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ORIGINAL RESEARCH

Electroanatomic Ratios and Mortality in Patients With Heart Failure: Insights from the ASIAN-HF Registry

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BACKGROUND: QRS duration (QRSd) is a marker of electrical remodeling in heart failure. Anthropometrics and left ventricular size may influence QRSd and, in turn, may influence the association between QRSd and heart failure outcomes.

METHODS AND RESULTS: Using the prospective, multicenter, multinational ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry, this study evaluated whether electroanatomic ratios (QRSd indexed for height or left ventricular end-diastole volume) are associated with 1-year mortality in individuals with heart failure with reduced ejection fraction. The study included 4899 individuals (aged 60±19 years, 78% male, mean left ventricular ejection fraction: 27.3±7.1%). In the overall cohort, QRSd was not associated with all-cause mortality (hazard ratio [HR], 1.003; 95% CI, 0.999–1.006, *P*=0.142) or sudden cardiac death (HR, 1.006; 95% CI, 1.000–1.013, *P*=0.059). QRS/height was associated with all-cause mortality (HR, 1.165; 95% CI, 1.046–1.296, *P*=0.005 with interaction by sex $p_{interaction}$=0.020) and sudden cardiac death (HR, 1.270; 95% CI, 1.021–1.580, *P*=0.032). QRS/left ventricular end-diastole volume was associated with all-cause mortality (HR, 1.22; 95% CI, 1.05–1.43, *P*=0.011) and sudden cardiac death (HR, 1.461; 95% CI, 1.090–1.957, *P*=0.011) in patients with nonischemic cardiomyopathy but not in patients with ischemic cardiomyopathy (all-cause mortality: HR, 0.94; 95% CI, 0.79–1.11, *P*=0.467; sudden cardiac death: HR, 0.734; 95% CI, 0.477–1.132, *P*=0.162).

CONCLUSIONS: Electroanatomic ratios of QRSd indexed for body size or left ventricular size are associated with mortality in individuals with heart failure with reduced ejection fraction. In particular, increased QRS/height may be a marker of high risk in individuals with heart failure with reduced ejection fraction, and QRS/left ventricular end-diastole volume may further risk stratify individuals with nonischemic heart failure with reduced ejection fraction.

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Key Words: electroanatomic remodeling ■ heart failure ■ height ■ left ventricle size ■ mortality ■ QRS ■ sudden cardiac death

Increased electrocardiographic QRS duration (QRSd) is a marker of electrical remodeling in heart failure with reduced ejection fraction (HFrEF). Prolonged QRSd has been associated with adverse outcomes in individuals with HFrEF.[1-7] However, this relationship may be confounded by age, sex, race, and obesity.[8-13] Differences in anthropometrics and left ventricular (LV) size are postulated to contribute to variations of QRSd with sex, race, obesity,[8,9,14] and to sex-based differences in response to cardiac resynchronization therapy.[14,15]

There is a need to better understand the relationship of QRSd to body size and LV size with respect

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CLINICAL PERSPECTIVE

What Is New?

- Increased electroanatomic ratios of QRS duration indexed for body size or left ventricular size were associated with increased mortality in individuals with heart failure with reduced ejection fraction, with influence of sex and heart failure cause.
- In particular, increased electroanatomic ratios of QRS/height may be a marker of high-risk in individuals with heart failure with reduced ejection fraction and increased electroanatomic ratios of QRS/left ventricular end-diastolic volume may further risk stratify individuals with nonischemic heart failure with reduced ejection fraction.

What Are the Clinical Implications?

- Our findings highlight electroanatomic ratios as predictors of mortality and underscore the importance of considering body and heart size in evaluating prognostic utility of QRS duration.
- Development of electroanatomic ratios to quantify the proportion of electrical and anatomic remodeling may serve as a model for understanding electroanatomic remodeling and association with outcomes, applicable as a framework for research in other cardiovascular conditions and across racial cohorts.

Nonstandard Abbreviations and Acronyms

ASIAN-HF	Asian Sudden Cardiac Death in Heart Failure
HFrEF	heart failure with reduced ejection fraction
QRSd	QRS duration
SCD	sudden cardiac death

to heart failure (HF) outcomes including mortality. We posit that ratios of QRSd to body size or LV size as electroanatomic ratios may provide quantitative insights into electrical and anatomic remodeling in individuals with HFrEF and association with outcomes. We hypothesize that increased electroanatomic ratios are associated with increased mortality in individuals with HFrEF. We further explore whether the association of electroanatomic ratio with mortality may be modified by sex or ischemic versus nonischemic cause of HF.

METHODS

The study data and materials used to conduct the research cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure because of the legal restrictions imposed by multinational jurisdictions.

Study Population

The ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry[16] is a contemporary multinational registry of individuals aged ≥18 years with symptomatic HF (stage C, with at least 1 episode of decompensated HF in the antecedent 6 months resulting in hospitalization or outpatient clinic treatment) and LV systolic dysfunction (ejection fraction [LVEF] <40% on baseline echocardiography). Participants were recruited between October 1, 2012 and December 31, 2015. Individuals with ≤1-year life expectancy, or unable or unwilling to give consent, or concurrently participating in a clinical trial were excluded. Ethics approvals were obtained from institutional review committee of each participating center and all participants gave informed consent.

Participants in the ASIAN-HF registry with available QRSd on baseline resting 12-lead ECG, baseline echocardiogram measurements of LV, and anthropometric parameters of height and weight were eligible for this study and included.

Electroanatomic Ratios

QRSd, LV end-diastolic volume (LVEDV), and height and weight measurements used were all uniformly based on measurements obtained for Visit 1 (baseline visit) of the ASIAN-HF registry for each subject. QRSd values were based on machine-automated measurements from resting 12-lead ECGs. LVEDV measurement values were based on transthoracic echocardiograms. Height and weight values were based on measurements by trained clinical or research staff. Electroanatomic ratios (Figure 1) were derived as the ratio of QRSd to anatomic measures of body size (such as height, as QRS/height) or LV size (measured by LVEDV, as QRS/LVEDV).

Outcomes of Interest

The primary outcome for this analysis was 1-year all-cause mortality. Secondary outcomes were 1-year cardiovascular mortality and 1-year sudden cardiac death (SCD). Mortality events were adjudicated in accordance with US Food and Drug Administration standardized definitions.[17] Details on death data collection and the adjudication process for the ASIAN-HF registry have been previously reported.[16] Each mortality event and its cause were adjudicated by an independent committee, based on review of data from

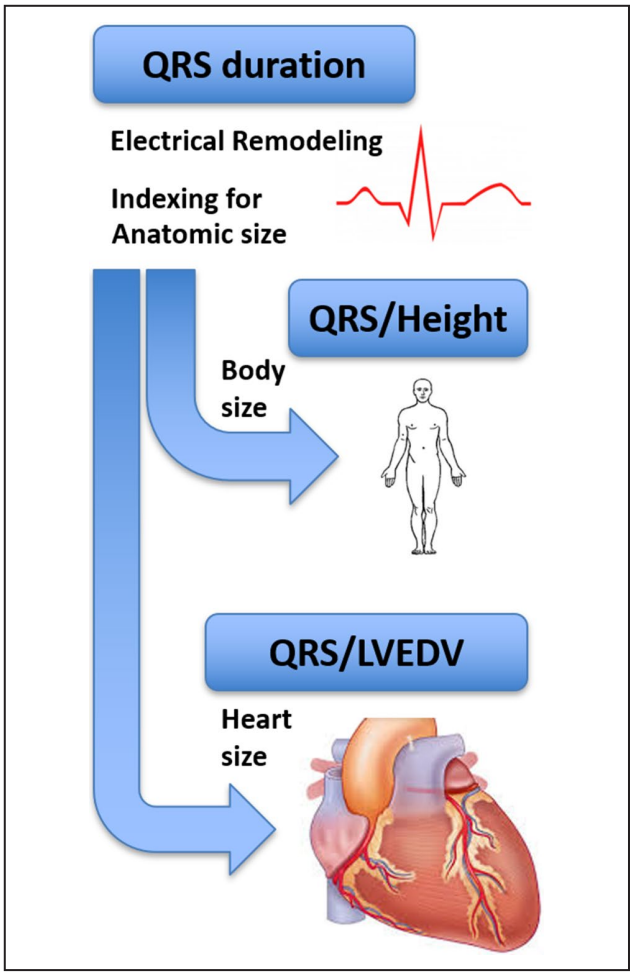

Figure 1. Schema of electroanatomic ratios.
Electroanatomic ratios were derived as the ratio of QRS duration to anatomic measures of body size (indexing QRS duration for height, as QRS/height) or left ventricular size (indexing QRS duration for LV end-diastolic volume, as QRS/LVEDV). LVEDV indicates left ventricular end-diastolic volume.

case report forms, death certificates, hospital discharge summaries, and any other relevant information requested by members of the event adjudication committee. All deaths were classified as cardiac or noncardiac. SCD was defined as unexpected observed or unobserved, and when sufficient information regarding preceding symptoms was available, SCD was defined as death that occurred within 1 hour of onset of cardiac symptoms.[16]

Statistical Analysis

Categorical variables were compared between subcohorts of men and women by Pearson χ^2 test. Continuous variables were compared using independent *t* tests. The Cox proportional hazards method was used to compute hazard ratios (HRs) for 1-year mortality for each electroanatomic ratio, first in univariable models then in multivariable models without violation of proportional hazards assumption. HRs of the electroanatomic ratios were computed per SD increase. Bonferroni adjustment was applied for multiple testing of electroanatomic ratios indexed for 3 and 5 measures of body and LV sizes, respectively.

The multivariable model, selected based on predictors of all-cause mortality in individuals with congestive HF,[18,19] incorporated age, ischemic cause of HF, previous hospitalization for HF, New York Heart Association (NYHA) class III-IV versus I-II, heart rate, systolic blood pressure, presence of S3, history of atrial fibrillation or flutter, history of ventricular tachycardia or fibrillation, presence of left bundle branch block (LBBB), β-blockade therapy, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy for analyses of all-cause and cardiovascular mortality. Multivariable model for SCD, developed based on published predictors of sudden death in patients with congestive heart failure,[18] included age, ischemic cause of HF, previous hospitalization for HF, NYHA class III-IV versus I-II, presence of S3, history of atrial fibrillation or flutter, history of ventricular tachycardia or fibrillation, β-blockade therapy, presence of LBBB, chronic kidney disease, and cardiac implantable electronic device therapy.

The interactions between sex or ischemic cause of HF with the association of each electroanatomic ratio with 1-year all-cause mortality were analyzed as prespecified subaims of this study. When interaction was detected (interaction $P<0.10$), additional subgroup-specific univariable and multivariable analyses of the affected electroanatomic ratios for all-cause mortality were conducted.

In 2 separate sensitivity analyses, we repeated the analyses for the primary outcome of 1-year all-cause mortality excluding participants with cardiac implantable electronic devices (CIED, inclusive of pacemakers and defibrillators) in 1 sensitivity analysis, and excluding participants with LBBB in the other sensitivity analysis.

Stata version 14 (Stata Corp, College Station, TX) and R statistical program version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. All *P* values were 2-sided and *P* values <0.05 were considered statistically significant.

RESULTS

Study Participants

Our study cohort consisted of 4899 individuals (3820 men and 1079 women; mean age: 60±19 years; mean LVEF: 27.3±7.1%) from the ASIAN-HF registry. Demographic and clinical characteristics of study

participants are summarized in Table 1. HFrEF was of ischemic cause in 50% of study participants and 35% of study participants were classified as NYHA class III-IV.

Small but statistically significant differences were seen between male and female participants in age, geographic distribution, LVEF, ischemic cause of HF, NYHA classification, and baseline diastolic blood pressure. Men and women also differed in history of prior hospitalization for HF, chronic kidney disease, and cancer.

Electroanatomic Parameters and Electroanatomic Ratios

Electroanatomic ratios of the overall study cohort and sex-specific subcohorts are summarized in Table 2. In the overall cohort, QRSd was 115.2±32.6 ms, LVEDV was 178.7±65.5 mL, and height was 1.64±0.09 m. While measures of QRSd, LVEDV, and height were larger in men than women, women had significantly higher ratios of QRS/height and QRS/LVEDV.

Electroanatomic Ratios and All-Cause Mortality

Of 4899 eligible study participants, 4445 (91%) had 1-year follow-up data available. Four hundred seventy-eight study participants (10.8% of 4445 study participants) died within 1 year. Similar rates were seen in men (379 of 3487; 11%) and women (99 of 958; 10.0%, *P*=0.636). The relationships between electroanatomic ratios and all-cause mortality are summarized in Table 3.

In the overall cohort, the association between QRSd alone and all-cause mortality was not statistically significant (Table 3, HR, 1.003; 95% CI, 0.999–1.006, *P*=0.142). While a modest interaction with sex was seen ($p_{interaction}$=0.06), QRSd alone was not significantly

Table 1. Demographic and Clinical Characteristics of Study Participants

	Overall Cohort (n=4899)	Subcohorts		
		Men (n=3820)	Women (n=1079)	*P* Value Men vs Women
Age (y; mean±SD)	60±19	60±13	61±14	0.006
Male (%)	3820 (78)	…	…	…
Northeast Asia/South Asia/Southeast Asia (%)	31%/ 28%/ 41%	30%/ 27%/ 43%	36%/ 30%/ 34%	<0.001
Height (m, mean±SD)	1.64±0.09		1.55±0.07	<0.001
Weight (kg, mean±SD)	67±16	70±15	59±13	<0.001
Body mass index (kg/m^2, mean±SD)	24.9±5.1	25.0±5.0	24.5±5.2	0.003
Body surface area (m^2, mean±SD)	1.74±0.20	1.79±0.21	1.58±0.20	<0.001
NYHA Class, I/II vs III/IV(%)	65% vs. 35%	67% vs. 33%	61% vs. 39%	0.002
Ischemic cause of HF (%)	50%	53%	38%	<0.001
LVEF % (mean±SD)	27.3±7.1	27.0±7.1	28.6±6.7	<0.001
QRSd (ms, mean±SD)	115.2±32.6	116.2±32.4	111.5±33.2	<0.001
Systolic blood pressure (mm Hg, mean±SD)	118±20	118±20	119±21	0.053
Diastolic blood pressure (mm Hg, mean±SD)	72±13	73±13	71±12	<0.001
Heart rate (bpm, mean±SD)	80±16	79±16	81±16	0.357
Previous hospitalization for HF (%)	63%	64%	58%	0.001
History of hypertension (%)	52%	52%	50%	0.245
History of stroke (%)	6.5%	6.6%	6.1%	0.614
History of atrial fibrillation/atrial flutter (%)	18%	18%	17%	0.534
History of ventricular tachycardia/ventricular fibrillation (%)	8.0%	8.2%	7.3%	0.334
ICD/PPM/CRT (%)	14%	14%	14%	0.698
Diabetes mellitus (%)	43%	43%	42%	0.616
Chronic kidney disease (%)	44%	43%	50%	<0.001
Cancer (%)	3.2%	2.5%	5.5%	<0.001
On BB (%)	78%	78%	76%	0.103
On ACEi/ARB (%)	76%	76%	74%	0.180
On mineralocorticoid receptor antagonist (%)	58%	59%	56%	0.145
On diuretic (%)	83%	82%	83%	0.464

ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, β-blocker; bpm, beats per minute; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PPM, permanent pacemaker; and QRSd, QRS duration.

Table 2. Electroanatomic Parameters and Electroanatomic Ratios of Study Participants

	Overall Cohort (n=4899)	Subcohorts		
		Men (n=3820)	Women (n=1079)	*P* Value Men vs Women
Electroanatomic parameters				
QRSd, ms	115.2±32.6	116.2±32.4	111.5±33.2	<0.001
Height, m	1.64±0.09	1.67±0.07	1.55±0.07	<0.001
LVEDV, mL	178.7±65.5	186.5±65.6	151.4±58.0	<0.001
Electroanatomic ratios				
QRS/height, ms/m	70.5±20.2	70.0±19.8	72.4±21.5	<0.001
QRS/LVEDV, ms/mL	0.73±0.36	0.69±0.31	0.85±0.47	<0.001

LVEDV indicates left ventricular end-diastolic volume; and QRSd, QRS duration.

associated with all-cause mortality in either sex when analyzed separately for men and women in the overall cohort (men HR, 1.093; 95% CI, 0.969–1.232, *P*=0.148; women HR, 1.087; 95% CI, 0.826–1.429, *P*=0.551, Figure 2). Interaction with LBBB ($p_{interaction}$=0.525), hypertension ($p_{interaction}$=0.233), and ischemic cause of HF ($p_{interaction}$=0.963) were not significant. There was a significant interaction between ethnicity and the relationship of QRSd with all-cause mortality ($p_{interaction}$=0.011).

QRSd indexed for body size was associated with all-cause mortality in the overall cohort (QRS/height: HR, 1.17; 95% CI, 1.05–1.30, *P*=0.005, similar relationships observed for QRS/body surface area [BSA], QRS/body mass index [BMI], Table 3). Sex-based differences were seen (Figure 2). In the overall cohort, QRS/height was associated with mortality in men (HR, 1.20; 95% CI, 1.07–1.36, *P*=0.003) but not in women (HR, 1.07; 95% CI, 0.84–1.38, *P*=0.57; $p_{interaction}$=0.020 for sex, similar interaction with sex for QRS/BSA, QRS/BMI, Table 3).

In the overall cohort, QRS/LVEDV was associated with all-cause mortality in univariable analysis (*P*=0.009). However, this association was no longer significant after multivariable adjustment (*P*=0.360) because of significant interaction with ischemic cause of HF ($p_{interaction}$=0.014) such that QRS/LVEDV was significantly associated with all-cause mortality in participants with nonischemic HF (HR, 1.22; 95% CI, 1.05–1.43, *P*=0.011) but not in participants with ischemic HF (HR, 0.94; 95% CI, 0.79–1.11, *P*=0.467, Figure 3). Hypertension ($p_{interaction}$=0.879), LBBB ($p_{interaction}$=0.280), and NYHA class ($p_{interaction}$=0.408) did not significantly modify the relationship between QRS/LVEDV and all-cause mortality.

Electroanatomic Ratios and Cardiovascular Mortality

Cardiovascular death occurred in 414 study participants (9.3% of 4445 study participants with 1-year follow-up data available) within 1 year. Similar rates were seen in men (333 of 3487, 9.6%) and women (81 of 958 women, 8.5%; *P*=0.302). The relationships between electroanatomic ratios and 1-year cardiovascular mortality are summarized in Table 3.

QRSd alone was not associated with 1-year cardiovascular mortality (HR, 1.002; 95% CI, 0.996–1.005, *P*=0.387) in the overall cohort. There was a trend toward association of increased electroanatomic ratio of QRSd indexed for anthropometrics with increased 1-year cardiovascular mortality (Table 3, QRS/height, HR, 1.121; 95% CI, 0.999–1.259, *P*=0.0503, similar for QRS/BSA and QRS/BMI) with significant interaction with sex ($p_{interaction}$=0.026 for QRS/height, similar for QRS/BSA and QRS/BMI). When analyzed separately by sex, QRS/height was significantly associated with 1-year cardiovascular mortality in men (HR, 1.158; 95% CI, 1.017–1.317, *P*=0.027) but not in women (HR, 1.089; 95% CI, 0.823–1.442, *P*=0.550; similar for QRS/BSA, QRS/BMI). The relationship of QRS/LVEDV and 1-year cardiovascular mortality was significantly affected by interaction with ischemic cause of HF ($p_{interaction}$=0.013).

Electroanatomic Ratios and SCD

SCD occurred in 122 study participants within 1 year (2.7% of 4445 study participants with 1-year follow-up data available). Similar rates were seen in men (98 of 3487, 2.8%) and women (24 of 958, 2.5%; *P*=0.609). The relationships between electroanatomic ratios and 1-year SCD are summarized in Table 4.

Whereas QRSd alone was not independently associated with SCD (HR, 1.006; 95% CI, 1.000–1.013, *P*=0.059), electroanatomic ratios of QRSd to anthropometrics were significantly associated with SCD. Increased QRS/height was strongly associated with increased 1-year SCD (QRS/height: HR, 1.270; 95% CI, 1.021–1.580, *P*=0.032; similarly for QRS/BSA and QRS/BMI, Table 4). Sex, cause of HF, LBBB, NYHA class, and hypertension did not significantly modify the relationships between QRSd indexed for anthropometrics with SCD.

QRS/LVEDV was significantly associated with SCD in participants with nonischemic HF (HR, 1.461;

Table 3. Electroanatomic Ratios and Mortality in Overall Cohort

	One-y All-Cause Mortality						One-y Cardiovascular Mortality					
	Unadjusted		Adjusted		Interaction for sex, *P* Value	Interaction for HF cause, *P* Value	Unadjusted		Adjusted		Interaction for sex, *P* Value	Interaction for HF cause, *P* Value
	HR	*P* Value	HR	*P* Value			HR	*P* Value	HR	*P* Value		
QRSd, ms	1.003 (1.00,1.005)	0.062	1.003 (0.999, 1.006)	0.142	0.06	0.963	1.002 (0.999, 1.005)	0.093	1.002 (0.998, 1.005)	0.387	0.099	0.810
Electroanatomic ratios, per SD												
QRS/height	1.145 (1.05, 1.242)	0.001	1.165 (1.046, 1.296)	0.005	0.020	0.940	1.132 (1.042, 1.230)	0.003	1.121 (0.999, 1.259)	0.053	0.026	0.617
QRS/BMI	1.189 (1.09, 1.29)	<0.001	1.182 (1.064, 1.314)	0.002	0.056	0.926	1.182 (1.087, 1.286)	<0.001	1.148 (1.026, 1.286)	0.016	0.095	0.493
QRS/BSA	1.151 (1.05, 1.25)	0.001	1.171 (1.048, 1.308)	0.005	0.020	0.940	1.136 (1.043, 1.238)	0.003	1.125 (0.999, 1.268)	0.053	0.026	0.617
QRS/LVEDV	1.138 (1.03, 1.253)	0.009	1.057 (0.939, 1.189)	0.360	0.177	0.014	1.093 (0.967, 1.235)	0.157	1.031 (0.885, 1.202)	0.691	0.454	0.013

Adjusted for age, ischemic cause of HF, previous hospitalization for HF, NYHA class III/IV versus I/II, heart rate, systolic blood pressure, presence of S3, atrial fibrillation/flutter, ventricular tachycardia/fibrillation, β-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, left bundle branch block, chronic kidney disease. BMI indicates body mass index; BSA, body surface area; HF, heart failure; HR, hazard ratio; LVEDV, left ventricular end-diastolic volume; NYHA, New York Heart Association; and QRSd, QRS duration.

95% CI, 1.090–1.957, *P*=0.011) but not in participants with ischemic HF (HR, 0.734; 95% CI, 0.477–1.132, *P*=0.162). While an interaction with sex was seen ($p_{interaction}$=0.035), QRS/LVEDV was not significantly associated with SCD in either sex when analyzed separately for men and women in the overall cohort (men: HR, 0.861; 95% CI, 0.601–1.233, *P*=0.413; women: HR, 1.320; 95% CI, 0.935–1.864, *P*=0.114).

Sensitivity Analyses

Sensitivity analyses excluded participants with CIED (520 participants with defibrillator and 140 participants with pacemaker, whose clinical and demographic characteristics were quite different from those without CIED, Table S1) or LBBB (679 participants). As shown in Table 5, results of sensitivity analyses were generally consistent with analyses in the entire cohort. While with the exclusion of patients with CIED, the association between QRSd and mortality became statistically significant, the HR remained marginal (HR, 1.005; 95% CI, 1.001–1.010, *P*=0.013, Table 5).

DISCUSSION

In this analysis of a large, real-world population with HFrEF, electroanatomic ratios relating QRSd to body and heart size were associated with mortality risk, whereas QRSd alone was not. Our study represents a novel investigation of electroanatomic ratios and presents a new pathway for future research.

QRSd and Mortality

In our study, QRSd alone was not associated with 1-year all-cause mortality, cardiovascular mortality, or SCD in the overall cohort. While the association between QRSd and all-cause mortality crossed into statistical significance in sensitivity analysis excluding participants with CIED, the effect size was very modest. These findings are overall consistent with prior observations from the Singapore Heart Failure Outcomes and Phenotypes (SHOP) cohort. In an analysis that assessed QRSd and outcomes in both Asian participants with HFrEF from the SHOP cohort and White participants with HFrEF from the Swedish HF Registry, a 10-ms increase in baseline QRSd conferred a significant increase in hazard for composite of HF hospitalization or all-cause death in White participants (HR, 1.06; 95% CI, 1.04 to 1.07, *P*<0.001) but not in Asian participants (HR, 1.01; 95% CI, 0.94 to 1.05, *P*=0.861) with HFrEF (defined by LVEF<50%).[8]

Race-based differences in the relationship of QRSd with all-cause mortality have also been seen in other contemporary studies, although with some heterogeneity in directionality. In an American cohort of

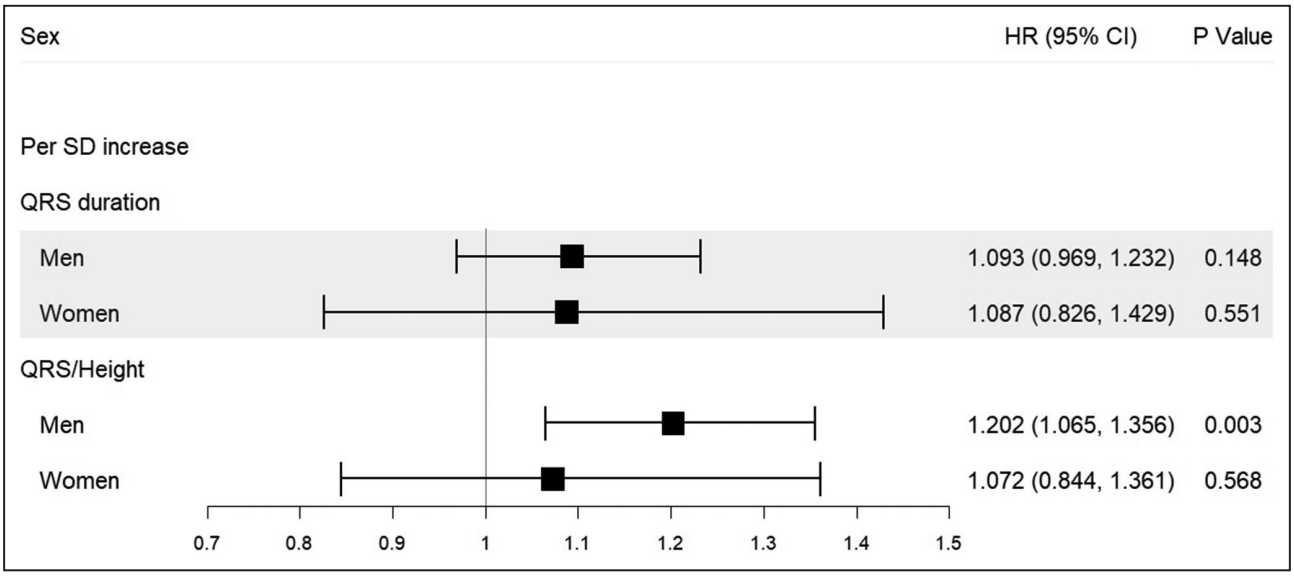

Figure 2. Sex modifies the relationship between electroanatomic ratios of QRS duration to height and all-cause mortality.
Sex modifies the relationship between electroanatomic ratios of QRS duration to height with all-cause mortality. Specifically, QRS/height was associated with all-cause mortality in men but not in women. HR indicates hazard ratio.

individuals with LVEF ≤35%, QRS prolongation was associated with increased all-cause mortality in Black but not White participants.[2] On the other hand, analysis of the Swedish HF Registry alone (European, White, LVEF <40%) found association of QRSd with increased all-cause mortality.[20,21]

Earlier studies[1,3,5,6] reporting an association between QRSd and all-cause mortality were conducted in predominantly White populations, with further important differences compared with our cohort including in medications (lower use of β-blockade,[1,3,5,6] use of mineralocorticoid not reported[1,3,5,6]), the nature of the study population (clinical trials[1,3]), length of follow-up for all-cause mortality,[3,5,6] and the sex composition of the study population (>98% men in 1 report[3]). Subsequent studies reporting an association between QRSd and all-cause mortality included post hoc analyses from the EVEREST (Efficacy of Vasopressin Antagonism in HF Outcome Study with Tolvaptan) trial and the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in HF) trial.[4,7] While the proportions of overall study population on angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, β-blockade, and mineralocorticoid antagonists in these studies[4,7] were similar to those observed in our study, these cohorts differed from ASIAN-HF in other respects. In addition to the inherent differences between clinical trials and registries, and the predominantly White racial composition compared with our cohort, the EVEREST population[7] was sicker (23% mortality at 9.9 months) and was recruited during acute

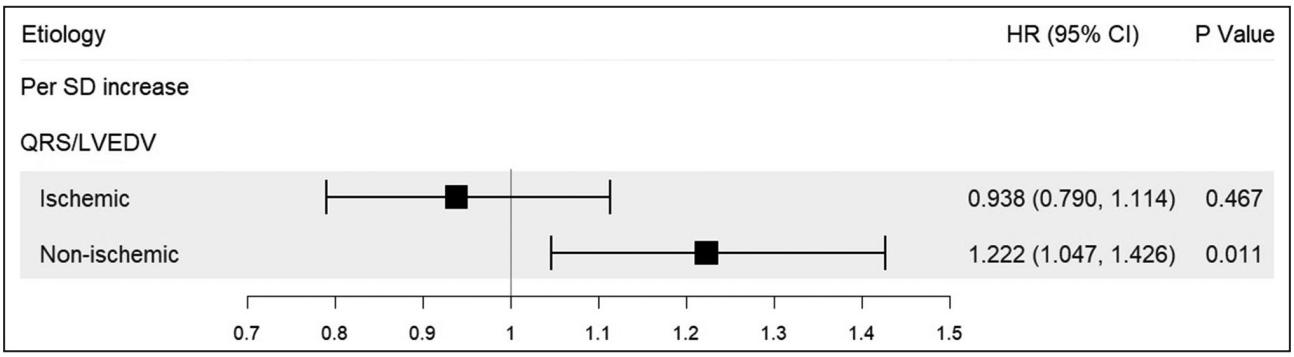

Figure 3. Cause of heart failure modifies the relationship between electroanatomic ratios of QRS duration indexed for left ventricular size and all-cause mortality.
QRS duration indexed for left ventricular size (QRS/LVEDV) was significantly associated with all-cause mortality in study participants with nonischemic cause of heart failure but not in study participants with ischemic cause of heart failure. HR indicates hazard ratio; and LVEDV, left ventricular end-diastolic volume.

Table 4. Electroanatomic Ratios and Sudden Cardiac Death in Overall Cohort

	One-Year Sudden Cardiac Death					
	Unadjusted		Adjusted		Interaction for Sex, *P* Value	Interaction for HF Cause, *P* Value
	HR	*P* Value	HR	*P* Value		
QRSd, ms	1.004 (1.000, 1.010)	0.071	1.006 (1.000, 1.013)	0.059	0.833	0.468
Electroanatomic ratios, per SD						
QRS/height	1.179 (1.020, 1.363)	0.026	1.270 (1.021, 1.580)	0.032	0.442	0.942
QRS/BMI	1.238 (1.067, 1.437)	0.005	1.329 (1.069, 1.651)	0.010	0.487	0.681
QRS/BSA	1.185 (1.021, 1.376)	0.026	1.279 (1.022, 1.602)	0.032	0.442	0.942
QRS/LVEDV	1.098 (0.841, 1.434)	0.491	1.064 (0.740, 1.531)	0.738	0.035	0.024

Adjusted for age, ischemic cause of HF, previous hospitalization for HF, NYHA class III-IV versus I-II, presence of S3, history of atrial fibrillation or flutter, history of ventricular tachycardia or fibrillation, β-blocker, presence of LBBB, chronic kidney disease, and cardiac implantable electronic device therapy. BMI indicates body mass index; BSA, body surface area; HF, heart failure; HR, hazard ratio; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; NYHA, New York Heart Association; and QRSd, QRS duration.

hospitalization. Furthermore, the EMPHASIS-HF population[4] had higher average BMI and a higher proportion of participants with ischemic HF cause compared with ASIAN-HF.

Race, medications, as well as design, demographic, and clinical characteristics of study populations likely contributed to differences in the relationship of QRSd and mortality across different studies.

Furthermore, it is worth noting that in our entirely racially Asian study population, a significant interaction was seen between (intraracial) ethnicity and the relationship of QRSd and mortality. Interethnic (intraracial) variations in QRSd have been previously reported between Asian subgroups.[9] This underscores the need to further consider QRSd in reference to body size and LV size, even within the same broad racial categorization. Analysis of interethnic variations in electroanatomic parameters, electroanatomic ratios, and associations with clinical outcomes is the subject of future planned analyses from our group. Our framework of electroanatomic ratios here provides a quantitative understanding of the extent of electrical and anatomic remodeling and the proportions of their respective remodeling beyond a measure of electrical remodeling as QRSd alone.

Electroanatomic Ratios of QRSd to Body Size

Interest in relating QRSd to anthropometrics is increasing but consensus on the ideal anthropometric measure is lacking. Recent studies in patients undergoing cardiac resynchronization therapy have reported associations of QRS/BSA with improvement in LVEF[22] and QRS/BMI with improvement in NYHA class and reduction of LV end-systolic volume.[23] In a patient-level meta-analysis, the greatest benefits of cardiac resynchronization therapy for reduction in all-cause mortality and the composite of mortality and HF hospitalization were observed in the shortest tercile of men.[24]

In our study, electroanatomic ratios of QRS/height, QRS/BSA, and QRS/BMI were strongly associated with all-cause mortality, cardiovascular mortality, and SCD. Independent associations of BSA and BMI with HF outcomes are known,[25-29] reproduced in analysis of our own data (Table S2), and may confound interpretation of their electroanatomic ratios. Weight was also independently associated with all-cause mortality in this study. Weight, and the inclusion of weight, may be further confounded by influence of nutrition, obesity, cachexia, adiposity, and fluctuation over time. On the other hand, height is not known to be an independent predictor of mortality in HF and was not in our data set (Table S2). We have therefore focused on height as the primary anthropometric parameter of body size for indexing of QRSd. The finding of a significant association of QRS/height with mortality in our study is novel and warrants further investigation in other populations with and without HF.

A significant interaction with sex was detected in the relationship of electroanatomic ratios of QRSd indexed for body size with all-cause and cardiovascular mortality in our study. Increased electroanatomic ratios of QRSd indexed for body size were associated with increased all-cause and cardiovascular mortality in men but not in women. Men and women with HFrEF are known to differ in cause of HF, prevalence of LBBB, prevalence of arrhythmias, and metabolism of, and response to, pharmacotherapies.[30-33] Pertinent to these known differences, our multivariable model included ischemic cause of HF, history of atrial fibrillation or atrial flutter, history of ventricular tachycardia or fibrillation, presence of LBBB, presence of β-blockade therapy, and presence of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy in addition to age, previous hospitalization for HF, NYHA class, heart rate, systolic blood pressure, and presence of S3. Yet, sex-specific associations of QRS/height (similarly for QRS/BSA

and QRS/BMI) with all-cause mortality and cardiovascular mortality remained. As the 1-year all-cause and cardiovascular mortality rates were similar in men and women in our study, sex differentially influenced the relationships of QRSd to body size with all-cause and cardiovascular mortality. Electroanatomic ratios of QRSd to body size, such as QRS/height, may uniquely identify men with HFrEF at higher risk for all-cause and cardiovascular mortality. In regard to SCD, the association with electroanatomic ratio of QRS indexed for anthropometrics was not influenced by sex. Excess electrical remodeling relative to body size, as increased QRS/height (and similarly for QRS/BSA and QRS/BMI), remains a potent marker for increased SCD risks in both men and women with HFrEF.

Electroanatomic Ratios of QRSd to LV Size

In our analysis, indexing of QRSd to LVEDV predicted mortality in patients with HFrEF with nonischemic cardiomyopathy but not ischemic cardiomyopathy. LVEDV is accepted as a volumetric measure of LV size and has been used previously in analysis of effects of cardiac resynchronization therapy on HF outcomes. Recent smaller studies have suggested QRS/LVEDV may help to identify patients with favorable response to cardiac resynchronization therapy[22,34,35] who may otherwise be at higher mortality risk.[35]

The cause-specific association of QRS/LVEDV with mortality outcomes may relate to differences between ischemic and nonischemic cardiomyopathy in electroanatomic remodeling. First, in ischemic cardiomyopathy, scars from myocardial infarction may create substrates for electrical remodeling and reentry arrhythmias without LV dilatation, making ischemic cardiomyopathy potentially less susceptible to influences of LVEDV. Second, as participants with nonischemic cardiomyopathy had larger LVEDV compared with participants with ischemic cardiomyopathy (in our study, 187.4±66.1 mL in nonischemic cardiomyopathy versus 173.3±64.6 mL in ischemic cardiomyopathy, $P<0.001$), increased electroanatomic ratios of QRS/LVEDV in participants with nonischemic cardiomyopathy may especially identify individuals with particularly marked electrical remodeling. Furthermore, a greater range of QRS and LVEDV values observed in the nonischemic cardiomyopathy subcohort compared with the ischemic cardiomyopathy subcohort may underscore nonischemic cardiomyopathy as a more heterogeneous classification with many different subtypes. With potentially greater heterogeneity of electrical and structural heart disease in nonischemic cardiomyopathy, further characterization of electroanatomic remodeling with electroanatomic ratios of QRS/LVEDV may be particularly helpful in distinguishing phenotypes in remodeling that may be associated with increased mortality risks.

Of note, our observation that increased QRS/LVEDV was strongly associated with increased SCD in participants with nonischemic cardiomyopathy is important, particularly in light of ongoing investigations to better define predictors of mortality in individuals with nonischemic cardiomyopathy[36-40] and ongoing debate regarding choice of device therapy.[39,40] Whether the electroanatomic ratio of QRS/LVEDV provides another dimension in risk stratification of patients with HF with nonischemic cardiomyopathy merits further studies.

Strengths and Limitations

This study is based on the ASIAN-HF registry. Although registry data may be susceptible to bias because of its nonrandomized nature, this study is strengthened by its large sample size, real-world, contemporary, prospectively collected and adjudicated multi-ethnic, multiregional data.

This study used the well-characterized ASIAN-HF registry, comprising entirely Asian patients. While this may limit initial direct generalizability of the results to other racial cohorts, potential anatomic differences among racial cohorts may in part be mitigated by this study's specific efforts to account for anatomic size. Furthermore, the use of the ASIAN-HF registry not only adds to needed knowledge on Asian-specific data given regional underrepresentation in HF studies,[16] but with the availability of well-characterized adjudicated data also permitted the execution of the conceptual approach of quantifying the proportions of electrical and anatomic remodeling as electroanatomic ratios and assessment of the association with clinical outcomes.

Study Implications and Future Directions

Our study has 2 important implications with impacts on future directions. First, electroanatomic ratios indexing QRSd for body and heart size identify adults with HFrEF at increased mortality risks, with ramifications for risk stratification, therapeutic strategies, and future research. Further research may be directed at assessment of the utility of electroanatomic ratios in risk stratification in HFrEF and whether treatment strategies may modify the elevated risks. Second, development of electroanatomic ratios to quantify the proportion of electrical and anatomic remodeling may serve as a framework for understanding electroanatomic remodeling and association with outcomes, applicable as a framework for research

Table 5. Sensitivity Analyses of Association of Electroanatomic Ratios with All-Cause Mortality

	Participants Without Cardiac Implantable Electronic Devices						Participants Without Left Bundle Branch Block					
	Unadjusted		Adjusted		Interaction for Sex, *P* Value	Interaction for HF Cause, *P* Value	Unadjusted		Adjusted		Interaction for Sex, *P* Value	Interaction for HF Cause, *P* Value
	HR	*P* Value	HR	*P* Value			HR	*P* Value	HR	*P* Value		
QRSd (ms)	1.003 (1.00, 1.006)	0.036	1.005 (1.00, 1.010)	0.013	0.045	0.389	1.003 (1.00, 1.006)	0.032	1.002 (0.998, 1.006)	0.274	0.552	0.679
Electroanatomic ratios, per SD												
QRS/height	1.145 (1.05, 1.242)	0.001	1.165 (1.04, 1.296)	0.005	0.020	0.940	1.214 (1.10, 1.331)	<0.001	1.163 (1.036, 1.304)	0.010	0.148	0.759
QRS/LVEDV	1.138 (1.03, 1.253)	0.009	1.057 (0.93, 1.189)	0.360	0.177	0.014	1.190 (1.06, 1.328)	0.002	1.103 (0.966, 1.260)	0.148	0.114	0.003

Adjusted for age, ischemic cause of HF, previous hospitalization for HF, NYHA class III/IV versus I/II, heart rate, systolic blood pressure, presence of S3, atrial fibrillation/flutter, ventricular tachycardia/fibrillation, β-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, left bundle branch block, chronic kidney disease. HF indicates heart failure; HR, hazard ratio; LVEDV, left ventricular end-diastolic volume; NYHA, New York Heart Association; and QRSd, QRS duration.

in other cardiovascular conditions and across racial cohorts.

CONCLUSIONS

Increased electroanatomic ratios of QRSd indexed for body size or LV size were associated with increased mortality in individuals with HFrEF, with influence of sex and HF cause. In particular, increased QRS/height may be a marker of high-risk in individuals with HFrEF, and QRS/LVEDV may further risk stratify individuals with nonischemic HFrEF.

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

Tables S1–S2
Appendix (ASIAN-HF Investigators)

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SUPPLEMENTAL MATERIAL

APPENDIX
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Table S1. Demographic and Clinical Characteristics of Study Participants With or Without Cardiac Implantable Electronic Device (pacemaker/defibrillator).

	Overall Cohort (n=4899)	**Without Device (n=3783)**	**With Device (n=660)**	***P*** **Without vs. With Device**
Age (years; mean±SD)	60 ± 19	59 ± 13	65 ± 12	<0.001
Male (%)	3820 (78)	2965 (78)	521 (79)	0.75
Northeast Asia/South Asia/Southeast Asia (%)	31%/ 28%/ 41%	27%/ 31%/ 42%	62%/ 12%/ 26%	<0.001
Height (m, mean±SD)	1.64 ± 0.09	1.64 ± 0.09	1.64 ± 0.09	0.11
Weight (kg, mean±SD)	67 ± 16	68 ± 16	64 ± 14	<0.001
Body mass index (kg/m^2, mean±SD)	24.9 ± 5.1	25.1 ± 5.1	23.9 ± 4.6	<0.001
Body surface area (m^2, mean±SD)	1.74 ± 0.20	1.75 ± 0.23	1.70 ± 0.21	<0.001
NYHA Class, I/II vs III/IV(%)	65% vs. 35%	66% vs 34%	62% vs 38%	0.050
Ischemic etiology of HF (%)	50%	51%	43%	<0.001
LVEF % (mean±SD)	27.3 ± 7.1	27.3 ± 7.0	26.8 ± 7.5	0.120
QRS duration (ms, mean±SD)	115.2 ± 32.6	111.4 ± 29.0	142.1 ± 37.8	<0.001
Systolic blood pressure (mmHg, mean±SD)	118 ± 20	119 ± 20	112 ± 18	<0.001
Diastolic blood pressure (mmHg, mean±SD)	72 ± 13	73 ± 13	67 ± 11	<0.001
Heart rate (bpm, mean±SD)	80 ± 16	81 ± 16	73 ± 13	<0.001
Previous hospitalization for HF (%)	63%	60%	83%	<0.001
History of Hypertension (%)	52%	52%	46%	0.002
History of Stroke (%)	6.5%	6.2%	9.2%	0.004
History of atrial fibrillation/atrial flutter (%)	18%	17%	31%	<0.001
History of ventricular tachycardia/ventricular fibrillation (%)	8.0%	4.0%	32%	<0.001
ICD/PPM/CRT (%)	14%	-	-	-
Diabetes (%)	43%	44%	39%	0.009
Chronic kidney disease (%)	44%	43%	52%	<0.001
Cancer (%)	3.2%	2.8%	6.4%	<0.001
On BB (%)	78%	78%	84%	0.002
On ACE/ARB (%)	76%	77%	73%	0.035
On mineralocorticoid receptor antagonist (%)	58%	59%	60%	0.80
On diuretic (%)	83%	84%	79%	0.006

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blocker; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PPM = permanent pacemaker.

Table S2. Anthropometrics and Mortality.

Height was not independently associated with mortality in our study, reinforcing height as the preferred anthropometric measure to use for deriving the key electroanatomic ratio of QRS duration indexing for body size. Body mass index (BMI) and body surface area (BSA) were independently associated with all-mortality, consistent with our consideration of the literature.

Per SD	**Primary Outcome of Interest: One-Year All-Cause Mortality**			
	Unadjusted		**Adjusted**	
	Hazard Ratio (95% Confidence Interval)	***p*-value**	**Hazard Ratio (95% Confidence Interval)**	***p*-value**
Height (m)	0.438 (0.161, 1.192)	0.106	0.424 (0.131, 1.372)	0.152
Body surface area (m^2)	0.329 (0.215, 0.505)	**<0.001**	0.362 (0.211, 0.621)	**<0.001**
Body mass index (kg/m^2)	0.947 (0.927, 0.967)	**<0.001**	0.958 (0.934, 0.982)	**0.001**

Adjusted for age, ischemic etiology of HF, previous hospitalization for HF, NYHA class III/IV versus I/II, heart rate, systolic blood pressure, presence of S3, atrial fibrillation/flutter, ventricular tachycardia/fibrillation, β-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, left bundle branch block, chronic kidney disease.