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Relationship between Prolonged QT Interval and Mortality in COVID-19 Patients at Ulin Hospital, Banjarmasin

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Abstract

BACKGROUND: QT prolongation in COVID-19 infection may be caused by SARS-CoV-2 infection, inflammation, ischemia, hypoxia, and the administration of drugs related to COVID-19. This condition is associated with a poor prognosis due to an increased risk of ventricular arrhythmias and sudden cardiac arrest.

METHODS: This study used an observational case-control design. Data were obtained consecutively using medical records of COVID-19 patients confirmed through RT-PCR swabs who died (case) and survived (control) at Ulin General Hospital, Banjarmasin. The number of samples in this study was 138 patients. The independent variables were prolonged QT interval (>430 m/s or QTc >450 m/s) and normal QT interval, while the dependent variable was the mortality of COVID-19 patients.

RESULTS: QT prolongation significantly increased the risk of death by 4 times (OR 4.48; 95% CI = 2.162-9.280; p = 0.000) compared to COVID-19 patients with normal QT intervals.

DISCUSSION: Prolonged QT intervals increased the risk of death in COVID-19 patients at Ulin General Hospital, Banjarmasin. These findings are in accordance with several other studies where this variable might be used as a prognostic factor in the mortality of hospitalized COVID-19 patients.

CONCLUSION: Prolonged QT intervals are associated with mortality in patients with COVID-19 at Ulin Hospital, Banjarmasin.

Introduction

The first case of COVID-19 was identified in Wuhan, the provincial capital of Hubei, in early December 2019. On January 7, 2020, the Chinese Center for Disease Control and Prevention (CDC) identified a new coronavirus taken from a throat swab from a patient and later termed 2019-nCov or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO) [1]. Cardiovascular complications such as acute myocardial injury, arrhythmias, coronary syndromes, strokes, and pulmonary thromboembolism are among the most frequently observed complications in COVID-19 patients [2].

QT interval prolongation is associated with "early after depolarization," which can produce early action potentials that lead to cardiac arrhythmias that can develop into ventricular fibrillation and sudden cardiac death. In the setting of SARS-CoV-2 infection, QT prolongation can be secondary to infection with the SARS-CoV-2 virus itself, inflammation, ischemia, hypoxia, and drug use related to COVID-19 [3]. Regardless of the patient's current treatment, the presence of QT prolongation at the time of initial hospital admission may indicate a poor prognosis [4]. Consequently, we were interested in investigating the association between a prolonged QT interval and mortality in COVID-19 patients at Ulin General Academic Hospital, Banjarmasin.

Methods

Study design, location, and period

This study uses a case-control-based observational study design. The study group was selected based on differences in risk factors, such as the group of patients with a prolonged QT interval and

a normal QT interval effect on mortality. This research was conducted at Ulin General Hospital, Banjarmasin, in the period of 2020–2022.

Population and sampling technique

The target population in this study were patients who died with a prolonged QT interval and was diagnosed with COVID-19 using the RT-PCR swab method. The accessible population was confirmed COVID-19 patients using the RT-PCR swab method who were treated at Ulin Hospital, Banjarmasin, with prolonged QT. The sampling technique was consecutive sampling according to the inclusion and exclusion criteria.

Sampling used a sequential technique (consecutive sampling), according to the inclusion and exclusion criteria.

Inclusion and exclusion criteria

The inclusion criteria for this study were patients (aged ≥18 years and ≤75 years) diagnosed with COVID-19 using the RT-PCR swab method who were treated at Ulin Hospital from 2020 to 2022. Patients were excluded if the medical record data were incomplete, patients aged <18 years and >75 years, patients were in critical condition before being infected with COVID-19, and patients had end-stage malignancy.

Research variables

The independent variables were prolonged and normal QT interval. The dependent variable was the mortality of a patient with confirmed COVID-19. We also account for confounding variables such as patient factors (age, sex, body mass index, smoking) and disease factors (asthma, COPD, pulmonary tuberculosis, DM, hypertension, CHD, stroke, chronic kidney disease, chronic liver disease, cancer, immunodeficiency, electrolyte disturbances (hypokalemia, hypocalcemia), and drugs that may cause QT interval prolongation).

Research flow and implementation

The study was conducted at Ulin Hospital, Banjarmasin, after obtaining approval from the Ethics Committee (No. 001/Kedokteran/Diklit/RSUDU/VIII/2020). Data tracking was carried out at the Medical Record Installation, Hospital Electronic Data Center, and Clinical Pathology Laboratory based on a diagnosis of COVID-19. Data on survived and deceased patients were collected, randomized, then tabulated, and statistically analyzed.

Statistical analysis

Descriptive data are arranged in the form of tables and percentages, which include data on patient characteristics in a distributive form, to find out which of the two variables affects mortality in confirmed COVID-19 patients being treated at Ulin Hospital, Banjarmasin. Patient characteristic were analyzed using descriptive analysis.

The probability ratio of the two groups is expressed by the odds ratio (OR) for bivariate analysis. The value of OR = 1 indicates that there is no difference in opportunity between the groups being compared; the value of OR <1 indicates a decrease in opportunity in the exposed group; and the value of OR >1 indicates an increase in opportunity in the exposed group compared to the unexposed group. This study used a significance limit of p <0.05 and a 95% confidence interval. The data was then analyzed using SPSS data processing software version 28.0.

Results

Baseline characteristics

The number of subjects in this study was 138 patients. Subjects were then divided based on their outcomes into 69 deceased patients and 69 survived patients. Descriptive analysis was then carried out on all subjects (Table 1). Bivariate analysis was performed using the Chi-square or Fischer's exact test if the Chi-square conditions were not met.

Table 1: Baseline characteristics of the study

Variable	Research sample population		
	Deceased (n = 69), n (%)	Survived (n = 69), n (%)	p-value
Age (years)			
≥60	49 (71.0)	52 (75.3)	0.564
<60	20 (29.0)	17 (45.9)	
Sex			
Male	48 (69.6)	55 (79.7)	0.171
Female	21 (30.4)	14 (20.3)	
Comorbidity			
Hypertension	20 (29.0)	23 (33.3)	0.581
Diabetes mellitus	15 (21.7)	14 (20.3)	0.834
Electrolyte disturbance	15 (19.7)	7 (10.1)	0.108
Smoking	12 (17.4)	4 (5.8)	0.033
Cardiovascular disease	3 (4.3)	2 (2.9)	1.000*
Asthma	1 (1.4)	14 (20.3)	0.000
TB	1 (1.4)	3 (4.3)	0.619*
Cancer	1 (1.4)	2 (2.9)	1.000*
CKD	1 (1.4)	0	1.000*
COPD	0	9 (13.0)	0.003
Immunodeficiency	0	1 (1.4)	1.000*
Cerebrovascular disease	0	0	N/A
Chronic liver failure	0	0	N/A
Receive therapy that may affect QT interval			
Yes (1 type of drug)	61 (88.4)	61 (88.4)	1.000
Hydroxychloroquine	51 (73.9)	60 (87.0)	0.053
Lopinavir/ritonavir	27 (45)	52 (46)	0.051
Oseltamivir	20 (37)	34 (63)	0.016
Azithromycin	22 (39.3)	34 (60.7)	0.039
Levofloxacin	41 (59.4)	28 (40.6)	0.027
NLR	45 (61.6)	28 (38.4)	0.004
Blood glucose	50 (47.6)	55 (52.4)	0.320
CRP	40 (58.8)	28 (41.2)	0.042
LDH	43 (59.7)	29 (40.3)	0.018
Severe COVID-19	23 (42.6)	31 (57.4)	0.308

*Fisher's exact test. N/A: Not available, TB: Tuberculosis, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, LDH: Lactate dehydrogenase.

Based on age, the subjects in this study were divided into ≥60 years and <60 years. The highest

mortality rate was found in patients aged ≥60 years in 49 (71.0%) subjects. There was no significant age difference between the survived and deceased groups (p = 0.564). Based on gender, most of the subjects in this study were male, around 103 (74.6%) subjects. Males also had the highest mortality rate, with 48 (69.6%) subjects. However, there was no significant difference in sex proportions between the survived and deceased groups (p = 0.171).

The most common comorbidity reported was hypertension in 43 subjects, of whom 20 (29.0%) were deceased. The second most common comorbidity was diabetes mellitus, which was suffered by 29 study subjects with 15 (21.7%) subjects deceased, followed by electrolyte disturbances in 22 subjects with 15 (19.7%) subjects deceased. There was a significant difference in the rates of asthma and COPD between the two groups (p < 0.05). Subjects with asthma (20.3% vs. 1.4%) and COPD (13.0% vs. 0.0%) comorbidities have a higher surviving rate, while smoking is associated with a higher death outcome (5.8% vs. 17.4%). There were no subjects with a history of cerebrovascular disease or chronic liver disease.

Therapies that may affect the QT interval in this study were defined as hydroxychloroquine, lopinavir/ritonavir, oseltamivir, azithromycin, and levofloxacin based on previous studies. There were 122 subjects who received drugs that could affect the QT interval, of whom 61 (88.4%) were deceased. The mortality rate based on the type of drug was 51 (73.9%) subjects who received hydroxychloroquine, 27 (45%) received lopinavir/ritonavir, 20 (37%) received oseltamivir, 22 (39.3%) received azithromycin, and 41 (59.4%) received levofloxacin. Subjects who received oseltamivir, azithromycin, and levofloxacin had a significantly higher death outcome (p < 0.05).

Laboratory test results from deceased patients showed that NLR increased in 45 (61.6%) subjects, GDS was elevated in 50 (47.6%), CRP was elevated in 40 (58.8%), and LDH was elevated in 43 (59.7%) subjects. Meanwhile, for the clinical degree of severity of COVID-19 disease in patients who deceased, there were 23 (42.6%) subjects.

QT interval analysis of mortality

In this study, the QT interval was divided into 2 categories: prolonged (QT interval is ≥430 ms with QTc ≥450 ms) and normal QT interval (QT interval is <430 ms with QTc <450 ms). Bivariate analysis of the association between QT interval and mortality in COVID-19 patients was carried out using the Chi-square test (significant if the p < 0.05). The probability ratio of QT prolongation to death was analyzed using the odds ratio (OR) as described in Table 2.

The majority of the subjects, 80 (58.0%), displayed a normal QT interval, while 58 (42.0%) displayed a prolonged QT interval. In the group of survived subjects, the majority, (52, (75.3%)) subjects showed a normal QT interval. Meanwhile, in the group of deceased subjects, the proportion of prolonged QT interval was higher (59.4%). There was a significant relationship between the QT interval and the outcome of COVID-19 patients (p = 0.000), with an OR of 4.48. This indicates that the risk of death in COVID-19 patients with a significantly prolonged QT interval is 4.48 times higher than in patients with normal QT intervals.

Table 2: The effect of the QT interval on mortality

QT interval	Outcome		Total	OR	p-value
	Deceased (n = 69), n (%)	Survived (n = 69), n (%)			
Prolonged	41 (59.4)	17 (24.6)	58 (42.0)	4.48	0.000*
Normal	28 (40.6)	52 (75.3)	80 (58.0)		
Total	69 (100.0)	69 (100.0)	138 (100.0)		

*p < 0.05. OR: Odds ratio.

Multivariate analysis

Multivariate logistic regression analysis using the enter method was performed for variables with p < 0.05 in bivariate analysis. These variables were smoking, asthma, COPD, antiviral therapy with lopinavir/ritonavir, oseltamivir, antibiotic therapy with azithromycin and levofloxacin, and laboratory parameters such as NLR, CRP, and LDH. For the COPD variable, multivariate analysis was not performed because it did not have a death outcome. The results of the multivariate analysis can be seen in Table 3.

Table 3: Multivariate analysis

Variables	AOR (95% CI)	p-value
Prolonged QT interval	4.03 (1.68–9.66)	0.002
Asthma	0.07 (0.01–0.59)	0.015
Smoking	1.81 (0.47–6.99)	0.390
Lopinavir/ritonavir	0.401 (0.16–1.00)	0.051
Oseltamivir	2.380 (1.179–4.804)	0.016
Azithromycin	2.075 (1.04–4.15)	0.039
Levofloxacin	2.18 (0.92–5.17)	0.077
NLR	2.746 (1.38–5.48)	0.004
CRP	2.001 (1.02–3.978)	0.042
LDH	2.281 (1.15–4.51)	0.018

AOR: Adjusted odds ratio, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, LDH: Lactate dehydrogenase.

Based on the results of multivariate analysis, QT prolongation, asthma, smoking, antiviral therapy with lopinavir/ritonavir, oseltamivir, antibiotic therapy with azithromycin, levofloxacin, and laboratory values of NLR, CRP, and LDH were independent predictors of mortality in COVID-19. As with bivariate analysis, a prolonged QT interval increased the risk of death by four times. The use of oseltamivir, azithromycin, and levofloxacin, as well as laboratory values of NLR, CRP, and LDH, had a significantly 2-fold risk of death. In our study, it was also found that asthma is a protective factor against mortality, with a 0.07-fold risk of death, which means that the probability of death is lower in COVID-19 patients with a history of asthma. Smoking and lopinavir/ritonavir therapy did not maintain significance in the multivariate analysis and are therefore not independent predictors of outcome in COVID-19.

Discussion

In this study, the highest mortality rate was observed in patients aged ≥60 years (71.0%) and males (69.6%), predominantly. There was no significant age and sex difference in our study, and this result was supported by a meta-analysis that stated that there was no significant relationship between age and hospital admission in COVID-19 patients (risk ratio [RR]: 1.013; 95% CI 0.998–1.028; p > 0.05) [5]. Previous studies have demonstrated that male COVID-19 patients had higher mortality rates due to higher levels of ACE2 expression, smoking habits, and more frequent activities outside the home to work during the pandemic [6], [7]. We assumed that there were other factors that confounded the sex relationship with COVID-19 mortality [8].

Hypertension (29.0%) and diabetes mellitus (21.7%) were the two most prevalent comorbidities we discovered in the group of deceased subjects. However, further analysis only showed significant differences between the survived and deceased groups in patients with a history of smoking (19,7%) and asthma (1.4%). Smoking has been found to significantly increase mortality risk in COVID-19 patients by 1.19 times (RR = 1.19, 95% CI = 1.12–1.27) [9]. The risk of death from COVID-19 is comparable to that of an active smoker in people with a history of smoking. This is most likely due to increased oxidative stress exposure from cigarette smoke in smokers, which exacerbates the inflammatory process in COVID-19 infection [10]. On the other hand, COVID-19 patients with comorbid asthma in our study had a significantly higher survival outcome, which is supported by previous studies that found that individuals with a history of asthma showed a 14% reduction in the need for hospitalization due to COVID-19 (95% CI = 0.77–0.99, p = 0.03). The mortality rate also decreased in individuals with a history of asthma (OR = 0.88; 95% CI = 0.77–1.01) [11]. This may be due to lower interferon levels in those patients, thereby reducing the incidence of cytokine storms in severe COVID-19. Individuals with a history of asthma may also comply more with health protocols because they are classified as a vulnerable population [12].

Therapy that may affect the QT interval in this study was antiviral therapy with oseltamivir and antibiotic therapy with azithromycin and levofloxacin. Patients who received oseltamivir, azithromycin, and levofloxacin therapy showed a higher deceased-than-survived outcome. This finding was consistent with previous studies, which found that oseltamivir increased the risk of mortality in COVID-19 patients who were hospitalized (HR = 1.13; 95% CI = 1.01–1.26), and the administration of oseltamivir early or late in the course of the disease did not change the risk [13]. A higher mortality rate was also found in COVID-19 patients who received antibiotics (RR = 3.37; 95% CI = 1.7–6.8). This may be because antibiotics are only given to severe and critical COVID-19 patients with a poor prognosis. In addition, the study also found that of all critically-severe COVID-19 patients who were given antibiotics, only 7% showed positive bacterial culture results, implying that the administration of antibiotics to COVID-19 patients was not on target [14].

The QT interval on the ECG is one of the indicators in the clinical evaluation of patients at high risk of experiencing ventricular arrhythmias and myocardial infarction, which is characterized by increased cardiac biomarkers of troponin and BNP [15]. QT prolongation (42.0%) in COVID-19 was found to be 4.48 times a significantly higher risk of death than normal QT interval. This finding was supported by a previous retrospective study in Dubai, which stated that a QTc interval >450 ms was significantly associated with ventilation requirements and increased mortality [15]. A study by Fishbein *et al*. found that delayed cardiac repolarization as indicated by QTc > 500 ms was an independent predictor of mortality in COVID-19 patients (OR= 1.41; 95% CI= 1.05–1.90) [16]. Banai *et al*. also found that prolonged QTc (≥440 ms for males and ≥450 ms for females) was an independent predictor of severe and critical COVID-19 (HR= 2.14; 95% CI = 1.3–3.5; p = 0.002). The 1-year mortality in COVID-19 patients with prolonged QTc was also higher than in COVID-19 patients with normal QTc (40.4% vs. 15.5%; p < 0.001), even after adjusting for other confounding variables (HR = 1.69; 95% CI = 1.06–2.68; p = 0.027) [17]. The activation of inflammatory cytokines following COVID-19 infection can suppress I_{Kr} (rapid delayed rectifier channel) in heterologous cells and myocytes, leading to longer repolarization. This is one mechanism that might explain the prolongation of the QT interval in COVID-19 [18].

In this study, the independent factors for mortality in COVID-19 were a prolonged QT interval, asthma co-morbidities, oseltamivir, azithromycin, and levofloxacin therapy, and NLR and LDH lab parameters. Oseltamivir, azithromycin, and levofloxacin use increased the risk of mortality by twofold. Previous research that found that antivirals reduced mortality was carried out in mild-moderate COVID-19 patients [19]. Meanwhile, our patient had severe-critical COVID-19, so it is possible that the effectiveness of antivirals will decrease. According to Tan *et al*., COVID-19 patients had a higher risk of death (OR = 2.83; 95% CI = 1.78–4.51) when they experienced abnormal heart rhythms, particularly ventricular arrhythmias characterized by QT prolongation [20]. Previous literature supported the results of multivariate analysis in this study.

The strengths of this study were: (1) an easy, fast, and minimally expensive assessment of the QT interval with an ECG so that it can be done routinely; (2) clinical evidence that the QT interval parameter was a predictor of mortality in COVID-19 patients; and (3) the analysis of confounding variables and laboratory data that might influence the outcome. However, the limitations of this study include: (1) a case-control study design that only evaluates the ECG at the time of initial admission to the hospital; (2)

a single-center design so it is difficult to generalize to the general population. Therefore, further research is needed with cohort design and a multi-center approach.

Conclusion

We found that prolonged QT intervals are associated with mortality in patients with COVID-19 at Ulin Hospital, Banjarmasin.

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