Baseline fragmented QRS is associated with increased all-cause mortality in heart failure with reduced ejection fraction: A systematic review and meta-analysis

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Abstract

Background: Recent studies suggested that fragmented (fQRS) is associated with poor clinical outcomes in heart failure with reduced ejection fraction (HFrEF) patients. However, no systematic review or meta-analysis has been done. We conducted a systematic review and meta-analysis to assess the association between baseline fQRS and all-cause mortality in HFrEF.

Methods: We comprehensively reviewed the databases of MEDLINE and EMBASE from inception to February 2018. Published studies of HFrEF that reported fQRS and outcome of all-cause mortality and major arrhythmic event (sudden cardiac death, sudden cardiac arrest, ventricular fibrillation, or sustained ventricular tachycardia) were included. Data were integrated using the random-effects, generic inverse-variance method of DerSimonian and Laird.

Results: Ten studies from 2010 to 2017 were included. Baseline fQRS was associated with increased all-cause mortality (risk ratio [RR] 1.63, 95% confidence interval [CI] 1.22–2.19, $p < 0.0001$, $I^2 = 73\%$) as well as major arrhythmic events (RR = 1.74, 95% CI 1.09–2.80, $I^2 = 89\%$). Baseline fQRS increased all-cause mortality in both Asian and Caucasian cohorts (RR = 2.17 with 95% CI 1.33–3.55 and RR = 1.45 with 95% CI 1.05–1.99, respectively) as well as increased major arrhythmic events in Asian cohort (RR = 1.50, 95% CI 1.05–2.13). Baseline fQRS also increased all-cause mortality in patients who had not received implantable cardioverter-defibrillator, significantly more than in patients who had received implantable cardioverter-defibrillator (RR = 2.46 with 95% CI 1.56–3.89 and 1.36 with 95% CI 1.08–1.71, respectively).

Conclusion: Baseline fQRS is associated with increased all-cause mortality up to 1.63-fold in HFrEF patients. Fragmented QRS could be a predictor of clinical outcome in patients with HFrEF.

Abbreviations: CI, confidence interval; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; ECG, electrocardiogram; EF, ejection fraction; fQRS, fragmented QRS; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICM, ischemic cardiomyopathy; MAE, major arrhythmic events; RR, risk ratio; SCD, sudden cardiac death; VF, ventricular fibrillation.

KEYWORDS

fragmented QRS, heart failure mortality

1 | INTRODUCTION

Heart failure (HF) is defined as a clinical syndrome with impairment of blood ejection or ventricular filling (Yancy et al., 2013). HF is a common cardiac problem which causes significant morbidity and mortality globally. It is estimated that up to twenty-three million people suffer from HF (McMurray, Petrie, Murdoch, & Davie, 1998), and approximately half of patients would die within 5 years of diagnosis (Levy et al., 2002; Roger et al., 2004). HF is mainly diagnosed on a clinical basis (Yancy et al., 2013). Its risk factors include, but is not limited to, coronary heart disease, cigarette smoking, hypertension, obesity, diabetes, and valvular heart disease (He et al., 2001). Heart failure with reduced ejection fraction (HFrEF), a subgroup of HF with documented ejection fraction (EF) less than forty percent, has been a focus of clinical trials. Most studied pharmacologic and device therapies specifically demonstrated benefits only in this group of HF patients (Yancy et al., 2013). Treatment of HFrEF includes lifestyle modification, management of underlying contributing factors, pharmacologic therapy, device therapy, cardiac rehabilitation, and preventive care. Several medications have been proven in their efficacy to reduce long-term morbidity and mortality. Device therapy has been recommended in stage C HF patients with strict indications and the risk and benefit should be thoroughly considered. Since the prognosis for HF varies widely, identifying patients at risk of poor clinical outcomes would be crucial. Several risk stratification tools or prognostic models have been proposed (Alba et al., 2013). However, surface ECG parameters have not been widely developed in HF risk stratification, even though ECG is one of the most accessible tool and usually available in most healthcare settings.

Fragmented QRS (fQRS), which reflects myocardial scarring, has been found to be associated with poor prognostic outcome in several cardiac conditions, including coronary artery disease (Xu et al., 2015), non-ischemic cardiomyopathy (Das et al., 2010), Brugada syndrome (Rattanawong et al., 2017), chronic total occlusion (Bonakdar et al., 2016), and hypertrophic cardiomyopathy (Rattanawong et al., 2018). Recent studies have demonstrated poor prognostic outcome in HFrEF patients whose baseline ECG was positive for fQRS. However, the results were inconclusive and no meta-analysis has been performed. Hence, we conducted a systematic review of the literature and meta-analysis to assess prognostic value of fQRS in HFrEF patients.

2 | METHODS

2.1 | Search strategy

We intended to identify all published reports relating the presence of fQRS and all-cause mortality or arrhythmic events in patients with

HFrEF. The published studies indexed in EMBASE and MEDLINE databases from inception to February 2018 were independently searched by two investigators (PC and PM), supplemented by manual searches through the references of the publications. We used a search strategy that included fragmented QRS and heart failure. Only English language publications involving human subjects were included.

2.2 | Inclusion criteria

The eligibility criteria included the following:

1. Cohort study (prospective or retrospective) or cross-sectional study reporting incidence or prevalence of all-cause mortality and major arrhythmic events (MAE), including ventricular fibrillation, sustained ventricular tachycardia, sudden cardiac arrest, or sudden cardiac death in heart failure with left ventricular dysfunction patients with and without baseline fQRS.
2. Heart failure with left ventricular dysfunction patients including heart failure patients who have left ventricular EF $\leq 40\%$ with or without implantable cardioverter-defibrillator (ICD) and/or cardiac resynchronization therapy (CRT) for primary or secondary prevention, dilated cardiomyopathy (DCM), or ischemic cardiomyopathy (ICM) with follow-up period ≥ 6 months.
3. Relative risk, hazard ratio, odds ratio, incidence ratio, or standardized incidence ratio with 95% confidence intervals (CI) or sufficient raw data for the calculation were provided.
4. Participants without baseline fQRS were used as controls.

The studies that include patients described fQRS on vectorcardiography, magnetocardiography, or signal-averaged ECG were excluded.

Study eligibility was independently determined by two investigators (CK and PM) and differences were resolved by mutual consensus. Newcastle–Ottawa quality assessment scale was used to evaluate each study in three domains: recruitment and selection of the participants, similarity and comparability between the groups, and ascertainment of the outcome of interest among cohort studies (Table S1).

2.3 | Data extraction

We used a standardized data collection form to obtain information from each study as followed: title of study, name of the first author, year of study, year of publication, country of origin, number of subjects enrolled, demographic data, and average follow-up time.

To ensure accuracy of data, all investigators conducted a data extraction process independently. Should there was any data discrepancy, we referred to original articles.

2.4 | Statistical analysis

We conducted a meta-analysis using random-effects model. We gathered the point estimates from each study by applying the generic inverse-variance method of Der Simonian and Laird. I^2 statistic and Q statistic were used to calculate the heterogeneity of effect size. The I^2 statistic ranges from 0% to 100% ($I^2 > 50\%$ reflects substantial heterogeneity, I^2 from 25% to 50% indicates moderate heterogeneity, and $I^2 < 25\%$ means low heterogeneity). Funnel plot and Egger's regression test were used to assess publication bias. All data analysis processes were done by the Stata SE 14.1 software from Stata Corp LP.

3 | RESULTS

3.1 | Description of included studies

Our search strategy generated ninety potentially relevant articles (fifty-four from EMBASE and thirty-eight from MEDLINE). Sixteen duplicated articles and two case reports were excluded, and 74 remaining articles underwent title and abstract review. Forty-nine studies were excluded by title and abstract review. Twenty-five remaining articles underwent full-length article review. Finally, seven retrospective cohorts, two prospective cohorts, and one cross-sectional study were included in the meta-analysis. Studies' characteristics are described in Table 1. In one study (Pei et al., 2012), we used the information from the subgroup analysis, since the characteristics of the subgroup fit with our criteria, while the characteristics of the main cohort did not.

3.2 | Quality assessment of included studies

We evaluated all included studies by using the Newcastle–Ottawa scale (zero-to-nine). The higher scores reflect higher study quality. Three domains were considered; selection, comparability, and ascertainment of outcomes. Included studies' score ranged from 7 to 8, indicating their high quality. Intrastudy risks of bias, including population characteristics, outcome definitions and assessment, follow-up duration, loss during follow-up, and identified limitations, were individually assessed. No intrastudy risk of bias was identified (Table S1).

3.3 | Meta-analysis results

Ten studies were included into the meta-analysis. Nine of 10 studies showed increased risk of all-cause mortality in patient with baseline fQRS. However, only one study (Cheema et al., 2010) showed non-significant negative association. Four cohorts from three studies showed significantly increased risk of all-cause mortality (Ozcan et al., 2013; Pei et al., 2012; Vandenberg et al., 2017). According to the overall analysis, baseline fQRS was significantly associated with the primary outcome of all-cause mortality (risk ratio [RR] = 1.63, 95% CI 1.22–2.19). Baseline fQRS was also significantly associated with secondary outcome of MAE (RR = 1.74, 95% CI 1.09–2.80). The statistical heterogeneity was substantial ($I^2 = 73\%$) for primary outcome

and high ($I^2 = 89\%$) for secondary outcome. No publication bias was detected by Egger test and funnel plot. To validate the result, we conducted a sensitivity analysis by omitting one study at a time. The results were not significantly different from the main results.

3.4 | Subgroups analyses

3.4.1 | Ejection fraction

Subgroup analysis based on EF was performed to compare between HFrEF patient with EF < 35% and nonspecific EF (EF ≤ 40%). Baseline fQRS significantly increased all-cause mortality and MAE (RR = 1.65 and 1.41, 95% CI 1.20–2.26 and 1.02–1.95, respectively) among patients with EF < 35%. Among HFrEF patients with nonspecific EF, baseline fQRS did not significantly increase all-cause mortality (RR 1.37, 95% CI 0.58–3.22), but significantly increased MAE (RR 7.63, 95% CI 5.15–11.29).

3.4.2 | ICD status

In subgroup of patients who had not received ICD placement, baseline fQRS significantly increased all-cause mortality more than in patients who had received ICD placement (RR = 2.46 and 1.36, 95% CI 1.56–3.89 and 1.08–1.71, respectively). Baseline fQRS increased MAE significantly in subgroup of patients who had not received ICD, but insignificantly in subgroup of patients who had received ICD (RR = 1.60 and 1.57, 95% CI 1.14–2.25 and 0.90–2.74, respectively).

3.4.3 | Ethnicities

Our analysis also indicated that baseline fQRS increased all-cause mortality in both Asian and Caucasian ethnicities (RR = 2.17 and 1.45, 95% CI 1.33–3.55 and 1.05–1.99, respectively). Baseline fQRS also increased MAE in Asian cohort (RR = 1.50, 95% CI 1.05–2.13). Nonetheless, in Caucasian cohort, baseline fQRS did not significantly increase MAE (RR = 1.85, 95% CI 0.97–3.52).

4 | DISCUSSION

This is the first meta-analysis to investigate the association between fQRS and prognostic outcomes in HFrEF patients. From included studies, most studies showed that fQRS was associated with increased all-cause mortality and increased MAE (Ahn, Kim, Joung, Lee, & Kim, 2013; Brenyo et al., 2012; Das et al., 2010; Forleo et al., 2011; Igarashi et al., 2017; Ozcan et al., 2013, 2014; Pei et al., 2012; Sha et al., 2011; Vandenberg et al., 2017), whereas one study revealed conflicting results (Cheema et al., 2010). The meta-analysis demonstrated that baseline fQRS was associated with increased all-cause mortality in HFrEF patients up to 1.63-fold. We also found that fQRS increased MAE up to 1.74-fold. The result suggested that fQRS could potentially be integrated as a risk stratification tool in such patients to aid clinical decision.

TABLE 1 The clinical characteristics and summary of included studiesw

First author	Country of origin	Year	Study type	Participant description	Exclusion criteria	Total population
Das et al.	USA	2010	Retrospective cohort	CAD and DCM receiving an ICD for primary or secondary prevention. LVEF $\leq 40\%$	Paced rhythm	361
Cheema et al.	USA	2010	Prospective cohort	LVEF $\leq 35\%$ of both ischemic and nonischemic etiologies.	N/A	842
Sha et al.	China	2011	Retrospective cohort	IDCM with LVEF $\leq 40\%$	HF due to CAD, secondary cardiomyopathy, valvular or congenital heart disease, or patients with orthotopic cardiac transplantation during follow-up. Paced rhythm at baseline.	128
Forleo et al.	Italy	2011	Retrospective cohort	IDCM or NIDCM, chronic stable HF with first ICD implantation. LVEF $\leq 35\%$	ICD for secondary prevention	394
Pei et al.	China	2012	Prospective cohort	CHF patients with DCM and ICM. (*Subgroup with LVEF $\leq 30\%$ was selected for analysis)	Malignant tumors, severe liver and kidney dysfunctions, or other uncontrollable systemic diseases, pregnancy	1570 (N/A for analyzed subgroup)
Brenyo et al.	USA	2012	Retrospective cohort	History of prior MI 1 month or more. LVEF $\leq 30\%$	N/A	1,040
Ozcan et al.	Turkey	2013	Retrospective cohort	Hospitalized for decompensated HF due to ischemic or nonischemic DCM	Bundle branch block, WPW syndrome, Brugada syndrome, or QRSd >120 ms, suspected subclinical myocardial involvement or presence of significant valvular heart disease or permanent pacemaker	227

Male (%)	Mean age (years)	fQRS definition	fQRS (n)	Mean duration of follow-up (months)	Outcome definition	Conclusion by authors
91	63.3 ± 11.4	RSR' patterns (QRS duration ≤120 ms), additional R', notching of the R or S wave, or more than two R' in two contiguous leads	84	16.6 ± 10.2	Arrhythmic events, all-cause mortality	fQRS predicts arrhythmic event in patients with ICM and NICM who received ICD for primary or secondary prevention of SCD, but does not predict mortality.
77.8	66 ± 12	RSR' patterns (QRS duration ≤120 ms), additional R', notching of the R or S wave, or more than two R' in two contiguous leads	274	40 ± 17	All-cause mortality, cause-specific mortality, appropriate shock in patients with ICD	fQRS was not associated with a higher risk for either all-cause or arrhythmic mortality.
68	53.6 ± 13.9	RSR' patterns (QRS duration ≤120 ms), additional R', notching of the R or S wave, or more than two R' in two contiguous leads	51	14 ± 5	All-cause mortality, ventricular arrhythmia, including appropriate ICD therapy for ventricular arrhythmia	fQRS predicts combined end point of all-cause mortality and ventricular tachyarrhythmias in IDCM patients with left ventricular dysfunction
84.8	66.4 ± 11.0	More than two peaks or notches present in the R or the S wave in two contiguous leads	103	26.3 ± 17.5	All-cause mortality, any appropriate ICD-delivered therapy	fQRS is not associated with an increased risk of subsequent appropriate ICD therapy or all-cause death.
78.0 (N/A for analyzed subgroup)	N/A for analyzed subgroup	RSR' patterns (QRS duration ≤120 ms), additional R', notching of the R or S wave, or more than two R' in two contiguous leads	N/A for analyzed subgroup	36	All-cause mortality, sudden cardiac death, including 3 appropriate ICD discharge, nonsudden cardiac death	Presence of J wave or fQRS in the inferior leads predicts SCD in DCM and ICM patients. fQRS might be an independent predictor for SCD in patients with CHF
97	N/A	RSR' patterns (QRS duration ≤120 ms), additional R', notching of the R or S wave, or more than two R' in two contiguous leads	339	20	SCD, combined appropriate ICD shock or SCD, all-cause mortality	fQRS predicts SCD or ICD shock for ventricular arrhythmia in patients with ischemic cardiovascular disease and depressed LV function. Inferior fQRS is strongly predictive of all-cause mortality and SCD in LBBB patients.
68.7	64.26	RSR' patterns (QRS duration ≤120 ms), additional R', notching of the R or S wave, or more than two R' in two contiguous leads	114	44.76 ± 16.92	Cardiovascular mortality, sudden cardiac death, rehospitalization for HF	Narrow fQRS predicts cardiovascular mortality in patients hospitalized for decompensated HF of both ischemic and nonischemic causes.

First author	Country of origin	Year	Study type	Participant description	Exclusion criteria	Total population
Ozcan et al.	Turkey	2014	Cross-sectional study	LV systolic failure in whom ICD had been implanted for primary prophylaxis.	ICD for secondary prevention	215
Vanderberk et al.	Belgium	2017	Retrospective cohort	Indicated for an ICD in primary prevention of SCD in ICM and non-ICM	N/A	407
Igarashi et al.	Japan	2017	Retrospective cohort	HF patients with NICM who received CRT	N/A	137

In this meta-analysis, we analyze fQRS regardless of its location. Pei et al. (2012), Vandenberg et al. (2017), and Brenyo et al. (2012), however, suggested particularly strong associations between fQRS in inferior lead and arrhythmic events or SCD. Pei et al. suggested that fQRS in inferior leads could be an independent predictor of SCD in CHF patients with ICM or DCM (Pei et al., 2012). MADIT II study, which included patients with history of myocardial infarction within 1 month whose EF $\leq$ 30%, suggested a particularly strong association between inferior fQRS and SCD or appropriate ICD therapy (Brenyo et al., 2012). Vandenberg et al. also reported a strong association between inferior fQRS and appropriate ICD therapy after implantation in patients receiving ICD for primary prevention of SCD (Vandenberg et al., 2017). Nonetheless, there were not enough data to conclude related clinical outcomes regarding specific location of fQRS. Thus, large-scale study is needed to warrant impact of fQRS in specific territory.

It is apparent that the association of fQRS and all-cause mortality was more pronounced in patients without ICD (2.46-fold when

compared to 1.36-fold in patients with ICD). This could be accountable from beneficial effect of ICD to the patients who are susceptible to MAE resulting in dramatically decreased mortality.

The explanation of the pathophysiology of fQRS associated with major arrhythmic events and all-cause mortality is still unclear. Recently, fQRS has been reported more in its prognostic effects of poor clinical outcomes in several cardiac conditions (Bonakdar et al., 2016; Das et al., 2010; Rattanawong et al., 2017; Xu et al., 2015). Suggested mechanism of fQRS is explained by electrical dyssynchrony of interventricular conduction (Sinha et al., 2016), which could result from a myocardial scar. Baseline fQRS was reported as a sensitive and specific tool to detect myocardial scars with sensitivity and specificity up to 85.6% and 89%, respectively (Das, Khan, Jacob, Kumar, & Mahenthiran, 2006; Sadeghi, Dabbagh, Tayyebi, Zakavi, & Ayati, 2016).

Several prognostic models or scoring systems have been introduced to predict the outcomes from clinical data in HF patients.

Male (%)	Mean age (years)	fQRS definition	fQRS (n)	Mean duration of follow-up (months)	Outcome definition	Conclusion by authors
72.5	58.2 ± 11.6	RSR' patterns (QRS duration ≤120 ms), additional R', notching of the R or S wave, or more than two R' in two contiguous leads	123	23.5 ± 12.1	All-cause mortality, appropriate ICD shock, combined endpoints of appropriate ICD shock and all-cause mortality	fQRS predicts arrhythmic events and appropriate ICD shocks, but not all-cause mortality in patients with systolic heart failure undergoing ICD implantation for primary prophylaxis
84.3	60.6 ± 11.9	(1) QRS duration ≤120 ms: RSR' pattern, ≥1 R prime or notching of R or S wave (2) QRS duration >120 ms: RSR' patterns with N2 R waves (R') or N2 notches in the R wave, or N2 notches in the downstroke or upstroke of the S wave	190	50 ± 40	All-cause mortality, first appropriate ICD shock	Inferior fQRS was a predictor of early arrhythmia. Anterior fQRS was related to mortality
67.2	63.8 ± 15.0	(1) QRS duration ≤120 ms: RSR' patterns, additional R', notching of the R or S wave, or more than two R' in two contiguous leads (2) QRS duration >120 ms: QRS, >2 notches in the R, or S waves in two contiguous leads	67	18	Composite of SCD or Vas including appropriate ICD or CRTD therapies	fQRS-post is independently associated with SCD or ventricular arrhythmic events.

Nonetheless, they faced several challenges, especially their applicability and generalizability to HF patients in real clinical settings (Alba et al., 2013). The Seattle Heart Failure Model (SHFM), which was proposed in 2006, was developed based on a database of 1,125 patients in the PRAISE clinical trial (Levy et al., 2006). The recruited patients in the trial were limited to patients in the United States and Canada with ejection <30% with the New York Heart Association classification functional class IIIB to IV heart failure thus external validity of the study was relatively limited. Published in 2012, the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) from 39,372 patients in 30 studies proposed the score based on 13 independent predictors of mortality in HF patients (Pocock et al., 2013). These predictors, by the order of predictive strength, included age, lower EF, the New York Heart Association classification, serum creatinine, diabetic status, not-prescribed beta-blocker, lower systolic BP, lower body mass, time since diagnosis, current smoker, chronic obstructive pulmonary disease,

male gender, and having not being prescribed with ACE-inhibitors or angiotensin-receptor blockers (Pocock et al., 2013). Several other models were developed to predict outcomes in patients with acute decompensated heart failure (Passantino, Monitillo, Iacoviello, & Scrutinio, 2015) or chronic heart failure—yet, none have become standard in clinical practice. This stressed the complexity in predicting outcome and the necessity to develop practical and widely applicable tools, and surface ECG clues could potentially be integrated into those prognostic predictors.

5 | LIMITATIONS

There are a few limitations in our study. First, as an observational nature of cohort studies, we did not demonstrate causal relationship between fQRS and poor prognostic outcome. Second, there is slight heterogeneity from variation among subjects included in each

FIGURE 1 Search methodology and selection process

Major arrhythmic events by ICD status

FIGURE 2 All-cause mortality (main result)

study and differences in definitions of MAE or cardiac events in each study. Third, we analyzed fQRS regardless of its location, since there was not enough information to identify specific location. Fourth, the indications of ICD implantation have often been revised in the past decades, hence, may affect the outcomes among recruited studies that included implanted ICD patients.

6 | CONCLUSION

Our study suggests that fQRS is significantly associated with increased all-cause mortality and MAE in HFrEF patients. Hence, fQRS could be considered as a potential element in risk stratification of HF patients. Since HFrEF patients are relatively heterogeneous, further

Major arrhythmic events

FIGURE 3 Major arrhythmic events (main result)

All-cause mortality by EF

Major arrhythmic events by EF

FIGURE 4 All-cause mortality and major arrhythmic event (subgroup analysis by EF)

All-cause mortality by ethnicities

Major arrhythmic events by ethnicities

FIGURE 5 All-cause mortality and major arrhythmic event (subgroup analysis by ethnicities)

All-cause mortality by ICD status

Major arrhythmic events by ICD status

FIGURE 6 All-cause mortality and major arrhythmic event (subgroup analysis by ICD status)

studies would be needed to validate its role in risk stratifying HFrEF patients in specific subsets of HFrEF for the best implementation in clinical settings.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Chanavuth Kanitsoraphan involved in conception design, data acquisition, and data interpretation, and drafted the manuscript. Pattara Rattanawong involved in conception design, data interpretation, statistical analysis, and corresponding. Poemlarp Mekraksakiet involved in data acquisition and data interpretation, and drafted the manuscript. Pakawat Chongsathidkiet and Tanawan Riangwiwat acquired the data. Napatt Kanjanahattakij, Wasawat Vutthikraivit, Saranapoom Klomjit, and Subhanudh Thavaraputta interpreted the data.

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SUPPORTING INFORMATION

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