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QTc prolongation in patients with COVID-19: a retrospective chart review

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ABSTRACT

Drug-induced corrected QT (QTc) prolongation can cause Torsade de Pointes (TdP) which leads to severe arrhythmia or sudden cardiac death. However, information on the prevalence of QTc prolongation in coronavirus disease 2019 (COVID-19) patients and risk factors is limited. A retrospective chart review was conducted in COVID-19 patients admitted to Chonburi Hospital from April to October 2020. The outcomes were the incidence of QTc prolongation and prevalence of risk factor QTc prolongation. We included 29 COVID-19 patients. After treatments were initiated, QTc prolongation occurred in 17 patients (58.62%). QT prolongation could be found as early as two days after the treatment initiation (median = 6 days interquartile range [IQR], 4–7). The median QTc interval in those 17 patients increased from 410 (IQR, 399.5–425.0) ms to 460 (453.50–466.50) ms, with the maximum QTc interval of 488 ms. They were treated with multiple drugs that were reported as a cause of QTc prolongation. 64.71% (n = 11) of them were treated with chloroquine. The median TdP risk score in patients with and without QTc prolongation was 3 (IQR, 2–3) and 2 (IQR, 1–2), respectively. The percentage of patients with comorbidities including atrial fibrillation, bradycardia, concomitant use of diuretics, diabetes, electrolyte imbalance was higher in patients with QTc prolongation. COVID-19 patients were treated with multiple drugs that were reported as a cause of QTc prolongation. COVID-19 patients with QTc prolongation had more comorbidities that are risk factors for QTc prolongation.

Keywords: COVID-19; long QT Syndrome; Thailand; Observation

INTRODUCTION

Multiorgan dysfunction, including cardiovascular problems, is one of the complications from coronavirus disease 2019 (COVID-19). Corrected QT (QTc) interval prolongation in the electrocardiography (ECG) of COVID-19 patients has been reported [1-5]. The severe ramification from QTc prolongation is Torsades de Points (TdP) which can cause malignant ventricular arrhythmias e.g. ventricular tachycardia/fibrillation and sudden cardiac death which leads to mortality [6]. QTc prolongation in COVID-19 can be multifactorial. Medication is one of the most important causes since several drugs for the treatment of COVID-19 that were recommended by health organizations had the potential for causing

QTc prolongation. In 2020, the National Institutes of Health and World Health Organization suggested therapeutic options that were currently under investigation for COVID-19 including azithromycin, chloroquine, hydroxychloroquine, darunovir/ritonavir, lopinavir/ritonavir, and remdesivir [7,8]. During that time in Thailand, the Department of Medical Services launched the guideline that recommended chloroquine, hydroxychloroquine, darunavir + ritonavir (DRV/r), or lopinavir + ritonavir (LPV/r), azithromycin, favipiravir for the treatment of COVID-19 patients [9].

There are several mechanisms involving the QTc prolongation by medications involving the treatment of COVID-19. The major mechanism is by inhibiting the human ether-a-go-go-related gene - K+ channel in myocytes, leading to the retardation of repolarization and prolonging the QT interval [6,10-12]. Drug interactions, especially via CYP3A4, also lead to an increased chance for QTc prolongation [13-15]. In addition, a report shows that COVID patients have an increase in systemic cytokine, especially interleukin-6 which stimulates ion channels in myocytes and inhibits CYP3A4 [16], increasing the risk for QTc prolongation. Other risk factors for QTc prolongation found in COVID-19 patients are elderly; risks for cardiovascular conditions; prior long QT syndrome or QTc prolongation; abnormal plasma electrolytes e.g. hypokalemia, hypomagnesemia; and bradycardia [13]. Although the mechanisms for QTc prolongation in COVID-19 patients are characterized, the prevalence reported in the literature is varied and limited in the Caucasian population. Therefore, this study aimed to investigate the prevalence of and risk factors for QTc prolongation in Thai patients with COVID-19.

METHODS

Study design and data collection
A retrospective chart review was conducted by reviewing an electronic patient database in the Hospital Information System (HIS) (Abstract-e-PHIS; Abstract Computer, Bangkok, Thailand). All COVID-19 patients admitted to Chonburi Hospital from April to October 2020 were eligible. Patients who did not receive treatment or did not have an electrocardiogram (EKG) were excluded. The first and the second author designed a case report form that allowed the deidentification of the patients. Data on patient demographics (age, sex, weight, height); vital signs (heart rate); patient history (smoking, alcohol consumption, concomitant diseases, current medications), laboratory data (renal and hepatic function, electrolytes, EKGs before and during the admission); and details of admission (duration of hospitalization, patient status after discharge) were collected. The study was approved by the Institutional Review Board of the hospital (registration number ชบ.0032.102.9/209).

Clinical outcome
The primary outcome was the difference in the QTc interval, which was calculated using Bazett's correction by attending physicians, from the baseline QTc. QTc interval prolongation was defined as QTc interval > 450 milliseconds (ms), 470 ms, and 460 ms in male adults, female adults, and adolescents of less than 15-year-old, respectively. Severe QTc prolongation was defined as a QTc interval of more than 500 ms [17,18].

The secondary outcomes were risk factors for TdP including having the following characteristics or using the following medication: older than 68-year-old, female, bradycardia (heart rate < 55 bpm), left ventricular systolic dysfunction, myocardial infarction, hypocalcemia (<8.6 mg/dL), hypokalemia (< 3.5 mmol/L), hypomagnesemia (<1.7 mg/dL), diuretics, treated with more than

one drug with potential for QTc prolongation [19,20]. Drugs with potential for QTc prolongation in this study were according to CredibleMed® which classified medications according to the risk for QTc/TdP into known risk, possible risk, and conditional risk [21].

Statistical analysis

Data on demographics, vital signs, patient history, laboratory, and details of admission data were analyzed by descriptive analysis using SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). Data were presented as percentage, mean ± standard deviation, or median (interquartile range [IQR]). The statistical comparison of data was performed using SPSS 21.0. Discrete (e.g. frequency of test per day) or continuous data (e.g. systolic blood pressure) were compared using an independent t-test with Welch's correction. Differences between proportions of categorical data (e.g. sex difference) were compared using Fisher's exact test.

RESULTS

There were 33 COVID-19 patients admitted to Chonburi Hospital during the study period. Three patients did not have EKGs and one did not receive medical treatment so they were excluded from this study. The included patients (n = 29) were in middle age (47.72 ± 16.13 years old); were overweight (body mass index [BMI], 24.35 ± 4.59 kg/m²); had normal QTc interval (410 [IQR, 399.0–424.0] ms). The majority of them were male (65.52%) and did not have comorbidities (60%) (**Table 1**). The patients were treated with several drugs including azithromycin, chloroquine, hydroxychloroquine, darunavir/ritonavir, favipiravir, lopinavir/ritonavir, and oseltamivir. Patients with QTc prolongation were significantly older, had significantly higher BMI, and had significantly lower estimated glomerular filtration rate (eGFR; p < 0.05; **Table 1**). The combination of each drug for the treatment regimen is described in **Table 2**, and the dose and duration of medications used are summarized in **Table 3**.

After the treatment for COVID-19 was initiated in 29 patients, QTc prolongation occurred in 17 patients (58.62%). In addition, among the 12 patients who did not have QTc prolongation, QTc interval rising occurred in 5 of them. The majority of QTc prolongation in COVID-19 patients

Table 1. Characteristics of included patients

Baseline characteristics	QTc prolongation (n = 17)	No QTc prolongation (n = 12)	p-value	Total (n = 29)
Age (yr)	57.45 ± 6.91	34.67 ± 11.87	< 0.01	47.72 ± 16.13
Female	2 (11.76)	8 (66.67)	< 0.01	10 (34.48)
Body mass index (kg/m²)	24.73 ± 5.02	23.83 ± 4.95	0.63	24.35 ± 4.59
Heart rate (beat per minute)	79.91 ± 11.61	79.50 ± 14.65	< 0.01	81.46 ± 12.50
Systolic blood pressure (mmHg)	126.50 (120.50–146.50)	108.50 (106.25–124.75)	0.01	123 (108.25–138.75)
Baseline QTc interval (millisecond)	410.0 (399.5–425.0)	411.0 (378.0–426.0)	0.52	410.0 (399.0–424.0)
Baseline eGFR (mL/min/1.73 m²)	81.45 (68.28–91.05)	103.15 (96.38–117.20)	< 0.01	92.55 (72.65–102.93)
Alcohol use	3 (17.65)	4 (33.33)	0.40	7 (24.14)
Smoking	1 (5.88)	3 (25.00)	0.28	4 (13.79)
Underlying disease				
Atrial fibrillation	1 (5.88)	0 (0.00)	1.00	1 (3.45)
Hypertension	2 (11.76)	0 (0.00)	0.50	2 (6.90)
Diabetes	4 (23.53)	0 (0.00)	0.12	4 (13.79)
COPD	1 (5.88)	0 (0.00)	1.00	1 (3.45)
Chronic kidney disease	1 (5.88)	0 (0.00)	1.00	1 (3.45)
Kidney transplantation	0 (0.00)	1 (8.33)	0.41	1 (3.45)
Hepatic dysfunction	0 (0.00)	1 (8.33)	0.41	1 (3.45)

Data were expressed as mean ± standard deviation, median (interquartile range) or number (%).
QTc, correct QT; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease.

Table 2. Medication treatment pattern in the treatment of coronavirus disease 2019

Core agents	Supplements (choose both)	Supplements (choose one)
Chloroquine 250–1,000 mg/day	Lopinavir/ritonavir 800/200 mg/day	Azithromycin 250–500 mg/day
OR	OR	AND/OR
Hydroxychloroquine 400–800 mg/day	Darunavir 600–1,200 mg/day	Favipiravir 3,200 mg/day on the first day and then 1,200 mg/day
		AND/OR
	Ritonavir 100–200 mg/day	Oseltamivir 150–300 mg/day

Table 3. Dose and duration of medications used for the treatment of coronavirus disease 2019

Medication	Dose (mg)/day	QTc prolongation case (n = 17)		No QTc prolongation case (n = 12)	
		No. (%)	Duration of drug use (days)[†]	No. (%)	Duration of drug use (days)[†]
Azithromycin	500	7 (41.18)	9.5 (7–12)	9 (75.00)	10 (9–11)
Chloroquine	250	0	NA	1 (8.33)	5 (5–5)
	500	7 (41.18)	5 (1–11)	2 (16.67)	7 (4–10)
	750	1 (5.88)	1 (1–1)	0	NA
	1,000	6 (35.29)	6 (2–10)	1 (8.33)	1 (1–1)
	Total*	11 (64.71)	5 (1–11)	3 (25.00)	4.5 (1–10)
Hydroxychloroquine	400	6 (35.29)	10 (6–15)	8 (66.67)	10.5 (7–12)
	800	0	NA	5 (41.67)	1.5 (1–11)
	Total	6 (35.29)	10 (6–15)	9 (75.00)	10 (1–12)
Darunavir/Ritonavir	600/100	1 (5.88)	1 (1–1)	0	NA
	900/100	5 (29.41)	12 (4–16)	1 (8.33)	8 (8–8)
	1,200/200	5 (29.41)	11 (6–16)	1 (8.33)	11 (11–11)
	Total	10 (58.82)	11 (1–16)	2 (16.67)	9.5 (8–11)
Favipiravir	1,200	5 (29.41)	9.5 (5–10)	0	NA
	3,200	3 (17.65)	1 (1–1)	0	NA
	Total	5 (29.41)	5.5 (1–10)	0	NA
Lopinavir/ritonavir	800/200	6 (35.29)	6 (3–11)	2 (16.67)	5.5 (5–6)
Oseltamivir	150	5 (29.41)	6 (1–9)	1 (8.33)	6 (6–6)
	300	2 (11.76)	8.5 (1–16)	0	NA
	Total	6 (35.29)	6 (1–16)	1 (8.33)	6 (6–6)

QTc, corrected QT; NA, not applicable.
*One patient could be treated by more than one dose of the drug; [†]Expressed as median (minimum–maximum).

occurred at day six (n = 17; median = 6; IQR, 4–7 days; range, 3–11 days) after the treatment of COVID-19. In patients with QTc prolongation, the ΔQTc interval rising from baseline and QTc interval after COVID-19 treatment were significantly higher than those in patients without QTc prolongation ($p < 0.05$). Details for QTc interval in all patients are demonstrated in **Table 4**. The

Table 4. Characteristics of QTc interval prolongation from the treatment of COVID-19 and its management

QTc interval	QTc prolongation	No QTc prolongation[‡]	p-value	Total
Characteristics	(n = 17)	(n = 12)		(n = 29)
QTc interval after COVID-19 treatment (millisecond)	460.00 (453.50–466.50), 449–488	433.00 (417.50–446.00), 341–460	< 0.01	451.00 (432.00–460.30.25), 341–488
QTc interval rising from baseline (millisecond)*	53.00 (39.00–64.00), 8–136	29.50 (13.25–47.75), 6–59	< 0.01	45.00 (33.00–59.00), 6–136
Duration of COVID-19 medication use (day)	11.00 (7.00–15.00), 6–21	11.00 (10.00–12.00), 5–17	0.64	11.00 (7.25–12.75), 5–21
Frequency of ECG test (day)	4.00 (2.50–5.00), 1–9	3.00 (2.25–4.75), 2–9	0.79	4.00 (2.50–5.00), 1–9
First date of QTc prolongation	6.00 (3.50–7.00), 3–11	NA	NA	6.00 (3.50–7.00), 3–11
Management[†]	(n = 17)	(n = 5)[‡]		(n = 22)
Continuing the same treatment regimen until discharge	13 (76.47)	3 (60.00)	0.58	16 (72.73)
Changing chloroquine + lopinavir/ritonavir to hydroxychloroquine with darunavir/ritonavir or with azithromycin	3 (17.64)	2 (40.00)	0.55	5 (22.73)
Decreasing chloroquine dosage	1 (5.88)	NA	NA	1 (4.55)

Values are presented as median (interquartile range), range, or number (%).
QTc, corrected QT; COVID-19, coronavirus disease 2019; ECG, electrocardiography; NA, not applicable.
*No QTc prolongation = 5 patients, total of QTc interval rising from baseline = 22 patients; [†]All patients with electrolyte imbalance were also treated for electrolyte imbalance; [‡]There were 12 patients without QTc prolongation. Five of them had the increased QT interval that intervention may have been required of which the data are presented in this table. Data of management of the rest of the patients without QTc prolongation (n = 7) are not shown here.

patients with QTc prolongation were older; had a higher male: female ratio; had approximately equal baseline QTc interval; had lower baseline eGFR; and had comorbidities (**Table 1**). In addition, patients with QTc prolongation had more TdP risk factors. The significant risk factors were electrolyte imbalance and hypocalcemia ($p < 0.05$). Although not statistically significant, they had more hypokalemia, hypomagnesemia, hypocalcemia, bradycardia, and furosemide usage than patients without QTc prolongation (**Table 5**). Also, the number of medications that patients with QTc prolongation (4.8 ± 1.29) and without QTc prolongation (4.0 ± 1.41) used were not different. Details of drugs prescribed to patients with and without QTc prolongation are demonstrated in **Table 5**.

From the total of 29 included patients, 22 patients required further management for the increase of QT interval. The management of QTc prolongation is shown in **Table 4**. Most

Table 5. The comparison of risk factors and drugs used in coronavirus disease 2019 patients with and without QTc prolongation

The risk factors and drugs used	QTc prolongation (n = 17)	No QTc prolongation (n = 12)	*p*-value
Number of TdP risk factors	3 (2–3)	2 (1–2)	0.08
Number of QTc prolonging drugs used in a patient during QTc interval prolongation	4.8 ± 1.29	4.0 ± 1.41	0.13
Number of patients with characteristics			
Bradycardia	2 (11.76)	0 (0.00)	0.50
Electrolyte imbalance	12 (70.59)	2 (16.67)	< 0.01
Hypokalemia	5 (29.41)	0 (0.00)	0.41
Hypomagnesemia	2 (11.76)	1 (8.33)	1.00
Hypocalcemia	12 (70.59)	2 (16.67)	< 0.01
Loop diuretics use	3 (17.65)	0 (0.00)	0.25
Hepatic dysfunction	0 (0.00)	1 (8.33)	0.41
Drugs with known TdP risk			
Azithromycin	7 (41.18)	9 (75.00)	0.13
Clarithromycin	0 (0.00)	1 (8.33)	0.41
Chloroquine	11 (64.71)	3 (25.00)	0.06
Domperidone	7 (41.18)	9 (75.00)	0.13
Haloperidol	1 (5.88)	0 (0.00)	1.00
Hydroxychloroquine	6 (35.29)	9 (75.00)	0.06
Levofloxacin	1 (5.88)	0 (0.00)	1.00
Ondansetron	13 (76.47)	7 (58.33)	0.42
Drugs with conditional TdP risk			
Loperamide	4 (23.53)	3 (25.00)	1.00
Metoclopramide	4 (23.53)	0 (0.00)	0.12
Omeprazole	2 (11.76)	1 (8.33)	1.00
Drugs with possible TdP risk			
Lopinavir/ritonavir	6 (35.29)	2 (16.67)	0.41
Enzyme inhibitors			
Darunavir/ritonavir	10 (58.82)	2 (16.67)	0.05
Other medications			
Favipiravir	5 (29.41)	0 (0.00)	0.06
Oseltamivir	6 (35.29)	1 (8.33)	0.19
QTc prolonging drugs			
Known TdP risk (K)	17 (100.00)	12 (100.00)	1.00
Conditional TdP risk (C)	8 (47.06)	3 (25.00)	0.27
Possible TdP risk (P)	6 (35.29)	2 (16.67)	0.41
Enzyme inhibitors (E)	10 (58.82)	3 (25.00)	0.13
K and C and P and E	0 (0.00)	1 (8.33)	0.41
K and (C or P) and E	7 (41.18)	1 (8.33)	0.09
K and (C or P)	7 (41.18)	2 (16.67)	0.23
K and E	3 (17.65)	2 (16.67)	1.00
K only	0 (0.00)	6 (50.00)	< 0.01

Data are shown as mean ± standard deviation or number (%).
QTc, corrected QT; TdP, torsade de pointes.

of the patients were treated with the same medications, albeit with the QTc prolongation, until the discharge. In these patients, routine monitoring was performed. Dosage regimen modification to hydroxychloroquine with darunavir/ritonavir or with azithromycin and dose reduction of chloroquine was also the management alternatives when QTc prolongation occurs, depending on the clinical judgment of the attending physicians. After the 29 patients were treated for COVID-19 for approximately two weeks (median admission time, 14 days; range, 5–40 days), 28 of them were fully recovered and discharged. One patient, who had QTc prolongation, passed away because of sepsis. This patient had an underlying heart failure and during the treatment developed hospital-acquired pneumonia, acute kidney failure, and septic shock. Other adverse events during the treatment occurred in patients without QTc prolongation which included vertigo and chest discomfort in one patient after the use of lopinavir/ritonavir.

DISCUSSION

This study found that the prevalence of QTc prolongation in COVID-19 infected Thai patients was 58.62%. In Thai healthy patients without COVID-19 infection, the prevalence was 14% [22]. This signifies the importance of the effect of COVID-19 and its treatment on QTc prolongation. In addition, in Chinese people without COVID-19 infection older than 35-year-old, the prevalence of QTc prolongation was 31.6% [23]. That study also found that age, the history of cardiovascular diseases, obesity, hypertension, diabetes, and hypokalemia with QTc prolongation potential significantly increase the prevalence QTc prolongation [23]. According to the guideline for the treatment of COVID-19 issued by the Department of Medical Services (updated version 1 May 2020) which were being used during the study period, the combination of 2–4 drugs, including chloroquine, hydroxychloroquine, DRV/r, or LPV/r, azithromycin were recommended for the treatment. If there was the progression of infiltration, as shown by chest X-ray, favipiravir with or without corticosteroids, may have been added to the treatment regimen, depending on the clinical symptoms of patients [9]. The medications recommended in the guideline which are azithromycin, chloroquine, hydroxychloroquine, protease inhibitors (darunavir, lopinavir, and ritonavir) are capable of QTc prolongation. Twenty-nine percent of the patients with QTc prolongation were treated with favipiravir, meaning that they had severe COVID-19 infection. Therefore, they were treated with more numbers of QTc prolonging drugs and with a higher dose of chloroquine. Borba shows that QTc prolongation is more likely when high dose chloroquine is used in combination with azithromycin than when the normal dose of chloroquine is used [3].

This study showed that patients with QTc prolongation were significantly older, had significantly higher BMI, and had significantly lower eGFR. These findings agreed with a retrospective cohort study showing that QTc prolongation occurs in COVID-19 patients treated with azithromycin and hydroxychloroquine, especially in the elderly, patients with BMI ≥ 30 kg/m^2 or with serum creatinine ≥ 1.5 mg/dL [24], The increase of QTc interval in the elderly might be caused by the physiological of the cardiovascular system and cardiac hypertrophy [25]. The prolongation of QTc interval with the elevation of BMI is believed to be caused by the increase of the cardiac output in individuals with high BMI, leading to subclinical cardiac hypertrophy [23,26]. Besides, Liu et al. [27] found that the more the progression of the stage of chronic kidney disease, the higher the risk of QTc prolongation. This is because chronic kidney disease is associated with electrolyte abnormalities, diabetes, and altered pharmacokinetics of medications [27].

Other factors also affect QTc prolongation in the patients. For example, there were other QTc prolonging medications that were concurrently used in this study e.g. domperidone, haloperidol, levofloxacin, and ondansetron. According to a study by García-Rodríguez D, loperamide, levofloxacin, metoclopramide, and ondansetron can cause QTc prolongation in COVID-19 patients [28]. We also found risk factors for QTc prolongation including electrolyte imbalances, bradycardia, comorbidities, and renal impairment, agreeing with other studies that found the relationship of these factors with QTc prolongation [13,14,18].

In patients with QT prolongation, the maximum QTc interval was 488 ms. Most of the patients 76.47%) were treated with the same treatment as when the treatment was initiated and the patients were corrected for electrolyte imbalance when occurred. This is in agreement with the European Society for Cardiology treatment guidelines which recommend reducing the dose of QTc prolonging drugs or changing the treatment to drugs with lower risks when QTc interval is more than 500 ms [29,30]. If the QTc interval is prolonged but is not more than 500 ms, the treatment can be continued with close monitoring for electrolytes [24]. In this study, QTc prolongation occurred within 3 days after the initiation of the drug treatment with the median onset of 6 days (range, 3–11 days; IQR, 4–7 days) and the frequency of ECGs was ECG every 4 (IQR, 2.50–5.00) (range, 1–9) days. This is in agreement with a retrospective study in COVID-19 patients (n = 201) who used chloroquine or hydroxychloroquine with or without azithromycin which also found the increase of QTc interval on the second day [30]. Other studies found that COVID-19 patients treated with azithromycin and hydroxychloroquine had QTc intervals longer than 500 ms in 2.9 ± 1.4 days [24], and in 3.6 ± 1.6 days after the treatment, especially in patients with acute kidney injury [2].

This study has several clinical applications. Our results, together with the result from other studies, suggest that COVID-19 patients treated with QTc prolonging medications should be monitored by ECGs within 2-4 days after the initiation of the treatment. Patients with electrolyte imbalances, bradycardia, cardiovascular diseases, diabetes mellitus, and furosemide usage should be monitor closely. Unnecessary QTc prolonging drugs should be discouraged in the patients. QTc prolonging medications for the treatment of COVID-19 can be used with careful monitoring. When QTc interval starts to increase but does not reach 500 ms, ECG monitoring every 1–2 days should be initiated. If the QTc interval is longer than 500 ms, changing the treatment to the drug without the incidence of QTc prolongation. Incidentally, this study has some limitations. Because of the small sample size, albeit using all patients during the study time frame, statistical analysis may be under power. In addition, the patients were not ECG monitored daily and after the treatment was finished so the onset, duration, and offset of the QTc prolongation; and QTc interval pattern after the cease of the QTc prolonging drug treatment and after the cure of COVID-19 was not clearly defined.

In conclusion, this retrospective chart review showed that QTc prolongation in COVID-19 patients was prevalent and mostly found among patients who used combined QTc prolonging medications. QTc prolongation was found more frequently in patients with electrolyte imbalances, bradycardia, cardiovascular diseases, and diabetes mellitus. Patients, especially those with risk factors, who used combined QTc prolonging medications should be closely monitored for QTc prolongation.

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