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Original Article

Evaluation of QTc-Interval Prolongation and Arrhythmogenic Indices and Associated Factors in Patients With COVID-19

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ABSTRACT

Background: Patients with a prolonged corrected QT (QTc) interval are at risk of arrhythmias, including Torsade de pointes (TdP). This interval could be affected by demographic characteristics, ischemia, and most importantly drugs. Furthermore, hospitalized patients tend to experience arrhythmias, accompanied by electrolyte abnormalities and the inflammatory status of diseases.

Methods: The present retrospective study recruited 135 patients with COVID-19. We observed the QTc interval on the third post-administration day and laboratory findings for possible risk factors for QTc-interval prolongation.

Results: Ischemic heart disease was markedly more common among patients with prolonged and severely prolonged QTc intervals. Laboratory findings showed a significantly higher neutrophil-to-lymphocyte ratio (NLR) in patients with prolonged or severely prolonged QTc intervals compared with those with normal QTc intervals and QTc intervals exceeding 500 milliseconds (P<0.001) on admission and the third day. Ribavirin caused the most elevation in the QTc interval after 3 days of hospitalization compared with other drugs. Forty percent of the patients who took ribavirin experienced a QTc interval exceeding 500 milliseconds, which was significant compared with other therapeutic regimens.

Conclusions: In addition to the well-known predisposing factors for the prolongation of QTc interval, we suggest focusing on the history of ischemic heart disease and inflammatory status (eg, by NLR) in patients with COVID-19 before making decisions to commence drugs that greatly affect QTc intervals. Further studies are required to shed light on the cardiac side effects of medications applied for COVID-19, particularly ribavirin. ***(Iranian Heart Journal 2022; 23(3): 77-87)***

KEYWORDS: COVID-19, Torsade de pointes, Arrhythmia, Electrocardiogram, Prolonged QTc

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In late December 2019, the catastrophic pandemic of Coronavirus (COVID-19) started in Wuhan, China, and rapidly spread globally. According to the World Health Organization (WHO), the novel Coronavirus (SARS-CoV-2) was responsible for more than 1.06 million deaths by October 9, 2020, worldwide. COVID-19 is still an unknown territory for physicians and healthcare systems. The clinical features constitute a spectrum from common cold-like symptoms to life-threatening complications such as acute respiratory distress syndrome (ARDS), multiple organ failure, metabolic acidosis,[5] and cardiac injuries (ie, myocarditis and acute coronary syndromes).[6] No effective treatment has been approved yet, and with the increasing rate of infected individuals, many clinicians have used different off-label medications with a wide range of complications. Early studies revealed that hydroxychloroquine, azithromycin, Kaletra (lopinavir/ritonavir), and ribavirin could be effective and viable therapy as they can reduce virus shedding and act as an antiviral agent.[7-9] Nevertheless, the challenge is that they are all known as a major reason for the prolongation of the corrected QT (QTc) interval.[10,11] QTc interval prolongation could indicate the prolongation of the refractory time caused by the prolonged ventricular repolarization period. This interval could be affected by the circadian rhythm, demographic features (eg, age and sex), electrolyte concentrations, ischemia, and most importantly drugs.[1] Hydroxychloroquine leads to a prolonged QTc interval by affecting sodium and calcium channels. [1] Studies have shown that in COVID-19 treatment, adding azithromycin to hydroxychloroquine can be associated with more frequent QTc prolongation in comparison with hydroxychloroquine alone,[12] perhaps due to drug interactions. However, there is a lack of information and testing on the effects of other drugs on the QTc interval during the COVID-19 pandemic. Patients with prolonged QTc intervals are rarely at risk of life-threatening arrhythmias, including Torsade de pointes (TdP). The risk of arrhythmias is only significant when the QTc interval reaches a level exceeding 500 milliseconds[13] or when hospitalized patients face complications. Furthermore, individuals tend to experience arrhythmias, accompanied by electrolyte abnormalities (ie, hypokalemia), stress, and fever, in the course of the disease progression.[2] A few studies on inflammatory diseases such as rheumatoid arthritis have proven that inflammatory mediators can also cause QTc- interval prolongation.[3,4]

In the present study, we aimed to determine possible risk factors for QTc prolongation in 135 patients with COVID-19 and evaluate their importance as prognostic factors.

METHODS

Patient Selection and Data Collection

The current retrospective, observational, multicenter study recruited 400 adult patients aged above 18 years admitted to the COVID-19 wards of Shohadaye Tajrish Hospital and Ayatollah Taleghani Hospital between February 20 and April 20, 2020. Patients were selected based on their clinical features (according to the CDC and WHO guidelines), typical chest computed tomography (CT) scan findings, and positive polymerase chain reaction (PCR) tests. We excluded patients who chronically used hydroxychloroquine, patients with incomplete first-day information, patients who were discharged early after admission, and patients with incomplete data on their hospital stay duration. We enrolled 135 individuals who had baseline and trends of laboratory tests and electrocardiograms (ECGs), as well as normal QTc intervals on admission and treatment for at least 1 day with hydroxychloroquine (400 mg twice a day) with or without azithromycin (500 mg once a day) or Kaletra (lopinavir-ritonavir) (400/100 mg twice a day) or Ribavirin (1200 mg twice a day).

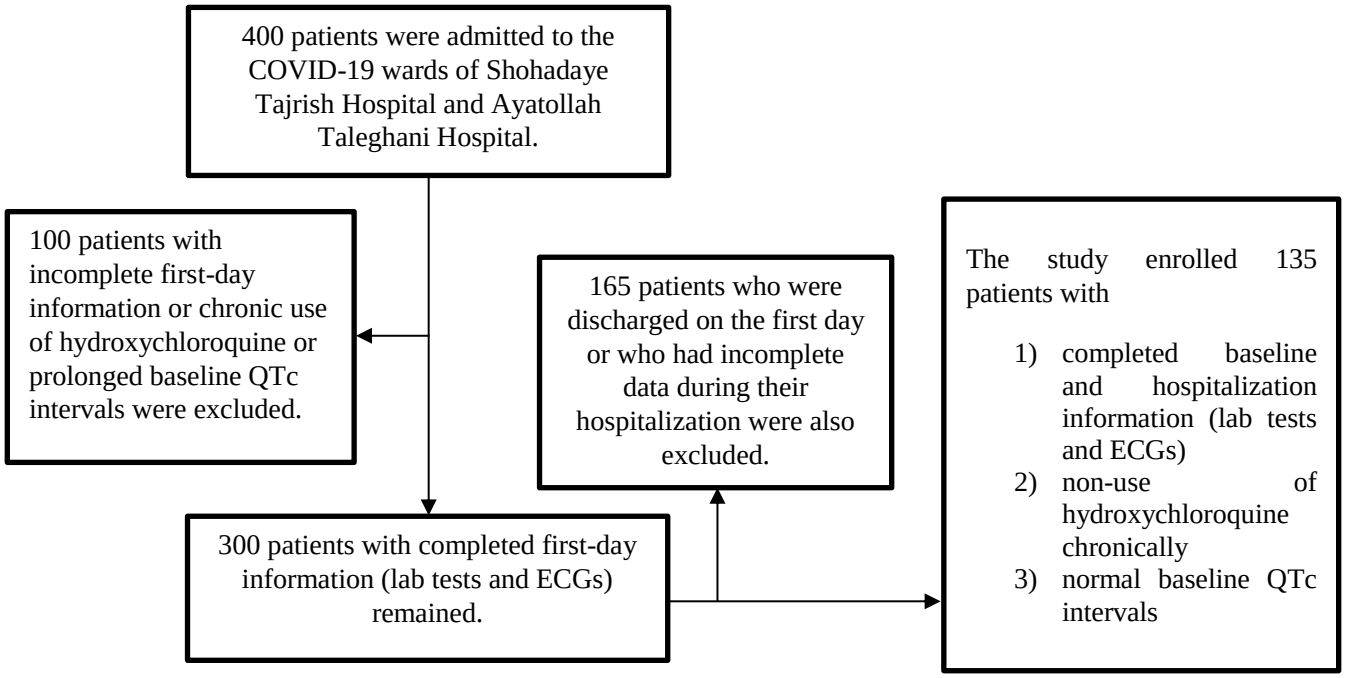

Figure 1: The diagram illustrates the patient selection flowchart.

We extracted information such as patient symptoms, past medical history, past drug history, physical findings, laboratory findings, and ECGs from the electronic medical record in both hospitals. ECGs were performed on admission and at least once after the administration of medications (on the third day of hospitalization). The ECGs were evaluated manually by 2 physicians trained and experienced in QT-interval measurements who were supervised by a senior cardiologist. Besides the QT interval, the QT dispersion in 12 leads was calculated. Lead II was selected for the measurement of the QT interval between the initiation of the Q wave and the steepest last limb of the T wave to its cross with the baseline. If there was difficulty reading and measuring the T wave on this lead, it was measured in leads I and V_6. The QT intervals and the QT dispersions were corrected using the Bazett formula. We observed the QTc interval on the third day of administration and defined a prolonged QTc interval as a QTc interval exceeding 440 milliseconds in men and a QTc interval exceeding 460 milliseconds in women and also a severe prolonged QTc as a QTc interval exceeding 500 milliseconds in both sexes, which is a risk factor of fatal cardiac arrhythmia. Laboratory tests were performed for all the patients on the day of admission, and they were measured with the same methods in both hospitals.

Statistical Analysis

Continuous variables were examined to determine the normality of the distribution using histograms, measures of skewness and kurtosis, and the Kolmogorov–Smirnov test. The normally distributed variables were described as the mean ± the standard deviation (SD), and the variables with skewed distributions were expressed as the median and the interquartile range (25%–75%). Categorical variables were summarized as frequencies (percentages). The independent samples *t* test was utilized

for the normally distributed continuous variables, and the Mann–Whitney *U* test was employed for the non-normally distributed variables. Comparisons of the categorical variables between the groups were conducted using the χ^2 test of independence. All the tests were 2-sided, and a *P* value of less than 0.05 was considered to indicate a statistically significant difference. All the statistical analyses were performed using the IBM SPSS, version 24.0 (IBM Corp, Armonk, NY, USA).

RESULTS

The study population was composed of 135 patients: 46 women (34.1%) and 89 men (65.9%). The average age of all the patients was 59.5 years (Table 1). The average age of the patients with prolonged and severe prolonged QTc intervals on the third day of hospitalization was 64.3 years (±14.19) and 69.91 years (±12.82), respectively, both significantly (*P*<0.001) higher than the average age in the group with normal QTc intervals (55.31±15.42 y). Patient history was taken at the time of admission. The important data that differed among the different QTc interval groups on the third day of admission was the past medical history of ischemic heart disease (IHD), which was markedly more common among the prolonged and severely prolonged QTc interval groups (*P*=0.057 and *P*=0.006, respectively). Of all the admission physical examinations and vital signs, the mean O_2 saturation was notably lower in both the prolonged QTc interval group (85.75%±10.53%) and the severely prolonged QTc interval group (83.14% ±12.26%) than in the normal QTc interval group (90.21%±5.59%) and the group with a QTc interval of less than 500 milliseconds (89.16%±7.21%) (*P*=0.001 and *P*=0.003, respectively) (Table 2).

Table 1: Baseline Demographic and laboratory data of all patients

	TOTAL PATIENTS N=135
Age mean (±SD)	59.50 (±15.47)
Sex N (%) female	46/135 (34.1%)
Systolic blood pressure mean (±SD)	119.64 (±15.20)
Diastolic blood pressure mean (±SD)	74.75 (±12.098)
Heart rate mean (±SD)	87.48 (±17.56)
Respiratory rate mean (±SD)	18.50 (±3.75)
T mean (±SD)	37.34 (±0.69)
Admission O_2 saturation mean (±SD)	88.18 (±8.47)
Death N (%)	44/135 (32.6%)
Intensive care unit N (%)	42/135 (31.1%)
PMH: IHD N (%)	36/119 (30.3%)
PMH: HTN (%)	30/119 (25.2%)
PMH: DM N (%)	30/119 (25.2%)
TISDALE SCORE >7	25/135 (18.5%)
7-10	106/135 (78.5%)
>11	4/135 (3%)

PMH, Past medical history; IHD, Ischemic heart disease; HTN, Hypertension; DM, Diabetes mellitus

Concerning the laboratory parameters measured for all the patients on admission, the neutrophil-to-lymphocyte ratio (NLR), the erythrocyte sedimentation rate (ESR), and the troponin level were markedly higher in the patients with prolonged and severely prolonged QTc intervals on the third day of admission than in the group with normal QTc intervals and the group with QTc intervals exceeding 500 milliseconds (Table 3). The mean white blood cell (WBC) count was significantly higher in the severely prolonged QTc interval group (*P*=0.041) (Table 3). The third-day laboratory findings showed a significantly higher NLR in the prolonged and severely prolonged groups than in the group with normal QTc intervals and the group with QTc intervals below 500 milliseconds (*P*≤0.001) (Table 3). On the third day of hospitalization, 54% of the patients with prolonged QTc intervals died as the disease progressed compared with 11.1% of the patients with normal QTc intervals (*P*<0.001). The death rate was

notably higher among the group with severely prolonged QTc intervals than in the group with QTc intervals of less than 50 milliseconds (*P*=0.000) (Table 2).

Of all the 63 patients who experienced prolonged QT intervals, 42 patients (66.7%) were in the moderate-risk group on admission according to the Tisdale score (score 7–10), which was statistically significant (*P*=0.005), in contrast with QT-interval prolongation among the low-risk group (score >7) and the high-risk group (score >11) (Table 2). The association between different therapeutic regimens and QTc interval changes on the third day of admission was recorded. The data showed that Kaletra and ribavirin made a significant impact on the QTc interval (*P*=0.011) compared with the other regimens (hydroxychloroquine and hydroxychloroquine + azithromycin). The mean QTc interval in the Kaletra group reached 443.96 milliseconds (±41.27), which caused a minimum change in the QTc interval on the third day of treatment. However, the ribavirin group reached 484.80 milliseconds (±61.36), which led to the most considerable change (Table 4). According to Table 5, 40% of the patients who took ribavirin experienced a QTc interval exceeding 500 milliseconds, which was significant compared with the other therapeutic regimes.

Table 2: Demographic data of the patients with different QTc intervals on the third day of hospitalization

	Prolonged QTc Interval (men >440 ms and Women > 460 ms) N=63	Normal QTc Interval (men >440 ms and Women > 460 ms) N=72	*P* value	Severely Prolonged QTc Interval (>500 ms) N=23	QTc Interval <500 ms N=112	*P* value
Age mean (±SD)	64.30 (±14.19)	55.31 (±15.42)	0.001	69.91(±12.82)	57.37 (±15.15)	0.000
N (%) Female	23/63 (36.5%)	23/72 (31.9%)	0.577	10/23 (43.5%)	36/112 (32.1%)	0.277
Systolic blood pressure mean (±SD)	121.81 (±27.00)	117.69 (±16.26)	0.283	119.78 (±27.24)	119.61 (±20.92)	0.973
Diastolic blood pressure mean (±SD)	74.69 (±15.01)	74.81 (±8.71)	0.954	73.18 (±12.57)	75.07 (±12.02)	0.506
Heart rate mean (±SD)	89.27 (±21.16)	85.89 (±13.58)	0.270	90.50 (±25.58)	86.87 (±15.57)	0.379
Respiratory rate mean (±SD)	18.68 (±4.39)	18.33 (±3.09)	0.618	18.10 (±3.54)	18.58 (±3.80)	0.592
T mean (±SD)	37.24 (±0.68)	37.46(±0.70)	0.542	37.00 (±0.53)	37.40 (±0.71)	0.132
Admission O_2 saturation mean (±SD)	85.75 (±10.53)	90.21 (±5.59)	0.001	83.14 (±12.26)	89.16 (±7.21)	0.003
Death N (%)	34/63 (54%)	8/72 (11.1%)	0.000	18/23 (78.3%)	24/112(21.4%)	0.000
Intensive care unit N (%)	33/63 (52.4%)	11/72 (15.3%)	0.000	18/23 (78.3%)	26/112 (23%)	0.000
PMH: IHD N (%)	22/57 (38.6%)	14/62 (22.6%)	0.057	12/22 (54.5%)	24/97 (24.7%)	0.006
PMH: HTN (%)	16/57 (28.1%)	14/62 (22.6%)	0.491	7/22 (31.8%)	23/97 (23.7%)	0.429
PMH:DM N (%)	15/57 (26.3%)	15/62 (24.2%)	0.790	8/22 (36.4%)	22/97 (22.7%)	0.182
Tisdale score >7	19/63 (30.2%)	6/72 (8.35%)	0.005	8/23 (34.8%)	17/112 (15.2%)	0.073
7-10	42/63 (66.7%)	64/73 (88.9%)		14/23 (60.9%)	92/112 (82.1%)	
>11	2/63 (3.2%)	2/73 (2.8%)		1/23 (4.3%)	3/112 (2.7%)	

PMH, Past medical history; IHD, Ischemic heart disease; HTN, Hypertension; DM, Diabetes mellitus

Table 3: Biomarker data of the patients with different QTc intervals on the third day of hospitalization

	Total Patients N=135	Prolonged QTc interval (men>440 ms and women > 460 ms) N=63	Normal QTc Interval (men <440 ms and women <460 ms) N=72	*P* value	Severely Prolonged QTc Interval (>500 ms) N=23	QTc Interval <500 ms N=112	*P* value
ADMISSION RBC COUNT MEAN (±SD)	4.19 (±0.91)	4.088 (±1.01)	4.28 (±0.82)	0.151	4.01 (±1.15)	4.23 (±0.85)	0.315
ADMISSION HCT % MEAN (±SD)	35.82 (±7.43)	34.85 (±8.07)	36.64 (±6.78)	0.255	34.95 (±9.54)	36.00 (±6.95)	0.548
ADMISSION HB G/DL MEAN (±SD)	11.77 (±2.52)	11.42 (±2.64)	12.08 (±2.40)	0.337	11.48 (±3.06)	11.84 (±2.41)	0.546
ADMISSION WBC COUNT MEAN (±SD)	8.50 (±6.68)	8.13 (±5.38)	8.82 (±7.64)	0.525	11.15 (±6.24)	7.96 (±6.67)	0.041
ADMISSION NLR MEAN (±SD)	6.35 (±5.15)	7.79 (±6.08)	5.10 (±3.79)	0.003	10.14 (±5.74)	5.53 (±4.65)	0.000
ADMISSION PLT COUNT MEAN (±SD)	195.24 (±102.4)	187.76 (±99.67)	201.54 (±105.02)	0.756	181.18 (±86.14)	198.13 (±105.6)	0.482
ADMISSION BUN MG/DL MEAN (±SD)	25.21 (±20.34)	31.31 (±24.55)	19.74 (13.66)	0.001	42.27 (±24.11)	21.63 (17.59)	0.002
ADMISSION CR MG/DL MEAN (±SD)	2.01 (±6.48)	2.94 (±9.33)	1.17 (±0.400)	0.126	1.77 (±0.86)	2.06 (±7.12)	0.845
ADMISSION NA MEQ/L MEAN (±SD)	138.18 (±4.48)	138.37 (±3.19)	138.01 (±3.19)	0.659	138.92 (±8.21)	138.02 (±3.23)	0.395
ADMISSION K MEQ/L MEAN (±SD)	4.21 (±0.50)	4.21 (±0.51)	4.20 (±0.50)	0.911	4.33 (±0.57)	4.20 (±0.50)	0.676
ADMISSION CPK IU/L MEAN (±SD)	248.96 (±386.4)	256.133 (±308.62)	242.25 (±450.63)	0.644	284.15 (±374.16)	239.93 (±391.52)	0.659
ADMISSION CK-MB IU/L MEAN (±SD)	31.21 (±40.94)	27.65 (±14.71)	34.54 (±44.24)	0.431	25.78 (±12.42)	32.68 (±45.68)	0.518
ADMISSION TROPONIN NG/ML MEAN (±SD)	0.24 (±0.70)	0.44 (±0.99)	0.06 (±0.07)	0.013	0.51 (±1.14)	0.16 (±0.48)	0.051
ADMISSION ESR MM/H MEAN (±SD)	40.20 (±26.20)	44.66 (±26.22)	35.50 (±25.57)	0.058	52.14 (±28.09)	37.59 (±25.17)	0.021
ADMISSION CRP MG/L MEAN (±SD)	53.52 (±49.56)	59.85 (±52.68)	47.19 (±45.81)	0.116	68.32 (±47.11)	50.13 (±49.72)	0.121
ADMISSION D-DIMER MG/L MEAN (±SD)	1412.52(±1950.4)	1924.00 (±2326.8)	608.82 (±722.43)	0.170	2623.00 (±3808.43)	1066.69 (±1023.81)	0.166
3RD DAY RBC COUNT MEAN (±SD)	4.00 (±0.88)	4.0417(±0.97)	3.96(±0.77)	0.696	3.96 (±0.83)	4.01(±0.89)	0.826
3RD DAY HCT % MEAN (±SD)	33.95 (±6.75)	34.41(±7.24)	33.38 (±6.16)	0492	34.75 (±6.71)	33.74(±6.79)	0.587
3RD DAY HB G/DL MEAN (±SD)	11.34 (±2.19)	11.35(±2.26)	11.33 (±2.13)	0.967	11.42(±2.26)	11.32 (±2.19)	0.870
3RD DAY WBC COUNT MEAN (±SD)	8.34 (±5.50)	9.21(±5.58)	7.49(±5.31)	0.155	11.44 (±5.88)	7.67 (±5.17)	0.011
3RD DAY NLR MEAN (±SD)	6.35 (±5.15)	7.88(±5.46)	3.86(±2.38)	0.000	11.36 (±6.07)	4.69 (±3.20)	0.000

3RD DAY PLT COUNT MEAN (±SD)	233.24 (±126.1)	220.10(±117.37)	226.94(±137.21)	0.805	194.17 (±122.195)	230.51 (±126)	0.291
3RD DAY BUN MG/DL MEAN (±SD)	26.17 (±20.93)	32.38 (±24.57)	18.71(±12.07)	0.004	40.81 (±18.97)	22.32(19.81)	0.001
3RD DAY CR MG/DL MEAN (±SD)	1.45 (±1.15)	1.73 (±1.46)	1.11 (±0.37)	0.017	1.80 (0.81)	1.36 (±1.21)	0.179
3RD DAY NA MEQ/L MEAN (±SD)	139.88 (±4.19)	140.21 (±4.36)	139.50 (±3.65)	0.457	141.22 (±6.36)	139.50 (±3.33)	0.136
3RD DAY K MEQ/L MEAN (±SD)	6.09 (±4.79)	3.98 (±0.51)	4.05 (±0.50)	0.575	3.89 (±0.44)	4.04 (±0.52)	0.284

Table 4: Sequentially measured QT intervals between the different therapeutic regimens

	All Patients N (%); mean (±SD)	HYDROXY N (%); mean (±SD)	HYDROXY+AZITHRO N (%); mean (±SD)	KALETRA N (%); mean (±SD)	RIBAVIRIN N (%); mean(±SD)	*P* value
QTC baseline	420.27 (±40.99)	428.18 (±39.46)	414.83 (±44.33)	416.09 (±36.38)	439.50 (±49.39)	0.106
QTC 3rd day	452.94 (±49.15)	451.91 (±55.84)	454.59 (±49.48)	443.96 (±41.27)	484.80 (±61.36)	0.011
QT 3rd-day QTC baseline	32.67 (±39.38)	23.73 (±40.82)	39.76 (±42.93)	27.87 (±36.94)	45.30 (±40.58)	0.197
QT dispersion baseline	49.53 (±35.00)	64.82 (±41.75)	47.31 (±37.46)	50.21 (±33.06)	41.80 (±34.47)	0.362
QT dispersion on the 3rd day	46.21 (±29.59)	55.64 (±31.82)	39.59 (±37.31)	46.12 (±20.84)	51.00 (±41.91)	0.381

Table 5: Percentage of QTc intervals >500 ms among the different therapeutic regimens on the third day of hospitalization

	QTC>500 ms	QTC<500 ms	*P* value
HYDROXYCHLOROQUINE	1/11 (9.1%)	10/11 (90.9%)	0.014
HYDROXYCHLOROQUINE+AZITHROMYCINE	6/28 (21.4%)	22/28 (78.6%)	
KALETRA	8/76 (10.5%)	68/76 (89.5%)	
RIBAVIRIN	8/20 (40%)	12/20 (60%)	

DISCUSSION

The study revealed the following 3 main findings:

1. Ribavirin can cause QT-interval prolongation.
2. The NLR may predict QT-interval prolongation in the course of the COVID-19 disease.
3. A past medical history of IHD can be a risk factor for QT prolongation.

It was found that the mean QT interval in patients with the ribavirin regimen was higher than that with other regimens, which based on our knowledge, there was no evidence from other studies proving that ribavirin can affect the QT interval.[14] On the other hand, although Kaletra is known as a drug that can prolong the QTc interval,[14] our analysis showed that this regimen had a minor effect on the mean QTc interval, which did not cause prolongation. The results regarding hydroxychloroquine in this study were not unexpected and are compatible with other studies insofar as it caused QTc-interval prolongation.[15,20,12] A previous study reported TdP arrhythmia with hydroxychloroquine in patients with COVID-19.[16] Nonetheless, in our study, the mean QTc interval after taking this medication was not at the arrhythmogenic range, with only 1% of the patients experiencing a QTc interval exceeding 500 milliseconds, without TdP arrhythmia or death (Table 5). The combination of hydroxychloroquine and azithromycin

caused a higher mean QTc interval than hydroxychloroquine alone, which is compatible with previous studies.[14,15]

Ribavirin is an RNA-polymerase inhibitor recommended for COVID-19 treatment according to Chinese guidelines.[17] Despite the lack of information on the QTc-prolongation mechanism of ribavirin, based on published results by the FDA, a cardiac arrhythmia rate of less than 1% was reported in patients treated with a combination of ribavirin and peginterferon α-2a.[18] Based on previous studies,[19] another drug that could suppress COVID-19 replication is ritonavir/lopinavir (Kaletra),[20] which leads to QTc prolongation by inhibiting the hERG current. The most frequently used drug during the COVID-19 pandemic is hydroxychloroquine, which can inhibit the virus-cell fusion and diminish viral copy.[20-22] Several clinical trial experiments have suggested that azithromycin can improve the effects of hydroxychloroquine on this disease.[14] Considering the risk of the QT prolongation of hydroxychloroquine, as a major concern during this pandemic, the mechanism of this complication (inhibition of the funny current channels [I_f], delayed rectifier potassium currents [I_{Kr}], and L-type calcium ion currents [I_{CaL}]) is fully understood in previous studies.[23] Therefore, the combination of this drug with azithromycin increases the QT-prolongation risk due to drug interactions.[12]

In the current study, laboratory findings, in addition to therapeutic regimens, were observed in order to investigate the relationship between the NLR and the risk of QT prolongation. The NLR is an inflammatory factor suggested as an independent prognostic factor in many diseases, especially COVID-19.[24,25] To our knowledge, this is the first study to reveal a relationship between the NLR and the QTc interval in patients with COVID-19. However, several experimental studies (especially on rheumatic arthritis) have provided evidence that inflammatory factors such as interleukin-1 (IL-1), tumor necrosis factor α (TNFα), and IL-6 can cause prolongation in the ventricular action potential time due to inflammatory channelopathies (rectified potassium current decrease by TNFα and L-type calcium current increase by IL-1 and IL-6).[2,3] Inflammatory factors such as C-reactive protein (CRP), IL-1, IL2, IL-6, and TNFα are not cost-effective for health organizations, hence their unavailability in many centers. The NLR measurement comes from a complete blood count test (CBC) with differentials, which is a widely available and inexpensive test that can also represent the inflammation state of patients and be used as a predictor of the severity of the COVID-19 disease.[26] Among other laboratory data, hypokalemia (especially K<3.5 mmol/lit) is a well-known factor that can cause QT prolongation. Low levels of potassium in the extracellular space paradoxically reduce IKr through enhanced inactivation or by the exaggerated competitive blocking of sodium, leading to QTc prolongation.[27] The average potassium level in the current study was 4.21 (±0.50) on admission day. The level decreased to 3.98 (±0.51) on the third day in the group with a prolonged QTc interval, which was not at a risk level. Consequently, it was not considered an influential factor in this study.

There are well-known risk factors for acquired QTc-interval prolongation such as being female, being old (>68 y/o), and having an electrolyte imbalance, which must be considered along with the reason for admission. These factors must be calculated in the Tisdale score before administering drugs for QT-interval prolongation.[28] James E. Tisdale and his team developed the Tisdale score in 2013 for evaluating the risk of drug-induced QTc-interval prolongation and TdP in

hospitalized patients. Based on this score, the patients are categorized into 3 levels: 1) low-risk (score <7), moderate-risk (score: 7-10), and high-risk (score >11) groups.[28] The majority of our patients were in the moderate-risk group. Although it was expected that the majority of the QTc-interval prolongation cases would belong to the moderate- and high-risk groups, as shown in Table 2, 66.7% of the patients with QTc prolongation were from the moderate-risk group, and 30.2% belonged to the low-risk group. The high percentage of low-risk patients exhibiting QTc prolongation is notable and is believed to be due to the inflammatory mechanisms of the COVID-19 disease. In addition to the aforementioned risk factors, our data revealed the importance of a past medical history of IHD as a risk factor for QTc prolongation. IHD is a significant cause of left ventricular systolic and diastolic function impairment.[29] According to previous studies, left ventricular diastolic dysfunction can lead to QTc prolongation.[30] Therefore, in patients with COVID-19, we suggest checking for a past medical history of IHD and the inflammatory state (especially with the NLR), in addition to other well-known risk factors, before the administration of drugs that affect the QT interval. Our data analysis indicated that more experiments on the cardiac effects of ribavirin might be necessary.

The present investigation has some limitations. Firstly, ECG was taken in some patients in the COVID-19 ward and was not a routine procedure; therefore, the data may have a bias. Secondly, in this cohort, we did not have COVID-19 patients without these therapeutic regimens as a control group. Thirdly, the patients received other drugs during hospitalization, and these drugs were not administered as the only drug that they received. Fourthly, we did not have the echocardiography data of the study population to prove systolic or diastolic dysfunction due to IHD. Many parameters may be confounded in this small cohort study because of the complexity of this disease.

Recommendations

The current study was conducted during the first peak of the COVID-19 pandemic and with a limited number of patients. Considering the importance of the outcomes of the current study, we highly recommend further experiments with larger samples and under different scenarios such as an equal ratio of males and females.

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