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The relationship between severe acute respiratory syndrome coronavirus 2 (SARS - COV - 2) pandemic and fragmented QRS

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A B S T R A C T

Objective: The aim of the study is to determine the frequency of fragmented QRS (FQRS) in patients with SARS - COV - 2.

Methods: A total of 125 consecutive patients over 20 years of age who were hospitalized for SARS - COV - 2 between 20th March 2020 and 18th May 2020 were included in the study. The data of the patients in the inpatient ward and in the intensive care unit were recorded separately. The duration of QRS and presence of FQRS were evaluated by two experienced cardiologists. The patients were divided into two groups as FQRS positive and FQRS negative considering presence of FQRS. Moreover, the frequency of FQRS in the patients in the inpatient ward and in the intensive care unit were compared with each other.

Results: FQRS was found in 24% of the patients who had SARS-COV-2. There was no difference between FQRS positive and negative groups in terms of age and gender. Heart rate was higher in FQRS positive group. C-reactive protein (7.25 ± 6.65 mg/dl vs. 4.80 ± 4.48 mg/dl; p = .02) levels were also significantly higher in the FQRS positive group. In patients with SARS-COV-2, intensive care unit requirement increased with increasing levels of troponin (p < .000). A positive correlation was detected between serum CRP levels and FQRS (r = 0.204, p = .024).

Conclusions: The frequency of FQRS is high in patients with SARS - COV - 2. Serum CRP levels increase with increasing frequency of FQRS in patients with SARS - COV - 2 indicating that patients with FQRS are exposed to more inflammation. Presence of FQRS in SARS - COV - 2 patients may be useful in predicting cardiovascular outcomes.

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A R T I C L E   I N F O

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Introduction

Pandemics are large-scale infectious disease outbreaks that can increase morbidity and mortality in a wide geographic area and cause significant economic, social and political disruption. Evidence suggests that the likelihood of a pandemic has increased in the last century due to increased global travel and integration, urbanization, changes in land use and more use of the natural environment. [1,2] Crucial points to struggle with a pandemic are to identify and limit the outbreaks that can lead to a pandemic and to maintain an adequate health care system [3].

The best known pandemics in the last century are Spanish flu in 1918, Asian flu in 1957, Hong Kong flu in 1968, and swine flu in 2009. Moreover, severe acute respiratory failure syndrome (SARS) in 2003, influenza (H1N1) in 2009, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, Ebola in 2014 and Zika virus in 2016 adversely affected many people worldwide and caused death of many people [4].

Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease caused by a new corona virus, SARS - COV - 2, which started in December 2019 in Wuhan, China, [4] Currently, it is a pandemic and increases distress, panic and anxiety in all human beings beside those exposed to the virus [5].

The recent reports have revealed that respiratory, neurological and cardiovascular systems are affected during the course of the SARS - COV - 2 infection [6]. Fragmented QRS (FQRS) is a depolarization disorder defined by the presence of an additional R wave (R') or the presence of a notch at the end of the R or S wave or presence of more than one R' in at least two consecutive leads corresponding to the areas fed by the major coronary arteries. [7] In a study, evaluating patients with coronary artery disease (CAD), those with FQRS had significantly higher all cause mortality and higher frequency of adverse cardiovascular outcomes (myocardial infarction, sudden cardiac death, revascularization) [8].
The aim of this study is to predict the course of the disease with the help of FQRS, a well-established predictor of future cardiovascular events, during the ongoing struggle against SARS-COV-2 all over the world and in our country.

Material and methods

In this retrospective study, 125 consecutive patients over 20 years of age who were hospitalized for SARS-COV-2 between 20th March and 18th May 2020 were included. Real-time reverse transcription polymerase chain reaction assay (RT-PCR) molecular method was applied for RNA analysis of SARS-CoV-2 virus isolated from the nasopharyngeal swab samples. The RT-PCR assay was performed using a SARS-CoV-2 (2019-nCoV) qPCR Detection Kit according to the manufacturer’s protocol (Bioeksen R&D Technologies Co Ltd).

Patients with cardiac pacemaker, diabetes mellitus, coronary artery disease (CAD), hypertension, congestive heart failure, severe heart valve disease or severe electrolyte imbalance were not enrolled in the study. Those with suspicious findings for CAD and hypertension on ECG were also excluded.

Data of patients with SARS-COV-2 were investigated retrospectively. Baseline demographical characteristics (age, gender, etc.) of the patients were recorded. Hospitalization in the regular inpatient ward and/or in the intensive care unit were separately analysed. Conventional blood sample parameters including hemoglobin, white blood cell, neutrophil, lymphocyte, monocyte, platelet, alanine aminotransferase, creatinin, sodium, potassium, troponin, ferritin, D-dimer and CRP levels were also recorded.

Electrocardiograms of the patients were taken using a conventional 12 channel ECG device at a 25 mm/s speed and 10 mm/mV amplitude in supine position. (Guangdong Biolight Meditech Co.) FQRS was described as notching in the R or S wave, RS' pattern or multiple R' in at least two consecutive leads corresponding to the areas fed by the major coronary arteries [7]. The duration of QRS and the presence of FQRS were evaluated by two separate cardiologists who were not aware of the clinical information of the patients and study design.

The patients were divided into two groups as FQRS positive and FQRS negative and the data of the patients were compared with each other. Moreover, the frequency of FQRS was compared between the patients in the regular inpatient ward and those in the intensive care unit.

This retrospective study was approved by the Republic of Turkey Ministry of Health (No. 2020-05-06T23_02_55) as well as the local ethical committee.

Statistical analysis

In all statistical analysis SPSS 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used. In order to test normality of distribution, Kolmogorov-Smirnov test was used. The numeric variables were expressed as mean ± SD while the categorical variables were expressed as percentage. Student–t-test or Mann Whitney U test was used to test the difference of the numeric variables between the groups. In order to test the difference of the categorical variables between the groups, Chi-square test was used. Point–biserial analysis was applied to evaluate the correlation between the fragmented QRS positivity, CRP and troponin levels. Linear regression analysis was performed to evaluate independent predictors of FQRS positivity. A p value of <0.05 was accepted as statistically significant.

Results

FQRS was found in 24% of patients who had SARS-COV-2. There was no significant difference between FQRS positive and negative groups in terms of age and gender. Heart rate was higher in the FQRS positive group. C-reactive protein (7.25 ± 6.65 mg/dl vs. 4.80 ± 4.48 mg/dl; p = .02) levels were also significantly higher in the FQRS positive group (Table 1).

The frequency of FQRS was similar when the patients in the inpatient ward were compared with those in the intensive care unit (Table 2).

The requirement for intensive care unit increased with increasing levels of troponin in patients with SARS-COV-2 (p < .000, Table 3). Moreover, a significant positive correlation was detected between serum CRP levels, heart rate and frequency of FQRS in patients with SARS-COV-2 (r = 0.204, p = .024, r = 0.187 p = .029).

Linear regression analyses revealed that serum CRP levels and heart rate were the independent predictors of presence of FQRS (Table 4).

Discussion

Our study results revealed that frequency of FQRS is significantly higher in patients with SARS-COV-2. In patients with FQRS, serum CRP levels are significantly higher and there is a positive correlation between frequency of FQRS and serum CRP levels. In the light of these data, it can be speculated that SARS-COV-2 patients with FQRS are exposed to more inflammation. Moreover, high frequency of FQRS in SARS-COV-2 patients may be a predictor of future adverse cardiovascular outcomes.

The new coronavirus SARS-COV-2 outbreak, first reported on December 8th 2019 in Hubei province of China, was adopted as a pandemic by the World Health Organization (WHO) on 11th March 2020. Based on the review of available data in public databases, the risk of infection and mortality have been found to be increased in males and older individuals [6].

Table 1

|                | Fragmented QRS | P value |
|----------------|----------------|---------|
|                | Positive (n = 30) | Negative (n = 95) |
| Age, years     | 67.73 ± 18.39 | 69.67 ± 15.44 | 0.56 |
| Gender, male, n (%) | 13 (43.3) | 50 (52.63) | 0.40 |
| Heart rate, bpm | 93.8 ± 19.59 | 85.27 ± 19.23 | 0.03 |
| Hemoglobin, g/dl | 12.38 ± 1.94 | 12.18 ± 2.47 | 0.72 |
| White blood cell, 10³ μl | 10.39 ± 6.63 | 10.84 ± 6.58 | 0.77 |
| Neutrophil, 10³ μl | 8.16 ± 6.49 | 8.11 ± 6.11 | 0.97 |
| Lymphocyte, 10³ μl | 1.53 ± 0.77 | 1.60 ± 1.18 | 0.81 |
| Monocyte, 10³ μl | 0.77 ± 0.38 | 0.71 ± 0.36 | 0.53 |
| Platelet, 10³ μl | 240.83 ± 75.50 | 249.47 ± 97.06 | 0.69 |
| Ferritin, mg/dl | 71.5 ± 24.74 | 347.0 ± 222.03 | 0.22 |
| Sodium, mEq/L | 137.7 ± 6.31 | 135.94 ± 4.19 | 0.46 |
| Potassium, mmol/L | 4.19 ± 0.47 | 4.52 ± 1.49 | 0.58 |
| Creatinin, mg/dl | 0.92 ± 1.25 | 0.94 ± 1.39 | 0.98 |
| Ferritin | 71.5 ± 24.74 | 347.0 ± 222.03 | 0.22 |
| CRP, mg/dl | 7.25 ± 6.65 | 4.80 ± 4.48 | 0.02 |
| QRS | 94.27 ± 9.22 | 97.42 ± 22.40 | 0.45 |

Table 2

|                | Fragmented QRS | P value |
|----------------|----------------|---------|
|                | Positive (n = 30) | Negative (n = 95) |
| Inpatient ward | 13 (43.3) | 44 (46.31) | 0.77 |
| Intensive care unit | 17 (56.7) | 51 (53.69) |

Data are given as mean ± SD, n (%), CRP: C-reactive protein.
In addition to pulmonary involvement in the form of interstitial pneumonia of varying degrees, the worst scenario due to this new identified virus is development of multiorgan failure. The cardiovascular (CV) system appears to have interactions with the SARS-CoV-2. Recent reports revealed that signs of myocardial damage were found in 20–40% of the patients presented with cardiac chest pain, fulminant heart failure, cardiac arrhythmias and cardiac arrest [6].

Severe SARS-CoV-2 is associated with systemic inflammation, pro-inflammatory cytokine storm and sepsis leading to multiorgan failure and death [9]. SARS-CoV-2 is associated with a predisposition to cardiac arrhythmia secondary to metabolic dysfunction, myocardial inflammation and activation of the sympathetic nervous system [10]. Following Acute Respiratory Distress Syndrome (ARDS), arrhythmia is the second most serious complication which was detected in 16.7% of the patients. Arrhythmia was observed in 7% of the patients who did not require ICU treatment and in 44% of cases admitted to ICU [11]. The most common types of arrhythmia seen in the patients with SARS-CoV-2 are atrial fibrillation, conduction block, ventricular tachycardia and ventricular fibrillation.

FQRS is a depolarization disorder that can be easily detected from a routine ECG recording. It represents the conduction delay caused by fibrotic tissue in the myocardium [7]. The fibrotic tissue increases the distance required by the electrical impulse to travel, slows the conduction velocity and ultimately causes inhomogeneous ventricular activation. This results in notching of the QRS complex in ECG [12]. It has been shown that FQRS detected in superficial ECGs of individuals with coronary artery disease or suspected coronary artery disease is associated with myocardial scar. In fact, presence of FQRS is more sensitive and has higher negative predictive value than Q wave in detecting scar tissue [13]. FQRS is also an independent marker for arrhythmic events and mortality in patients with CAD [7]. Biochemical, echocardiographic and radiological methods have been described in detecting myocardial fibrosis, but these are mostly sophisticated and expensive methods [14]. A recent study showed that FQRS was useful in predicting scar areas detected by magnetic resonans imaging [15]. FQRS can be easily detected from routine ECG recordings and does not require special equipment and training [16].

Although the frequency of FQRS differs in different studies; in a prospective study, routine 12-lead resting ECGs of 1500 consecutive healthy adults (707 males, age 38 ± 12 years) were screened and 5.1% (76) were found to have FQRS [17]. In our study, this rate was 24.2% in patients with SARS-CoV-2. The higher frequency of FQRS in patients SARS-CoV-2 may be a predictor of arrhythmic events and mortality. Moreover, a number of studies have shown that cardiac complications, including fulminant myocarditis, are potential consequences of SARS-CoV-2 infection. Heart failure was reported in 23% of SARS-CoV-2 patients in a recent report from China. In the subgroup analysis, frequency of heart failure was 52% and 12% in the victims and survivors, respectively [18]. In our study, we found that sinus tachycardia was more frequent and was an independent predictor of FQRS. Increased heart rate in these patients may be a sign of subtle myocardial systolic dysfunction.

Serum creatine kinase (CK), lactate dehydrogenase (LDH) and C-reactive protein (CRP) levels are increased in most of the patients hospitalized for SARS-CoV-2 [19]. Serum CRP levels positively correlate with lung lesions in the early stage of SARS-CoV-2 and may reflect the severity of the disease [20]. Moreover, it has been shown that in patients with severe SARS-CoV-2, CRP levels increase significantly even before detection of the lung lesions in computerized tomography (CT) [21]. These findings demonstrate the significance of CRP levels in patients with SARS-CoV-2. In our study, high levels of CRP and correlation between CRP levels and FQRS suggest that myocardial exposure may also be associated with inflammation.

Although exact mechanism for the effects of SARS-CoV-2 on the cardiovascular system is not known, various mechanisms associated with other viral diseases can also apply to the patients with SARS-CoV-2. In other viral diseases, patients with heart failure have an increased risk of decompensation. Moreover, viral diseases can potentially deteriorate atherosclerotic plaques with systemic inflammatory responses [22]. In the SARS and MERS-CoV epidemics, early reports revealed acute myocardial infarction in almost two out of five deaths. [23,24]. Considering the possibility of cardiac involvement in patients with SARS-CoV-2, presence of FQRS can be used to predict adverse cardiovascular events.

Serum troponin levels were found to be increased in 8–12% of the patients with SARS-CoV-2. In severe forms of SARS-CoV-2 infection, troponin levels have significantly increased compared to milder disease forms [25]. In our study, serum troponin levels were also significantly increased in patients in the intensive care unit. However, we were not able to determine a positive correlation between FQRS and troponin levels.

Limited number of patients and lack of echocardiographic evaluation can be considered as limitations of our study. On the other hand, to the best of our knowledge, this is the first study to evaluate the relationship between serum levels of CRP and frequency of FQRS in patients with SARS-CoV-2.

Consequently, FQRS is more frequently seen in patients with SARS-CoV-2. There is a positive correlation between frequency of FQRS and serum CRP levels. FQRS can be used to predict increased inflammation and adverse cardiovascular events.

### Declaration of Competing Interest

None.

### References

[1] Jones KE, Patel NG, Levy MA, Storey D, Balk D, et al. Global Trends in Emerging Infectious Diseases. Nature. 2008;451(718):990–3 [PMC free article] [PubMed].

[2] Morse SS. Factors in the Emergence of Infectious Diseases. Emerg Infect Dis. 1995;1(1):7–15 [PMC free article] [PubMed].

[3] Smolinsky MS, Hamburg MA, Ledenbergh J, editors. Microbial threats to health: Emergence, detection, and response. Washington, DC: National Academies Press; 2003.

[4] Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? Int J Epidemiol. 2020;1–10.

[5] Shuja KH, Ageel M, Jaffar A, Ahmed A. COVID-19 pandemic and impending global mental health implications. Psychiatr Danub. 2020;32(1):32–5. https://doi.org/10.24869/psyd.2020.32 PubMed PMID: 32303027.
[6] Guzik Tomasz J, Mohiddin Saidi A, Dimarco Anthony, Patel Vimal, Savvatis Kostas, Marelli-Berg Federica M, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020. https://doi.org/10.1093/cvr/cva106; cva106.

[7] Das MK Saha C, El Masry H, et al. Fragmented QRS on a 12-lead ECG: a predictor of mortality and cardiac events in patients with coronary artery disease. Heart Rhythm. 2007;4(11):1385–92.

[8] Cheema A, Khalid A, Wimmer A, Bartone C, Chow T, Spertus JA, et al. Fragmented QRS and mortality risk in patients with left ventricular dysfunction. Circ Arrhythm Electrophysiol. 2010 Aug;3(4):339–44. https://doi.org/10.1161/CIRCEP.110.940478.

[9] Iwata-Yoshikawa N, Okamura T, Shimizu Y, Hasegawa H, Takeda M, Nagata N. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. J Virol. 2019;93:e01815–8.

[10] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020. https://doi.org/10.1001/jama.2020.1585.

[11] Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl). 2020. https://doi.org/10.1097/CMA.0000000000000744.

[12] Gardner PI, Ursell PC, Fenoglio Jr JJ, Wit AL. Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarcts. Circulation. 1985;72:596–611.

[13] Das MK, Khan B, Jacob S, Kumar A, Mahenthiran J. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation. 2006;113:2495–501.

[14] Jellis C, Martin J, Narula J, Marwick TH. Assessment of nonischemic myocardial fibrosis. J Am Coll Cardiol. 56:89–97.

[15] Homsi M, Alsayed L, Das MK, Mahenthiran J. Fragmented QRS complexes on a 12-lead ECG is a marker of greater myocardial scarring related to coronary artery disease by magnetic resonance imaging. J Am Coll Cardiol. 2008;51:A31.

[16] Das Mithilesh Kumar, Maskoun Waddah, Shen Changyu, Michael Mark A, Suradi Hussam, Desai Mona, et al. Fragmented QRS on twelve-lead electrocardiogram predicts arrhythmic events in patients with ischemic and nonischemic cardiomyopathy. Heart Rhythm. 2010;7(1):74–80. https://doi.org/10.1016/j.hrthm.2009.09.065.

[17] Tian Ying, Zhang Ying, Yan Qian, Mao Jun, Dong Jianzeng, Ma Changsheng, et al. Fragmented QRS complex in healthy adults: prevalence, characteristics, mechanisms, and clinical implications. Int J Heart Rhythm. 2017;2(1):34–9.

[18] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.

[19] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.

[20] Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect. 2020;50(4):332–4. https://doi.org/10.1016/j.medmal.2020.03.007 [Epub 2020 Mar 31].

[21] Tan Chaochao, Huang Ying, Shi Fengxia, Tan Kui, Ma Qionghui, Chen Yong, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol. 2020 Apr;13. https://doi.org/10.1002/jmv.25871. Online ahead of print.

[22] Cole JE, Park I, Ahern DJ, Kassiteridi C, Danso Abeam D, Goddard ME, et al. Immune cell censs in murine atherosclerosis: cytometry by time of flight illuminates vascular myeloid cell diversity. Cardiovasc Res. 2018;114:1366–71.

[23] PJH Kusters, Lutgens E, TTP Seijkens. Exploring immune checkpoints as potential therapeutic targets in atherosclerosis. Cardiovasc Res. 2018;114:368–77.

[24] Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet. 2003;361:1767–72.

[25] Lippi G, Lave CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. Prog Cardiovasc Dis. 2020. https://doi.org/10.1016/j.pcad.2020.03.001.