Serum Ionized Calcium Levels May Be More Closely Related To The Admission Qtc Interval Than Total Calcium Levels In Patients Hospitalized With Covid-19

Murat Çap[1*], Ferhat Işik[1], Önder Bilge[1], Bernas Altintaş[1], Flora Ozkalayci[2], Abdurrahman Akyüz[1], Burhan Aslan[1], Ümit Inci[1], Rojhat Altindag[1], Ilyas Kaya[1], Kemal Güneş[3], Ibrahim Halil Tanboğa[2]

[1]Department of Cardiology, University of Health Sciences Diyarbakır Gazi Yaşargil Education and Research Hospital, Diyarbakır, Turkey
[2]Department of Cardiology, Hisar Intercontinental Hospital, İstanbul, Turkey
[3]Department of Biochemistry, University of Health Sciences Diyarbakır Gazi Yaşargil Education and Research Hospital, Diyarbakır, Turkey

ABSTRACT

Hypocalcemia prolongs the QTc interval. Total calcium (TCa) measurement can be misleading in cases where the concentration of albumin is abnormal. We aimed to investigate which calcium level—ionized calcium (iCa) or TCa—may be more closely related to the QTc interval in COVID-19 patients in whom hypocalcemia and hypoalbuminemia are observed frequently.

Adult patients hospitalized for COVID-19 were included in this study. ICa levels were obtained from the venous blood gas sample examined during the emergency department admission, and the TCa levels were obtained from the biochemistry results on admission. The pH-adjusted iCa (Corrected-iCa) and albumin-adjusted TCa (corrected-TCa) were calculated. The QT interval was measured from the admission ECG and corrected for heart rate using the Bazett formula.

Hundred and thirty-two patients were included in the study. The mean age was 50±19 years, and 62 (47%) patients were female. Median iCa level was 1,13 mmol/L (1,08-1,18 interquartile range (IQR)), median TCa level was 2.13 mmol/L (2.02-2.22 IQR). 76 patients (57%) had hypocalcemia (iCa<1,16 mmol/L). The median QTc interval was 431 ms (414-450 IQR). In the multivariable linear regression analysis, a significant relationship was observed between the QTc interval and iCa and corrected-iCa levels (β=-2.22, standard error (SE) =27.839, p=0.028, β=-2.16, SE=29.407, p=0.033), but no significant relationship was observed between TCa and corrected-TCa levels (β=-1.02, SE=3.959, p=0.312, β=-0.44, SE=4.635, p=0,650).

A significant relationship was observed between iCa levels and the QTc interval, which was longer in patients with hypocalcemia, but there was no significant relationship observed with TCa levels.

Keywords: Hypocalcemia; COVID-19; QTc interval; Calcium levels

Introduction

Coronavirus disease 2019 (COVID-19), which was declared a pandemic by the World Health Organization in March 2020, continues to threaten human health globally. (1,2) Although the primary target organ is the lung; pathological changes are observed in many other organs and tissues. Electrolyte abnormalities such as hypocalcemia, hypokalemia, and hyponatremia are among the pathological conditions observed in patients with COVID-19. (3,4) Studies on patients with COVID-19 reported a high frequency of hypocalcemia with both low ionized calcium (iCa) and total calcium (TCa) levels in the emergency department (ED) and during hospitalisation. (5,6,7,8) Although the mechanism of hypocalcemia is not well known, it may be due to vitamin D deficiency, insufficient intestinal absorption, effects of cytokines on parathyroid hormone, low albumin levels. (5,8) Among these electrolyte abnormalities, hypocalcemia is

*Corresponding Author: Murat Çap, Department of Cardiology, University of Health Sciences Diyarbakır Gazi Yaşargil Education and Research Hospital, Diyarbakır, Turkey

E-Mail: murat00418@hotmail.com, phone: +90 (412) 258 00 60, fax: +90 (412) 258 00 50

ORCID ID: Murat Çap: 0000-0003-1164-2124, Ferhat Işik: 0000-0002-1438-3327, Önder Bilge: 0000-0001-8214-972X, Bernas Altintaş: 0000-0003-1662-3061, Flora Ozkalayci: 0000-0003-2816-0199, Abdurrahman Akyüz: 0000-0003-2491-6593, Burhan Aslan: 0000-0002-8994-7414, Ümit Inci: 0000-0002-7412-1222, Rojhat Altindag: 0000-0002-2479-9318, Ilyas Kaya: 0000-0003-1998-6722, Kemal Güneş: 0000-0001-5104-5901, Ibrahim Halil Tanboğa: 0000-0003-4546-9227
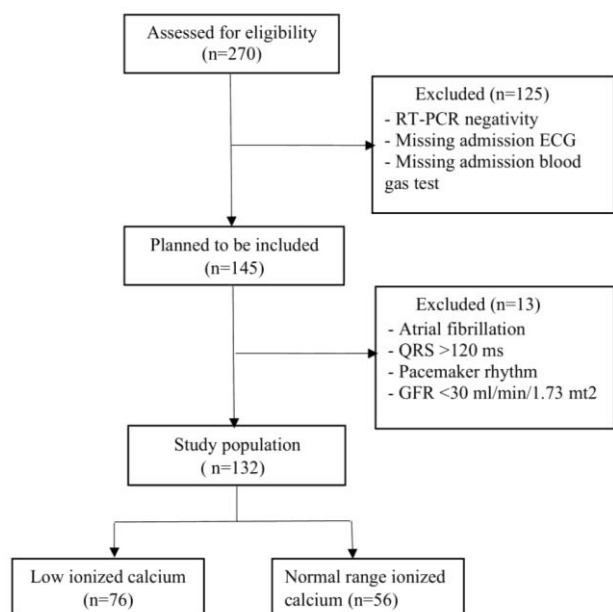
Fig. 1. Flow-Chart of Patient Selection

associated with disease severity. (5,6,7,8)

Previous studies have demonstrated that hypocalcemia prolongs the QT interval. (9,10) In a large-scale study conducted in the general population, QT interval was found to be inversely associated with total and ionised calcium. (11) In patients with COVID-19, prolongation of the QT interval and arrhythmic events may occur due to either primary cardiac injury or electrolyte abnormalities such as hypocalcemia. Forty percent of calcium is bound to proteins, especially albumin. Albumin levels can decrease significantly in patients with COVID-19. (12) Due to protein abnormalities such as hypoalbuminemia, a decrease in TCa levels can be observed in COVID-19 patients. Corrected calcium (corrected-TCa) can be calculated by adjusting albumin levels. Studies have shown that in critically ill patients, corrected-TCa is not more reliable in predicting the accuracy of calcium levels from total calcium; however, it may be more appropriate to evaluate hypocalcemia by iCa levels in these patient groups. (13,14) Considering the effect of hypocalcemia on QTc interval, it is unclear which form of calcium level is more physiologically related to the QTc interval in patients with COVID-19. It is also unclear which form of calcium level will be considered for replacement in hypocalcemic patients with long QTc. We aimed to investigate which form of calcium (iCa or TCa) may be more closely related to the QTc interval in COVID-19 patients in whom hypocalcemia and hypoalbuminemia can be observed frequently.

Materials and Methods

Adult patients hospitalized for COVID-19 at the our hospital between 15 April and 15 May 2020 were recruited for this single-center, retrospective observational study. Patients with negative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) results, atrial fibrillation, pacemaker rhythm, no electrocardiogram (ECG) recording, and without iCa and TCa levels were excluded from the study. Patients with a QRS> 120 ms were excluded because the widening of the QRS complex caused QT interval prolongation without significant changes in the repolarisation time. (15) Patients with a GFR <30 ml / min / 1.73 mt2 were excluded as they had more than one electrolyte abnormality including hypocalcemia, anticoagulant therapy used in the renal replacement procedure caused hypocalcemia, and long QTc could be observed. A total of 132 patients met the inclusion criteria and were included in the study. The patients were divided into two groups: those with low iCa and those with normal range iCa. The flowchart of patient selection is shown in Figure 1.

The demographic, clinical, and laboratory parameters of the patients during their hospitalization were obtained from the hospital's electronic medical records.ICa levels were obtained from venous blood gas tests performed in the first evaluation in the ED and were measured by ion-selective electrode potentiometry (ABL 800, Radiometer, Copenhagen, Denmark) on whole blood. The collected specimens were venous blood obtained from peripheral vessels. To avoid any dilutional or chemical interference, only lyophilised heparin syringes were used for sample collection (Ayset-72 IU lyophilised lithium heparin syringe with hypodermic needle-2 ml). Specimens were transported immediately to the emergency laboratory by hand at room temperature. As the measurement laboratory was close to the emergency room, the transport time between sampling and analysis was 15 min maximum. Until the blood gas sample is analysed, pH changes may occur due to CO_2 loss, which may cause changes in iCa levels. Therefore, pH-adjusted iCa (corrected-iCa) levels were calculated according to standardised pH 7.4 levels. The corrected-iCa level was calculated using the following equation: iCa corrected= iCa-actual [1-0.53(7.4-pH actual)]. TCa levels were obtained from the biochemistry results on admission and were measured using the Arsenazo-III method photometrically (ARCHITECT c8000, ABOTT,
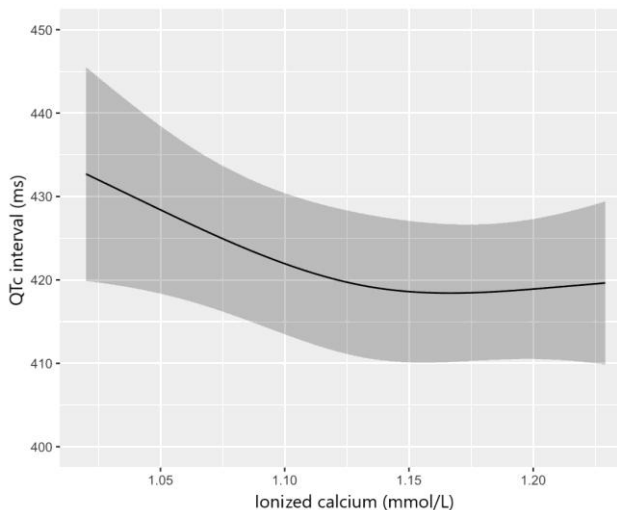
Fig. 2a. Partial Effect Plot Of Ionized Calcium For Predict Qtc Interval In Model 1

Figure 2b. Partial Effect Plot Of Total Calcium For Predict Qtc Interval In Model 3

USA) on serum obtained after centrifugation (10 min at 3000xg × g at room temperature) of whole blood collected in plastic tubes with gel separator and clot activator (SST II Advance, Becton Dickinson). Albumin levels were lower in COVID-19 patients. (12) Therefore, albumin-corrected TCa levels were calculated. The corrected-TCa level was calculated using the following equation: corrected calcium (mmol/L) = total calcium (mmol/L) + 0.02 × (40 - albumin [g/L]) The TCa reference range was defined as 2.15-2.56 mmol/L and the iCa reference range was defined as 1.16-1.32 mmol / L. (16) Hypocalcemia was characterized as an iCa concentration of less than 1.16 mmol/L.

Myocardial injury was defined as the presence of at least one cardiac troponin value above the 99th percentile upper reference limit. The following criteria were used to characterize the systemic inflammatory response syndrome (SIRS): Tachycardia (heart rate >90 beats/min), hypothermia or fever (temperature <36 °C or >38 °C), and leukopenia or leukocytosis (white blood cells >12.000/mm3 or < 4.000/mm3). SIRS was diagnosed when two or more of these four conditions were met. A glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 mt2 is considered chronic kidney disease (CKD).

QTc Interval Measurement: During ED admission, standard 12-lead electrocardiogram (ECG) images were obtained at a paper speed of 25 mm/second and a calibration of 10 mm/mV. Two experienced cardiologists manually measured the QT interval after the images were transferred to a computer via a scanner. In the circumstance that lead II was unavailable, lead V5 was used. One of the remaining leads was chosen after both
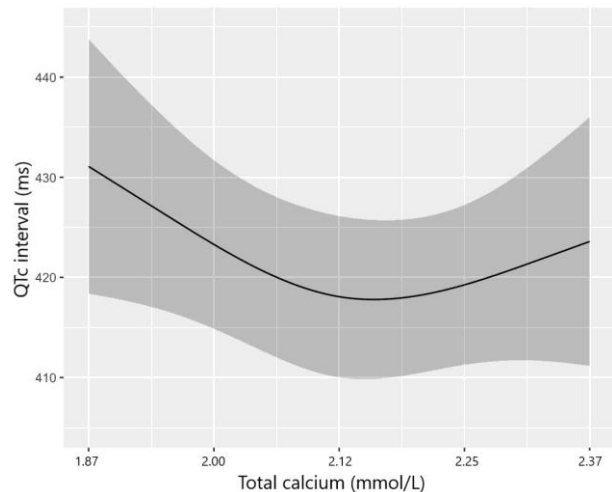
leads II and V5 were considered unsuitable. The QT interval was calculated by averaging 3 to 5 beats from the beginning of the QRS complex to T-wave termination. The end of the T-wave was described as the nadir between the T- and U-waves in cases where the T-wave was interrupted by a U-wave. QT intervals were corrected for heart rate using the Bazett formula (QTc = QT / (R-R) 1/2). Prolonged QTc was described as a QTc interval of >450 ms in men and >470 ms in women. (17)

This research was approved by the local institutional ethics committee. The research protocol conformed to the Declaration of Helsinki.

Statistics Analysis: R software version 3.2.2 was used for statistical analysis (R Project, Austria Vienna). Shapiro-Wilk test and histogram were used to determine the distribution of continuous variables, and if continuous variables showed normal distribution, they were given as mean and standard deviation, when not normally distributed, they were given as median and interquartile range 25-75% (IQR).Categorical variables are expressed as percentages. Chi-square test was used to compare categorical variables between groups. Continuous variables were compared by Mann Whitney U tests or Student's t test according to the distribution of data. Multivariable linear regression analysis was used to evaluate the relationship between the QTc interval and candidate predictors (age, sex, potassium levels, calcium level, SIRS, coronary artery disease, myocardial injury, beta-blocker use, chronic renal disease, diuretic use). A basal model was constructed without adding calcium. Then, each type of calcium level (iCa, corrected-iCa, TCa, and corrected-TCa) was sequentially added to the basal

Table 1. Demographic characteristics, clinical, laboratory, and electrocardiographic findings of the study population

	Total (n=132)	Low iCa (n=76)	Normal range iCa (n=56)	P value
Age(year)	50±19	56±17	40±18	<0.001
Gender(female)	62(47%)	34(44%)	28(50%)	0.549
Hypertension	27(20%)	20(26%)	7(14%)	0.084
Diabetes mellitus	22(17%)	16(21%)	6(10%)	0.181
Smoking	35(26.5%)	27(35%)	17(30%)	0.663
Congestive heart failure	2(2%)	2(3%)	0(0%)	0.508
Coronary artery disease	9(7%)	8(10%)	1(2%)	0.078
Chronic obstructive pulmonary diease	9(7%)	6(8%)	3(5%)	0.733
Chronic renal disease	12(9%)	9(12%)	3(5%)	0.330
Myocardial injury	9(7%)	7(6%)	2(2%)	0.184
≥2 SIRS criteria	40(30%)	29(38%)	11(20%)	0.032
Beta blocker use	9(7%)	7(9%)	2(3%)	0.301
Diuretic use	12(9%)	9(12%)	3(5%)	0.330
Radiographic finding of pneumonia	123(93%)	74 (97%)	49(87%)	0.021
İntensive care unit admission	24(18%)	20(26%)	4(7%)	0.009
Lenght of stay hospital (day)	7(6-9)	8(6-10)	6(6-9)	0.184
Temperature (°C)	37.3(36.8-3.78)	37(36.8-38)	36.7(37-37.5)	0.004
Systolic blood pressure (mmHg)	110(100-120)	110(105-121)	110(100-120)	0.372
Diastolic blood pressure (mmHg)	70(65-75)	70(67-75)	70(65-75)	0.788
White blood cell (103/uL)	6.31(4.73-8.03)	6.15(4.58-7.42)	6.57(5.27-8.48)	0.047
Neutrophil (103/uL)	4.31(2.86-5.63)	4.20(2.9-5.51)	4.51(2.86-6.20)	0.546
Lymphosit (103/uL)	1,37(0.96-1.97)	1.20(0.92-1.67)	1.66(1.30-2.29)	<0.001
Hemoglobin g/dL	13.9(12.8-14.8)	13.8(13-14.7)	14(12.8-14.9)	0.714
Plathelet(103/uL)	203(170-252)	181(151-216)	239(197-271)	<0.001
C-reactif protein (mg/L)	28(2-74)	41 (23-80)	2.2 (2-38)	<0.001
D-dimer (ng/mL)	185(120-316)	235(158-349)	152(82-246)	0.001
Ferritin (µg/L)	232(79-459)	306(151-616)	129(50-211)	<0.001
Lactic dehydrogenase (IU/L)	260(202-331)	292(246-267)	223(184-258)	<0.001
Procalsitonin (ng/mL)	0.07(0.04-016)	0.09(0.05-0.21)	0.05(0.03-0.11)	0.005
Creatinine (mg/dl)	0.79(0.69-0.97)	0.81(0.72-1.04)	077(0.67-0.87)	0.015
Potassium (mmol/L)	3.98(3.72-4.28)	3.95(3.77-4.26)	3.99(3.64-4.32)	0.877
Albumin (g/L)	39(36-43)	38(36-41)	42(38-46)	<0.001
Total calcium (mg/dL)	2.13(2.02-2.22)	2.05(2.00-2.12)	2.22(2.17-2.29)	
Corrected calcium (mg/dL)	2.14(2.08-2.20)	2.11(2.04-2.16)	2.19(2.14-2.25)	
Ionized calcium (mmol/L)	1.13(1.08-1.18)	1.09(1.06-1.12)	1.19(1.17-1.21)	
Corrected Ionised calcium(mmol/L)	1.12(1.08-1.16)	1.09(1.05-1.11)	1.17(1.14-1.19)	
pH	7.38(7.36-7.41)	7.39(7.37-7.41)	7.36(7.34-7.39)	<0.001
pCO2 (mmHg)	41(37-47)	41(36-46)	42(38-48)	0.057
Heart rate (beat/min)	83(74-91)	91(81-100)	84(75-98)	0.111

QRS duration (ms)	92(84-100)	94(86-104)	90(80-98)	0.039
QT interval (ms)	355(334-375)	352(338-382)	356(328-370)	0.287
QTc interval (ms)	431(414-450)	439(423-456)	423(407-441)	<0.001
Number of patients with Prolonged QTc	21(16%)	2(2%)	19(14%)	0.002

Continuous variables are presented given as mean±SD or median (interquartile range) and categorical variables were expressed as number (%). SIRS, Systemic Inflammatory Response Syndrome; iCa, ionized calcium

Table 2. Multivariate linear regression analysis between QTc (ms) interval and candidate predictors without adding calcium (Basal model)

Age(year)	2.59	0.123	0.010
Gender(female)	2.13	4.068	0.035
Chronic Renal Disease	-1.71	8.314	0.090
Myocardial Injury	1.34	7.803	0.181
B blocker use	-0.89	9.331	0.376
SIRS	2.86	4.443	0.005
Potassium (mmol/L)	-1.83	4.866	0.069
Coronary artery disease	2.68	9.547	0.008
Diuretic use	0.82	8.165	0.411

SIRS, Systemic inflammatory response syndrome

model, and four different models were constructed. Variables with very low frequencies were not included in the model. Continuous variables were included into the model using restricted cubic spline transformation. The models were compared using the assessment of fit (likelihood ratio chi-square), quality (Akaike and Bayesian information criteria, AIC and BIC respectively), adjusted R^2, and partial R^2. In all statistical analyses, a two tailed P value of <0.05, was considered statistically significant.

Results

Hundred and thirty-two COVID-19 patients whose diagnosis was confirmed by RT-PCR were included in our study. The mean age was 50±19 years, and 62 (47 %) patients were female. The median iCa level was 1,13 mmol/L (1.08-1.18 IQR) and the median TCa was 2.13 (2.02-2.22 IQR) mmol/L. Seventy-six patients (57%) had hypocalcemia (iCa<1.16mmol/L). The patients were divided into two groups: those with hypocalcemia (Group 1, n=76) and those without hypocalcemia (Group 2, n=56). In the hypocalcemia group, C-reactive protein (CRP), procalcitonin, ferritin, lactic dehydrogenase (LDH), and D-dimer levels were higher, while lymphocyte and albumin levels were lower. The demographic characteristics, clinical finding, laboratory results, and electrocardiographic parameters of the study population are presented in Table 1.

There were 18 patients with normal TCa levels, but low iCa levels, and two patients with normal TCa but mildly high iCa levels. The highest total value with low iCa was 2.4 mmol/L and the patient's iCa value was 1.08 mmol/L. The QTc interval of the same patient was observed to be prolonged at 456 ms and calcium replacement was found in 11 of all patients during hospitalisation.

The median QTc interval was 431 ms (414-450 IQR). Prolonged QTc was observed in 21 patients, of which 19 had low iCa levels. In 9 of these 19 patients, corrected-TCa levels were normal and only 4 received calcium replacement. In two patients, the QTc interval was above 500 ms.

A significant relationship was observed between QTc interval and age (β=2.59, standard error [SE]=0.123, p=0.010), gender (β=2.13, SE=4.068, p=0.035), SIRS (β=2.86, SE=4.443, p=0.005), and CAD (β=2.68, SE=9.547, p=0.008) in the basal model using multivariable linear regression analysis (Table 2). In models 1 and 2, a significant relationship was observed between the QTc interval and iCa and corrected-iCa (β=-2.22, SE=27.839, p= 0.028, β=-2.16, SE=29.407, p=0.033). However, in models 3 and 4, no significant relationship was observed between QTc interval and TCa and corrected-TCa (β-1.02, SE=3.959, p=0.312, β=-0.44, SE=4.635, p=0,650) (Table 3). The performance analysis indicated that

Table 3. Multivariable linear regression analysis by adding each calcium level to the basal model

	β coefficient	Standard Error	P value
iCa (Model 1)	-2.22	27.8390	0.028
Corrected-iCa (Model 2)	-2.16	29.407	0.033
TCa (Model 3)	-1.02	3.959	0.312
Corrected-TCa (Model 4)	-0.44	4.625	0.658

iCa, ionized calcum; TCa, total calcium

Table 4. Likelihood ratio, AIC, BIC, adjusted R2 and partial R2 values of models

	Likelihood ratio	AIC	BIC	Adjusted R2	Partial R2
Basal Model	39.5	1191	1222	0.207	
Model 1	44.7	1187	1222	0.232	0.030
Model 2	44.5	1188	1222	0.230	0.029
Model 3	40.6	1192	1226	0.207	0.006
Model 4	39.7	1193	1227	0.201	0.001

AIC and BIC, (lower value denotes better model), Harrel c-index statistics measures the discriminative ability of the model, and values closer to 1.0 are better. Likelihood Ratio x2 and R2 higher value represent better model performance

the best performances were observed in models containing iCa levels (Models 1 and 2) (Table 4). In model 1, the interactions between potassium and iCa were assessed (p=0,12). Partial effect plots of iCa predicting QTc intervals are shown in Figure 2a. In model 3, the interactions between potassium and TCa were assessed (p=0,22) and a partial effect plot of TCa predicting QTc intervals is shown in Figure 2b.

Discussion

In COVID-19, hypocalcemia and prolongation of the QTc interval can be seen due to various reasons. In these patient groups, there is not enough data to examine the relationship between the QTc interval and calcium level and which calcium level should be used for QTc monitoring. The results of this study demonstrated a significant relationship between iCa levels and QTc intervals in patients with COVID-19. Furthermore, QTc intervals were extended as iCa levels decreased. No significant relationship between total calcium levels (TCa and corrected-TCa) and QTc intervals was observed. Again, hypocalcemia was common among these patients. Additionally, ferritin, CRP, LDH, procalcitonin, and D-dimer levels were higher, while albumin and lymphocyte counts were lower in the low iCa group.

In COVID-19, cardiac injury and pathological changes in many other organs and tissues may occur in addition to lung involvement. One pathological condition observed in COVID-19 patients is electrolyte abnormalities. Hypocalcemia is one of these electrolyte abnormalities and has been identified as one of the major biochemical features of patients with COVID-19. (5-8,18). Studies evaluating calcium levels in these patients have reported a high frequency of hypocalcemia with both low iCa and TCa levels in ED and during hospitalisation. (5-8,18) In one of these studies, hypocalcemia was observed in 83% according to iCa levels in patients with COVID-19. (5) In another study evaluating severe COVID-19 patients, 62.5% of the patients had hypocalcemia. Hypocalcemia (iCa <1.16 mmol/L) was observed in 57% of the patients in our study. Hospitalisation of patients with mild symptoms and the low rate of severe patients and comorbidity may explain the low rate of hypocalcemia in our study population. Several studies have demonstrated that hypocalcemia is associated with disease severity in patients with COVID-19, and patients with hypocalcemia have higher ICU admission rates and mortality. (5,8,18) Inflammatory parameters such as CRP, LDH, procalcitonin, and D-dimer were higher, and albumin and lymphocyte levels were lower in patients with hypocalcemia. (5,8) Similarly, in our study of the hypocalcemic group, higher levels of CRP, ferritin, LDH, procalcitonin, and D-dimer were observed, while lymphocyte and albumin levels were lower. The mechanism of hypocalcemia in these patients is unclear. Low levels of calcium may be due to a decrease in intestinal absorption, vitamin D deficiency, decrease in albumin levels, the effect of

inflammatory processes on PTH, or the direct effect of the virus. (5,8,19)

It has been observed that extending QTc intervals, which reflects ventricular electrical activity, may cause arrhythmias such as torsade de pointes. (20,21,22) In a study evaluating the relationship between admission serum iCa levels and in-hospital mortality and long-term mortality in hospitalised patients, patients with low serum iCa levels were found to have an increased risk of ventricular arrhythmia. (23) Low serum iCa levels can cause QT prolongation and arrhythmias, such as Torsad de pointes. (24) Since inward calcium currents are one of the factors determining the plateau configuration of the action potential, hypocalcemia prolongs phase 2 of the action potential and thus prolongs the repolarisation duration. (25,26,27) In our study, the QTc interval was also observed to be longer in the low-iCa group. Approximately 40% of serum calcium is bound to proteins, especially albumin, 10% to anions, and approximately 50% is in free form (ionised calcium). In clinical practice, TCa levels are mostly used to monitor calcium levels. The total serum calcium concentration varies substantially with the concentration of albümin. (28) Albumin is a negative acute phase reactant and, as in COVID-19, a decrease is observed in its levels secondary to infection. (12,29) For this reason, corrected-TCa levels calculated by adjusting the TCa according to the albumin level can be used. However, studies have shown that corrected-TCa levels do not provide better information in critically ill patients than in TCa. However, iCa levels can provide more accurate information for determining the calcium levels in these patients. (13,14) In our study, a negative correlation was observed between calcium levels and the QTc interval. In the multivariable regression analysis, a significant relationship was observed between ionized calcium levels (iCa and corrected-iCa) and the QTc interval, but no significant relationship was observed between total calcium levels (TCa and corrected-TCa). iCa is the active form of calcium in the blood. Due to the protein abnormalities observed in COVID-19 patients, TCa and Correct-TCa levels can be monitored inaccurately, as determining precise calcium levels can be difficult. (12) Again, even if TCa or corrected TCa levels are normal in patients, there may be variations in iCa levels due to pH changes among other reasons, which in turn may change the QTc interval. Therefore, iCa may provide physiologically important information concerning

calcium levels. In our study, although TCa level were normal in 18 patients, iCa levels were low and seven patients had a prolonged QTc. Calcium replacement has been shown to shorten QTc intervals in hypocalcemic patients with QTc prolongation. (26) In the Diagnosis and Management of CV Diseases Guidance has recommended that total calcium levels should be kept above 2,25 mmol/L in COVID-19 patients (30); however, this may cause unnecessary and excessive calcium replacement in hypocalcemic patients because of low albumin levels or may cause patients with normal TCa and low iCa to be overlooked. In our hospital, calcium monitoring was performed according to corrected TCa levels due to hypoalbuminemia. It was found that only 4 of 19 patients with low iCa and prolonged QTc received calcium replacement. Corrected-TCa values in 9 patients and TCa values in 6 of them were within the normal range. A small number of patients received calcium replacement, probably because of corrected-TCa levels within the normal range.

Although the number of patients is small, given the relationship between iCa levels and QTc intervals, the use of iCa levels in COVID-19 patients can provide very important physiological information about QTc prolongation. Arrhythmias that may occur due to reasons such as myocardial injury and drugs can be prevented with calcium replacement in COVID-19 patients with hypocalcemia and prolonged QTc.

In conclusion, a significant relationship was observed between ionized calcium levels (iCa and corrected-iCa) and QTc interval in COVID-19 patients. Further, the QTc interval was longer in patients with hypocalcemia. No significant relationship was observed between total calcium (TCa and corrected-TCa) levels and the QTc interval. Evaluation of ionised calcium levels, which are more closely related to QTc, in COVID-19 patients with prolonged QTc can provide more physiologically important information.

Limitations: The most important limitation of this study was the small sample size. Studies with larger sample sizes are needed to evaluate the relationship between different calcium levels and QTc interval. Again, due to the hospitalisation of patients with mild symptoms in the initial stages of the pandemic, severe patients and patients with comorbidities were lower. Yet hypocalcemia rates may be higher in patients with severe diseases. Another limitation is that variables that can affect the QTc interval, such as CHF, could not be

included in the multivariable analysis due to the small sample size.

References

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020. https://www.who.int/dg/speeches/detail/who-directorgeneral-s-opening-remarks-at-the-media-briefing-on-covid19—11-march-2020. Accessed March 24, 2020.

2. World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-theinternational-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov). Accessed March 24, 2020.

3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.

4. Lippi G, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Ann Clin Biochem 2020; 57: 262-265.

5. L. Di Filippo, A.M. Formenti, P. Rovere-Querini et al. Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19. Endocrine 2020; 68: 475-478.

6. L. Di Filippo, A.M. Formenti, A. Giustina, Hypocalcemia: the quest for the cause of a major biochemical feature of COVID-19. Endocrine (2020) https://doi.org/10.1007/s12020-020-02525-9

7. F. Cappellini, R. Brivio, M. Casati, A. Cavallero, E. Contro, P. Brambilla, Low levels of total and ionized calcium in blood of COVID-19 patients. Clin. Chem. Lab. Med 2020; 58: 171-173.

8. J. Liu, P. Han, J. Wu, J. Gong, D. Tian, Prevalence and predictive value of hypocalcemia in severe COVID-19 patients. J. Infect. Public Health 13(9), 1224–1228 (2020).

9. El-Sherif N, Turitto G. Electrolyte disorders and arrhythmogenesis. Cardiol J 2011; 18: 233-245.

10. Sohaib SM, Papacosta O, Morris RW, Macfarlane PW, Whincup PH. Length of the QT interval: determinants and prognostic implications in a population-based prospective study of older men. J Electrocardiol 2008; 41: 704-710.

11. Zhang Y, Post WS, Dalal D, et al. Serum 25-hydroxyvitamin D, calcium, phosphorus, and electrocardiographic QT interval duration: findings from NHANES III and ARIC. J Clin Endocrinol Metab 2011; 96: 1873-1882.

12. Huang J, Cheng A, Kumar R, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol 2020; 92: 2152-2158.

13. Slomp J, van der Voort PH, Gerritsen RT, Berk JA, Bakker AJ. Albumin-adjusted calcium is not suitable for diagnosis of hyper- and hypocalcemia in the critically ill. Crit Care Med 2003; 31: 1389-1393.

14. Ridefelt P, Helmersson-Karlqvist J. Albumin adjustment of total calcium does not improve the estimation of calcium status. Scand J Clin Lab Invest 2017; 77: 442-447.

15. Bogossian H, Linz D, Heijman J, Bimpong-Buta NY et al. QTc evaluation in patients with bundle branch block. Int J Cardiol Heart Vasc 2020; 30: 100636.

16. Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. Elsevier Health Sciences; 2012.p.1422-1490. Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. Elsevier Health Sciences 2012; 1422-1490.

17. Rautaharju PM, Surawicz B, Gettes LS, et al. American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology. American College of Cardiology Foundation. Heart Rhythm Society AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. Circulation 2009; 119: 241-250.

18. J.K. Sun, W.H. Zhang, L. Zou et al. Serum calcium as a biomarker of clinical severity and prognosis in patients with coronavirus disease 2019; 12: 11287-11295 (2020).

19. Cappellini F, Brivio R, Casati M, Cavallero A, Contro E, Brambilla P. Low levels of total and ionized calcium in blood of COVID-19 patients. Clin Chem Lab Med 2020 58: 171-173.

20. Straus SM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden

cardiac death in a population of older adults. J Am Coll Cardiol 2006; 47: 362-367.

21. Zhang Y, Post WS, Dalal D, et al. QT-interval duration and mortality rate: results from the Third National Health and Nutrition Examination Survey. Arch Intern Med 2011; 171: 1727-1733.

22. Beinart R, Zhang Y, Lima J, et al. The QT interval is associated with incident cardiovascular events: the MESA study. J Am Coll Cardiol 2014; 64: 2111.

23. Thongprayoon C, Cheungpasitporn W, Chewcharat A et al. Hospital mortality and long-term mortality among hospitalized patients with various admission serum ionized calcium levels. Postgrad Med 2020; 132: 385-390.

24. Mosebach CM, Kluger J. Probable Hypocalcemia Induced Ventricular Fibrillation and Torsades de Pointes following Blood Product Administration. Cureus 2018; 10: 3765.

25. Bronsky D, Dubin A, Waldstein SS, et al. Calcium and the electrocardiogram. I. The electrocardiographic manifestations of hypoparathyroidism. Am J Cardiol 1961; 7: 823-832.

26. Eryol NK, Colak R, Ozdoğru I et al. Effects of calcium treatment on QT interval and QT dispersion in hypocalcemia. Am J Cardiol 2003; 91: 750-752.

27. Grandi E, Pasqualini FS, Pes C, Corsi C, Zaza A, Severi S. Theoretical investigation of actionpotential duration dependence on extracellular Ca2+ in human cardiomyocytes. J Mol Cell Cardiol. 2009, 46: 332-342.

28. Thongprayoon C, Cheungpasitporn W, Chewcharat A et al. Serum ionised calcium and the risk of acute respiratory failure in hospitalised patients: a single-centre cohort study in the USA. BMJ Open 2020; 10: e034325.

29. 29.Gulhar R, Jialal I. Physiology, Acute Phase Reactants. [Updated 2020 Mar 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;2020 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519570/

30. The European Society for Cardiology. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance. (Last update: 28 May 2020)