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Does prolonged QTc predict pulmonary involvement in COVID-19 patients?

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ABSTRACT

Objectives: Coronavirus disease 2019 (COVID-19) is a disease with high mortality due to acute respiratory distress syndrome (ARDS) secondary to viral pneumonia. In addition to its effects on the respiratory system, coronavirus is known to have serious systemic effects on the cardiovascular system. In this study, we aimed to investigate the association between prolonged QTc duration and COVID-19 specific pulmonary involvement

Methods: Between December 2020 and February 2021, 112 patients who were diagnosed with COVID-19 in our COVID-19 outpatient clinic and met the inclusion criteria were evaluated for the association between cardiac variables (heart rate, PR width, QRS width, fragmented QRS, and corrected QT [QTc] interval), other patient characteristics and lung involvement.

Results: A significant difference was found between the QTc intervals of COVID-19 patients with and without lung involvement ($p < 0.026$). In the ROC analysis for the QTc interval, which was found to be significant in the multivariate regression analysis, the cut-off value of 419.5 ms had a sensitivity of 72% and a specificity of 51.6% in predicting pulmonary involvement.

Conclusions: Prolonged QTc duration may be useful in predicting COVID-19 pulmonary involvement in patients admitted to the emergency department.

Keywords: COVID-19, electrocardiography, prolonged QTc, pulmonary involvement

Coronavirus disease 2019 (COVID-19) is a complex disease that has affected more than 500 million patients and caused more than six million deaths since its emergence [1]. COVID-19 is typically characterized by symptoms such as shortness of breath, fever, cough, fatigue, malaise, and taste and smell impairment. Because it primarily affects the lungs, the disease can rapidly progress to interstitial pneumonia and severe respiratory failure [2]. COVID -19 disease may also have adverse effects on the cardiovascular system along with respiratory system involvement. It is known that the disease can lead to many cardiac pathologies, including myopericarditis, pericardial effusion, hypoxia, direct cytotoxic effect, and acute coronary syndrome [3, 4].

The major cause of mortality in COVID-19 is the development of acute respiratory distress syndrome (ARDS) due to viral pneumonia, and the incidence of ARDS has been reported to exceed 15% in patients hospitalized for COVID-19 [5, 6]. Although the main

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cause of mortality and morbidity is respiratory system involvement, the effects of COVID -19 on the cardiovascular system (acute coronary syndrome, pericardial effusion, arrhythmia, etc.) have also been demonstrated [7].

Inflammation and hypoxia caused by COVID-19 pneumonia are thought to affect the QT interval. The main causes of arrhythmias in COVID-19 patients are myocardial damage, systemic and local inflammation, electrolyte imbalance, and drugs used in treatment [8, 9]. There is increasing evidence that interleukins, particularly interleukin 6 (IL-6), may prolong the corrected QT (QTc) interval by affecting the action potential through a direct action on cardiomyocyte ion channels [10].

Female gender, advanced age, electrolyte imbalances, diuretic use, and renal failure are some of the known risk factors for prolonged QTc interval [11]. Many viral infections, such as human immunodeficiency virus (HIV) and dengue fever, have been independently associated with a prolonged QT interval [12]. In an animal study, coronavirus infection was associated with a prolonged QT interval in rabbits [13]. There are publications on QTc interval prolongation in COVID -19 patients in the absence of conventional risk factors [14].

Although there are studies in the literature showing an association between COVID-19 disease and QTc interval prolongation, the complexity of this association is not yet clear [15]. Prolonged QTc interval is an ECG parameter that has been associated with malignant arrhythmias, and QTc interval assessment is an easily applicable method in the emergency department [16].

Electrocardiography (ECG) is an important diagnostic method in detecting myocardial damage or arrhythmias in COVID -19 patients and may play a role in the treatment strategies of COVID-19 patients. In this study, we aimed to investigate the association between a prolonged QTc interval and pulmonary involvement in COVID-19.

METHODS

Selection of Patients

The study was prospectively conducted with patients who presented to the COVID -19 outpatient clinic of Manisa City Hospital between December 2020 and February 2021. The study was conducted with the approval of the non-interventional ethics committee of Istanbul Medipol College (E-10840098-772.02-2485). The records of a total of 139 patients over 18 years of age and without suspected pregnancy who presented to the hospital with symptoms of COVID -19 disease were analyzed after obtaining written informed consent. Exclusion criteria were the presence of pulmonary edema, electrolyte disturbances, ECG abnormalities (ST segmental changes, atrial fibrillation, pacemaker rhythm, bundle branch block, and arrhythmia), and use of medications that prolong the QT interval (amiodarone, citalopram, clomipramine, sotalol, clarithromycin). Twenty-seven patients were excluded from the study based on these exclusion criteria, and 112 patients were evaluated. Patient data were divided into two groups: COVID-19 patients without pulmonary involvement (group 1) and COVID-19 patients with pulmonary involvement (group 2).

ECG Analysis

ECG was recorded at a rate of 25 mm/sec with a calibration of 1 mV/cm and a filter setting of 0.05-150 Hz. The parametric ECG values included HR (heart rate), PR (interval between the onset of the P wave and the beginning of the R wave), QRS (interval between the onset of the Q wave and the end of the S wave), and QT interval measurements. The heart rate corrected QT (QTc) interval was measured using the Bazett correction formula ($QTc = QT / \sqrt{RR(sec)}$).
QT was automatically calculated as the interval from the beginning of the Q wave to the end of the T wave and corrected for heart rate using the Bazett formula (QTc). All ECGs were recorded with a Philips PageWriter TC30 Cardiograph (Koninklijke Philips, Eindhoven, The Netherlands). The ECG examination was evaluated by a cardiologist. Among the selected patients, those whose chest CT scans had a high probability of pulmonary involvement with COVID-19 according to radiological reports were classified as COVID-19 pneumonia.

Statistical Analysis

SPSS 26.0 software (SPSS Inc. Chicago, IL) was used for statistical analysis. After checking the conformity of the data to the normal distribution with the

Table 1. Demographic characteristics of the patients and their distribution according to groups

	Group 1 (n = 62)	Group 2 (n = 50)	*p* value
Age (years), Mean ± SD	62.55 ± 10.20	58.94 ± 7.03	0.029*
Gender, n (%)			0.150#
Male	30 (48.4)	31 (62)	
Female	32 (51.6)	10 (38)	
Hypertension, n (%)	18 (29)	21 (42)	0.152#
Diabetes Mellitus, n (%)	11 (17.7)	10 (20)	0.761#
CAD, n (%)	10 (16.1)	16 (32)	**0.048**#
Heart Failure, n (%)	4 (6.5)	7 (14)	0.182#
COPD, n (%)	7 (11.5)	11 (22)	0.125#
CRF, n (%)	0 (0)	4 (8)	**0.037**#
PCR positivity, n (%)	26 (41)	41 (82)	**0.001**#

COPD = chronic obstruction pulmonary disease, CAD = coronary artery disease, CRF = chronic renal failure, PCR = polymerase chain reaction, SD =standard deviation

*t-test, #Chi-square test

Kolmogorov-Smirnov test, parametric tests for continuous variables with normal distribution were preferred. Data were analyzed by descriptive statistics (number, percentage, mean, standard deviation), T-test, Mann-Whitney U and Chi-square test, logistic regression, and ROC (Receiving operator characteristic) curve. The significance level accepted was $p < 0.05$.

RESULTS

Patient demographics and their distribution among groups are shown in Table 1. Coronary artery disease (CAD), chronic renal failure (CRF), and PCR test positivity were significantly higher in the group with pulmonary involvement (group II). Compared to the group without lung involvement (group I), the mean age of group II was significantly lower ($p = 0.029$). The cardiac variables (heart rate, PR, QRS, fQRS, and QTc) of the groups are shown in Table 2. The mean QTc interval of subjects in group II was significantly higher.

Univariate and multivariate logistic regression analyzes performed to determine the relationship between the variables and lung involvement are shown in Table 3. Age, PCR, and QTc variables were included in the multivariate logistic regression model. Multivariate logistic regression analysis revealed that lower age (odds ratio [OR]: 0.929; 95% CI: 0.879-0.982, $p = 0.009$), PCR positivity ([OR]: 7.28; 95%

Table 2. Distribution of cardiac variables according to groups

	Group 1 (n = 62)	Group 2 (n = 50)	*p* value
Heart rate (beat/min)	82.52 ± 15.49	85.46 ± 15.23	0.316*
PR (ms)	140.59 ± 17.86	141.74 ± 16.82	0.730*
QRS (ms)	84.51 ± 9.66	84.04 ± 11.69	0.814*
fQRS, n (%)	21 (34.4)	11 (22.4)	0.169#
QTc (ms)	421.70 ± 22.66	436.52 ± 30.72	**0.004***

Data are shown as mean±standard deviation or n (%).

f QRS = fragmented QRS, PCR = polymerase chain reaction

*t-test, #Chi-square test

Table 3. Univariate and multivariate regression analysis results of variables in predicting lung involvement

	Univariate		Multivariate	
	Odds ratio (95% CI)	***p* value**	**Odds ratio (95% CI)**	***p* value**
Age	0.955 (0.914-0.998)	**0.039**	0.929 (0.879-0.982)	**0.009**
CAD	2.44 (0.994-6.022)	0.051		
CRF	2177379136 (0.00-0.00)	0.999		
PCR positivity	6.3 (2.615-15.212)	**< 0.001**	7.28 (2.691-19.362)	**< 0.001**
QTc	1.02 (1.006-1.040)	**0.015**	1.023 (1.003-1.043)	**0.026**

CAD = Coronary artery disease, CRF = chronic renal failure

CI: 2.691-19.362, $p < 0.001$) and prolonged QTc duration ([OR]: 1.023; 95% CI: 1.003-1.043, $p = 0.026$) were significantly associated with lung involvement.

The prediction point for the QTc interval, which plays a role in predicting pulmonary involvement, was determined using ROC curve analysis (Fig. 1). In the analysis, the QTc interval with a value of 419.5 ms predicted pulmonary involvement with 72% sensitivity and 51.6% specificity (AUC:0.651, 95% CI:0.549-0.753, $p = 0.006$).

DISCUSSION

Although COVID-19 mainly targets lung tissue, it may have direct or indirect adverse effects on the heart. COVID-19-related conditions such as myopericarditis, complete AV block, acute coronary syndromes, decompensated heart failure, and pulmonary embolism have been reported in the literature [17, 18]. On the other hand, several studies have described an abnormal immune-inflammatory response to SARS-CoV-2 infection. Another study showed that the levels of interleukin (IL)-1β, IL-6, IL-8, IL-10, and soluble TNF receptor 1 (sTNFR1) were increased in patients with SARS-CoV-2 infection compared with healthy subjects [19]. In a recent meta-analysis, elevated levels of other immune-inflammatory parameters such as C-reactive protein, white blood cell count, and procalcitonin were shown to be significantly associated with disease severity [20]. Considering that inflammation can also lead to QTc interval prolongation, SARS-CoV-2 infection may prolong QTc duration through an inflammatory response [21]. Thus, prolonged QTc duration in SARS-CoV-2 infection may be a direct consequence of viral activity or may be mediated by inflammation. This helps to explain why a prolonged QTc interval is independently associated with mortality [22]. Ay *et al*. [23] reported that there may be an association between QTc interval prolongation and mortality in COVID-19 patients. Again, some studies have emphasized that the cardiac effects of COVID-19 disease increase mortality [23, 24]. QTc interval prolongation is thought to be one of the reasons for the increased mortality in COVID-19 [25]. Prolongation of the QTc interval due to hydroxychloroquine and azithromycin, which are used in the treatment of COVID-19, has also been reported in the literature

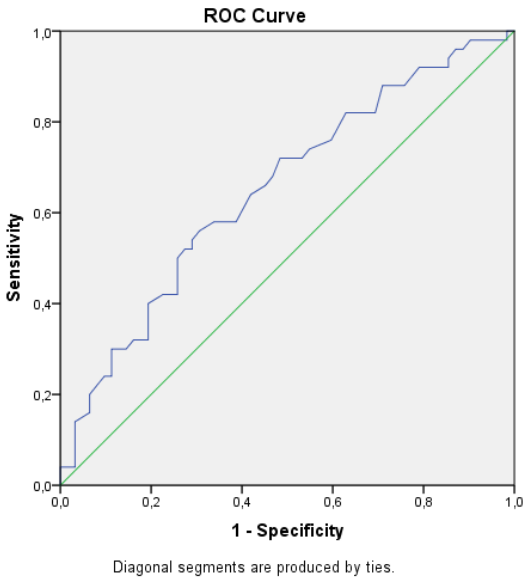

Fig 1. Evaluation of the effectiveness of the QTc interval in predicting pulmonary involvement using the ROC curve.

[26]. In a study comparing the QTC value at admission of covid-19 patients, it was found that 10% had a QTc interval and QTc prolongation was independently associated with increased mortality. This result supports our thesis that QTc can be used as a predictive factor at the time of admission [22].

Although the role of ECG in the early diagnosis of cardiovascular complications and mortality in COVID-19 is well known, the role of ECG abnormalities in predicting pulmonary involvement in COVID-19 pneumonia has not been found in the literature.

In this study, we investigated the relationship between ECG findings, patient characteristic variables, and pulmonary involvement in patients hospitalized with COVID-19 symptoms and diagnosed with COVID-19.

In our study, Group II had higher CRF and CAD rates than Group I. This suggests that COVID -19 positive patients with chronic diseases should be closely monitored because of the risk of pulmonary involvement and mortality (Table 1). The fact that the mean age of group I patients was higher than the mean age of group II patients (Table 1) suggests that younger patients were exposed to a higher viral load because of the isolation of the elderly population during the pandemic. Since CRF patients are dialysis-dependent and dialysis treatment is provided under hospital conditions, these patients have a higher COVID-19 viral load. These patients are at higher risk, not only for nosocomial opportunistic infections but also because they are transported to the hospital by public transportation.

In our study, pulmonary involvement was found to be significantly associated with QTc interval in univariate and multivariate regression analysis (Table 3) (Fig. 1). In the ROC analysis for the QTc interval, which was found to be significant in the multivariate regression analysis, the cut-off value of 419.5 ms had a sensitivity of 72% and a specificity of 51.6% in predicting pulmonary involvement. The most common ECG abnormality resulting from COVID-19-associated hypoxia is QTc interval prolongation. Significant prolongation of the QTc interval has been noted, particularly in elderly patients with right ventricular contractile defect, and a high mortality rate has been reported in these patients [21].

In our study, the relationship between pulmonary involvement and QTc was clearly demonstrated by excluding patients who were taking medications that might affect the QT interval. Because of this relationship, the use of drugs that prolong the QTc interval may worsen the clinical picture in patients with increased lobular involvement. Therefore, QTc and pulmonary involvement should be considered when prescribing these drugs, and QTc times should be monitored during treatment.

A significant increase in mortality has been observed in patients with severe COVID-19 pneumonia [27]. Considering the association between prolonged QTc interval and COVID-19 pulmonary involvement in our study, we believe that close cardiac monitoring is also important in this group of patients at risk of mortality

CONCLUSION

The presence of a prolonged QT interval on the ECG of COVID-19 patients at the time of hospital admission may be helpful in predicting pulmonary involvement. It should be kept in mind that these patients should be monitored closely, as this may lead to cardiac complications. To this end, we think that ECG, which is an inexpensive and non-invasive tool available in all healthcare facilities, as well as the use of smartwatches or devices that can perform remote cardiac monitoring, can be easily used to predict pulmonary involvement in COVID-19 pneumonia.

Authors' Contribution

Study Conception: AS, ÖFR; Study Design: SK, ÇC; Supervision: ÖFR; Funding: N/A; Materials: AS, ÇC; Data Collection and/or Processing: EB; Statistical Analysis and/or Data Interpretation: FR; Literature Review: FR, EB; Manuscript Preparation: AS, ÖFR and Critical Review: FA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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REFERENCES

1. World Health Organization, 2021. The impact of COVID-19 on health and care workers: a closer look at deaths (No. WHO/HWF/WorkingPaper/2021.1). World Health Organization.
2. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res 2020;116:1666-87.
3. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, Jain SS, et al. COVID-19 and cardiovascular disease. Circulation 2020;141:1648-55.
4. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259-60.
5. Zhou M, Zhang X, Qu J. Coronavirus disease 2019 (COVID-19): a clinical update. Front Med 2020;14:126-35.
6. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395:1763-70.
7. Kwenandar F, Japar KV, Damay V, Hariyanto TI, Tanaka M, Lugito NPH, et al. Coronavirus disease 2019 and cardiovascular system: a narrative review. Int J Cardiol Heart Vasc 2020;29:100557.
8. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355-62.
9. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
10. Ciceri F, Castagna A, Rovere-Querini P, De Cobelli F, Ruggeri A, Galli L, et al. Early predictors of clinical outcomes of COVID-19 outbreak in Milan, Italy. Clin Immunol 2020;217:108509.
11. Yang P, Kanki H, Drolet B, Yang T, Wei J, Viswanathan P, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. Circulation 2002;105:1943-8.
12. Chastain DB, Veve MP, Wagner JL. Abnormal QTc syndrome in HIV-infected patients: a systematic review of prevalence and risk factors. Antivir Ther 2019;24:459-65.
13. Alexander LK, Keene BW, Yount BL, Geratz JD, Small JD, Baric RS. ECG changes after rabbit coronavirus infection. J Electrocardiol 1999;32:21-32.
14. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846-8.
15. Changal K, Paternite D, Mack S, Veria S, Bashir R, Patel M, et al. Coronavirus disease 2019 (COVID-19) and QTc prolongation. BMC Cardiovasc Disord 2021;21:158.
16. Malik M, Camm AJ. Evaluation of drug-induced QT interval prolongation. Drug Saf 2001;24:323-51.
17. Angeli F, Spanevello A, De Ponti R ,Visca D, Marazzato J, Palmiotto G, et al. Electrocardiographic features of patients with COVID-19 pneumonia. Eur J Intern Med 2020;78:101-6.
18. Szekely Y, Lichter Y, Taieb P, Banai A, Hochstadt A, Merdler I, et al. Spectrum of cardiac manifestations in COVID-19: a systematic echocardiographic study. Circulation 2020;142:342-53.
19. Lazzerini PE, Acampa M, Capecchi PL, Hammoud M, Maffei S,Bisogno S, et al. Association between high sensitivity C-reactive protein, heart rate variability and corrected QT interval in patients with chronic inflammatory arthritis. Eur J Intern Med 2013;24:368-74.
20. Feng X, Li S, Sun Q, Zhu J, Chen B, Xiong M, et al. Immune-inflammatory parameters in COVID-19 cases: a systematic review and meta-analysis. Front Med (Lausanne) 2020;7:301.
21. Alareedh M, Nafakhi H, Shaghee F, Nafakhi A. Electrocardiographic markers of increased risk of sudden cardiac death in patients with COVID-19 pneumonia. Ann Noninvasive Electrocardiol 2021;26:e12824.
22. Farré N, Mojón D, Llagostera M, Belarte-Tornero LC, Calvo-Fernandez A, Valles E, et al. Prolonged QT interval in SARS-CoV-2 infection: prevalence and prognosis. J Clin Med 2020;9:2712.
23. Ay MO, Kozaci N, Ay OO, Kaya H, Bulut M, Yuksel M, et al. QTc interval and electrocardiographic findings of COVID-19 patients. Ann Clin Anal Med 2021;12:1031-6.
24. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. J Cardiovasc Electrophysiol 2020;31:1003-8.
25. Krittanawong C, Kumar A, Hahn J, Wang Z, Zhang H, Sun T, et al. Cardiovascular risk and complications associated with COVID-19. Am J Cardiovasc Dis 2020;10:479-89.
26. Diaz-Arocutipa C, Brañez-Condorena A, Hernandez AV. QTc prolongation in COVID-19 patients treated with hydroxychloroquine, chloroquine, azithromycin, or lopinavir/ritonavir: A systematic review and meta-analysis. Pharmacoepidemiol Drug Saf 2021;30:694-706.
27. Mahendra M, Nuchin A, Kumar R, Shreedhar S, Mahesh PA. Predictors of mortality in patients with severe COVID-19 pneumonia - a retrospective study. Adv Respir Med 2021;89:135-44.