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ORIGINAL RESEARCH ARTICLE

QRS fragmentation as a possible electrocardiographic diagnostic marker in patients with acute myocarditis: preliminary histopathological validation

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Abstract

Aims We aim to assess the reproducibility of QRS fragmentation (fQRS) on a multi-centre dataset of patients with acute myocarditis (AM), including a histopathological validation in a subgroup with biopsy-proven disease. Electrocardiogram (ECG) in patients with myocarditis is usually considered aspecific. ST changes and conduction anomalies have been commonly reported so far. We have previously described fQRS in patients with AM.

Methods and results Patients admitted between 2008 and 2019 in two centres with a diagnosis of AM were included. Standard ECG, echocardiography, and cardiac magnetic resonance (CMR) findings were recorded at baseline and at follow-up (FU). Eighty patients were analysed, 66 men (82%), with median age of 34 (26–43) years. Twenty-two patients had biopsy-proven AM. At presentation, 61 patients (76%) displayed fQRS. Median ejection fraction (EF) was 55% (43–60). Seventy-two patients (90%) underwent CMR and displayed late gadolinium enhancement (LGE). ECG leads showed that fQRS correlated with distribution of LGE. In patients with positive biopsy, fQRS was present in 18 (81%). Median FU was 419 days (224–956). Complete FU was available for 64 patients (80%), and 33 patients (52%) displayed persistence of fQRS. Median EF was 60% (57–64). Eleven patients underwent a repeated biopsy at FU, eight of whom had persistent inflammation and fQRS. Fifteen patients (23%) had ventricular tachycardia, 14 of whom still showed fQRS.

Conclusions In this cohort fQRS was confirmed as an additional useful ECG sign. Persistence of fQRS was associated with ongoing inflammation and with a poorer outcome in terms of ventricular function and occurrence of arrhythmias.

Keywords QRS fragmentation; Myocarditis; Diagnosis

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Introduction

Diagnosis of acute myocarditis (AM) is based on a multi-parametric assessment including clinical presentation, electrocardiogram (ECG), non-invasive cardiac imaging, serum biomarkers of myocardial damage, and endomyocardial biopsy (EMB). Although EMB represents the diagnostic gold standard and provides valuable information to guide specific treatments with immunosuppressive medications, ECG is still the first-line assessment, along with clinical profile and increase of serum biomarkers, in patients presenting with suspected AM, particularly those with symptoms overlapping with acute coronary syndromes.[1–3] On the other hand, ECG is usually considered a blunt diagnostic tool as changes are deemed to be aspecific and transient. Clinical prognostic variables are also still poorly defined. Persistence of inflammation in EMBs is recognized as a risk factor.[4] Additional new ECG features, expression of structural changes within the myocardium, might be particularly useful in the clinical practice to support diagnosis and clinical follow-up.

Fragmentation of QRS (fQRS) is one of the most promising diagnostic and prognostic indexes described in a wide range of myocardial heart diseases characterized by the presence of infiltrates and/or of myocardial fibrosis.[5] Different patterns

of fragmentation have been described; the common characteristics are the presence of discernible multiple notches in either the R or S component of the QRS.[6] fQRS has been extensively studied in ischaemic heart disease and has been shown to be correlated with ventricular function and cardiac events at follow-up, irrespective of the presence of Q wave and extension of myocardial necrosis.[7,8] Although some of the histopathological features described in ischaemic and non-ischaemic cardiomyopathies overlap with those typical of AM, fQRS has never been described in patients with this particular disease.

We hypothesize that pathological changes observed in patient with AM, similarly to other model of disease, might affect the local electrical activation leading to anisotropic conduction expressed as fQRS in one or more leads.[6]

We have previously described the association of fQRS with late gadolinium enhancement (LGE) at cardiac magnetic resonance (CMR) in patients with AM referred to a single centre.[9]

This study aims to validate the observation of fQRS as additional electrocardiographic diagnostic sign on a larger cohort of patients with AM, including a subgroup with biopsy-proven disease. We also sought to investigate if persistence of fQRS might predict ongoing structural changes at biopsy or CMR at follow-up.

Methods

Patients admitted between 2008 and 2019, in two centres, with acute onset of symptoms were retrospectively assessed. Diagnosis was based on a consistent clinical presentation with increase of myocardial necrosis markers associated with presence of oedema/LGE on the CMR, according to the Lake Louise criteria.[10] In addition to the classic Dallas criteria, myocarditis was defined biopsy proven in the presence of abnormal inflammatory infiltrate within the myocardium: $\geq$14 leucocytes/mm^2 including up to 4 monocytes/mm^2 and $\geq$7 cells/mm of CD3-positive T-lymphocytes. Coronary angiography was performed whenever deemed appropriate to exclude ischaemic heart disease. Standard 12 leads ECG was recorded with filter range 0.16–100 Hz, with paper speed 25 mm/s, and 50 mm/s, and 10 mm/mV, taking particular care in optimizing contact of the electrodes with the skin. fQRS was defined as presence of an additional R wave (R′) or notching in the nadir of the S wave, or the presence of $>$1 R′ in at least two contiguous leads.[11] All ECGs were reviewed independently and blindly by two authors (P. F. and I. P.). In case of disagreement, fQRS was confirmed or ruled out after discussion. In order to take into account different laboratory metrics, the peak levels of C-reactive protein and troponin were normalized calculating the ratio with the upper normal reference value.

All available information at last follow-up, including clinical assessment, echocardiography, standard, and 24 h ECG recording, was retrieved. Significant arrhythmias were defined as any ventricular tachycardia consisting of at least 4 beats. CMR and EMB were also repeated in selected patients, according to institutional protocol, to assess the effect of specific therapies and to guide risk stratification. Distribution of LGE was categorized into three patterns according to the myocardial segment involved: anterior/septal, inferior/lateral, and spotted. The subgroup of patients with biopsy-proven myocarditis was used to validate fQRS in both the acute phase and follow-up.

Statistical methods

Continuous variables were reported as median ± standard deviation or median and inter-quartile ranges and compared by Student *t*-test or Wilkinson rank sum test, as appropriate. Normality of continuous variables was assessed by visually inspecting the distribution histograms. Categorical variables were presented as counts and percentages and compared by χ^2 or Fisher exact test.

A *P* value of 0.05 was assumed as cut-off for statistical significance. Analysis was performed with STATA 11.0 by Stata Corp.

Results

Clinical presentation and in-hospital management

Eighty patients were included in the analysis (66 male, 82%), 68 (85%) Caucasian. Median age was 34 years (26–43). In 22 (27%) patients, the diagnosis was biopsy proven; in 14 (17%) patients, both biopsy and CMR were positive; and in the remaining, only CMR was performed (*Figure 1*). Biopsy showed lymphocytic, eosinophilic, and giant cell myocarditis in 19 (86%), 2 (9%), and 1 (5%) patients, respectively.

Seventy-three patients (91%) reported typical prodromal symptoms, in particular flu-like and gastrointestinal syndrome, in 61 (76%) and 12 (15%), respectively. The most common symptom at presentation was chest pain in 66 (82%). Seven patients (9%) presented with cardiac arrest and 10 (12%) with cardiogenic shock or low cardiac output syndrome. ECG was pathologic in 76 (95%): 24 (30%) were aspecific, and 45 (56%) showed transient ST-T changes. fQRS was visible in 61 (76%) patients. At first examination, there was agreement on fQRS diagnosis in all cases but three, giving an inter-observer variability *K* coefficient of 0.93 (95% CI 0.86–1). ECG leads involved roughly matched the distribution of LGE at CMR (*Figure 2*).

In patients with ST-T changes, a significantly higher normalized release of troponin was observed: 414 (98–761) vs.

Figure 1 Diagram summarizing prevalence of QRS fragmentation in different categories of patients. fQRS, fragmented QRS; CMR, cardiac magnetic resonance.

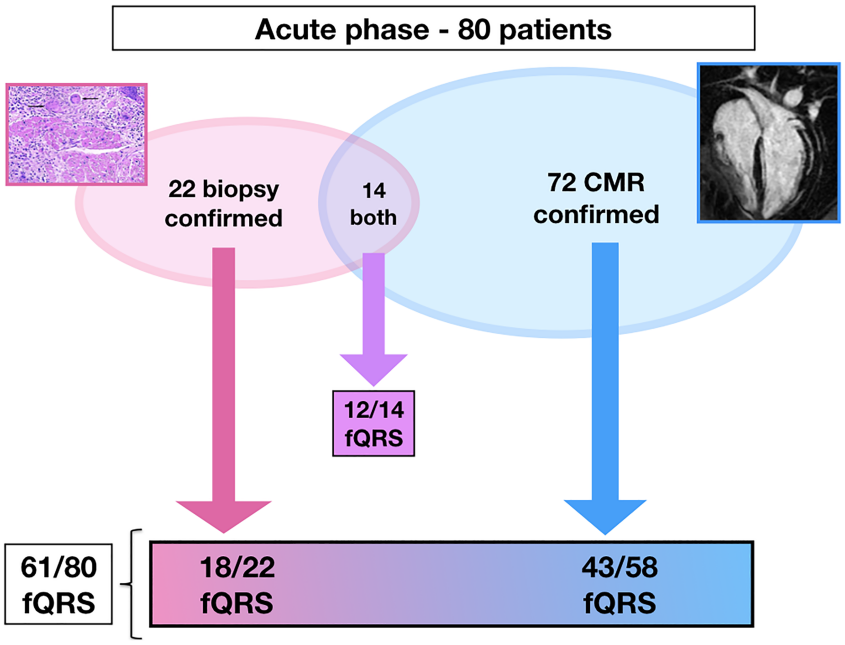
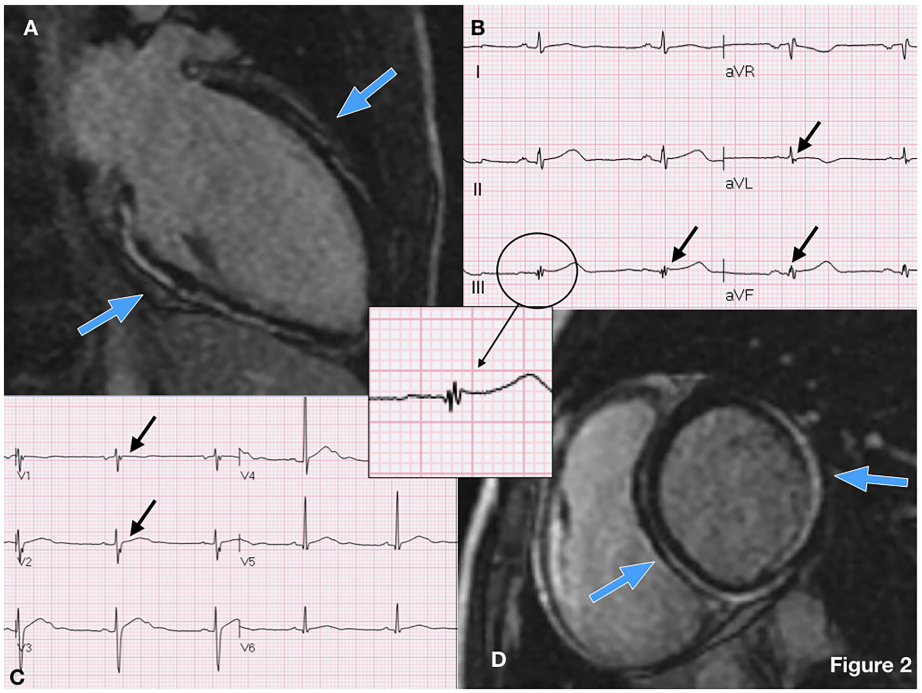


Figure 2 Illustration of correlation between LGE distribution and ECG leads displaying fragmentation. ECG, electrocardiogram; fQRS, fragmented QRS; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement. (A) CMR long-axis view. Blue arrows indicate LGE. (B)ECG showing fQRS in the peripheral leads (black arrows). (C)ECG showing fQRS in precordial leads (black arrows). (D) CMR short axis view. Blue arrows indicate LGE.



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83 (20–182), P = 0.003. Ventricular arrhythmias, either sustained or not sustained, occurred in 25 (31%) patients. fQRS was not associated with occurrence of ventricular arrhythmias in the acute phase. Median echocardiographic ejection fraction (EF) at admission was 55% (43–60). Seventy patients (87%) underwent CMR during the acute phase, which showed anterior/septal, inferior/lateral, and spot LGE in 14 (19%), 37 (51%), and 21 (29%) patients, respectively. Ischaemic heart disease was excluded by coronary angiography in 44 (55%) patients who had a medium-high probability of coronary artery disease.

Median troponin peak at presentation was 191 (29–642) times the upper limit of the normal institutional range, while C-reactive protein was 5.9 (3.4–13.6) times. Median BNP peak was 293 (66–980) pg/mL.

No correlation between troponin, C-reactive protein, and BNP levels were observed. Furthermore, levels of troponin, C-reactive protein, and BNP did not significantly differ patients displaying fQRS: 200 (29–635) vs. 171 (50–642), P = 0.9; 5.9 (3.3–13.5) vs. 6.6 (3.7–16.9), P = 0.5; and 304 (69–990) vs. 293 (56–741), P = 0.9, respectively.

C-reactive protein was significantly lower in patients presenting with gastrointestinal symptoms 4.6 (1.6–6) vs. 6.6 (3.5–14.2), P = 0.03, and in patients with chest pain, 5.6 (3.4–11.5) vs. 15 (5.3–26) P = 0.03. On the other hand, chest pain was not associated with a significantly different level of troponin.

Early inotropic support and mechanical circulatory support at admission were needed in 14 patients (17%) and 6 patients (7%), respectively. This latter group included four patients who underwent extracorporeal membrane oxygenator (ECMO) and two Impella. All patients received conventional heart failure medications, while 15 patients (19%) were treated with different combinations of immunosuppressive therapy (*Tables 1* and *2*).

One patient who presented with cariogenic shock and needed ECMO support died in hospital.

Table 1 General demographics and clinical characteristics of the population

	n = 80
Age (years), median (IQR)	34 (26–43)
Male, *n* (%)	66 (82)
Caucasian ethnicity	68 (85)
Prodromal symptoms, *n* (%)	73 (91)
Flu-like syndrome, *n* (%)	61 (76)
Gastrointestinal disorders	12 (15)
Clinical presentation/in-hospital course	
Chest pain, *n* (%)	66 (82)
Cardiac arrest, *n* (%)	7 (9)
Shock/LCO, *n* (%)	10 (12)
Inotropic support, *n* (%)	14 (17)
Mechanical circulatory support, *n* (%)	6 (7)
Laboratory findings	
C-reactive protein ratio (peak), median (IQR)	5.9 (3.4–13.6)
Troponin ratio (peak), median (IQR)	191 (29–642)
BNP peak (pg/mL), median (IQR)	293 (66–980)
EMB performed, *n* (%)	22 (27)
Coronary angiography performed	44 (55)
Immunosuppressive therapy, *n* (%)	15 (19)
Recurrence of AM, *n* (%)	11 (14)

AM, acute myocarditis; BNP, brain natriuretic peptide; EMB, endomyocardial biopsy; IQR, inter-quartile range; LCO, low cardiac output.

Table 2 Electrocardiographic, echocardiographic, and cardiac magnetic resonance findings at admission and follow-up

	Admission	Follow-up
ECG, *n* (%)	80 (100)	64 (80)
QRS fragmentation, *n* (%)	61 (76)	33 (51)
Rhythm identification, *n* (%)	80 (100)	71 (88)
Ventricular arrhythmia, *n* (%)	25 (31)	15 (21)
Echocardiography, *n* (%)	80 (100)	64 (80)
EDD (mm), median (IQR)	49 (47–52)	48 (45–51)
Pericardial effusion, *n* (%)	16 (20)	0
LVEF (%), median (IQR)	55 (43–60)	60 (55–63)
CMR, *n* (%)	70 (87)	54 (67)
LVEDVi (mL/m^2), median (IQR)	78 (70–92)	79 (69–88)
LVEF (%), median (IQR)	59 (53–64)	60 (57–64)
LGE, *n* (%)	70 (100)	40 (74)
Antero-septal LGE, *n* (%)	14 (19)	9 (17)
Infero-lateral LGE, *n* (%)	37 (51)	22 (41)
Other-pattern LGE, *n* (%)	21 (29)	9 (17)

ECG, electrocardiogram; EDD, end-diastolic diameter; IQR, inter-quartile range; LGE, late gadolinium enhancement; LVEDVi, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction.

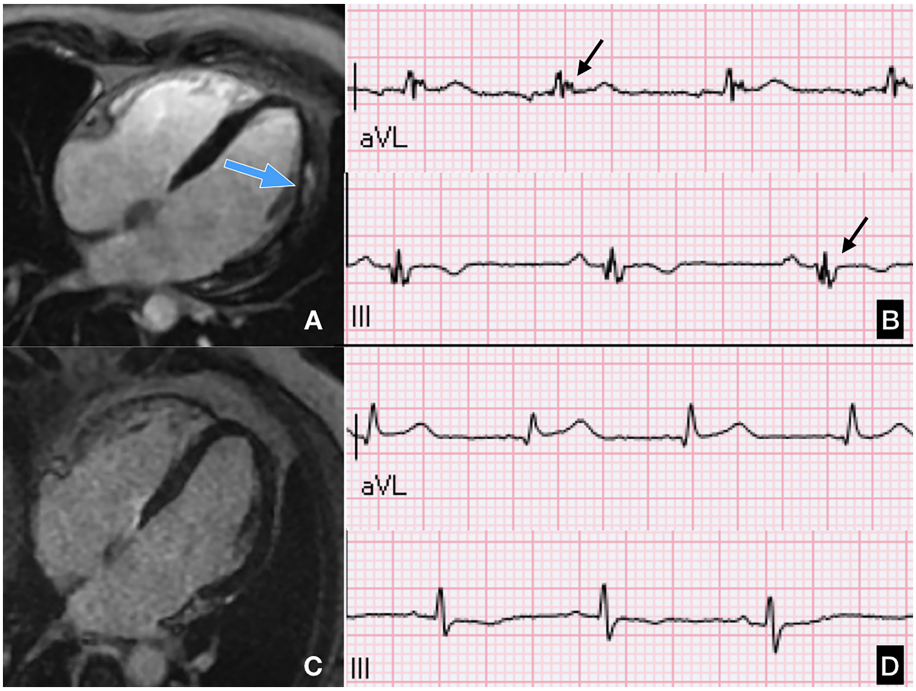
Follow-up

Complete follow-up was available in 64 (80%) patients with a median of 419 days (224–956). CMR was available in 54 (67%) patients, showing persistence of LGE in 40 (74%). fQRS was present at follow-up in 33 (51%) patients. Inter-observer variability K coefficient at follow-up was 0.91 95% CI (0.83–0.9). There was a significant association between persistence of fQRS and both LGE and biopsy positivity at follow-up: 25 patients out of 40 with LGE persistence displayed also fQRS ($P < 0.01$); likewise, all the eight patients have persistently positive biopsies (*Figures 3* and *4*).

Significant arrhythmias were recorded at follow-up in 15 (21%) patients, six of whom underwent implantable cardioverter defibrillator implantation (*Table* 2). All patients but one with significant arrhythmic burden showed persistence of fQRS.

Eleven patients had relapses of AM (14%). At last follow-up, median EF was 60% (55–63) and was found to be lower in patients with persisting fQRS: 56 ± 7% vs. 61 ± 6% P = 0.002. Thirteen (17%) patients displayed incomplete recovery of systolic function, which was associated with persistence of fQRS: 11 out of 33 with fQRS vs. 2 out of 31 without fQRS. On the other hand, of 51 patients who had complete recovery at follow-up, 22 (43%) still displayed fQRS (P = 0.03).

Figure 3 ECG normalization mirroring LGE disappearance in a sample patient. ECG, electrocardiogram; fQRS, fragmented QRS; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement. (A) CMR four chamber view. Blue arrows indicate LGE. (B) ECG showing fQRS in the peripheral leads. (C) The same patient at follow-up (10 months later); CMR of four chambers showing LGE disappearance. (D) ECG normalization in the same leads at follow-up.



Discussion

ECG is strongly recommended in patients with suspected AM presenting with typical or atypical chest pain or rhythm disturbances. In the literature statements, the most common findings discussed are ST changes, helping to identify AM mimicking acute coronary syndromes.[1] However, these signs, as well as bundle branch blocks, are aspecific and may be only occasionally and transiently present.[5] fQRS has been previously described in different cardiac conditions such as ischaemic, congenital, and arrhythmogenic cardiomyopathy, in which it has also a prognostic role.[12] This electrocardiographic feature is deemed to be the expression of a local slowing of electrical conduction across the myocardial muscle due to structural changes.

This feature has never been systematically reported in patients with AM, although the documentation of oedema and fibrosis in this disease represents a putative substrate for the development of fQRS. In a series of patients in previously published data, we observed that fQRS consistently mirrored the evidence and persistence of LGE on the CMR.[9] In that preliminary report, diagnosis of AM was based on clinical finding and CMR. In the present analysis, we included a group of patients with biopsy-proven myocarditis from another centre in which the observation of fQRS in both the acute phase and at follow-up was confirmed. Interestingly, the presence of fQRS in the acute phase was not associated with higher troponin nor with BNP levels. In a proportion of patients, fQRS disappeared at follow-up. This finding seems to be associated with a better prognosis in terms of mechanical function. On the other hand, a non-negligible proportion of patients whose ventricular function normalized had fQRS at follow-up. Hence, we can speculate that despite a tight association between fQRS and LGE, ECG is a sensitive but not specific predictor of incomplete EF recovery. Persistence of fQRS, but not its presence at admission, seems to be associated with a higher arrhythmic burden at follow-up. This is in agreement with a similar observation in ischaemic and non-ischaemic cardiomyopathy in which fQRS was associated with a higher risk of arrhythmic events.[11] This observation is particularly intriguing, as criteria for stratification of arrhythmic risk in patients with myocarditis are still poorly defined despite that many potential arrhythmic trigger have been recognized.[13] In the subset of patients who had undergone CMR, similarly to ischaemic and non-ischaemic cardiomyopathy, fQRS and LGE distribution appeared correlated, confirming our preliminary observation.[9,14]

Interestingly, persistence of fQRS was also significantly correlated with evidence of ongoing disease at biopsy, supporting the pathophysiologic link between histological

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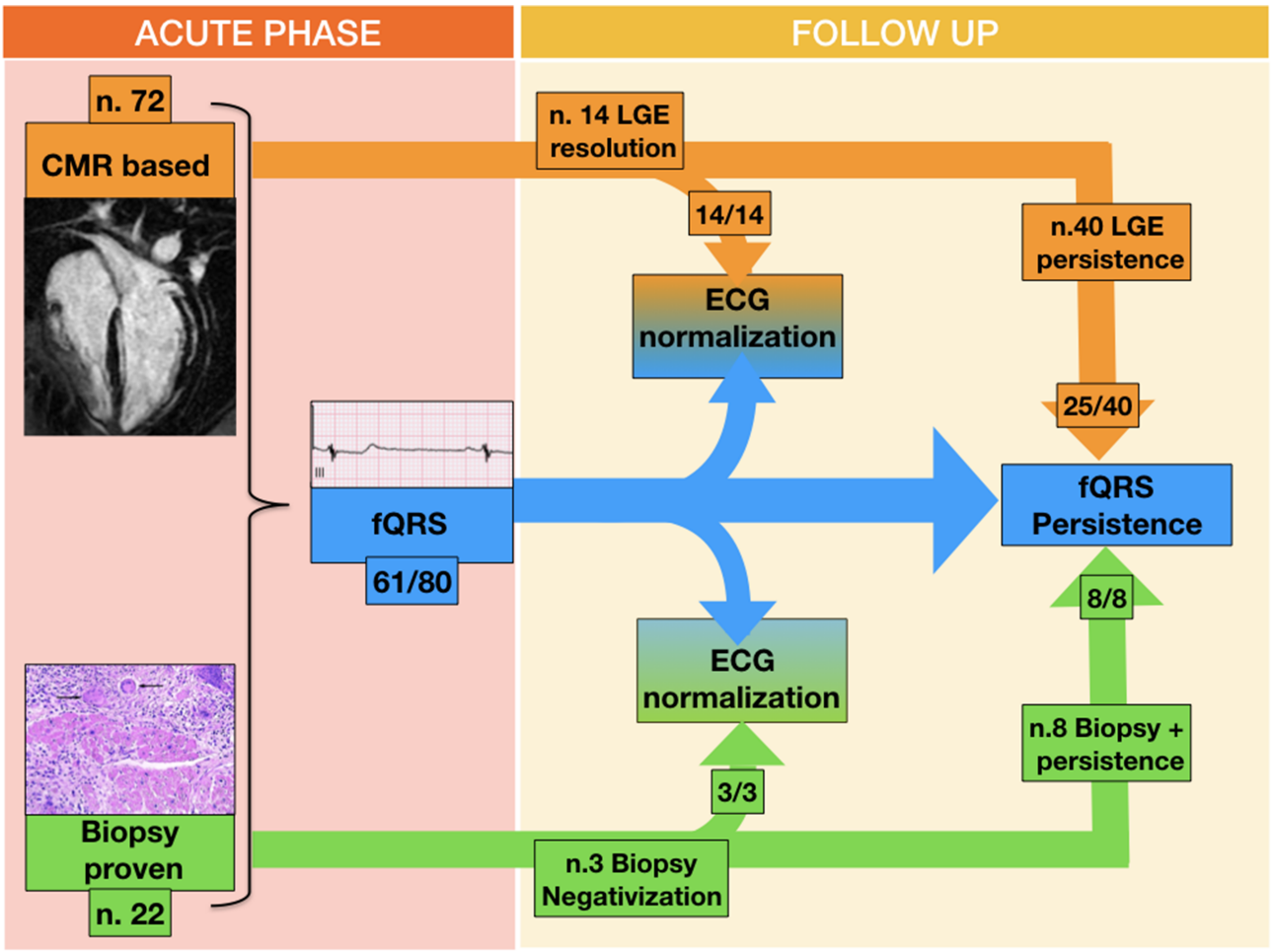
Figure 4 Diagram summarizing association among fQRS LGE and biopsy positivity at admission and during follow-up. fQRS, fragmented QRS; LGE, late gadolinium enhancement; CMR, cardiac magnetic resonance.



and electrical changes in this particular model of structural disease. If confirmed on larger samples, fQRS might be used as a simple clinical bedside tool to support the initial suspect of AM and to predict histological persistence of disease, which has been recognized as a detrimental prognostic factor.[4]

Limitations

A major limitation of this study is the retrospective design, suggesting caution about reproducibility of fQRS diagnosis in the general population. Furthermore, the histopathological feature in AM may change overtime; therefore, a variable latency in fQRS appearance may be supposed. On the other hand, given the dynamic healing process of myocarditis, the heterogeneity of the follow-up might have affected the rate of ventricular function recovery and ECG normalization.

Owing to the retrospective design of the study, some follow-up ECGs were missing, potentially causing an underestimation of fQRS persistence. Finally, the limited number of events at follow-up does not allow to draw conclusions about the prognostic significance of fQRS.

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Conflict of interest

None declared.

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