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ORIGINAL ARTICLE

Evaluation of Symptomatic and Asymptomatic Outpatients in the Post-COVID-19 Period With Electrocardiographic Ventricular Depolarization and Repolarization Parameters

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Abstract

Background: A recently identified viral illness called coronavirus disease 2019 (COVID-19) is spreading quickly. Numerous cardiovascular issues such as arrhythmias and electrocardiogram (ECG) alterations have been linked to COVID-19.

Objective: In this investigation, we compared ECG indicators of depolarization and repolarization heterogeneity between symptomatic individuals who complained of palpitations and chest discomfort following COVID-19 and those who did not.

Methods: In this prospective case-control study, 56 post-COVID-19 patients who did not have any symptoms of chest discomfort or palpitations were included in the control group and compared with a study group comprising 73 post-COVID-19 patients who presented at the outpatient clinic with complaints of chest pain and palpitation. Electrocardiographic (ECG) measures were used to assess depolarization and repolarization of the ventricles. These measures included the Tpeak-Tend (Tp-e) interval, QT dispersion (QTd), Tp-e/QT ratio, Tp-e/QTc ratio, frontal QRS-T (fQRS-T) angle, and fragmented QRS (FQRS). Two cardiologists recorded the patients' ECG data. A statistically significant result was defined as a p value less than 0.05.

Results: The results of multivariate analysis including FQRS, Tp-e interval, Tp-e/QT, and Tp-e/cQT showed that presence of FQRS (OR: 6.707, 95% CI: 1.733-25.952; p = 0.006) was an independent predictor of symptomatic post-COVID -19 patients.

Conclusion: In our study, FQRS was found to be significantly higher in symptomatic post-COVID-19 patients than in non-symptomatic post-COVID-19 patients, while Tp-e interval was found to be lower.

Keywords: COVID-19; cardiac Arrhythmias; Electrocardiography.

Introduction

The coronavirus disease 2019 (COVID-19) is caused by the coronavirus family's seventh member, which can infect humans.[1] The first instance of COVID-19 was discovered in December 2019 in Wuhan, China, and the sickness quickly spread to all countries, causing a terrible epidemic. COVID-19 has been linked to serious cardiovascular complications.[2] A significant body of study has been conducted to identify possible risk factors for serious adverse cardiac events. Following COVID-19, many individuals seek treatment at cardiology outpatient clinics for chest discomfort and palpitations. Many of these people have no risk factors for cardiovascular disease or a history of cardiac or arrhythmic disease".[3]

QT dispersion (QTd), the interval between T wave peak and T wave tip (Tp-e), and the frontal QRS-T (fQRS-T) angle have all been proposed as indications of regional and transmural heterogeneity of cardiac repolarization. It has been found that systemic viral

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Central Illustration: Evaluation of Symptomatic and Asymptomatic Outpatients in the Post-COVID-19 Period With Electrocardiographic Ventricular Depolarization and Repolarization Parameters

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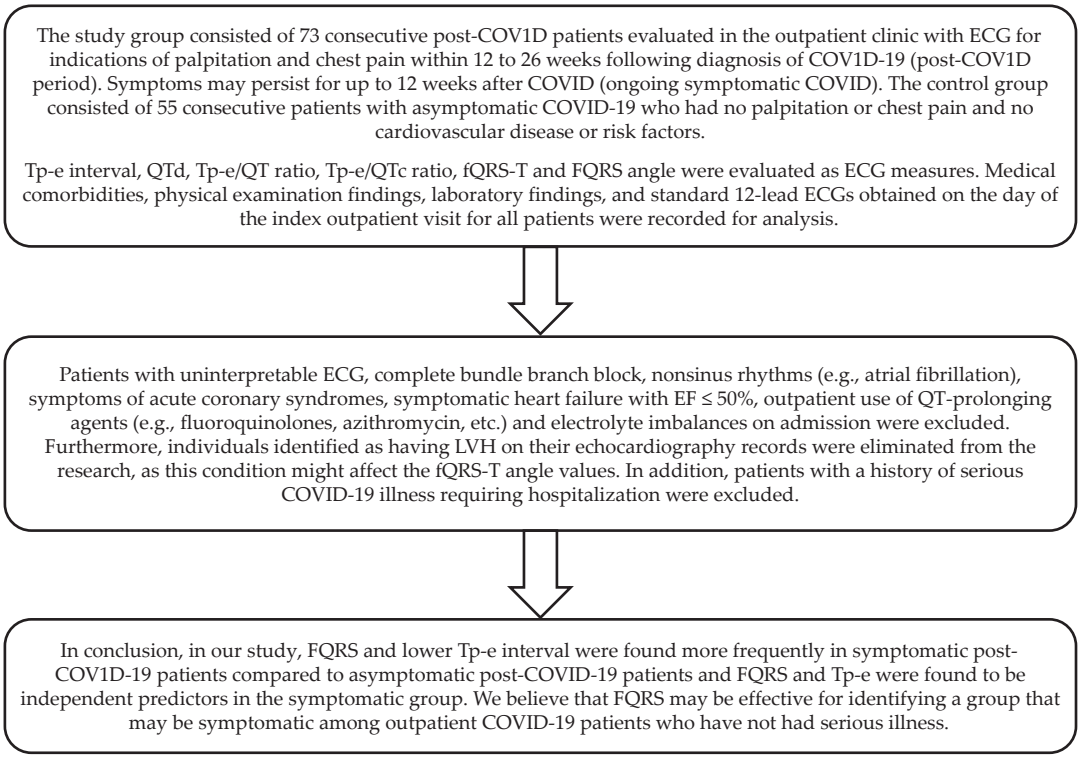

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ECG: electrocardiogram; Tp-e: Tpeak-Tend; QTd: QT dispersion; fQRS-T: frontal QRS-T; FQRS: fragmented QRS; EF: ejection fraction; QTc: corrected QT.

infections[4] and systemic inflammatory disorders[5] have a significant impact on these ECG indicators. However, the effect of COVID-19 on cardiac repolarization is not well understood. Unlike prior research, this study was designed to look at the influence of repolarization and depolarization heterogeneity on several ECG markers in post-COVID-19 symptomatic patients vs. non-symptomatic COVID-19 patients.

The presence of an extra Rwave (R′), a notch at the end of the R or S wave, or more than one R′ in at least two consecutive leads that correspond to the regions supplied by the main coronary arteries are characteristics of fragmented QRS (FQRS), a depolarization disorder.[6] A wide range of cardiac disorders, including coronary artery disease (CAD), cardiomyopathies, valvular heart disease, aortic dissection, pulmonary embolism, congenital heart disease, and cardiac channelopathies, have been studied in the literature on fQRS during the past several years.[7] It was shown that patients with FQRS on surface ECGs had higher death rates and worse prognosis.[8]

The aim of this study was to evaluate the electrocardiogram (ECG) markers of depolarization and repolarization heterogeneity in symptomatic patients presenting to the outpatient clinic with post-COVID palpitations and compare them to the same markers in post-COVID-19 patients without these symptoms.

Methods

Study participants

The research group was made up of 73 consecutive post-COVID patients who were assessed using an ECG in the outpatient clinic for signs of palpitations and chest discomfort between 12 and 26 weeks after being diagnosed with COVID-19 (the post-COVID period). Symptoms may still be present up to 12 weeks following COVID (ongoing symptomatic COVID).

The control group was made up of 55 consecutive individuals with COVID-19 who were asymptomatic, free of chest discomfort or palpitations, and had no cardiovascular disease or risk factors. The sample size of our investigation was determined using data from a study by Yenerçağ et al.[9]

Electrocardiographic measures included Tpeak-Tend (Tp-e) interval, QTd, Tp-e/QT ratio, Tp-e/QTc ratio, fQRS-T, and FQRS angle (Nihon Kohden, Tokyo, Japan). For analysis, all patients' medical comorbidities, physical examination results, laboratory results, and standard 12-lead ECGs acquired on the day of their index outpatient visit were documented.

All patients had transthoracic echocardiography utilizing Philips HD 11 XE ultrasound equipment (Andover, MA, USA).

Individuals who exhibited symptoms of acute coronary syndromes, complete bundle branch block, nonsinus rhythms (like atrial fibrillation), symptomatic heart failure with ejection fraction (EF) ≤ 50%, outpatient use of QT-prolonging agents (like azithromycin, fluoroquinolones, etc.), and/or electrolyte imbalances upon admission were excluded. Moreover, participants with LVH noted on their echocardiogram reports were excluded from the study since this illness may have an impact on the fQRS-T angle readings. Furthermore, those who had previously experienced severe COVID-19 disease that necessitated hospitalization were not included.

ECG recordings

All patients had 12-lead ECG (Nihon Kohden, Tokyo, Japan) recorded at rest in the supine position with speed of 25 mm/s, height of 10 mm/mV, and filter range of 0.16–100 Hz. Surface ECGs were scanned and imported into Adobe Photoshop CC 2019 (Adobe Photoshop Version: 20.0.0; Adobe Inc.) on a desktop computer. After setting the measurement scales, intervals were computed at 200% magnification.

Clinical ECG equipment cannot identify the spatial QRS-T angle due to their three-dimensional nature and lack of a vector that displays the postero-anterior axis of the heart. As a result, the spatial QRS-T angle—which was appropriate when utilizing 12-lead ECG—was replaced with the fQRS-T angle.[10,11] The fQRS-T angle was simply computed by subtracting the QRS angle from the T angle in the ECG because the majority of ECG machines automatically provide the QRS and T axes. The Tp-e interval was established from the T wave's peak until its termination. The longest Tp-e interval was reported by measuring the Tp-e interval from precordial leads.[12] In cases with complex T waves (biphasic, triphasic, etc.), the interval between the nadir of the first component of the T wave and the end of the T wave was measured.[13,14] The time elapsed between the start of the QRS complex and the conclusion of the T wave was named the QT interval. All leads had their QT intervals measured, and the longest QT interval was noted. The difference between the greatest and minimum QT interval in several leads was used to calculate QTd. Heart rate was calculated using the measured R-R interval. Bazett's formula ($QTc = QT\sqrt{(R\text{-}R\ interval)}$) was used to compute the corrected QTd and corrected QT interval (QTc). These values were used to determine the Tp-e/QT ratios. In a standard 12-lead ECG (0.5-150 Hz), FQRS is defined as the presence of extra R' waves or a notch in the nadir of the R or S wave (fragmentation) in two contiguous leads belonging to a coronary region. Two different cardiologists measured patients' ECG data. These values were computed for every research subject. When there was substantial disagreement, a third independent cardiologist calculated the ECG parameters, and the results were agreed upon. The intraclass correlation coefficients for both intraobserver and interobserver variability were greater than 95% for every measurement assessed.

Statistical analyses

The SPSS 22.0 statistical package for Windows, (SPSS Inc., Chicago, IL, USA) was utilized for all statistical analyses. The Kolmogorov-Smirnov test was utilized to determine whether distributions were normal. The mean ± standard deviation was used to specify quantitative variables with normal distribution, whereas the median (interquartile range) was used to specify variables with irregular distribution. Counts and percentage values were displayed for categorical variables. The Mann Whitney U test and Student's *t* test (unpaired) were used to assess group differences. The chi-square test was used to compare categorical variables. Using factors that were significant in univariate analysis ($P < .05$), multivariate logistic regression (stepwise backward conditional) analysis was performed to identify independent predictors of the sample group. A statistically significant result was defined as a p value less than 0.05.

Results

A total of 128 patients with a history of COVID-19 were included in the final analyses. Of these patients, 73 were in the symptomatic group with complaints of chest pain and palpitation and 55 were in the asymptomatic group. The general characteristics of the patients are shown in Table 1. There were no significant differences between the groups in terms of clinical characteristics or hematological or biochemical parameters, except for smoking status (3 (5.5%) vs. 3 (17.8%), p = 0.037) and ALT levels (23 (13-26) vs. 19 (13-21), p = 0.024).

When we compare the ECG parameters between the two groups (Table 2), there were no significant differences between groups for QRS duration, QT interval, cQT interval, QTd, or fQRS-T angle. There were significant differences between the groups in terms of Tp-e interval, Tp-e/QT, Tp-e/cQT, and FQRS. Tp-e interval, Tp-e/QT, and Tp-e/cQT were found to be higher in asymptomatic post-COVID-19 patients, with statistically significant differences. In contrast, FQRS was detected in more patients in the symptomatic group.

The results of multivariate analysis of FQRS, Tp-e interval, Tp-e/QT, and Tp-e/cQT showed that FQRS (OR: 6.707, 95% CI: 1.733-25.952; p = 0.006) and Tp-e interval (OR:0.880, 95% CI: 0.788-0.983; p = 0.023) were independent predictors of symptomatic post-COVID-19 patients (Table 3).

Discussion

To the best of our knowledge, this study is the first in the literature to compare ECG ventricular depolarization and repolarization parameters between symptomatic and asymptomatic groups of post-COVID patients. To summarize the main findings of our study, presence of FQRS and a lower Tp-e interval were found in more patients whose symptoms continued after COVID-19 disease than in asymptomatic patients.

Tp-e interval and Tp-e/QT ratios have been utilized as event predictors in several clinical situations, such as cardiac failure, Brugada syndrome, hypertrophic cardiomyopathy, and bradyarrhythmia and even in the general population. In comparison to a healthy control group, Yenerçag et al. found that patients with COVID-19 infection had longer Tp-e intervals and higher Tp-e/QT and Tp-e/QTc ratios before initiation of therapy.[9] Conversely, our research revealed statistically significant differences in Tp-e interval, Tp-e/QT, and

Table 1– Comparison of demographic features and laboratory characteristics of asymptomatic and symptomatic post-COVID-19 patients

	Asymptomatic post-COVID-19 patients (n = 55)		Symptomatic post-COVID-19 patients (n = 73)		p
Age (years)	41	±13	38	±11	0.306
Sex, n (%) (Female)	23	(41.8)	41	(56.2)	0.109
Smoking, n (%)	3	(5.5)	13	(17.8)	0.037
Hypertension, n (%)	8	(14.5)	7	(9.5)	0.390
Diabetes, n (%)	3	(5,4)	4	(5.4)	0.995
Hemoglobin (g/dL)	14.55	±1.71	14,49	±1.84	0.832
Htc (%)	43.45	±4.81	43,73	±4.85	0.743
WBC (10^3/mL)	7.23	±1.76	7,40	±1.99	0.711
Lymphocytes (10^3/mL)	2.28	(1.82-2.65)	2,29	±0.79	0.878
Platelets (10^3/mL)	269	±74	280	±61	0.337
Glucose (mg/dL)	104	±31	94	±21	0.055
Creatine (mg/dL)	0.74	±0.24	0,74	±0.18	0.686
eGFR (mL/min/1.73 m^2)	105.09	±17.42	107,88	±17.40	0.227
ALT (U/L)	23	(13-26)	19	(13-21)	0.024
AST (U/L)	20	±10	18	±5	0.954
CRP (mg/L)	1.69	(0.68-5.72)	1.82	(0.80-3.50)	0.939
Sodium (mEq/L)	139	±3	139	±2	0.645
Potassium (mEq/L)	4.27	±0.39	4.20	±0.37	0.402
Calcium (mg/dL)	9.49	±0.48	9.33	±0.42	0.344
TSH (mIU/L)	1.62	(1.31-2.39)	1.55	(2.35-2.27)	0.879
T3 (nmol/L)	3.38	±0.59	3,11	±0.61	0.893
T4 (nmol/L)	1.28	±0.26	1,34	±0.47	0.687

ALT: Alanine Transaminase; AST: Aspartate Transferase; WBC: White Blood Cells, Htc: Hematocrit; eGFR: Estimated Glomerular Filtration Rate; TSH: Thyroid Stimulating Hormone; T3: Triiodothyronine; T4: Thyroxine; CRP: C-Reactive Protein.

Table 2 – Comparison of electrocardiographic (ECG) findings of groups.

	Group 0 (Asymptomatic post-COVID-19 patients)		Group 1 (Symptomatic post-COVID-19 patients)		p
Heart rate, bpm	82	±15	83	±16	0.992
QRS duration, ms	93	±11	94	±14	0.630
Tp-e interval, ms	65	±9	61	±14	0.009
QT interval, ms	382	±31	376	±32	0.284
cQT interval, ms	439	±26	433	±27	0.139
QTd, ms	56	±19	53	±20	0.431
Tp-e/QT	0.17	±0.03	0.16	±0.04	0.031
Tp-e/cQT	0.15	±0.02	0.14	±0.03	0.034
FQRS, n(%)	3	(5)	16	(22)	0.01
fQRS-T angle (°)	41	(13-60)	39	(14-53)	0.925

Tp-e: peak-to-end interval of the T wave; cQT interval: corrected QT interval; FQRS: Fragmented QRS; fQRS-T angle: frontal QRS-T angle; QTd: QT dispersion.

Table 3 – Logistic regression models for post-COVID-19 patients

	Univariate			Multivariate		
	Univariate OR, 95% CI		p	Multivariate OR, 95% CI		p
Tp-e interval	0.968	(0.937-0.999)	0.04	0.880	(0.788-0.983)	0.023
Tp-e/QT	0.000	(0.000-6.376)	0.102	-	-	-
Tp-e/cQT	0.000	(0.000-10.700)	0.111	-	-	-
FQRS	4.865	(1.341-17.660)	0.016	6.707	(1.733-25.952)	0.006

Tp-e: peak-to-end interval of the T wave; cQT interval: corrected QT interval; FQRS: Fragmented QRS; OR: odds ratio; CI: confidence interval.

Tp-e/cQT between asymptomatic and symptomatic post-COVID-19 individuals. The biggest difference in our study was that the control group consisted of patients with a history of COVID-19 infection, even if they had been asymptomatic, rather than a healthy control group. For this reason, different results were obtained for the ventricular repolarization markers Tp-e interval, Tp-e/QT, and Tp-e/cQT between symptomatic and asymptomatic post-COVID-19 patient groups compared to other studies including healthy control groups. We think that there is a need for studies of this subject involving more patients and centers.[15]

QT interval prolongation is a traditional ECG indicator of vulnerability to torsades de pointes (TdP) or malignant arrhythmias. Handheld devices can streamline monitoring for COVID-19 patients, particularly those on QT-prolonging medications like azithromycin or hydroxychloroquine for SARS-CoV-2.[16] However, in our study, no significant difference was found between the groups in terms of QT or cQT intervals. We think that this may be due to the fact that our patient groups consisted of outpatients who did not have serious COVID-19 infections and therefore did not use drugs that prolong the QT interval.

Elevated Alanine Transaminase (ALT) levels have been detected in COVID-19 disease, especially due to hypoxic and drug toxicity, depending on the severity of the disease.[17] Our study and control groups were outpatients with no history of serious COVID-19 infection and were seen at least 12 weeks after the COVID-19 disease. However, while there was a significant difference between groups in ALT levels, median ALT levels were within the normal reference range in both groups.

A typical ECG recording can be used to quickly identify FQRS, a depolarization condition. It represents the myocardium's fibrotic tissue-induced conduction delay.[6] Research has demonstrated a correlation between myocardial scarring and FQRS, which is seen in the superficial ECGs of patients with CAD or suspected CAD.[18] According to one study, f-QRS was detected in 24.2% of patients with COVID-19.[19] In our study, a similar rate was found in symptomatic post-COVID-19 patients (22%). Interestingly, the rate in asymptomatic post-COVID-19 patients was low, at 5%. Although a relationship between FQRS and the severity of COVID-19 disease has been proven,[20] we think that as shown in our study it may be effective for identifying a group that may be symptomatic among COVID-19 patients who have not had serious illness. In a recently

published paper, Yildirim et al.[8] studied 114 patients with COVID-19. Especially in patients with COVID-19, FQRS was been found to be an indicator of poor clinical outcomes. In another retrospective study, Bektas et al. suggested that presence of FQRS in patients with COVID-19 may be useful for predicting cardiovascular outcomes.[19] In our study, FQRS was detected in more symptomatic post-COVID-19 patients than in patients in the asymptomatic group. Interestingly, although both groups had a history of COVID-19 infection, FQRS was detected in significantly more patients in the symptomatic group and was identified as an independent predictor. Another interesting aspect of our study is that even after more than 12 weeks had passed since the COVID-19 illness, the ECG findings of patients remain, even if they do not have a history of serious COVID-19.

Limitations

Our research has several limitations. Since our initial sample size of 130 COVID-19 patients was small, a larger cohort study is needed to validate our findings. The absence of control (prior to COVID-19 infection) and/or recovery data is the study's main drawback. We will never know whether the COVID-19 infection is to blame for the prolongation or not.

Conclusion

In summary, our investigation revealed that symptomatic post-COVID-19 patients exhibited a higher frequency of FQRS and smaller Tp-e intervals than asymptomatic post-COVID-19 patients. Furthermore, FQRS and Tp-e were identified as independent predictors in the symptomatic group (**Central Illustration**). We postulate that FQRS would be useful in identifying the subset of outpatient COVID-19 patients who have not experienced a severe illness and who might exhibit symptoms. Our results require long-term, large-scale research to be supported.

Author Contributions

Conception and design of the research: Karakayalı M, Altunova M, Rencüzoğulları I; acquisition of data: Karakayalı M, Ilis D, Omar T, Guzel E; analysis and interpretation of the data and statistical analysis: Artac I, Karabağ Y; writing of the manuscript: Karakayalı M; critical revision of the manuscript for intellectual content: Karakayalı M, Altunova M, Rencüzoğulları I, Karabağ Y.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Faculty of Medicine of Kafkas University under the protocol number 80576354-050-99/177. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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