Fragmented QRS is a marker of mortality in patients with severe COVID-19: A retrospective observational study

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Abstract

Objective: In this study, we aimed to investigate the association of fragmented QRS (f-QRS) with in-hospital death in patients with severe novel coronavirus disease 2019 (COVID-19).

Methods: This was a retrospective and observational study. A total of 201 consecutive patients with severe COVID-19 were enrolled. Demographic data, laboratory parameters, medications, electrocardiographic (ECG) findings, and clinical outcomes were recorded. Patients with and without f-QRS were compared, and predictors of all-cause in-hospital mortality were analyzed.

Results: A total of 135 patients without f-QRS (mean age of 64 years, 43% women) and 66 patients with f-QRS (mean age of 66 years, 39% women) were included. C-reactive protein (CRP), D-dimer, troponin I, ferritin levels, and CRP to albumin ratio were significantly higher in patients with f-QRS. The need for invasive mechanical ventilation (63.6% vs. 41.5%, p=0.003) and all-cause in-hospital mortality [54.5% vs. 28.9%, log rank p=0.001, relative risk 1.88, 95% confidence interval (CI) 1.16–4.78] were significantly higher in patients with f-QRS. A number value of f-QRS leads ≥2 yields sensitivity and specificity (85.3% and 86.7%, respectively) for predicting in-hospital all-cause mortality. Multivariable analysis showed that f-QRS (odds ratio: 1.041, 95% CI: 1.021–1.192, p=0.040) were independently associated with in-hospital death.

Conclusion: This study revealed that the presence of f-QRS in ECG is associated with higher in-hospital all-cause mortality in patients with severe COVID-19. f-QRS is an easily applicable simple indicator to predict the risk of death in these patients.

Keywords: coronavirus disease 2019, electrocardiography, fragmented QRS, mortality

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Introduction

In December 2019, the Chinese city of Wuhan drew attention with cases of pneumonia of unknown origin. When the cause of pneumonia was investigated, a virus (which was later called 2019 novel coronavirus) was found (1). The World Health Organization (WHO) announced a standard format of coronavirus disease 2019 (COVID-19) for this novel coronavirus pneumonia on February 11, 2020; and on the same day, the International Committee on Taxonomy of Viruses named this novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). Given the rapid spread of this virus, COVID-19 was declared a pandemic by the WHO on March 11, 2020 (3).

Mortality owing to COVID-19 is generally caused by the respiratory system. Complications arising from the cardiovascular system are another important cause of mortality. Cardiac complications due to COVID-19 may be because of myocardial injury (mainly owing to ischemia or myocarditis), arrhythmia, new onset, or worsening of pre-existing heart failure, thromboembolic events, and medical therapy (4).

In a study evaluating the electrocardiography (ECG) data of patients with COVID-19, it is recommended that patients with delayed ventricular conduction should be monitored more closely (5). Fragmented QRS (f-QRS) is a relatively new parameter of proven prognostic value in various populations. Its presence on ECG is associated with myocardial scarring and ven-

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HIGHLIGHTS

- Fragmented QRS (f-QRS) is a marker that shows myocardial scar and can be easily determined by electrocardiography (ECG).
- The presence of f-QRS on ECG is independently associated with all-cause in-hospital mortality in patients with severe coronavirus disease 2019 (COVID-19).
- The need for invasive mechanical ventilation was higher in critically ill patients with COVID-19 and f-QRS.
- There is a positive correlation between the presence of f-QRS with C-reactive protein (CRP) and CRP to albumin ratio.

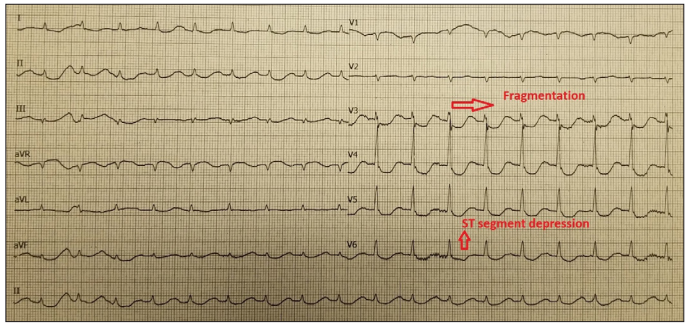

Figure 1. ECG sample with fragmented QRS and ST segment depression

tricular conduction disturbances, which may predispose a patients to ventricular arrhythmias (6-9). f-QRS can be defined as the presence of additional R′ waves or a notch in the nadir of the R or S wave (fragmentation) in 2 contiguous leads corresponding to a coronary territory in a routine 12-lead ECG (0.5–150 Hz) (Fig. 1) (10). The f-QRS is an easily detectable parameter in the standard 12-lead ECG and has been associated with mortality in many cardiovascular events (11).

The number of studies investigating the association between the presence of f-QRS and clinical outcomes in severe COVID-19 is limited. Therefore, we aimed to assess the relationship between f-QRS and in-hospital mortality in patients critically ill with COVID-19.

Methods

The study was designed retrospectively at Merkez Efendi State Hospital, which is a pandemic hospital in Manisa City of Turkey. The Ministry of Health, Republic of Turkey, gave approval for the study. The research protocol complied with the Declaration of Helsinki and was approved by Celal Bayar University Medicine Faculty, Non-Interventional Clinical Trials Ethics Committee (decision #85252386-050.04.04.04). Consecutive 201 patients with severe COVID-19 followed from June 01 to September 30, 2020, in the intensive care unit (ICU) were included in this study. Patients who did not require follow-up in the ICU were not included in the study. A total of 218 hospitalized patients in the ICU with the diagnosis of COVID-19 were examined retrospectively. Four patients with DDD-pacemaker and 1 patient with VVI-pacemaker were excluded from the study, and 12 patients were excluded from the study because electrocardiographic data were not available. In the final analysis, 201 patients were included in the study. SARS-CoV-2 PCR tests (SARS-CoV-2 with qPCR Detection Kit and Bio-Speedy) were positive for all the patients. The ECGs were obtained and evaluated on admission to the ICU. The patients were divided into 2 groups as patients with fragmented and non-fragmented QRS. The ECG recording device was MAC 2000, GE Medical Systems Information Technologies, Inc., Milwaukee, Wisconsin, USA. The ECG data of all the patients were extracted from the hospital archive and electronic medical records. All demographic characteristics (age and sex), symptoms, pre-existing comorbidities, laboratory parameters, drugs, and outcome data were recorded by investigating the medical history of the patients. Chest computed tomography (CT) findings of all the patients were categorized according to radiology reports. Patients who needed mechanical ventilation owing to respiratory failure were recorded. The all-cause in-hospital mortality of the patients was recorded. We followed all the patients during their hospital stay. Fifty patients were randomly selected to repeat the analysis of the QRS complex, this time blinded, by the same operator and by a second operator to establish the interobserver and intraobserver variability.

Statistical analysis

In this study, which was conducted to determine the association between f-QRS complex and disease severity in patients with COVID-19, power was determined by taking at least 0.80 and 1st type error as 0.05 for each variable. The categorical variables were expressed in frequencies and percentages. Categorical variables were compared using the χ^2 test. Baseline continuous variables were presented as mean ± standard deviations (SD) or median (interquartile range), depending on the distribution of the data. Whether the continuous measurement averages were normally distributed or not was checked with the Kolmogorov-Smirnov (n>50) and Skewness-Kurtosis tests, and parametric tests were applied because the variables were normally distributed. The continuous variables were compared using the t-test or the Mann-Whitney U test as appropriate. Independent t-test was performed to compare the measurement averages according to the f-QRS factor. Survival analysis (Kaplan-Meier method) and log-rank test were used to determine the effects of some factors on survival rates. f-QRS cut-off values to predict mortality were determined by the area under the curve (AUC) and receiver operating characteristic (ROC) analysis. Spearman correlation co-efficients were calculated to determine relationships between measurements. To determine interobserver and intraobserver variability, we used the intraclass correlation coefficient (ICC) for continuous variables and the kappa coefficient for categorical variables. An ICC <0.4 was considered poor, ICC of 0.4–0.75 fair to good; ICC > 0.75 excellent. Binary logistic regression analysis was applied to identify

predictors of in-hospital mortality. For all analyses, p<0.05 was considered statistically significant. Analyses are performed with the Statistical Package for the Social Sciences version 24.0 (SPSS Inc, Chicago, Illinois, USA).

Results

A total of 201 consecutive patients critically ill with COVID-19 were included in this study. The number of patients with f-QRS was 66, and the number of patients without it was 135. Baseline characteristics of study population are given in Table 1. The mean age of all population was 65 years. There were no significant differences in age, sex, smoking, alcohol use, body mass index, or blood pressure between the two groups. Prevalence of the symptoms on admission such as fever, cough, headache, diarrhea, fatigue, muscle ache, chest pain, or taste dysfunction were also similar between the two groups. Palpitations were more common in patients with f-QRS. There was only one difference in terms of comorbid conditions between the patients with fragmented and non-fragmented QRS. Renal failure was more common in patients with f-QRS. However, there was no statistical difference in hemodialysis. Other comorbid conditions were similar in both the groups. There was no significant difference in terms of CT thorax findings and length of in-hospital stay (days) in the 2 groups. The need for invasive mechanical ventilation (63.6% vs. 41.5%, p=0.003) and all-cause in-hospital mortality [54.5% vs 28.9%, log rank p=0.001, relative risk 1.88, 95% confidence interval (CI) 1.16–4.78] were significantly higher in patients with f-QRS (Fig. 2).

Laboratory parameters and medications are given in Table 2. Serum D-dimer, troponin I, and ferritin levels were statistically significantly higher in patients with f-QRS. However, serum albumin levels were significantly lower in the f-QRS group. C-reactive protein (CRP) and CRP to albumin ratio (CAR) were higher in patients with severe COVID-19 and f-QRS. There was no significant difference between the two groups in other laboratory parameters. No statistically significant difference was found between the use of cardiovascular (antihypertensive, antihyperlipidemic, and antiaggregant) drugs in the groups. There was no difference in the use of hydroxychloroquine in patients with and without f-QRS. However, the use of azithromycin, favipiravir, and immunosuppressive agents or steroids was more common in patients with f-QRS.

ECG parameters are given in Table 3. The mean heart rate was significantly higher in patients with f-QRS. The rates of atrial fibrillation, atrioventricular block, premature atrial contractions, premature ventricular contractions, right bundle-branch block, and left bundle-branch block were similar in both the groups. ST segment depression was higher in patients with f-QRS. When we look at the localization of ST segment depression, it was found more in the anterior derivation. T-wave inversion was observed at a similar rate in both the groups as were PR and QT distance. QRS wave width was determined to be more in patients with f-QRS. When corrected QT (QTc) was calculated, it was found to be more in patients with f-QRS. Left

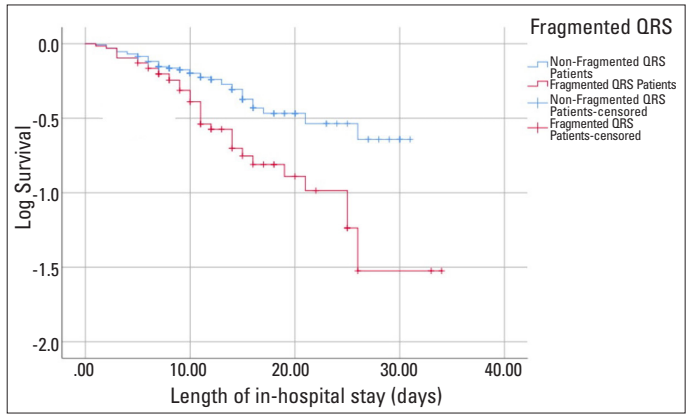

Figure 2. Kaplan-Meier survival rates for patients with and without fragmented QRS

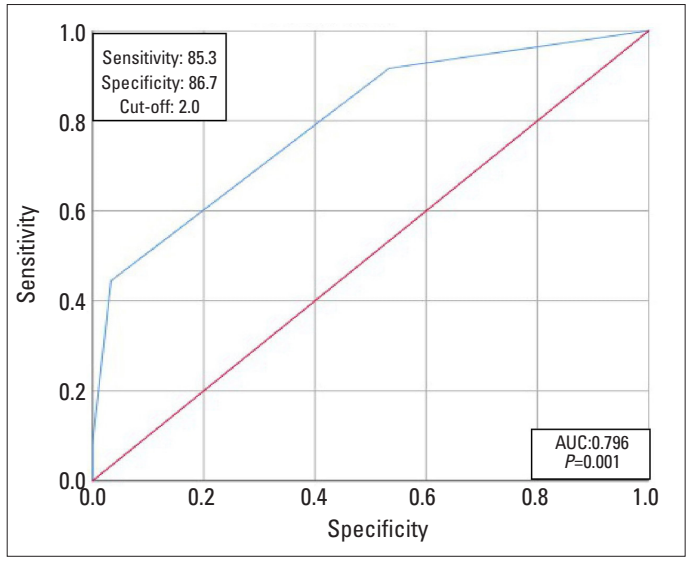

Figure 3. Receiver operating characteristic curve analysis for the number of leads with fragmented QRS to predict mortality

ventricular hypertrophy and right ventricular hypertrophy were similar in both the groups.

ROC analysis of the number of leads with f-QRS to predict all-cause in-hospital mortality is shown in Figure 3. The ROC curve showed that the optimal cut-off value for the number of f-QRS leads is ≥2. A number value of f-QRS leads ≥2 yields sensitivity and specificity (85.3% and 86.7%, respectively) for predicting in-hospital all-cause mortality.

f-QRS locations were grouped as anterior, lateral, and inferior. f-QRS was observed in 2 different regions in 17 patients. The effect of f-QRS detection region on mortality was evaluated by logistic regression. f-QRS increased mortality by 2.6 times when observed in lateral leads, 2.5 times when observed in inferior leads, and 3.7 times when observed in anterior leads (Table 4).

After adjustment for potential confounders, multivariable analyses showed that urea (OR: 1.030, 95% CI: 1.013–1.048, p=0.002), CAR (OR: 1.238, 95% CI: 1.011–1.421, p=0.021), D-dimer (OR:1.316, 95% CI:1.009–1.454, p=0.033), age (OR: 1.064, 95% CI: 1.018–1.113, p=0.006), hypertension (OR: 3.507,

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Table 1. Baseline characteristics of study population

	Patients with non-fragmented QRS (n=135)	Patients with fragmented QRS (n=66)	*P*-value
Age, years	64.08±13.21	66.29±13.72	0.273
Female sex, n (%)	58 (43.0)	26 (39.4)	0.630
Smoking, n (%)	55 (40.7)	24 (36.4)	0.551
Alcohol use, n (%)	17 (12.6)	5 (7.6)	0.285
Body mass index, kg/m^2	26.26±3.40	26.58±3.69	0.543
Systolic blood pressure, mm Hg	137.53±24.60	133.23±21.74	0.229
Diastolic blood pressure, mm Hg	83.64±16.70	80.47±15.46	0.197
Symptoms at admission, n (%)			
Fever	78 (57.8)	35 (53.0)	0.524
Cough	43 (31.9)	22 (33.3)	0.833
Shortness of breath	89 (65.9)	40 (60.4)	0.460
Headache	2 (1.5)	1 (1.5)	0.212
Diarrhea	6 (4.4)	1 (1.5)	0.287
Fatigue, tiredness	14 (10.4)	7 (10.6)	0.959
Palpitation	0	3 (4.5)	0.013
Muscle ache	9 (6.7)	3 (4.5)	0.551
Sore throat	5 (3.7)	6 (9.1)	0.115
Chest pain	3 (2.2)	1 (1.5)	0.736
Taste dysfunction	3 (2.2)	2 (3.0)	0.730
Comorbidities, n (%)			
Diabetes mellitus	55 (40.7)	19 (28.8)	0.099
Hypertension	84 (62.2)	35 (53.0)	0.213
Anemia	27 (20.0)	15 (22.7)	0.655
Renal failure	21 (15.6)	19 (28.8)	0.027
Dialysis	7 (5.2)	7 (10.6)	0.156
CAD	26 (19.3)	15 (22.7)	0.567
PCI/CABG	18 (13.3)	10 (15.2)	0.727
Peripheral vascular disease	2 (1.5)	1 (1.5)	0.212
Chronic heart failure (HFrEF)	10 (7.4)	6 (9.1)	0.679
Chronic obstructive pulmonary disease	8 (5.9)	8 (12.1)	0.128
Hyperlipidemia	21 (15.6)	9 (13.6)	0.720
Malignancy	4 (3.0)	3 (4.5)	0.566
CVA/TIA	8 (5.9)	7 (10.6)	0.236
Thorax CT findings, n (%)			
No significant finding	6 (4.4)	1 (1.5)	0.287
Ground glass opacity	122 (90.4)	60 (90.9)	0.902
Pneumonic consolidation	15 (11.1)	10 (15.2)	0.415
Pleural effusion	13 (9.6)	7 (10.6)	0.828
Invasive mechanical ventilation, n (%)	56 (41.5)	42 (63.6)	0.003
Length of in-hospital stay (days)	12.82±6.94	12.70±7.49	0.907
In-hospital mortality, n (%)	39 (28.9)	36 (54.5)	0.001

CABG - coronary artery by-pass graft; CAD - coronary artery disease; CT - computed tomography; CVA - cerebrovascular accident; HFrEF - heart failure with reduced ejection fraction; PCI - percutaneous coronary intervention; TIA - transient ischemic attack

Table 2. Laboratory parameters and medications

	Patients with non–fragmented QRS (n=135)	Patients with fragmented QRS (n=66)	*P*-value
Laboratory parameters			
Urea, mg/dL	49.00 (35.00–69.50)	54.50 (40.25–84.50)	0.132
Serum creatinine, mg/dL	0.87 (0.71–1.25)	1.05 (0.70–1.61)	0.193
Serum potassium, mmol/L	4.05±0.60	4.06±0.68	0.932
Serum calcium, mg/dL	8.31±0.69	8.21±0.69	0.317
Uric acid, mg/dL	5.40 (4.30–7.20)	5.75 (3.60–7.70)	0.641
Albumin, g/dL	3.49±0.53	3.31±0.62	0.031
Aspartate transaminase, u/L	32.00 (21.50–47.50)	36.00 (27.25–54.75)	0.126
Alanine transaminase, u/L	21.00 (14.00–37.50)	30.00 (16.00–36.50)	0.963
D–dimer, ng/mL	501.00 (268.00–1147.00)	763.50 (444.50–1776.75)	0.007
Troponin–I, ng/mL	0.006 (0.003–0.045)	0.021 (0.007–0.165)	0.002
Ferritin ng/mL	352.40 (157.25–731.45)	688.55 (340.30–1136.25)	0.003
Hemoglobin, g/dL	11.61±1.91	11.62±2.21	0.973
Leukocyte, $x10^3/\mu L$	10851.85±5069.71	11974.24±6711.99	0.188
Lymphocyte, $x10^3/\mu L$	1177.78±642.78	1126.82±785.67	0.625
C–reactive protein, mg/dL	146.79±104.79	175.94±94.41	0.041
C–reactive protein/albumin ratio, mg/g	40.13±36.64	56.93±35.91	0.032
Medications, n (%)			
Acetylsalicylic acid	51 (37.8)	31 (47.0)	0.213
Clopidogrel	16 (11.9)	10 (15.2)	0.513
ACEI/ARB	61 (45.2)	21 (31.8)	0.070
Beta–blocker	30 (22.2)	17 (25.8)	0.578
Dihydro–calcium channel blockers	28 (20.7)	13 (19.7)	0.863
Non–dihydro–calcium channel blockers	4 (3.0)	2 (3.0)	0.979
Aldosterone antagonists	8 (5.9)	5 (7.6)	0.655
Statin	20 (14.8)	9 (13.6)	0.823
Hydroxychloroquine	130 (96.3)	64 (97.0)	0.807
Azithromycin	84 (62.2)	51 (77.3)	0.033
Favipiravir	89 (65.9)	53 (80.3)	0.036
Immunosuppressive agent or steroid	49 (36.3)	35 (53.0)	0.024
Vitamin B	135 (100)	66 (100)	–
Vitamin C	135 (100)	66 (100)	–

ACEI - angiotensin-converting enzyme inhibitor; ARB - angiotensin-receptor blocker

95% CI: 1.206–10.194, p=0.021), renal failure (OR: 6.611, 95% CI: 1.152–37.941, p=0.034), troponin-I (OR: 1.493, 95% CI: 1.054–1.853, p=0.039), and f-QRS (OR: 1.041, 95% CI: 1.021–1.192, p=0.040) were independently associated with in-hospital death Table 5).

There was a positive correlation between f-QRS and CRP (r=0.261; p=0.034) and CAR (r=0.335; p=0.006). However, there was no correlation between f-QRS and D-dimer (r=0.065; p=0.605), troponin I (r=0.136; p=0,277), and ferritin (r=0.070; p=0,578). However, there was a negative correlation between the frequency of f-QRS and albumin (r=–0.385; p=0.001) (Table 6).

When we compared the ECG parameters of the survivors and non-survivors, it was found that the prevalence of f-QRS was higher in non-survivors. There was no significant difference in PR and QRS durations. The mean QTc interval was longer in non-survivors. Heart rate was significantly higher in non-survivors. ST segment depression was observed more in non-survivors, and T-wave inversion was similar in both the groups (Fig. 4).

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Table 3. Electrocardiographic findings

	Patients with non-fragmented QRS (n=135)	Patients with fragmented QRS (n=66)	*P*-value
Heart rate, bpm	87.01±21.20	95.11±23.49	0.015
Atrial fibrillation, n (%)	3 (2.2)	3 (4.5)	0.363
Atrioventricular block, n (%)	4 (3.0)	3 (4.5)	0.566
First degree	4 (3.0)	3 (4.5)	0.566
Second degree	0	0	-
Third degree	0	0	-
Atrial premature contractions, n (%)	11 (8.1)	9 (13.6)	0.222
Ventricular premature contractions, n (%)	15 (11.1)	10 (15.2)	0.415
Right bundle branch block, n (%)	5 (3.7)	6 (9.1)	0.115
Left bundle branch block, n (%)	3 (2.2)	2 (3.0)	0.335
ST segment elevation, n (%)	0	0	.
ST segment depression, n (%)	14 (10.4)	15 (22.7)	0.019
Lateral	6 (4.4)	3 (4.5)	0.974
Inferior	2 (1.5)	2 (3.0)	0.460
Anterior	8 (5.9)	10 (15.2)	0.031
T wave inversion, n (%)	15 (11.1)	13 (19.7)	0.099
Lateral	8 (5.9)	6 (9.1)	0.408
Inferior	5 (3.7)	5 (7.6)	0.236
Anterior	3 (2.2)	3 (4.5)	0.248
PR interval, ms	146.77±24.62	145.95±25.31	0.831
QRS interval, ms	84.67±13.45	89.45±17.30	0.033
QTc interval, ms	438.84±29.51	449.48±32.44	0.021
Left ventricular hypertrophy, n (%)	19 (14.1)	9 (13.6)	0.933
Right ventricular hypertrophy, n (%)	3 (2.2)	1 (1.5)	0.736

Figure 4. Comparison of ECG parameters in surviving and deceased patients

Higher serum urea, aspartate transaminase, alanine transaminase, D-dimer, troponin I, ferritin, CRP levels, and CAR were detected in non-survivors. There was no statistical difference between non-survivors and survivors in terms of the use of hydroxychloroquine, azithromycin, and favipiravir (Table 7).

First, we carried out a study of the reproducibility of the electrocardiographic data by analyzing interobserver and intraobserver variability. The ICC for intraobserver correlation was 0.988 (95% CI: 0.980–0.933) for the estimation of the f-QRS number and was 0.973 (95% CI: 0.952–0.984) for the calculation of the f-QRS when interobserver correlation was examined. These findings correspond to excellent interobserver and intraobserver correlations. There was also excellent reproducibility in the detection of QRS fragmentation for intraobserver (Kappa: 1.0) and interobserver (Kappa: 0.960) agreement.

Discussion

In this study, we investigated whether the presence of f-QRS on ECG is a predictor for all-cause mortality in patients

Table 4. Impact of the location of fragmented QRS on mortality

	OR	95% CI lower	95% CI upper	*P*-value
Fragmented QRS lateral leads (n=20)	2.641	1.090	7.499	0.022
Fragmented QRS inferior leads (n=29)	2.540	1.108	5.822	0.028
Fragmented QRS anterior leads (n=34)	3.785	1.657	8.648	0.002

CI - confidence interval; OR - odds ratio

Table 5. Multivariable logistic regression analysis for associated factors with all-cause in-hospital mortality

	OR	95% CI Lower	95% CI Upper	*P*-value
Age	1.064	1.018	1.113	0.006
Hypertension	3.507	1.206	10.194	0.021
Renal failure	6.611	1.152	37.941	0.034
Troponin-I	1.493	1.054	1.853	0.039
C-reactive protein/ albumin ratio	1.238	1.011	1.421	0.021
D-dimer	1.316	1.009	1.454	0.033
Urea	1.030	1.013	1.048	0.002
f-QRS	1.041	1.021	1.192	0.040

CI - confidence interval; OR - odds ratio

Table 6. Correlation analyses between fQRS and laboratory parameters in patients with COVID-19

Laboratory parameters	r value	*P*-value
Serum creatinine, mg/dL	0.231	0.063
Serum calcium, mg/dL	-0.071	0.572
D-dimer, ng/mL	0.065	0.605
Troponin, ng/mL	0.136	0.277
Ferritin ng/mL	0.070	0.578
C-reactive protein, mg/dL	0.261	0.034
C-reactive protein / albumin ratio, mg/g	0.335	0.006
Albumin, g/dL	-0.385	0.001

in the ICU with COVID-19. Our study has several important findings. First, all-cause in-hospital mortality was significantly higher in patients with f-QRS. Second, serum CRP, D-dimer, troponin I, ferritin levels, and CAR are significantly higher in these patients. Third, there is a positive correlation between the presence of f-QRS with CRP and CAR. Serum albumin level is lower in patients with f-QRS. Considering these data, we believe that inflammation is more in s patients with severe COVID-19 and f-QRS. Finally, the presence of f-QRS in critically ill patients with COVID-19 is independently associated with in-hospital death.

The impact of the COVID-19 pandemic continues around the world. The most common indication requiring follow-up in ICU is respiratory failure because of pulmonary involvement. Acute respiratory distress syndrome caused by pulmonary involvement is the most common cause of death from COVID-19 (12). Patients with COVID-19 with cardiovascular comorbidities tend to have higher disease severity and case fatality rates (13, 14). It is not known how underlying cardiovascular disease (CVD) contributes to the severity of COVID-19 disease. However, it is thought that hyperinflammation plays a role in this. As the immune system encounters the virus and gets to know its antigens, it produces large amounts of proinflammatory cytokines and chemokines. In some patients, this activation becomes so great that a cytokine storm develops, resulting in thrombotic propensity and multi-organ failure, and eventually death (15, 16). High levels of biomarkers can be observed in patients with severe COVID-19 because of increased inflammation. CRP, D-dimer, ferritin, albumin, and troponin I are some of these biomarkers and are helpful parameters to the clinician in risk stratification of patients with severe COVID-19 (17-22). In addition, many studies have shown that CAR is a valuable prognostic factor to detect the inflammatory state in different inflammatory diseases (23). In our study, high CRP, D-dimer, CAR, troponin I, and low albumin levels were detected in patients with severe COVID-19. Importantly, the prevalence of f-QRS was higher in these patients. These data suggest that there may be an association between f-QRS and inflammation.

Myocardial cells are a potential target of SARS-CoV-2 (24). In addition, fulminant myocarditis because of inflammatory mononuclear infiltration in myocardial tissue under high viral load has been described (25, 26). Endothelial cell infection has been reported in many organs, including the heart vessels, and another possible mechanism of myocardial lesion and troponin elevation has been mentioned (27). Increasing inflammation caused by COVID-19 causes myocardial injury. The incidence of severe ventricular dysfunction and cardiac arrhythmia owing to this injury is increasing. Myocardial injury is a common complication in hospitalized patients with or without pre-existing CVD and is associated with in-hospital mortality and a poor prognosis (28). Compared with non-ICU admissions, there was a larger proportion of arrhythmias found in ICU admissions in 2 studies (1.2%–16.7% and 40%–44%, respectively) (29, 30). The mean QTc interval was longer in the f-QRS group in our study. However, the rate of favipiravir and azithromycin use was also higher in the same group. Therefore, in patients with f-QRS, the difference in QT interval and its predictive value for adverse arrhythmic events can be considered in patients with or without any drugs that prolong QT intervals. However, the mean QTc interval was longer in non-survivors. Prolonged QTc may be contributing to increased malignant arrhythmias in patients with severe COVID-19. QT prolonging drugs should be used more carefully in patients with severe COVID-19.

f-QRS is an ECG finding reflecting impaired ventricular depolarization owing to heterogeneous electrical activation of the injured myocardium. f-QRS is recognized as a new and useful

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Table 7. Assessment of ECG, laboratory parameters, and medicine among survivors and non-survivors

	Survivor (n=126)	Non–survivor (n=75)	*P*-value
Number of f-QRS leads, n	1.57±0.57	2.44±0.77	0.001
Heart rate, bpm	84.99±18.20	97.53±26.04	0.001
PR interval, ms	148.22±23.08	143.36±27.52	0.056
QRS interval, ms	85.90±15.51	86.80±14.03	0.223
QTc interval, ms	435.65±31.05	462.16±30.46	0.033
ST segment depression, n (%)	8 (6.3)	21 (28)	0.001
T wave inversion, n (%)	13 (10.3)	15 (20)	0.055
Urea, mg/dl	45.50 (33.00–60.75)	60.00 (46.50–102.00)	0.001
Serum creatinine, mg/dL	0.87 (0.71–1.30)	1.04 (0.73–1.50)	0.134
Albumin, g/dl	3.60±0.48	3.16±0.60	0.043
Aspartate transaminase, u/L	28.00 (19.00–39.00)	45.00 (34.50–69.00)	0.001
Alanine transaminase, u/L	25.50 (14.00–33.00)	31 (16.00–43.00)	0.023
D-dimer, ng/mL	432.50 (253.75–795.50)	1098.00 (535.50–2426.00)	0.001
Troponin I, ng/mL	0.006 (0.002–0.013)	0.078 (0.011–0.227)	0.001
Ferritin ng/mL	330.75 (126.20–739.90)	613.10 (348.30–1093.40)	0.001
C-reactive protein, mg/dL	146.33±85.29	227.20±106.18	0.001
C-reactive protein/albumin ratio, mg/g	41.88±25.41	75.38±42.06	0.001
Hydroxychloroquine, n (%)	120 (95.2)	74 (98.7)	0.200
Azithromycin, n (%)	86 (68.2)	49 (65.3)	0.334
Favipiravir, n (%)	87 (69.0)	55 (73.3)	0.519

marker of myocardial scar or fibrosis (31). Q wave and f-QRS were compared in terms of myocardial scar in patients who underwent nuclear stress test, and specificity of f-QRS was found to be superior to Q wave (7). In patients with left ventricular dysfunction, the presence of myocardial fibrosis may cause ventricular arrhythmias. Cardiac MRI studies in patients with ischemic and non-ischemic cardiomyopathy have shown that myocardial fibrosis represents an arrhythmogenic substrate (32, 33). Imaging methods used in the detection of myocardial fibrosis are more expensive and complex than f-QRS, which is easily detected on an ECG device. In a study, the rate of detection of f-QRS in patients with COVID-19 was calculated as 24.2% (34). Only patients with severe COVID-19 disease who were followed up in the ICU were included in our study, and the f-QRS rate was calculated as 32.84%. We observed that patients with f-QRS included in our study needed more mechanical ventilation and that mortality was higher in these patients. The mean heart rate and symptom of palpitation were found to be higher in the ECG in patients with f-QRS. At the same time, more ST depression was observed in this group. ST segment depression is a sign of myocardial ischemia and has been associated with increased mortality in COVID-19 (35, 36). Sinus tachycardia may indicate increased myocardial oxygen demand (37). In a study of patients with COVID-19, ST-T segment abnormal change rate and sinus tachycardia were observed to correlate with disease severity. ST-T segment changes and sinus tachycardia increased as the disease severity increased (38). ST-T segment change and sinus tachycardia may be related to myocardial damage caused by SARS-CoV-2.

Especially in patients with COVID-19, f-QRS may be a predictor of poor clinical outcomes. In a recently published paper, Yildirim et al. (39) studied 114 patients with COVID-19. In this study, similar to our results, hospitalization duration, ICU requirement, all-cause mortality, and cardiac mortality were found to be higher in patients with COVID-19 with f-QRS. However, this study revealed that there was a positive relationship between QRS duration and duration of hospital stay, need for ICU, and mortality, but there was no relationship between T inversion and mortality (39). In contrast, no relationship was found between QRS duration and mortality in our study. However, there was a significant difference in the QRS duration of patients with and without f-QRS. In another retrospective study, Bektas et al. (34) suggested that presence of f-QRS in patients with COVID-19 may be useful in predicting cardiovascular outcomes. Similarly, Barman et al. (40) found that the presence of f-QRS in patients with SARS-CoV-2 infection was independently associated with ICU admission.

Fragmentation in ECG is a predictor of QTc prolongation (41). Prolongation of the electrocardiographic QT interval is an established risk factor for torsades de pointes (42). QT prolonging drugs such as hydroxychloroquine and azithromycin can be used in the treatment of patients with COVID-19 (43). Therefore, fragmentation in ECG may contribute arrhythmic events.

In a study, the presence of 3 f-QRS leads was identified as an independent predictor of cardiac death or hospitalization for heart failure in patients with prior myocardial infarction (44). In another study, f-QRS in anterior leads was found to be associated with higher GRACE risk score and Killip class (45). In our study, the lead with f-QRS cut-off value was found to be ≥2. A significant increase in mortality was observed with f-QRS seen in at least 2 different derivations. The association of f-QRS with mortality in the anterior derivations was more determined than the inferior and lateral leads.

Study limitations

Our study had several limitations. Its retrospective nature and relatively small patient population are major limitations. f-QRS can be seen in cardiovascular diseases such as coronary artery disease, atrial fibrillation, and heart failure. We did not have ECG data of the patients before the hospitalization. In addition, it is not clear whether f-QRS develops because of COVID-19 as serial ECG follow-up was not performed after hospitalization. Lack of echocardiographic data can be considered as a limitation of our study.

Conclusion

The presence of f-QRS in ECG is associated with higher in-hospital all-cause mortality in patients with severe COVID-19. Furthermore, f-QRS is positively correlated with serum CRP level and CAR and negatively correlated with serum albumin, which are indicators of inflammation. The prevalence of prolonged QTc is higher in patients with f-QRS. Therefore, during the pandemic period where the number of patients increases every day, the presence of f-QRS in ECG, which is an inexpensive and easily accessible marker, can be used to determine the mortality risk of critically ill patients with COVID-19.

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