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Fragmentation of the QRS Complex Is Associated with Right Ventricular Dilatation and Mortality in Critically Unwell Coronavirus Disease 2019 Patients

ABSTRACT

Background: QRS fragmentation (fQRS) is a depolarization disorder that can be detected on routine electrocardiography (ECG). Current evidence suggests that fQRS is a prognosticator of adverse cardiovascular events. This study aimed to assess the relationship between fQRS and all-cause mortality in critically unwell coronavirus disease 2019 (COVID-19) patients and to investigate the significance of associated abnormalities on echocardiography.

Methods: A retrospective cohort study of COVID-19 patients in a critical care setting was performed. Electrocardiography was performed on presentation to hospital, admission to the critical care unit, and at subsequent points according to clinical need. Transthoracic echocardiography was performed at clinical discretion to assess for structural and functional cardiac abnormalities. Primary outcome was in-hospital mortality and secondary outcome was the need for mechanical invasive ventilation.

Results: Totally, 212 consecutive patients were included of which 120 (57%) exhibited fQRS and inferior leads were involved in 88% of the patients. Overall, fQRS was a significant predictor of mortality [65% vs. 44% $P=.003$; multivariate odds ratio=2.96, 95% confidence interval (CI): 1.42-6.40, $P=.005$] and inferior fQRS itself was a significant predictor of mortality ($P=.03$). There was no significant association between fQRS and the need for invasive mechanical ventilation. A total of 112 patients underwent echocardiography. There was a greater incidence of right ventricular (RV) dilatation in the fQRS group (16% vs. 2% respectively, $P=.02$) and pulmonary hypertension (33% vs. 14% respectively, $P=.03$) based on echocardiographic criteria.

Conclusion: Our study demonstrates that fQRS is significantly associated with RV dilation, pulmonary hypertension, and mortality in critically unwell COVID-19 patients.

Keywords: COVID-19, fragmentation, QRS, pulmonary hypertension

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by the severe acute respiratory syndrome (SARS-CoV-2) virus that causes a spectrum of mild-to-severe illness, manifesting most commonly within the hospitalized critically unwell population as a severe pneumonitis progressing to respiratory failure and multiorgan dysfunction. On March 11, 2020, the World Health Organization declared a global COVID-19 pandemic which was followed by national lockdowns, mass hospitalizations, and a significant expansion in critical care capacity to facilitate the use of mechanical ventilation.[1] The global research effort has since focused on establishing effective treatment options, as well as biochemical and bedside prognostic markers of disease severity.

Fragmentation of the QRS complex (fQRS), characterized by various RSR' or notching patterns, is a depolarization disorder that can be detected from routine 12-lead electrocardiography (ECG) (Figure 1). In a general population, the prevalence of fQRS was found to be 19.7%, with a greater prevalence observed in those with underlying cardiac disease.[2] There is established evidence that the

ORIGINAL INVESTIGATION

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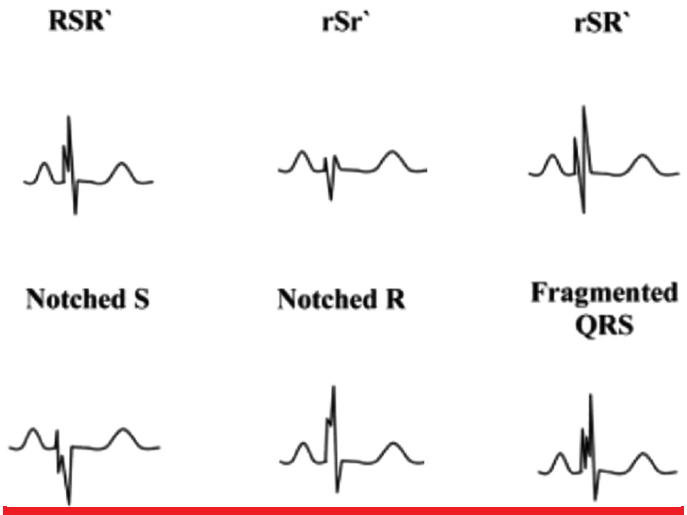

Figure 1. Morphologies of QRS fragmentation on electrocardiogram where QRS duration is <120 ms. Figure adapted from (11).

presence of fQRS on ECG is strongly indicative of myocardial scarring in patients with coronary artery disease and a marker of further cardiac events.[3,4] It is pathologically also present in those with cardiomyopathy, valvular, and congenital heart disease.[5] Fragmented QRS has previously been shown to have a high positive predictive value and specificity for the presence of dysfunctional segmental myocardial contractility.[6] Until recently its significance in the COVID-19 population had not been assessed, but there is emerging evidence in these patients that fQRS is linked to an increased risk of all-cause mortality and need for invasive mechanical ventilation.[7,8]

In contrast to previous studies that have focused on the cardiac population, our focus pertained to the critically ill COVID-19 population. We aimed to explore the relationship between fQRS and all-cause mortality, and to investigate the significance of associated cardiac structural and functional abnormalities on transthoracic echocardiography (TTE) in this population.

METHODS

Population and Demographics

This was a retrospective case-cohort study of consecutive patients treated for COVID-19 in a critical care setting (high dependency or intensive care unit) at our institution in the United Kingdom between February 2020 and May 2021. Data were collected from the local electronic patient health record. Those who had pre-existing ceilings of treatment were excluded. Patients with active COVID-19 were defined as those with positive real-time reverse transcriptase-polymerase chain reaction assay for SARS-CoV-2 on nasopharyngeal swab. Patient demographics and comorbidities classified using the Charlson Comorbidity Index were extracted from patient records.[9]

Primary and secondary outcomes were in-hospital mortality and the need for mechanical invasive ventilation respectively. Known prognostic laboratory markers of cytokine storm were also recorded. These included peak values for platelets, leukocytes, neutrophils, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, troponin T, D-dimer, creatinine kinase (CK), alanine aminotransferase (ALT), and trough values for lymphocyte count.[10] Where values were above or below the range quantifiable by the laboratory, the highest or lowest quantifiable value was used, respectively.

Electrocardiography

Standard 12-lead surface ECG (0.5-150 Hz, 25 mm/s, 10 mm/mV) recordings performed throughout the admission were collated. All patients had ECGs recorded on initial presentation to the hospital, on admission to the critical care unit, and at subsequent points thereafter at the treating team's discretion. For each patient, the longest PR interval (in ms), longest QRS duration (in ms), largest ST segment change (in mm), and longest Bazett's corrected QT interval (in ms) measured throughout the admission were recorded. Any new arrhythmic events were also recorded.

In ECGs with a QRS duration ≤120 ms, fQRS was defined as notching in the R or S wave, RSR' pattern or multiple R' (Figure 1).[11] In patients with a QRS >120 ms, fQRS was defined as the presence of >2 notches on the R wave or the S wave.[12] Fragmented QRS was considered present if these changes appeared on at least 1 ECG recording and in at least 2 consecutive leads corresponding to the major coronary artery territories. The territories were categorized as anterior (V1-V5), lateral (I, aVL, and V6), and inferior (II, III, and aVF).

Three authors independently analyzed all ECGs performed on all patients while being blinded to the patient's outcome to assess for the presence of fQRS. Where there was disagreement between the initial assessors, the ECG was evaluated by a fourth senior cardiologist author to serve as a tiebreak. Agreement between the initial assessors was high, with 9% of ECGs sent to the fourth author.

Echocardiography

Transthoracic echocardiography was performed at the critical care team's discretion by experienced British Society of Echocardiography (BSE) accredited technicians according to the BSE COVID-19 consensus pathway.[13] The time interval between ECG and TTE was based on clinical need during the critical care admission. Technically inadequate studies were excluded. Left ventricular ejection fraction was calculated by the Simpson's biplane method.

HIGHLIGHTS

- In this cohort study of 212 patients, fragmentation of the QRS complex (fQRS) was a significant predictor of in-hospital mortality in critically unwell coronavirus disease 2019 patients.
- Fragmented QRS was associated with right ventricular (RV) dilatation and pulmonary hypertension on echocardiography.
- A possible mechanism could include a relationship between conduction delay within RV myocardial tissue as a result of pressure and volume overload.

Diastolic dysfunction was defined as present if severity was grade II or above according to European Association of Cardiovascular Imaging (EACVI) guidelines.[14] A dilated left ventricle (LV) internal end-systolic diameter (LVIDs) was defined as >41 mm in males and >37 mm in females, while a dilated LVID (LVIDd) was defined as >56 mm in males and >51 mm in females.[15] Left atrial dilatation was defined as a volume of >54 mL. The presence of any regional wall abnormalities was also recorded.

The right atrium (RA) and right ventricle (RV) were assessed in a dedicated focused view. Right atrial dilatation was defined as an area of >22 cm^2 for males and >19 cm^2 for females.[15] Right ventricle dilatation was defined as a basal diameter >47 mm in males and >43 mm in females. Right ventricle systolic dysfunction was defined as a fractional area change <35% in females or <30% in males, a tricuspid annular plane systolic excursion <17 mm or an RV s′ <9 cm/s. Pulmonary hypertension was marked as present if the echocardiographic probability of pulmonary hypertension was high: defined as peak tricuspid regurgitation velocity (TRV) > 3.4 m/s or peak TRV 2.9-3.4 m/s with ≥2 supporting signs of pulmonary hypertension.[16]

Statistical Analysis

Continuous variables were assessed for normality using Kolmogorov–Smirnov and Shapiro–Wilk tests. When normally distributed, continuous variables were expressed as mean ± SD and compared using the independent samples *t*-test. Non-normal data were presented as median with interquartile range and compared using the Mann–Whitney *U*-test. Categorical variables were summarized as frequencies and percentages and compared using either the Fisher's exact test or chi-squared test. A multiple logistic regression analysis was carried out using covariates implicated in COVID-19 patient outcomes. Mortality was used as a binary outcome, against which the recorded parameters were assessed. All parameters were included in the analysis; however, peripheral vascular disease and malignancy were excluded due to the low incidence among the study population. Significance was determined by a confidence interval entirely greater than 1 and a *P*-value less than .05. All statistical analyses were performed using GraphPad Prism 9 for MacOS using a *P*-value of less than .05 to determine statistical significance.

Ethics

This study was approved by our Research, Quality Improvement, and Audit department with the reference number FH205. All data were collected locally, anonymized, and handled in accordance with local data protection guidelines.

RESULTS

A total of 212 patients were included for this study (Figure 2), with 6% of those treated for COVID-19 excluded from the final analysis due to incomplete data. Baseline characteristics and clinical data of all patients in our cohort are summarized in Table 1. In this study population, 120 patients (57%) exhibited fQRS during their admission. There was a high incidence of mortality and a requirement for invasive mechanical ventilation (58% and 71% of the total population respectively). Older age was a significant predictor of mortality but not invasive mechanical ventilation. Gender and ethnicity were not significant predictors of mortality or invasive mechanical ventilation. Overall, the most common comorbidities were hypertension and diabetes mellitus (47% and 42% of the total population, respectively). There was a low prevalence of pre-existing heart failure in the patient cohort overall (3%). Diabetes mellitus, ischemic heart disease and the Charlson Comorbidity Score were significantly associated with mortality; however, neither specific comorbidities nor overall co-morbidity burden were associated with invasive mechanical ventilation. Certain laboratory markers were associated with mortality, including peak leukocyte, peak neutrophil, trough lymphocyte, peak CRP, peak troponin T, and peak LDH concentrations. Peak CRP concentrations were associated with the need for invasive mechanical ventilation.

Presence of fQRS was significantly associated with mortality (65% presence in mortality group vs. 44% in survivor group, $P = .003$). The inferior leads (II, III, and aVF) were most commonly involved (88% of patients) (Table 3) and inferior fQRS alone was a significant predictor of mortality ($P = .03$). On multivariate logistic regression, fQRS remained a significant independent predictor of mortality (odds ratio (OR) = 2.96, 95% CI: 1.42-6.40, $P = .005$) along with age (OR = 1.07, 95% CI: 1.02-1.13, $P = .01$) and peak leukocyte count (OR = 1.35, 95% CI:

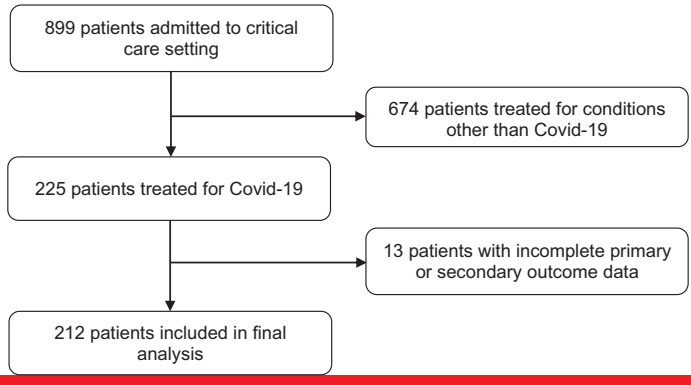

Figure 2. Patient inclusion flow diagram.

Table 1. Summary of Patient Demographics and Comparison of Data to Analyze Mortality, Use of Invasive Mechanical Ventilation, and Use of Echocardiography

	Mortality			Invasive Mechanical Ventilation			Echo Performed		
	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*
n	88 [42%]	124 [58%]		62 [29%]	150 [71%]		100 [47%]	112 [53%]	
Mean age ± SD (years)	54.6 ± 11.7	62.4 ± 9.6	**<.001***	58.8 ± 12.0	59.4 ± 10.8	.741	60.1 ± 11.3	58.5 ± 11.0	.299
Gender, female	29 [33%]	37 [30%]	.654	21 [34%]	45 [30%]	.626	29 [29%]	37 [33%]	.555
Ethnicity			.271			.294			.167
Caucasian	47 [53%]	54 [44%]		34 [55%]	67 [45%]		53 [53%]	48 [43%]	
Asian	37 [42%]	66 [53%]		25 [40%]	78 [52%]		42 [42%]	61 [54%]	
Afro-Caribbean	4 [5%]	4 [3%]		3 [5%]	5 [3%]		5 [5%]	3 [3%]	
Comorbidities									
Chronic respiratory disease	19 [22%]	22 [18%]	.487	16 [26%]	25 [17%]	.131	24 [24%]	17 [15%]	.119
Ischemic heart disease	9 [10%]	28 [23%]	**.027***	9 [15%]	28 [19%]	.554	14 [14%]	23 [21%]	.277
Heart failure	2 [2%]	5 [4%]	.702	4 [6%]	3 [2%]	.198	3 [3%]	4 [4%]	1.000
Hypertension	38 [43%]	62 [50%]	.333	26 [42%]	74 [49%]	.367	41 [41%]	59 [53%]	.099
Peripheral vascular disease	0	3 [2%]	.268	2 [3%]	1 [1%]	.205	1 [1%]	2 [2%]	1.000
Stroke	5 [6%]	8 [6%]	1.000	7 [11%]	6 [4%]	.059	4 [4%]	9 [8%]	.262
Liver disease	5 [6%]	7 [6%]	1.000	2 [3%]	10 [7%]	.516	6 [6%]	6 [5%]	1.000
Diabetes Mellitus	29 [33%]	59 [48%]	**.035***	22 [35%]	66 [44%]	.285	33 [33%]	55 [49%]	**.018***
CKD	8 [9%]	13 [10%]	.818	8 [13%]	13 [9%]	.448	10 [10%]	11 [10%]	1.000
Malignancy	3[3%]	6 [5%]	.738	3 [5%]	6 [4%]	.723	6 [6%]	3 [3%]	.312
Connective tissue disease	4 [5%]	2 [2%]	.236	2 [3%]	4 [3%]	1.000	4 [4%]	2 [2%]	.424
Median Charlson CMI score (IQR)	2(2)	3(2)	**<.001***	2 (3)	3 (3)	.497	3(3)	3(3)	.704
Blood parameters									
Leukocytes peak × 10^9/L, median (IQR)	13.82 (10.2)	18.4 (13.4)	**<.001***	15.47 (13.3)	17.09 (10.5)	.129	15.25 (10.4)	18.15 (11.5)	.197
Neutrophils peak × 10^9/L, median (IQR)	11.90 (9.0)	15.65 (11.5)	**<.001***	12.99 (12.0)	15.2 (8.6)	.119	13.3 (9.5)	15.8 (10.3)	.147
Lymphocytes trough × 10^9/L, median (IQR)	0.61 (0.5)	0.42 (0.4)	**<.001***	0.52 (0.6)	0.45 (0.5)	.294	0.53 (0.5)	0.43 (0.44)	**.029***
Platelets peak × 10^9/L, mean ± SD	369.15 ± 163.4	348.23 ± 137.3	.314	337.21 ± 156.2	365.06 ± 145.2	.216	350.29 ± 147.0	362.82 ± 150.6	.271
D-dimer peak ng/mL, median (IQR)	2609 (6413)	2536 (5843.8)	.968	2522 (6187)	2589.5 (5997.3)	.912	2542 (7706)	2577.5 (5950.5)	.842
CRP peak mg/L, mean ± SD	213.01 ± 115.6	253.00 ± 114.5	**.014***	206.79 ± 120.8	248.60 ± 112.7	**.017***	221.66 ± 113.7	249.28 ± 117.7	**.043***
Ferritin peak µg/L, median (IQR)	1196 (1653)	1314 (1750)	.162	1131 (2257.3)	1278 (1543)	.779	1314 (1667.5)	1196 (1606)	.772
Troponin T peak ng/L, median (IQR)	18.5 (32.3)	23 (54)	**.032***	20 (34.3)	20 (56)	.418	15 (24.5)	28 (72)	**<.001***
LDH peak U/L, median (IQR)	498 (290)	568 (280)	**.024***	554 (245)	528 (313.5)	.697	571 (369)	500.5 (264.8)	.089
CK peak U/L, median (IQR)	157 (396.5)	283 (487.5)	.067	227 (556)	267.5 (455)	.575	242.5 (444)	257 (507)	.849
ALT peak U/L, median (IQR)	74 (87)	82 (93)	.136	75.5 (106.75)	83 (77.5)	.412	75 (92)	86.5 (85)	.263
Fragmented QRS, presence	39 [44%]	81 [65%]	**.003***	37 [60%]	83 [55%]	.648	57 [57%]	63 [56%]	1.000

Values in bold indicate statistical significance.
ALT, alanine aminotransferase; CK, creatinine kinase; CKD, chronic kidney disease; CMI, Co-morbidity Index; CRP, C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase.

Table 2. Multivariate Logistic Regression Model to Identify Predictors of Mortality for Critically Unwell Coronavirus Disease 2019 Patients

	Odds Ratio	95% CI	*P*
Age	1.07	1.015-1.130	**.014***
Gender, female	0.8297	0.3499-1.956	.669
Fragmented QRS	2.96	1.420-6.400	**.005***
Comorbidities			
Chronic respiratory disease	0.9615	0.3708-2.521	.936
Ischemic heart disease	1.328	0.4309-4.252	.624
Heart failure	0.8169	0.06412-10.54	.873
Hypertension	0.9444	0.4184-2.132	.890
Stroke	0.9287	0.1896-4.890	.928
Liver disease	2.439	0.4907-13.46	.285
Diabetes mellitus	2.298	0.9153-5.972	.080
CKD	0.6351	0.09661-3.976	.629
Malignancy	0.8402	0.07184-10.69	.888
Connective tissue disease	0.09288	0.007474-0.8092	**.040***
Median Charlson CMI score (IQR)	1.023	0.6544-1.667	.924
Blood parameters			
Leukocyte peak × 10^9/L, median (IQR)	1.351	1.051-1.827	**.034***
Neutrophil peak × 10^9/L, median (IQR)	0.7845	0.5674-1.035	.114
Lymphocyte trough × 10^9/L, median (IQR)	0.5616	0.2087-1.432	.234
Platelet peak × 10^9/L, mean ± SD	0.9962	0.9933-0.9988	**.006***
D-dimer peak ng/mL, median (IQR)	1	0.9999-1.000	.181
CRP peak mg/L, mean ± SD	1.003	0.9999-1.007	.060
Ferritin peak μ g/L, median (IQR)	1	0.9998-1.000	.866
Troponin T peak ng/L, median (IQR)	1	0.9992-1.001	.605
LDH peak U/L, median (IQR)	1.001	0.9997-1.003	.134
CK peak U/L, median (IQR)	1	0.9997-1.000	.649
ALT peak U/L, median (IQR)	1.001	0.9994-1.003	.408

Values in bold indicate statistical significance.
ALT, alanine aminotransferase; CK, creatinine kinase; CKD, chronic kidney disease; CMI, Co-morbidity Index; CRP, C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase.

1.05-1.83, *P* = .03) (Table 2). Connective tissue disease was negatively associated with mortality.

Upon assessing other ECG parameters in those with fQRS compared to those without, there was no significant difference in PR interval, QRS duration, ST segment change, and QTc interval (Table 3). There was also no significant difference in the incidence of arrhythmic events. In total, 112 patients had TTE performed. These patients were not associated with any significant increase in mortality compared to those who did not undergo TTE (58% mortality in TTE group vs. 59%, *P* = .89). Demographic data were also similar between those who underwent TTE compared to those who did not. However, there was a greater incidence of diabetes mellitus in the TTE group as well as higher peak troponin T and CRP concentrations and lower trough lymphocyte counts. There was a greater incidence of RV dilatation (16% vs. 2%, *P* = .02) and pulmonary hypertension (33% vs. 14%, *P* = .03) based on echocardiographic probability criteria in the fQRS group (Table 3). Notably, there was no difference in RV or LV function between the 2 groups nor any difference in other echocardiographic parameters.

DISCUSSION

The presence of fQRS reflects myocardial conduction abnormality. It arises when myocardial tissue is replaced by scar or fibrosis, resulting in an irregular course of myocardial activation that retards or blocks conduction.[17] Slow conduction within these zones facilitates re-entry, predisposing to the development of ventricular tachyarrhythmias.[18] It has been proposed that the manifestation of fQRS may be a surrogate marker of cardiac events among patients with coronary artery disease[12] and its presence might be utilized as a prognosticator of response to treatment in patients with cardiomyopathy.[19]

Our study clearly demonstrates that fQRS is a strong predictor of mortality in COVID-19, corroborating recent literature.[7,8,20] This is the first study that we are aware of demonstrating a significant relationship between fQRS, RV dilatation and pulmonary hypertension on TTE. Right ventricle dilatation corresponded to fQRS within the inferior leads in 88% of patients. We propose that fQRS in patients with severe COVID-19 arises from structural changes within

Table 3. Summary of Electrocardiographic and Echocardiographic Parameters in Patients with Non-fragmented QRS vs. Fragmented QRS

	n	Non-fragmented QRS	Fragmented QRS	*P*
Fragmented QRS, territory involved	212			
Inferior (II, III, aVF)			106 [88%]	
Anterior/septal (V1-4)			22 [18%]	
Lateral (V5-6, I, aVL)			28 [23%]	
ECG parameters	212			
PR interval (s), mean ± SD		157 ± 24.26	162 ± 31.41	.228
QRS duration (s), median (IQR)		97 (14.5)	99 (21)	.112
ST change (s), median (IQR)		0 (0)	0 (0)	.704
QTc interval (s), median (IQR)		447 (51.5)	442 (63.5)	.881
New arrhythmias		7 [8%]	12 [11%]	.632
Echo performed	112	49	63	
LVEF %, median (IQR)		58% (6.25)	57.5% (4)	.609
LV diastolic dysfunction		15 [31%]	11 [17%]	.118
RWMA		8 [16%]	9 [14%]	.796
Dilated LA		14 [29%]	10 [16%]	.112
Dilated RA		4 [8%]	9 [14%]	.383
Dilated LVIDs		3 [6%]	1 [2%]	.317
Dilated LVIDd		4 [8%]	1 [2%]	.166
Dilated RV dimension		1 [2%]	10 [16%]	**.022***
RV dysfunction		10 [20%]	10 [16%]	.622
Pulmonary hypertension		7 [14%]	21 [33%]	**.028***

IQR, interquartile range; LA,= left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; LVIDs, left ventricular internal dimension (systole); LVIDd, left ventricular internal dimension (diastole); RA, right atrium; RV, right ventricle; RWMA, regional wall abnormalities.

the RV in response to pressure and volume overload leading to aberrant conduction and an abnormal depolarization segment. We suggest that RV dilatation and pulmonary hypertension translates to the higher mortality seen within this sub-group. To date, a few retrospective analyses with small sample sizes have corroborated our findings of increased all-cause mortality and need for invasive mechanical ventilation in COVID-19 patients exhibiting fQRS on ECG.[7,8,20] Özdemir et al[7] and Bektas et al[20] hypothesized that the higher mortality observed in those with fQRS was related to cytokine storm and subsequent myocardial injury. The aforementioned studies were conducted relatively early in the pandemic, whereas our timescale looked at data from patients as late as May 2021, when the RECOVERY trial had led to the protocolization of treatment in COVID-19 with dexamethasone (June 2020) and interleukin 6 (IL-6) inhibitors tocilizumab and sarilumab (February 2021).[21,22] While this study demonstrated an association between certain markers and mortality (namely peak leukocyte, peak neutrophil, trough lymphocyte, peak CRP, peak troponin T, and peak LDH concentrations), novel treatments may have contributed to cytokine storm playing less of a role in our study group.

To our knowledge, our study is the first to incorporate TTE and electrocardiographic data to explore the relationship between cardiac structure, function, and fQRS in COVID-19. While the link between myocardial scarring and fQRS is increasingly accepted in cardiac patients, we suggest the mechanism of fQRS in the COVID-19 critical care population is more complex. Here, several pathophysiological processes likely contribute to RV dilatation and pulmonary hypertension, either as a direct consequence of COVID-19 pneumonitis, or in combination with pre-existing respiratory pathology and mechanical ventilation. Hypoxemia from pneumonitis increases RV afterload via pulmonary vasoconstriction which is compounded in latter stages by poor CO_2 clearance as the lung loses compliance. Mechanical ventilation necessitates the generation of higher mean airway pressures and alveolar overdistension, which contribute to pulmonary artery hypertension, RV pressure overload followed by volume overload, and subsequent failure. In situ pulmonary thrombosis and coronary artery hypoperfusion in hypovolemic septic shock also directly attenuate RV function.[23] Finally, acutely elevated RV pressure can decrease the preload of the LV and lead to RV ischemia or infarction.

We therefore propose that in critically ill COVID-19 patients, especially those ventilated, fQRS is not only a predictor of mortality but of structural changes in the RV with accompanying pulmonary arterial hypertension. We postulate that fQRS in this context is a phenomenon of abnormal myocardial activation arising from structural and electrical changes within the RV in response to pressure and volume overload, and from the cumulative effect of the above physiological processes. It is not unreasonable to assume that areas of redundant myocardium, irrespective of underlying pathomechanisms, remain substrate for reentry and ventricular tachycardias. While not studied formally, in some of

our study patients fQRS was transient or episodic suggesting that the depolarization segment abnormality might be dynamic and corresponding to episodes of acute right heart strain and pulmonary arterial hypertension. This implies that fQRS could be acute and reversible, related to myocardial stretch and stunning, however further study is required to assess this phenomenon.

Other relevant findings from this study included older age and increased comorbidity burden (specifically ischemic heart disease and diabetes mellitus) to be significantly associated with mortality, in agreement with previous studies.[24,25] Patients who underwent TTE were characterized by worsened blood markers of cytokine storm and cardiac injury (CRP, troponin T, and lymphocyte counts). This appropriately reflects how this group of patients would have fulfilled the clinical criteria to warrant TTE.

Our hypotheses and findings require validation in further, larger studies. Longer-term data, utilizing more sophisticated functional imaging modalities such as perfusion magnetic resonance imaging, might elucidate the natural history and clinical significance of electrocardiographic and TTE abnormalities following hospitalization. The other question remains whether myocardial scarring and fibrosis are long-term sequelae from protracted high-pressure ventilation and a high burden of parenchymal +/- vaso-occlusive disease. Nevertheless, emphasis is laid upon recognition of fQRS by clinicians, which should prompt TTE assessment and consideration of targeted lung-protective ventilation and pharmacotherapy to best offload the RV.

Study Limitations

Despite achieving significant results in a number of outcomes, we acknowledge the risk of a type 2 error occurring with our experimental sample size. Therefore, we were unable to discount an association between fQRS, RV dilatation, and pulmonary hypertension and those variables that did not achieve statistical significance with observed effect sizes. The high mortality rate observed may have also generated a bias.

During the 15-month period of our study, treatment protocols for COVID-19 were rapidly changing, as were the variants of SARS-COV-2 identified within the population. Changes in protocol overlapping with our study, namely, dexamethasone (June 2020) and IL-6 inhibitors tocilizumab and sarilumab (February 2021), may have contributed to cytokine storm being less prominent in our study group. These factors make it difficult to generalize to populations where acuity and standard treatment were different.

We also acknowledge that extracting information from medical notes requires second-hand interpretation and may not be representative of the full clinical picture. There was also clear limitations given we relied on observational, retrospective data with no clear protocol in terms of clinician decisions to monitor ECG and TTE parameters. Electrocardiograms were performed on admission to hospital, critical care, and then at clinician discretion rather than at defined time points. TTE was also performed based on clinical discretion, meaning the time interval between ECG and TTE varied between each patient. Therefore, a definitive relationship between fQRS and RV volume and pressure overload cannot be confirmed for certain. Finally, we have no data to ascertain abnormalities in patient pre-morbid ECGs, TTE, or ongoing data post-critical care admission. This remains an area for future study.

CONCLUSION

Our study is the first to demonstrate a possible relationship between fQRS, RV dilatation, pulmonary hypertension, and mortality in critically ill COVID-19 patients. The mechanism surrounding fQRS in these patients may reflect anomalous myocyte activation arising from mechanical and electrical delay within RV myocardial tissue in response to pressure and volume overload. We suggest RV dilatation and pulmonary hypertension are important prognosticators within the context of current treatment protocols for severe COVID-19. Furthermore, our findings may be of particular interest when considering therapeutic options targeted at lung-protective ventilation and pulmonary arterial vasodilation to improve outcomes. Acknowledgment of the importance of fQRS could also lead to improvement in ECG analysis algorithms to facilitate broader clinical application for diagnosis and prognostication.

Ethics Committee Approval: As an analysis using clinically collected, nonidentifiable data, this work does not fall under the remit of National Health Service Research Ethics Committees. This study was approved by our institution's Research, Quality Improvement, and Audit Department with the reference number FH205. It was not appropriate or possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of our study.

Informed Consent: As a non-interventional, observational study, specific informed consent was not required by the Research, Quality Improvement and Audit department.

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