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QRS duration and cardiovascular mortality in Asian patients with heart failure and preserved and reduced ejection fraction

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The QRS duration has been well established as a predictor of mortality in patients with heart failure with reduced ejection fraction (HFrEF) [1]. In patients with heart failure with preserved ejection fraction (HFpEF), some studies have shown that prolonged QRS duration has been associated with increased morbidity and mortality [2, 3]. However, these studies were based mainly on Western cohorts with scarce data from Asia, where normal ranges for QRS duration may differ [4, 5]. The aim of this study was to examine the association between QRS duration and mortality in an Asian heart failure cohort.

Consecutive patients who were admitted with heart failure as the primary diagnosis from two institutions from 1 January 2008 to 31 December 2009 were included. Those with paced rhythms were excluded. The QRS interval was measured by trained staff on a 12-lead electrocardiogram upon admission. HFpEF was defined as heart failure patients with ejection fraction (EF) ≥ 50% and ≥ grade 1 diastolic dysfunction on the echocardiogram or N-terminal-pro-B-type natriuretic peptide (NT-proBNP) level > 220 pg/mL heart failure with non-preserved EF (HFnpEF) was defined as EF < 50%. The outcomes were obtained from national registries. All patients were followed-up till December 2014. The primary outcomes were all-cause mortality and cardiovascular mortality. Ethics approval was obtained from the institutional review board.

Cox proportional hazard modelling was used to identify predictors of all-cause and cardiovascular mortality. Variables significant on univariate analysis ($p < 0.05$) were selected for the multivariate models. Multivariate Cox proportional hazard models were then performed for each heart failure cohort to calculate hazard ratios (HR) and associated 95% confidence intervals (CI) for mortality. QRS duration was analyzed both as a continuous and categorical variable. The optimal QRS cut-off was assessed by area under receiver operating characteristics (AUROC) curve. Data was analyzed using the Statistical Package for the Social Sciences (SPSS®, version 23.0). A p value of < 0.05 was taken to be statistically significant.

A total of 666 HFpEF (mean age 73.1 ± 10.5, 36.3% male, mean LVEF 61 ± 8%) and 1032 HFnpEF (mean age 66.3 ± 12.4 years, 64.3% male, mean LVEF 29 ± 13%) were included. The clinical characteristics are summarized in Table 1.

In patients with HFpEF, 5-year overall and cardiovascular mortality was 57% (n = 381) and 28% (n = 189) respectively. QRS duration as a continuous variable was a significant predictor of cardiovascular (adjusted HR 1.010; 95% CI 1.002–1.018; p = 0.011) but not overall mortality (p = 0.190). A cut-off of 100 ms was found to provide the optimal discriminatory AUC compared to other cut-offs including 90 ms, 110 ms and 120 ms. A QRS ≥ 100 ms was a significant predictor of cardiovascular mortality (adjusted HR 1.468; 95% CI 1.014–2.126; p = 0.042) but not overall mortality (adjusted HR 1.287; 95% CI 0.993–1.668; p = 0.056).

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Table 1. Clinical characteristics of the study population.

	Preserved ejection fraction (n = 666)			Reduced ejection fraction (n = 1032)		
	< 100 ms (n = 482)	≥ 100 ms (n = 184)	P	< 100 ms (n = 484)	≥ 100 ms (n = 548)	P
Demographics						
Mean age (SD)	73.0 (10.5)	72.6 (11.0)	0.634	65.9 (12.8)	66.8 (12.1)	0.239
Male	141 (29.3%)	101 (54.9%)	< 0.001	272 (56.2%)	394 (71.9%)	< 0.001
Race:						
Chinese	360 (74.7%)	136 (73.9%)	0.452	328 (67.8%)	372 (67.9%)	0.545
Malay	55 (11.4%)	24 (13.0%)		95 (19.6%)	94 (17.2%)	
Indian	59 (12.2%)	18 (9.8%)		51 (10.5%)	71 (13.0%)	
Others	8 (1.7%)	6 (3.3%)		10 (2.1%)	11 (2.0%)	
Clinical characteristics						
Prior CAD	204 (42.3%)	69 (37.5%)	0.258	193 (39.9%)	298 (54.4%)	< 0.001
Prior MI	80 (16.6%)	34 (18.5%)	0.564	179 (37.0%)	210 (38.3%)	0.658
Atrial fibrillation	164 (34.0%)	73 (39.7%)	0.173	94 (19.4%)	127 (23.2%)	0.142
Diabetes mellitus	225 (46.7%)	86 (46.7%)	0.989	304 (62.8%)	277 (50.5%)	< 0.001
Hypertension	388 (80.5%)	139 (75.5%)	0.159	324 (66.9%)	386 (70.4%)	0.226
Hyperlipidemia	297 (61.6%)	96 (52.2%)	0.027	306 (63.2%)	355 (64.8%)	0.603
Stroke	86 (17.8%)	36 (19.6%)	0.607	66 (13.6%)	78 (14.2%)	0.782
PVD	24 (5.0%)	12 (6.5%)	0.431	35 (7.2%)	38 (6.9%)	0.853
COPD	61 (12.7%)	30 (16.3%)	0.220	48 (9.9%)	74 (13.5%)	0.075
Ever smoker	116 (24.1%)	67 (36.4%)	0.001	202 (41.7%)	279 (50.9%)	0.003
Systolic BP (SD) [mmHg]	143.1 (29.1)	140.3 (31.3)	0.266	139.8 (30.5)	133.6 (29.2)	0.001
Diastolic BP (SD) [mmHg]	73.2 (16.5)	72.4 (17.5)	0.608	80.6 (19.3)	75.6 (18.3)	< 0.001
Heart rate (SD)	84.4 (22.9)	78.8 (22.9)	0.005	92.8 (21.0)	84.4 (18.3)	< 0.001
QRS duration (SD)	85.1 (8.1)	115.7 (17.5)	< 0.001	87.9 (7.6)	123.9 (24.2)	< 0.001
NT-proBNP (SD) [pg/mL]	5079.9 (7141.8)	8282.3 (11909.7)	0.061	11741.1 (14600.0)	12389.6 (15358.1)	0.537
Creatinine (SD) [μmol/L]	121.4 (84.8)	145.9 (125.3)	0.015	133.4 (98.4)	141.2 (92.7)	0.186
Sodium (SD) [mmol/L]	136.4 (4.9)	136.2 (5.2)	0.706	136.0 (7.3)	135.8 (8.7)	0.713
Potassium (SD) [mmol/L]	4.2 (0.8)	4.2 (0.8)	0.451	4.3 (0.8)	4.3 (1.8)	0.895
Hemoglobin (SD) [g/dL]	11.7 (2.0)	12.0 (2.1)	0.085	12.4 (2.1)	12.6 (2.0)	0.046
Discharge medications						
ACEI/ARB	284 (58.9%)	114 (62.0%)	0.475	360 (74.4%)	415 (75.7%)	0.617
Beta-blocker	240 (49.8%)	98 (53.3%)	0.423	314 (64.9%)	369 (67.3%)	0.405
Spironolactone/Aldosterone antagonist	35 (7.3%)	17 (9.2%)	0.395	90 (18.6%)	145 (26.5%)	0.003
Nitrate	192 (39.8%)	84 (45.7%)	0.173	245 (50.6%)	312 (56.9%)	0.042
Diuretic	365 (75.7%)	148 (80.4%)	0.176	424 (87.6%)	476 (86.9%)	0.722
Digoxin	88 (18.3%)	37 (20.1%)	0.584	130 (26.9%)	158 (28.8%)	0.481
ASA	196 (40.7%)	87 (47.3%)	0.122	282 (58.3%)	331 (60.4%)	0.485
Clopidogrel	63 (13.1%)	16 (8.7%)	0.118	89 (18.4%)	90 (16.4%)	0.405
Warfarin	86 (17.8%)	33 (17.9%)	0.978	52 (10.7%)	70 (12.8%)	0.313
Lipid-lowering	301 (62.4%)	112 (60.9%)	0.707	357 (73.8%)	395 (72.1%)	0.545

CAD — coronary artery disease; MI — myocardial infarction; PVD — peripheral vascular disease; COPD — chronic obstructive pulmonary disease; BP — blood pressure; NT-proBNP — N-terminal-pro-B-type natriuretic peptide; ACEI/ARB — angiotensin converting enzyme/angiotensin receptor blocker; ASA — acetylsalicylic acid

In patients with HFnpEF, 5-year overall and cardiovascular mortality was 65% (n = 673) and 43.0% (n = 444). QRS duration as a continuous variable was a significant predictor of both overall (adjusted HR 1.005; 95% CI 1.001–1.008; p = 0.004) and cardiovascular mortality (adjusted HR 1.006; 95% CI 1.002–1.010; p = 0.003). A cut-off of 100 ms was found to provide the optimal discriminatory AUC compared to other cut-offs including 90 ms, 110 ms and 120 ms. QRS ≥ 100 ms was a significant predictor of both overall (adjusted HR 1.262; 95% CI 1.047–1.522; p = 0.015) and cardiovascular mortality (adjusted HR 1.336; 95% CI 1.058–1.688; p = 0.015; Table 2).

In this Asian HFnpEF cohort, it was found that QRS prolongation predicted both overall and cardiovascular mortality. This is in-line with current literature [1] and lends further evidence to the detrimental impact of QRS prolongation across different ethnicities.

Of greater interest are the results from the HFpEF cohort. In two non-Asian studies, QRS prolongation in HFpEF impacted upon overall mortality [2, 3]. In one of the few Asian studies to-date, Gisberts found a significant association of QRS duration on overall mortality in HFrEF patients, but not in HFpEF patients [4]; cardiovascular mortality was not assessed. The neutral all-cause mortality finding was similar to that of our HFpEF cohort. However, a significant relationship with cardiovascular mortality was additionally found in the HFpEF patients of the current study. This is pathophysiologically plausible with QRS prolongation indicative of cardiac abnormalities [6]. Of note, the cut-offs in the above two non-Asian studies was found to be 120 ms [2, 3]; a cut-off of 100 ms to was found have greater discriminatory value in the Asian cohort. This may be a result of body size or ethnicity [4, 5]. It was found that the average QRS duration in a healthy community-based cohort of Chinese, Malays and Indians was 89 ms in males and 83 ms in female [5]. In the Framingham heart study, the average QRS duration in a healthy Caucasian male was 97 ms and 87 ms in females [7]. Several studies have shown that increasing body size results in increasing QRS duration [5] and this may account for the lower QRS cut-offs as seen in the present study with known smaller body sizes of Asians. The differences in findings between the current HFpEF and HFnpEF cohort are likely the result of both conditions being separate disease entities. Multiple studies have previously shown distinct clinical and prognostic differences between these groups [8].

Table 2. QRS duration, all-cause and cardiovascular (CV) mortality.

	Unadjusted overall mortality		Unadjusted CV mortality		Adjusted overall mortality		Adjusted CV mortality	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Preserved ejection fraction								
QRS duration (continuous)	1.007 (1.002–1.013)	0.012	1.013 (1.006–1.020)	< 0.001	1.004 (0.998–1.011)	0.190*	1.010 (1.002–1.018)	0.011**
QRS duration (categorical)								
< 100 ms								
≥ 100 ms	1.347 (1.086–1.671)	0.007	1.674 (1.246–2.250)	0.001	1.287 (0.993–1.668)	0.056*	1.468 (1.014–2.126)	0.042**
Reduced ejection fraction								
QRS duration (continuous)	1.005 (1.002–1.007)	0.001	1.007 (1.004–1.010)	< 0.001	1.005 (1.001–1.008)	0.004^	1.006 (1.002–1.010)	0.003^^
QRS duration (categorical)								
< 100 ms								
≥ 100 ms	1.249 (1.072–1.454)	0.004	1.488 (1.230–1.800)	< 0.001	1.262 (1.047–1.522)	0.015^	1.336 (1.058–1.688)	0.015^^

HR — hazard ratio; CI — confidence interval; other abbreviations — see Table 1. *Adjusted for age, gender, left ventricular hypertrophy, prior MI, atrial fibrillation, stroke, PVD, smoker, diastolic BP, NT-proBNP, creatinine, sodium, potassium, hemoglobin, ACEI/ARB, beta-blocker, warfarin; **Adjusted for age, ethnicity, left bundle branch block, left ventricular hypertrophy, prior MI, hyperlipidemia, stroke, PVD, systolic BP, NT-proBNP, creatinine, potassium, haemoglobin, warfarin; ^ Adjusted for age, heart rate, coronary artery disease, prior MI, atrial fibrillation, diabetes mellitus, hypertension, hyperlipidaemia, stroke, PVD, systolic BP, diastolic BP, NT-proBNP, creatinine, hemoglobin, ACEI/ARB use, beta-blocker use, nitrates use, ASA use; ^^ Adjusted for age, heart rate, right ventricular hypertrophy, CAD, prior MI, atrial fibrillation, diabetes mellitus, hyperlipidemia, stroke, PVD, systolic BP, diastolic BP, NT-proBNP, creatinine, hemoglobin, ACEI/ARB, aldosterone antagonist

HFpEF remains a difficult clinical condition to manage due to its limited therapeutic options. Risk stratification is challenging and has fewer established prognostic markers [9]. An electrocardiogram is readily available and thus QRS duration could potentially be used as a simple risk stratification tool for clinicians. QRS prolongation has been linked to mechanical desynchrony in HFpEF [10]. In appropriate HFrEF patients, the use of cardiac resynchronization therapy has been shown to provide mortality and symptomatic benefit, but how this eventually translates to therapeutic options for HFpEF is less clear. Regardless, HFpEF patients with prolonged QRS duration identifies a subset at higher risk of adverse outcomes; greater efforts must be taken to optimize the holistic care of these patients including control of cardiovascular risk factors.

Limitations of the present study include primary use of hospitalized patients with heart failure; more stable patients in an outpatient/community setting may have been different. Secondly, the current cohort consisted of patients who were mainly of Chinese, Malay and Indian ethnicity which reflects the population distribution in Singapore; the data should be validated in other Asian ethnicities. Thirdly, the uptake of guideline directed medical therapy in the present cohort reflects real-world practice and this cohort was recruited from 2008 to 2009; the potential impact of heart failure therapies, especially the more contemporary medications, will be the work of future studies. Lastly, the QRS duration was only available from the admission electrocardiogram. Changes in QRS duration over time was not captured.

In the present Asian heart failure cohort, QRS duration is a significant predictor of cardiovascular mortality in both HFpEF and HFnpEF patients. QRS duration also significantly predicted overall mortality in HFnpEF patients.

Conflict of interest: None declared

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