). They are also susceptible to increased pharmacodynamic and pharmacokinetic drug-drug interactions due to increased drug use.
- In COVID-19 patients, there is a significant relationship between pulmonary involvement scoring in chest CT and the need for intensive care, intubation and mortality.
- According to the Radiological Society of North America (RSNA) classification, the type of lung involvement is not a mortality predictor.

What's new

- Although QT interval prolongation is more common in patients with critical disease, it was observed in our study that the presence and type of lung involvement has no effect on QT interval prolongation in COVID-19 patients who do not need intensive care.
- Drugs that can prolong the QT interval are safe in terms of arrhythmic events and mortality for COVID-19 patients who do not need intensive care.

2 | MATERIALS AND METHODS

This retrospective study was conducted with patients who were hospitalized and started medical treatment based on a possible diagnosis of COVID-19 according to the COVID-19 treatment algorithm of the TR MoH.[11] Inclusion criteria were as follows: (a) a diagnosis of COVID-19 by PCR test (SARS-CoV-2, qPCR Detection Kit by Bio-Speedy); (b) >18 years of age and being treated in the in-patient ward, not the ICU; (c) being in sinus rhythm; (d) electrocardiography (ECG) taken before and on the fifth day of the treatment; (e) being treated with only HCQ, HCQ/azithromycin, HCQ/moxifloxacin, or HCQ/favipiravir combinations; (f) having chest CT imaging available. According to the hospital protocol created under the guidance of TR MoH COVID-19 treatment recommendations and the literature data, the patients were administered a 5-day HCQ treatment, with a total dose of 400 mg given orally twice a day as the loading dose on the first day and 200 mg twice a day on following days. For the patients with signs of pneumonia, 500 mg azithromycin was administered orally once a day for 3 days, or favipiravir was administered orally for 5 days with a dose of 1600 mg twice a day on the first day as a loading dose, and then 600 mg twice a day on the following 4 days as a maintenance dose. The patients with suspected atypical pneumonia and/or findings of secondary infection were administered 500 mg Moxifloxacin intravenously once a day for 5 days. The patients' daily blood calcium, magnesium, and potassium levels

were measured, and electrolyte replacement was performed for the patients with electrolyte imbalance.

Exclusion criteria were: (a) QRS width ≥120 milliseconds before treatment, any bundle branch block, pre-excitation syndromes, QTc interval ≥500 milliseconds and/or a heart rate <50/min at baseline ECG; (b) implantable-cardioverter defibrillator or cardiac resynchronization therapy, or cardiac pacemaker; (c) rhythm other than sinus; (d) pregnancy; (e) use of other drugs (antipsychotics, antidepressants, antiarrhythmics, other antimicrobials etc) that may cause QTc prolongation; (f) chronic kidney failure (estimated glomerular filtration rate <60 mL/min according to the Cockcroft-Gault formula).

All the patients had 12-channel ECGs recorded at a speed of 50 mm/sec (Nihon Kohden ECG 1250). The ECGs were taken before and on the fifth day of the treatment. Rhythm, heart rate, bundle branch block, QRS distance, QT interval, and QTc interval were recorded and calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$). Although the Bazett formula is a widely used method for calculating QTc, it provides overcorrection at high heart rates. Therefore, in our study, we used the Framingham method in patients with a heart rate of 100/min and above.[12] The ECG measurements of QT intervals and heart rate were performed by two cardiologists blind to the patient data.

The patients' age, gender, body mass index (BMI), accompanying comorbid conditions, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive peptide (CRP), angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker values, antihypertensive use, and prognosis were recorded. The patients with missing data in their files were called to complete their data.

RT-PCR tests were conducted using nasopharyngeal and oropharyngeal swabs (SARS-CoV-2, qPCR Detection Kit by Bio-Speedy). For all patients, imaging was performed in the supine position throughout the end of inspiration based on conventional CT scans (Somatom go. Now; Siemens Healthineers). Because this was retrospective study, a standard CT protocol was not used. All CT images were 1.25 mm sections, and multiplanar images were reformed. In the radiology clinic of our centre, the lung findings on the COVID-19 patients' chest CT images were classified as typical, atypical, indeterminate, or negative according to the Expert Consensus Statement Classification of the Radiological Society of North America (RSNA). The reporting of COVID-19-related chest CT findings was as follows: Typical appearance = peripheral, bilateral, ground-glass opacity (GGO) with or without consolidation or visible intralobular lines (crazy-paving), multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines (crazy-paving), reverse halo sign, or other findings of organizing pneumonia (seen at the later stages of the disease); Indeterminate appearance = multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and nonrounded or non-peripheral, and few very small GGO with a nonrounded and non-peripheral distribution; Atypical appearance = isolated lobar or segmental consolidation without GGO, discrete small nodules (centrilobular, tree-in-bud), lung cavitation, and smooth interlobular septal thickening with pleural effusion; and Negative for pneumonia = no CT features to suggest pneumonia.[13]

Approval of the TR MoH COVID-19 Research Assessment Commission and the Ethics Committee of Celal Bayar University (Istanbul, Turkey) was obtained for the study.

Statistical analysis was performed using IBM SPSS Statistics 26, and figures were constructed using JASP (Version 0.14.1). Continuous variables were reported as the mean ± standard deviation and categorical variables were reported as numerical values and percentages. Comparisons of characteristics between patients according to chest CT findings were made with chi-square test or Fisher's exact test for categorical variables and one-way ANOVA for continuous variables. QTc interval and heart rate change were evaluated in prespecified subgroups, including patient's medication and chest CT findings. Changes in baseline versus control QTc intervals and heart rates were compared using a paired *t* test. A two-way ANOVA was conducted that examined the effects of treatment regime and chest CT findings on Δ QTc (change in corrected QT interval). The assumption of normality was assessed by the Kolmogorov-Smirnov test. Pearson's correlation was used to measure the degree of association between two variables. All probability values were 2-sided, and a *P* value cutoff of <.05 was used to determine statistical significance.

3 | RESULTS

A total of 344 patients were included in the study sample. Table 1 shows the clinical characteristics of the study population. Median follow-up was 8 days for the cohort (ranging between 5 and 12). The patients' mean age was 46.34 years and mean BMI (calculated as weight in kilograms divided by height in meters squared) was 26.72 kg/m^2. Of them, 56.1% were males and 19.4% were smokers. The prevalence of medical comorbidities was observed to be high: 11.3% of the patients had a history of hypertension, 12.2% had a history of diabetes mellitus, 4.9% had a history of coronary heart disease, 0.8% had a history of heart failure, and 10.7% had a history of chronic obstructive pulmonary disease. The laboratory test results are presented in Table 1. All patients received HCQ; 15 (4.4%) patients received HCQ plus azithromycin, 146 (42.4%) patients received HCQ plus moxifloxacin, and 17 (4.9%) patients received HCQ plus favipiravir.

The patients were divided into four groups according to their chest CT findings: negative, indeterminate, atypical, or typical. No significant differences were found between the groups' age, gender, and BMI. Although diabetes was observed at a lower level in patients with atypical chest CT findings compared to the other groups, there were no significant differences between the groups in terms of the other comorbid conditions. Haemoglobin levels were slightly lower in patients with indeterminate chest CT findings, but no anaemia requiring erythrocyte transfusion was observed in any group. Serum creatinine, potassium, AST, ALT, WBC, and CRP levels were also similar between groups. In addition, no statistically significant difference was found between the groups in terms of treatment

TABLE 1 Clinical characteristics of study population

	Total	Negative	Indeterminate	Atypical	Typical	*P* value
	344	109 (31.7%)	66 (19.2%)	63 (18.3%)	106 (30.8%)	
Age, y (mean ± std)	46.34 ± 17.68	43.56 ± 15.88	50.62 ± 17.63	46.38 ± 19.65	46.34 ± 17.68	.087
Gender (Male) n (%)	193 (56.1%)	66 (60.6%)	30 (45.5%)	38 (60.3%)	59 (55.7%)	.224
BMI, kg/m^2 (mean ± std)	26.72 ± 4.51	26.40 ± 4.50	26.91 ± 4.51	26.86 ± 4.93	26.85 ± 4.30	.846
Comorbidities, n (%)						
HT	39 (11.3%)	9 (8.4%)	9 (14.1%)	8 (13.3%)	13 (12.5%)	.639
DM	42 (12.2%)	9 (8.4%)	12 (18.8%)	2 (3.3%)	19 (18.3%)	.009*
CHD	17 (4.9%)	3 (2.8%)	2 (3.1%)	3 (5.0%)	9 (8.7%)	.220
HF	3 (0.8%)	1 (0.9%)	0 (0%)	0 (0%)	2 (1.9%)	.501
COPD	37 (10.7%)	14 (13.1%)	5 (7.8%)	7 (11.7%)	11 (10.6%)	.758
Smoking	67 (19.4%)	26 (24.3%)	7 (10.9%)	12 (20%)	22 (21.2%)	.203
Laboratory data, (mean ± std)						
Creatinin, mg/dL	0.77 ± 0.20	0.75 ± 0.16	0.74 ± 0.19	0.79 ± 0.21	0.78 ± 0.22	.336
Potassium, mEq/L	4.18 ± 0.41	4.20 ± 0.37	4.19 ± 0.40	4.13 ± 0.42	4.20 ± 0.44	.749
AST, μ/L	31.88 ± 23.93	31.31 ± 16.47	38.95 ± 43.90	28.52 ± 14.10	30.07 ± 15.36	.053
ALT, μ/L	37.31 ± 50.93	35.61 ± 29.11	51.72 ± 98.91	29.03 ± 29.71	34.99 ± 28.79	.062
WBC, $10^3/\mu L$	7.08 ± 3.39	6.39 ± 2.38	7.38 ± 4.75	7.34 ± 3.24	7.46 ± 3.31	.083
Hg, g/dL	13.38 ± 2.02	13.83 ± 1.63	12.93 ± 2.13	13.51 ± 1.89	13.12 ± 2.31	.014*
CRP, mg/dL	2.63 ± 4.83	2.09 ± 3.42	2.67 ± 3.97	2.75 ± 4.43	3.10 ± 6.50	.491
Medications, n (%)						
HCQ alone	166 (48.3%)	48 (44%)	36 (54.5%)	29 (46%)	53 (50%)	.557
HCQ +AZT	15 (4.4%)	3 (2.8%)	2 (3%)	6 (9.5%)	4 (3.8%)	.238
HCQ +MOX	146 (42.4%)	53 (48.6%)	25 (37.9%)	25 (39.7%)	43 (40.6%)	.455
HCQ +FAV	17 (4.9%)	5 (4.6%)	3 (4.5%)	3 (4.8%)	6 (5.7%)	.983
Mortality, n (%)	8 (2.3%)	2 (1.8%)	1 (1.5%)	3 (4.8%)	2 (1.9%)	.461

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; AZT, Azithromycin; BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; FAV, Favipiravir; HCQ, hydroxychloroquine; HF, heart failure; Hg, haemoglobin; HT, hypertension; MOX, Moxifloxacin; Std, standard deviation; WBC, white blood cell count.

*Statistically significant.

regimens. According to the chest CT findings, 44% of the patients in the negative group, 54.5% in the indeterminate group, 46% in the atypical group, and 50% in the typical group received HCQ alone.

All patients had a baseline ECG before starting treatment and a repeat ECG after the 5-day treatment. As compared to baseline, QTc was significantly increased after treatment (404.40 ± 25.87 vs 422.69 ± 27.26 milliseconds, $P < .001$). There was also significant QT prolongation in all groups when evaluated according to chest CT findings after treatment (Table 2). However, there was no significant difference between the groups in terms of mean QTc interval values at the beginning of treatment (*P*:.127) and after the treatment period (*P*:.205). Similar findings were also observed in heart rate changes, as no significant changes were observed in mean heart rate among the groups at admission (*P*:.648) and post-treatment (*P*:.229) ECGs, according to chest CT findings (Table 3). In addition, when the patients were evaluated according to their in-hospital treatment regime, there was a significant QT prolongation in all groups after treatment. Although no significant changes were seen in HR in the patients who received AZT or FAV in combination with HCQ, after the treatment, a significant decrease was found in HR in the other groups (HCQ alone and HCQ +MOX) and all patients (80.74 ± 14.86 vs 72.23 ± 12.27 beats/min, $P < .001$ in all patients) (Table 2). There was no statistically significant difference in Δ QTc between treatment groups (F:2,280; *P*:.079), and between groups when evaluated according to chest CT findings (F:1,186; *P*:.315). An interaction between treatment regime and chest CT findings could not be demonstrated (F:0,721; *P*:.690) (Table 4).

Out of 344 patients with serial ECGs, QTc intervals ≥500 milliseconds were observed in 6 (1.74%) after treatment. Of these patients, 4 had typical, 1 had atypical, and 1 had indeterminate chest CT findings. In addition, 10 patients (2.9%) had an increase in QTc interval of 60 milliseconds or more from baseline. Of these patients, 4 had typical, 3 had negative, 2 had atypical, and 1 had indeterminate chest CT findings. No instances of ventricular tachycardia,

TABLE 2 Comparison of pre-treatment vs post-treatment ECG parameters of study population by chest computed tomography findings and in-hospital treatment regimes

	Baseline QTc	Control QTc	*P* value	Baseline HR	Control HR	*P* value
All (n:344)	404.40 ± 25.87	422.69 ± 27.26	<.001*	80.74 ± 14.86	72.23 ± 12.27	<.001*
Chest CT findings						
Negative (n:109)	403.47 ± 24.56	423.92 ± 25.82	<.001*	79.96 ± 16.13	71.96 ± 12.60	<.001*
Indeterminate (n:66)	410.50 ± 25.02	424.48 ± 26.57	<.001*	81.70 ± 15.33	73.47 ± 12.36	<.001*
Atypical (n:63)	399.93 ± 26.09	416.06 ± 26.44	<.001*	79.30 ± 14.18	69.61 ± 10.17	<.005*
Typical (n:106)	403.87 ± 27.10	424.27 ± 29.34	<.001*	81.78 ± 13.67	73.30 ± 12.91	<.001*
Treatment regime						
HCQ alone (n:166)	402.62 ± 25.25	417.66 ± 23.60	<.001*	79.98 ± 14.46	70.91 ± 11.77	<.001*
HCQ +AZT (n:15)	392.80 ± 29.52	408.73 ± 22.26	<.05*	80.93 ± 13.78	73.93 ± 11.85	.064
HCQ +MOX (n:146)	407.35 ± 24.75	428.01 ± 29.22	<.001*	80.65 ± 15.51	72.36 ± 12.20	<.001*
HCQ +FAV (n:17)	406.70 ± 34.81	438.17 ± 32.38	<.005*	88.64 ± 12.84	81.94 ± 14.23	.079

Note: Data are presented as mean ± standard deviation. QTc interval were recorded and calculated according to Bazett's formula. The Framingham method was used in patients with heart rates above 100/min.

Abbreviations: AZT, Azithromycin; CT, computed tomography; FAV, Favipiravir; HCQ, hydroxychloroquine; HR, heart rate; MOX, Moxifloxacin; QTc, corrected QT interval.

*Statistically significant.

ventricular fibrillation, or significant conduction delay were observed during follow-up.

4 | DISCUSSION

In this study, the patients were divided in to four groups according to their chest CT findings: typical, atypical, indeterminate, or negative. There was no significant difference between the groups in terms of the drugs used. Although a significant QT interval prolongation was observed in all groups after the treatment, no significant difference was found between the groups in this regard. There was also no significant difference between the groups in terms of bradycardia.

COVID-19 is highly contagious; therefore, fast and reliable diagnostic methods are required. Early diagnosis and treatment reduce the morbidity and mortality rates and allow to decrease the transmission rate in the community by isolating the patients, especially those who are asymptomatic. The RT-PCR test was used as a diagnostic method in the early stages of the epidemic; however, since its sensitivity was around 60%, chest CT imaging has become an additional diagnostic method routinely used in many centres due to its sensitivity of over 90% and its rapid results.[4] In addition, chest CT imaging greatly contributes to monitoring the progression of the disease and evaluating the effectiveness of the treatment.[5]

Although a considerable time has passed since the beginning of the epidemic and many treatment methods have been used, the desired level of success has not yet been achieved and current treatments have side effects. One of these side effects is QT interval prolongation, which forms the basis of the present study. HCQ, an antirheumatic and antimalarial drug, was used extensively in the early stages of the epidemic; however, contradictory study results have been published. Upon the recommendation of the WHO, HCQ is no longer used in many countries, but it is still listed in the COVID-19 treatment guide in Turkey. It has been reported to prolong the QTc interval in COVID-19 patients but to rarely cause arrhythmias.[14] As per guideline recommendations, patients received a total of 2400 mg of HCQ for 5 days in the present study. Azithromycin, a macrolide-group antibiotic with known immunomodulatory and anti-inflammatory effects, has been shown to reduce the viral load more when combined with HCQ for the treatment of COVID-19.[15] While it has been shown to significantly prolong the QTc interval, the incidence of associated malignant arrhythmia and arrhythmic death is quite low.[16] In accordance with the TR MoH COVID-19 treatment guidelines, moxifloxacin, a broad-spectrum antibiotic from the fluoroquinolone group commonly used in atypical pneumonia cases, has also been used for the treatment of the patients with clinical suspicion of COVID-19 and signs of atypical pneumonia on chest CT. Moxifloxacin causes QTc interval prolongation, as all fluoroquinolones do.[17] Although azithromycin was used more at the beginning of the pandemic, moxifloxacin was used more in the later period. For this reason, the number of patients using azithromycin in our study is limited. Favipiravir, an RNA polymerase enzyme inhibitor from the antiviral drug group, was one of the first drugs used in the treatment of COVID-19 around the world and is still extensively used in Turkey. Favipiravir is reported to be effective in the treatment of many RNA viruses, especially influenza and Ebola virus; however, there are data showing that it has no effect on QT interval. On the other hand, there is also a case report stating that it can cause prolongation.[18,19] Since the present study consisted of non-ICU patients, the number of patients using favipiravir was low. In this study, as in the above-mentioned studies, a significant prolongation in the control QTc intervals was observed in all the HCQ

TABLE 3 Comparison of ECG parameters between groups according to chest computed tomography findings

	Negative	Indeterminate	Atypical	Typical	
	109 (%31.7)	66 (%19.2)	63 (%18.3)	106 (%30.8)	*P*
Baseline QTc, ms	403.47 ± 24.56 (398.81-408.14)	410.50 ± 25.02 (403.83-416.25)	399.93 ± 26.09 (393.36-406.50)	403.87 ± 27.10 (400.11-410.20)	.127
Control QTc, ms	423.92 ± 25.82 (419.02-428.83)	424.48 ± 26.57 (418.52-431.35)	416.06 ± 26.44 (409.40-422.72)	424.27 ± 29.34 (418.59-429.95)	.205
Δ QTc, ms	20.44 ± 18.74 (16.89-24.00)	14.89 ± 17.96 (10.47-19.31)	16.12 ± 20.13 (11.05-21.19)	19.44 ± 19.30 (15.71-23.18)	.197
Baseline HR, ms	79.96 ± 16.13 (76.87-83.05)	81.70 ± 15.33 (77.90-85.50)	79.30 ± 14.18 (75.70-82.90)	81.78 ± 13.67 (79.13-84.42)	.648
Control HR, ms	71.96 ± 12.60 (69.54-74.37)	73.47 ± 12.36 (70.41-76.54)	69.61 ± 10.17 (67.02-72.19)	73.30 ± 12.91 (70.77-75.82)	.229

Note: Data are presented as mean ± standard deviation and 95% confidence interval.

Abbreviations: HR, heart rate; QTc, corrected QT interval; Δ QTc, change in corrected QT interval.

TABLE 4 Comparison of Δ QTc values by chest computed tomography findings and in-hospital treatment regimes

	Chest CT findings*											
	Negative (n:109)			Indeterminate (n:66)			Atypical (n:63)			Typical (n:106)		
Treatment regime**	n	Mean ± std	95% CI	n	Mean ± std	95% CI	n	Mean ± std	95% CI	n	Mean ± std	95% CI
HCQ alone (n:166)	48	16.87 ± 14.14	12.76 to 20.98	36	13.69 ± 15.32	8.50 to 18.88	29	13.20 ± 20.69	5.33 to 21.07	53	16.03 ± 16.35	11.48 to 20.59
HCQ +AZT (n:15)	3	28.00 ± 10.81	1.12 to 54.87	2	19.00 ± 15.55	−120.76 to 158.76	6	15.50 ± 24.61	−10.33 to 41.33	4	21.00 ± 12.75	0.70 to 41.29
HCQ +MOX (n:146)	53	23.56 ± 22.51	17.36 to 29.77	25	15.00 ± 22.10	5.87 to 24.12	25	20.04 ± 18.22	12.51 to 27.56	43	20.72 ± 21.48	14.1 to 27.33
HCQ +FAV (n:17)	5	17.20 ± 12.13	2.13 to 32.26	3	25.66 ± 13.20	−7.13 to 58.46	3	13.00 ± 27.07	−54.25 to 80.25	6	38.83 ± 21.45	16.32 to 61.34
All (n:344)	109	20.44 ± 18.74	16.89 to 24.00	66	14.89 ± 14.89	10.47 to 19.31	63	16.12 ± 20.13	11.05 to 21.19	106	19.44 ± 19.30	15.71 to 23.18

Note: F:0.721; *P*:0.690; η^2_p:0.019 for chest CT findings and treatment regime interaction

P:.147 for homogeneity of variances with using Levene's test

Abbreviations: AZT, Azithromycin; CT, computed tomography; FAV, Favipiravir; HCQ, hydroxychloroquine; MOX, Moxifloxacin; Std, standard deviation; Δ QTc, change in corrected QT interval.

*F:1,186; *P*:.315; η^2_p:0,011 for chest CT findings.; **F:2,280; *P*:.079; η^2_p:0,020 for treatment regime.

alone, HCQ + AZT, HCQ + MOX, and HCQ + FAV groups according to the basal QTc intervals. However, arrhythmia and arrhythmic death were not observed.

Independent risk factors for QTc prolongation are female gender, a history of acute myocardial infarction, presence of hypokalaemia, presence of heart failure, use of two or more drugs to prolong QTc, presence of sepsis, advanced age (>68), a QTc interval ≥450 milliseconds on baseline ECG, and the use of loop diuretics.[9] QTc interval prolongation can be observed more frequently in critical patients or those being followed-up in the ICU due to the higher number of risk factors and the increased pharmacodynamic and pharmacokinetic drug-drug interactions due to increased drug use.[20] In the present study, a positive correlation was observed between age and both basal QTc and control QTc intervals, supporting the above data. On the other hand, no correlation was found between BMI and QTc intervals (Table 5 and Figure 1). The low number of patients with a QTc interval ≥500 milliseconds in the present study compared to other studies, and the absence of arrhythmic events can be explained by the fact that the subjects were younger, non-ICU patients in the present study.[21]

Francone et al compared the severity and prognosis of COVID-19 with the CT-based semi-quantitative pulmonary involvement scores. They found a significant relationship between the severity of the disease and the laboratory parameters such as CRP, D-dimer, and CT scores. They also found that the significant relationship between a high CT score and mortality was predictive of increased mortality.[22] Abbasi et al similarly determined that a high chest CT score is an independent predictor of mortality. They also found a significant correlation between chest CT score and the need for intensive care and intubation. However, the analysis made in terms of typical, atypical and indetermined involvement findings according to the RSNA classification indicated that the RSNA classification did not predict mortality, unlike the CT scoring.[23] In a study by Barman et al, no significant relationship was found between the disease severity and QTc interval prolongation in COVID-19 patients, but the number of patients with a QTc interval >500 milliseconds was found to be significantly higher among those with more severe disease.[24]

TABLE 5 Correlation coefficients (r) between age, BMI and QTc intervals

	Pearson's r	*P*	CI (%95)
Age-baseline QTc	0.360	<.001*	0.264 to 0.448
Age-control QTc	0.445	<.001*	0.356 to 0.526
BMI-Baseline QTc	−0.028	.612	−0.135 to 0.080
BMI-control QTc	−0.033	.547	−0.140 to 0.075
Baseline QTc-control QTc	0.693	<.001*	0.633 to 0.744

Abbreviations: BMI, body mass index; QTc, corrected QT interval.
*Statistically significant.

5 | CONCLUSIONS

As a result, this study concluded that the absence or presence of typical, atypical, or indeterminate pneumonic involvement according to the RSNA classification (regardless of the severity of the involvement) does not correlate with QTc interval prolongation in non-ICU COVID-19 patients using drugs that can prolong the QTc interval. The patient groups in this study consisted of individuals whose disease was not severe and who did not require intensive care. They also did not have many associated risk factors that would prolong the QT interval. Larger prospective studies are needed to evaluate the effects of treatments on QT interval and bradycardia using the scoring system that evaluates the severity of pneumonic involvement together with the RSNA classification in COVID-19 patients.

6 | LIMITATIONS

The present study was conducted with non-ICU patients; however, the severity of pneumonic involvement may be higher among ICU patients, and thus, the findings may be different from those obtained from the patient groups in the present study. Another limitation of the study is that no scoring system was used to calculate the severity of involvement in patients with pneumonic involvement.

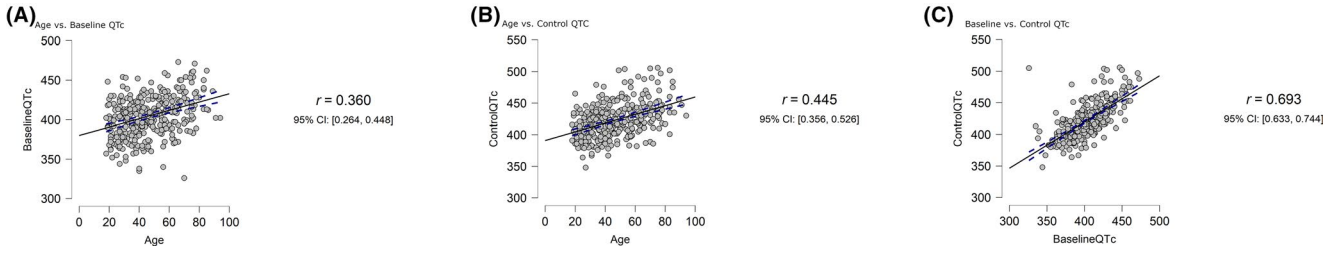

FIGURE 1 Scatterplot showing the correlation between age and QTc intervals. A, Correlation between age (y) and baseline QTC interval (ms). B, Correlation between age (y) and control QTc interval (ms). C, Correlation between baseline and control QTc intervals (ms)

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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