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ORIGINAL ARTICLE

Left ventricular mass index-to-QRS-voltage ratio predicts outcomes in heart failure with preserved ejection fraction

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Abstract

Aims Increased left ventricular mass index (LVMI) disproportionate to electrocardiographic QRS voltage has been reported to be associated with cardiac fibrosis and amyloid infiltration to myocardium. This study aimed to assess whether the LVMI-to-QRS-voltage ratio predicts clinical outcomes in heart failure with preserved ejection fraction (HFpEF).

Methods and results The Japanese Heart Failure Syndrome with Preserved Ejection Fraction (JASPER) registry is a nationwide, observational, and prospective registration of Japanese patients hospitalized with HFpEF (EF $\geq$ 50%). LVMI was assessed by echocardiography using the cube formula. QRS voltage was assessed by Sokolow–Lyon voltage criteria. We divided 290 patients in the registry who met inclusion criteria into five groups according to the quintile values of their LVMI-to-QRS-voltage ratio. In the highest quintile group ($\geq$71.8 g/m^2/mV), approximately 50% of the patients had concentric hypertrophy and 30% had eccentric hypertrophy. These patients had the highest proportion of atrial fibrillation (61.4%) and history of pacemaker implantation (12.1%) among the five groups ($P < 0.05$). During the mean follow-up of 587 ± 300 days, 31.4% of all patients met the composite endpoint of all-cause death or rehospitalization for HF. Even after adjustment for demographic and baseline variables, the highest quintile group had a significantly higher incidence of the composite endpoints than the lowest quintile group ($<$30.7 g/m^2/mV) (hazard ratio: 2.205, 95% confidence interval: 1.106–4.395, $P < 0.05$).

Conclusions A high LVMI-to-QRS-voltage ratio is independently associated with poor outcomes in patients with HFpEF.

Keywords Left ventricular mass; QRS voltage; Amyloidosis; HFpEF

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Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a common phenotype of older patients with HF, and the number of HFpEF patients has been increasing in recent years with the aging of the population.[1] Despite increasing awareness of the clinical significance of HFpEF, there is still no established treatment for these patients.[2] One reason is that HFpEF represents a heterogeneous population, and phenotyping of HFpEF is essential to develop effective treatments.[3]

Left ventricular hypertrophy (LVH) including concentric hypertrophy (CH) or eccentric hypertrophy (EH) has been reported to be associated with poor prognosis in patients with HFpEF.[4] LVH reflects not only cardiac fibrosis but also amyloid infiltration in some HFpEF patients, because it has been reported that 13–19% of patients with HFpEF have transthyretin amyloidosis (ATTR).[5–7] In particular, LVH with

low QRS voltage, or increased left ventricular (LV) mass disproportionate to electrocardiographic QRS voltage, is a key sign reflecting infiltration of the myocardium.[8] A recent study reported that a high ratio of LV mass index (LVMI) to QRS voltage predicts poor prognosis in patients with cardiac amyloidosis.[9] However, it is unknown whether this ratio of LVMI to QRS voltage can predict clinical outcomes in populations containing various types of HFpEF. Therefore, the present study aimed to evaluate the prognostic significance of the LVMI-to-QRS-voltage ratio by assessing data from a nationwide Japanese registry of HFpEF, the JASPER registry.

Methods

Patient recruitment

The JASPER registry is a multicentre, observational, prospective cohort that includes 535 consecutive patients aged 20 years and older who required hospitalization with HFpEF between July 2012 and March 2015.[10] The diagnosis of acute HF was determined by at least two experienced cardiologists according to the Framingham criteria. Preserved LV systolic function was defined as LV ejection fraction $\geq$ 50% by the modified Simpson method or LV fractional shortening $\geq$ 25% by echocardiography. Patients with acute coronary syndrome, receiving haemodialysis, or with a history of heart transplantation were excluded. Patient demographic data including vital signs, co-morbidities, laboratory and echocardiographic data, and concomitant medications were obtained from the discharge assessment. Follow-up was performed at 12 and 24 months after discharge through direct contact with patients or their physicians in the hospital or outpatient clinic setting, or via patient interview by telephone and mail by dedicated coordinators and investigators.

In the current study, because patient information was anonymized and de-identified prior to analysis, written informed consent was not obtained from each patient. However, the study was publicized by posting a summary of the protocol on the National Cerebral and Cardiovascular Center website, where a notice clearly informed patients of their right to refuse enrolment. These procedures for informed consent and enrolment were in accordance with the detailed regulations described in the guidelines, and this study, including the procedure for enrolment, was approved by the Institutional Review Board of each site and registered under the Japanese UMIN Clinical Trials Registration (UMIN000010601).

The flow chart of patient selection in the present analysis is shown in *Figure 1*. Of 535 patients enrolled in the JASPER registry, the following patients were excluded: patients who died during their hospitalization (n = 7); patients without body surface area data, or echocardiogram during hospitalization (n = 16); patients without electrocardiogram (ECG) assessment during hospitalization (n = 206); and patients whose QRS voltage on ECG showed abnormal values (SV1 + RV5 $\geq$ 10 mV) that were not physiologically possible and assumed to be input errors (n = 16) considering previously reported studies.[11,12] A total of 290 patients were included in this analysis.

Each LVMI-to-QRS-voltage ratio was calculated by dividing the value of LVMI by the value of QRS voltage as previously described.[9] LVMI was assessed by echocardiography using linear measurements recommended by the American Society of Echocardiography as follows[13]: LVMI (g/m^2) = 0.8{1.04[([LV end-diastolic dimension (LVEDD) + end-diastolic interventric-

Figure 1 Flow chart of patient selection. Q1, first quintile; Q2, second quintile; Q3, third quintile; Q4, fourth quintile; Q5, fifth quintile.

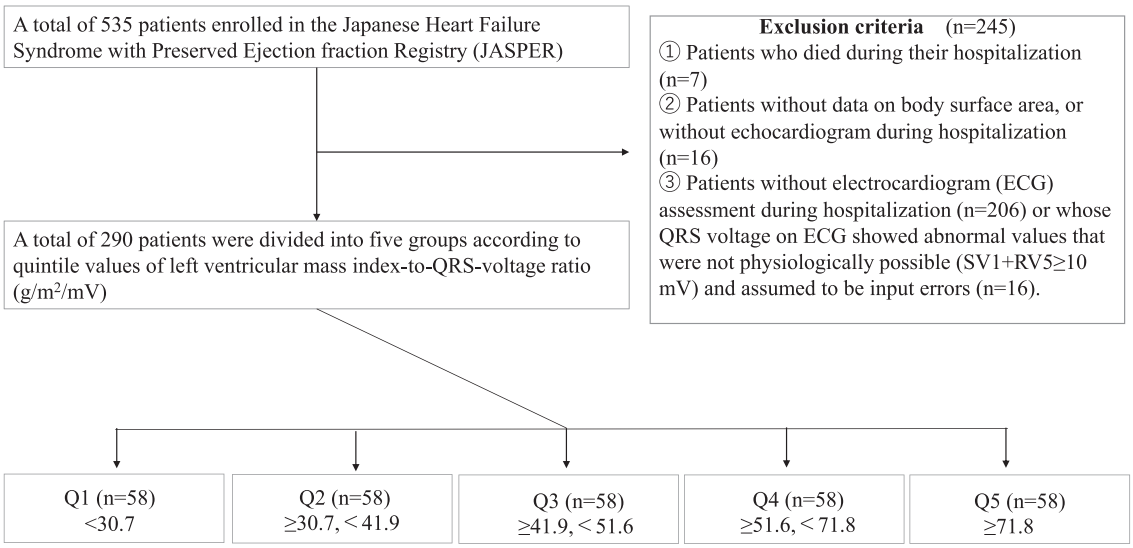

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Table 1 Patient characteristics among five groups according to the quintile values of left ventricular mass index-to-QRS-voltage ratio

	Q1 (n = 58)	Q2 (n = 58)	Q3 (n = 58)	Q4 (n = 58)	Q5 (n = 58)	P value
LVMI-to-voltage ratio (g/m^2/mv)	24.7 [21.5–27.3]	36.7 [35.2–39.6][a]	46.9 [44.5–49.1][a, b]	61.4 [56.6–65.9][a, b, c]	93.1 [79.8–113.5][a, b, c, d]	<0.001
Age (n = 290) (years)	78.5 [72.0–84.0]	80.0 [71.0–84.8]	78.0 [73.0–82.0]	79.0 [71.3–83.0]	80.0 [72.3–83.8]	0.936
Male (n = 290), n (%)	25 (43.1)	33 (56.9)	32 (55.2)	28 (48.3)	31 (53.4)	0.586
BMI (n = 284) (kg/m^2)	21.5 [19.6–24.4]	21.8 [18.7–24.4]	21.9 [20.3–24.9]	23.2 [20.3–25.7]	21.6 [19.5–24.8]	0.315
SBP (n = 290) (mmHg)	116.5 [103.0–129.3]	115.0 [106.0–128.0]	117.00 [104.0–127.3]	115.0 [104.5–122.8]	113.5 [103.5–126.5]	0.966
HR (n = 290) (b.p.m.)	64.0 [60.0–75.0]	61.0 [56.3–71.5]	68.0 [60.0–73.8]	66.0 [60.0–72.8]	65.50 [60.0–71.0]	0.230
Prior HF admission (n = 284), n (%)	17 (32.1)	15 (27.8)	21 (36.8)	18 (33.3)	26 (46.4)	0.325
NYHA class III/IV (n = 274), n (%)	4 (7.1)	4 (7.3)	3 (5.3)	7 (13.0)	4 (7.7)	0.697
Co-morbidity						
CAD (n = 287), n (%)	10 (17.5)	16 (28.1)	20 (34.5)	21 (36.2)	9 (15.8)	0.032
Hypertension (n = 288), n (%)	44 (75.9)	50 (86.2)	47 (81.0)	47 (82.5)	44 (77.2)	0.633
Diabetes/IGT (n = 287), n (%)	23 (40.4)	25 (43.9)	22 (37.9)	25 (43.1)	23 (40.4)	0.971
Atrial fibrillation (n = 285), n (%)	22 (37.9)	19 (33.9)	28 (49.1)	27 (47.4)	35 (61.4)[b]	0.033
COPD (n = 282), n (%)	2 (3.6)	8 (14.3)	7 (12.5)	6 (10.5)	6 (10.5)	0.340
CVD (n = 285), n (%)	12 (20.7)	13 (23.2)	11 (19.3)	12 (21.1)	13 (22.8)	0.986
Prior PM implant (n = 290), n (%)	2 (3.4)	1 (1.7)	1 (1.7)	1 (1.7)	7 (12.1)	0.041
Medications						
ACE-I/ARB (n = 290), n (%)	43 (74.1)	45 (77.6)	45 (77.6)	44 (75.9)	45 (77.6)	0.995
Beta-blocker (n = 290), n (%)	38 (65.5)	41 (70.7)	41 (70.7)	40 (69.0)	35 (60.3)	0.751
MRA (n = 290), n (%)	16 (27.6)	17 (29.3)	15 (25.9)	20 (34.5)	23 (39.7)	0.510
Loop diuretics (n = 290), n (%)	42 (72.4)	41 (70.7)	43 (74.1)	43 (74.1)	43 (74.1)	0.996
Tolvaptan (n = 290), n (%)	1 (1.7)	1 (1.7)	3 (5.2)	5 (8.6)	3 (5.2)	0.402
Laboratory values						
Haemoglobin (n = 285) (g/dL)	11.70 [9.9–13.3]	11.4 [10.2–12.4]	11.1 [10.2–12.6]	11.4 [9.9–12.6]	10.5 [9.5–12.1]	0.149
Sodium (n = 285) (mEq/L)	140.0 [137.0–141.0]	140.0 [138.0–141.0]	140.0 [138.0–141.0]	140.0 [137.3–142.0]	138.0 [135.3–140.8]	0.058
BUN (n = 285) (mg/dL)	22.2 [16.9–33.0]	26.5 [21.0–41.8]	22.0 [17.7–32.0]	25.0 [19.3–35.8]	28.4 [20.1–43.9]	0.052
eGFR (n = 285) (mL/min/1.73 m^2)	47.0 [30.2–59.4]	40.8 [22.7–58.6]	46.0 [26.2–57.1]	42.0 [28.2–60.3]	39.6 [27.9–48.9]	0.392
Albumin (n = 226) (g/dL)	3.7 [3.4–4.0]	3.6 [3.3–4.0]	3.5 [3.1–3.9]	3.5 [3.3–4.0]	3.5 [3.3–3.8]	0.402
Total cholesterol (n = 152) (mg/dL)	172.0 [142.0–195.0]	173.0 [146.8–200.8]	155.0 [142.0–178.0]	159.5 [132.3–196.0]	148.5 [133.5–171.3]	0.130
BNP (n = 242) (pg/mL)	152.4 [75.1–229.8]	127.8 [89.6–255.4]	169.1 [68.5–308.3]	151.3 [88.6–244.5]	196.9 [88.6–356.3]	0.564
Echocardiography						
LVEF (n = 185) (%)	65.0 [56.5–71.3]	61.0 [55.1–65.1]	64.0 [59.0–67.8]	62.0 [53.0–66.0]	60.0 [56.1–68.5]	0.187
LAVI (n = 118) (mL/m^2)	56.2 [48.0–82.3]	47.3 [41.0–70.3]	46.4 [34.1–62.7]	56.0 [39.0–67.7]	61.2 [47.8–87.6]	0.134
E′ (septal) (n = 164) (cm/s)	5.0 [3.2–6.9]	5.4 [4.1–6.7]	5.1 [3.7–6.5]	5.7 [4.6–7.5]	4.9 [3.6–6.6]	0.360
E′ (lateral) (n = 87) (cm/s)	8.0 [6.4–9.8]	7.0 [6.4–8.8]	7.2 [6.0–8.0]	8.3 [6.7–9.3]	8.4 [6.2–10.4]	0.675
E/E′ (septal) (n = 164)	15.7 [13.0–19.0]	17.0 [10.6–21.7]	16.1 [13.8–19.3]	15.2 [11.8–18.9]	18.6 [13.0–25.6]	0.308
E/E′ (lateral) (n = 87)	10.7 [9.0–12.3]	10.1 [9.0–14.5]	8.7 [7.1–10.6]	10.0 [8.3–11.3]	11.4 [10.2–13.8]	0.252
TRPG (n = 175) (mmHg)	28.5 [24.0–35.0]	29.0 [22.5–35.3]	26.5 [21.8–31.0]	26.5 [21.3–35.0]	31.0 [24.8–34.8]	0.527
IVSd (n = 290) (mm)	10.0 [8.0–12.0]	11.0 [9.0–12.0]	10.9 [9.0–12.0]	10.6 [9.0–12.0]	11.0 [10.0–13.0][a]	0.020
LVDd (n = 290) (mm)	43.0 [39.4–48.0]	47.2 [42.0–49.0]	46.4 [42.7–52.0][a]	49.0 [45.5–53.0][a]	49.0 [46.0–54.0][a]	<0.001
LVMI (n = 290) (g/m^2)	97.8 [77.9–123.7]	114.3 [99.3–133.4]	115.7 [94.9–136.0]	123.4 [111.8–138.1][a]	132.6 [114.4–155.2][a, b, c]	<0.001
RWT (n = 290)	0.47 [0.38–0.54]	0.46 [0.38–0.53]	0.43 [0.38–0.54]	0.42 [0.37–0.49]	0.47 [0.39–0.54]	0.301

(*Continues*)

Table 1 (continued)

	Q1 (n = 58)	Q2 (n = 58)	Q3 (n = 58)	Q4 (n = 58)	Q5 (n = 58)	P value
Electrocardiogram						
SV1 + RV5 (n = 290) (mv)	4.25 [3.30–5.50]	3.10 [2.58–3.75][a]	2.41 [2.02–3.02][a, b]	2.00 [1.79–2.29][a, b, c]	1.37 [1.16–1.60][a, b, c, d]	<0.001
LBBB (n = 273), n (%)	1 (1.7)	3 (5.2)	0 (0.0)	4 (6.9)	5 (8.6)	0.131
Abnormal Q wave (n = 278), n (%)	4 (7.1)	6 (10.9)	4 (7.0)	8 (14.5)	10 (18.2)	0.294

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; E/E′, ratio of the early transmitral flow velocity and early mitral annular velocity; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; IGT, impaired glucose intolerance; IVSd, end-diastolic interventricular septal thickness; LAVI, left atrial volume index; LBBB, left bundle branch block; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PM, pacemaker; Q1, first quintile; Q2, second quintile; Q3, third quintile; Q4, fourth quintile; Q5, fifth quintile; RWT, relative wall thickness; SBP, systolic blood pressure; TRPG, transtricuspid pressure gradient.
Continuous variables are expressed as medians [interquartile ranges].
[a]$P < 0.05$ for Q1.
[b]$P < 0.05$ for Q2.
[c]$P < 0.05$ for Q3.
[d]$P < 0.05$ for Q4.

ular septal thickness (IVSd) + end-diastolic posterior wall thickness (PWd)]^3 − LVEDD^3)]} + 0.6 and normalized to body surface area.

For each LV measurement, the value of the echo at the time of discharge was used, but if the echo data at the time of discharge were not available, the echo measurement at the time of admission was used instead. QRS voltage was assessed by Sokolow–Lyon voltage criteria (SV1 + RV5 mV). We divided patients into five groups according to the quintile values of the LVMI-to-QRS-voltage ratio as follows: Q1, <30.7 g/m^2/mV; Q2, ≥30.7 < 41.9 g/m^2/mV; Q3, ≥41.9 < 51.6 g/m^2/mV; Q4, ≥51.6 < 71.8 g/m^2/mV; and Q5, ≥71.8 g/m^2/mV. LV geometry was classified into the following four groups according to previously described criteria[13]: normal geometry (N): no LVH and relative wall thickness (RWT) ≤ 0.42; concentric remodelling (CR): no LVH and RWT > 0.42; CH: LVH and RWT > 0.42; and EH: LVH and RWT ≤ 0.42. LVH was defined as LVMI > 115 g/m^2 in men and >95 g/m^2 in women as previously described.[13]

We evaluated the composite endpoint of all-cause death and first events of unplanned rehospitalization for HF after discharge.

Statistical analysis

Continuous variables are expressed as medians and interquartile ranges. Differences in continuous variables were compared using the Kruskal–Wallis test. Categorical variables were compared using Fisher's exact test. Differences between pairs were assessed using the Bonferroni test. The event-free survival curve after discharge was estimated by the Kaplan–Meier method. Cox proportional hazards models were used to assess the effect of a high LVMI-to-QRS-voltage ratio on the primary outcome and its interaction with each subgroup. To adjust for differences in the patients' background, age, sex, and all baseline characteristics that were associated with differences in quintile values of the LVMI-to-QRS-voltage ratio ($P < 0.1$) were entered into the multivariate Cox proportional hazard analysis. A P value < 0.05 was considered statistically significant. All analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (Version 2.13.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

The median age of the cohort was 79 (72–84) years, and 51.4% of the patients were men. A history of hospitalization for HF was found in 33.5% of the patients, and 7.6% of the

patients were in New York Heart Association (NYHA) functional class III. The most common LV geometry was CH (43.4%), followed by EH (20.7%), CR (19.7%), and N (16.2%). The prevalence of coronary artery disease (previous history of myocardial infarction or coronary revascularization including percutaneous coronary intervention or coronary artery bypass grafting) and atrial fibrillation were 26.2% and 45.2%, respectively. Non-cardiac co-morbidities, that is,

Figure 2 Characteristics of LV geometry among the five groups according to the LVMI-to-QRS-voltage ratio. CH, concentric hypertrophy; CR, concentric remodelling; EH, eccentric hypertrophy; LV, left ventricular; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; N, normal geometry; RWT, relative wall thickness. [a]$P < 0.05$ for Q1; [b]$P < 0.05$ for Q2.

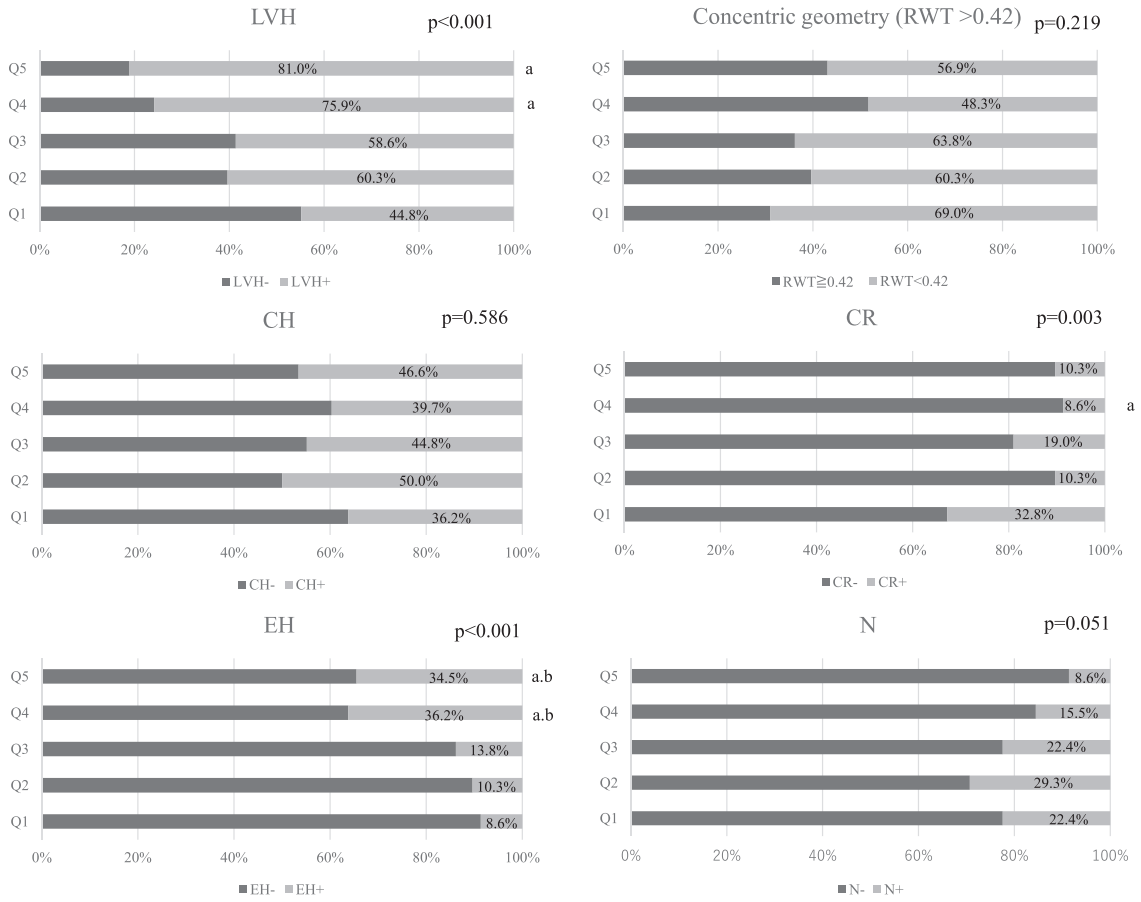


Table 2 Multivariate Cox regression analysis for predicting the composite endpoint of all-cause death and heart failure rehospitalization

	Unadjusted hazard ratio (95% confidence interval)	*P* value	Adjusted hazard ratio[a] (95% confidence interval)	*P* value
LVMI (per g/m^2)	1.004 (0.999–1.010)	0.130		
QRS voltage (per mV)	0.954 (0.821–1.109)	0.541		
LVMI-to-QRS-voltage ratio (per g/m^2/mV)	1.008 (1.001–1.014)	0.016	1.010 (1.003–1.017)	0.007
LVMI-to-QRS-voltage ratio (per quintile value)				
Q1	1.000 (reference)		1.000 (reference)	
Q2	1.062 (0.536–2.102)	0.863	0.993 (0.470–2.099)	0.985
Q3	1.046 (0.528–2.071)	0.898	1.120 (0.530–2.369)	0.767
Q4	0.766 (0.368–1.593)	0.476	0.786 (0.353–1.752)	0.556
Q5	2.130 (1.152–3.939)	0.016	2.205 (1.106–4.395)	0.025
LVMI-to-QRS-voltage ratio ≧ 70.5 (g/m^2/mV) (cut-off value)	2.233 (1.435–3.474)	<0.001	2.202 (1.349–3.596)	0.002

LVMI, left ventricular mass index; Q1, first quintile; Q2, second quintile; Q3, third quintile; Q4, fourth quintile; Q5, fifth quintile.
[a]Adjusted for age, sex, coronary artery disease, atrial fibrillation, prior pacemaker implant, sodium, and blood urea nitrogen.

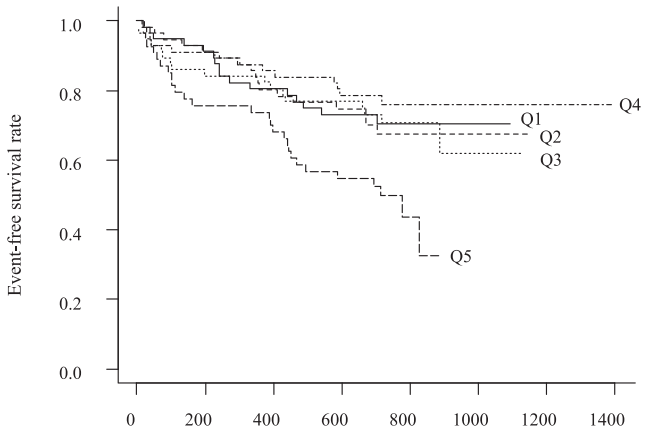
chronic obstructive pulmonary disease, diabetes mellitus, anaemia (haemoglobin levels < 13 g/dL in men and <12 g/dL in women), and severe renal dysfunction (chronic kidney disease stages 4–5; estimated glomerular filtration rate < 30 mL/min/1.73 m^2), were found in 10.0%, 40.7%, 71.7%, and 29.7% of the patients, respectively.

Table 1 and *Figure 2* show the patient characteristics for five groups according to the quintile values of the LVMI-to-QRS-voltage ratio. Patients in the highest quintile group (Q5) had the highest proportion of atrial fibrillation (61.4%) and previous history of pacemaker implantation (12.1%) as well as the lowest proportion of coronary artery disease (15.8%) among the five groups ($P < 0.05$). Regarding laboratory data, serum sodium level tended to be lowest and blood urea nitrogen level tended to be highest in the Q5 group although these differences were not significant. On echocardiogram and ECG, patients in the Q5 group had the highest value of LVMI and the lowest value of QRS voltage among the groups. *Figure 2* shows the characteristics of LV geometry among the five groups. Patients in both the Q4 and Q5 groups had a relatively higher prevalence of LVH among the five groups (Q4: 75.9%, Q5: 81.0%, $P < 0.05$). In the classification of LV geometry, the prevalence of CH did not differ among the five groups, but that of EH was relatively greater in the Q4 and Q5 groups (Q4: 36.2%, Q5: 34.5%, $P < 0.05$). Patients in the Q1 group had the highest prevalence of CR among the groups (Q1: 32.8%, $P < 0.05$). There were no significant differences in the prevalence of concentric geometry among the groups.

Effects of the left ventricular mass index-to-QRS-voltage ratio on primary endpoints

During the mean follow-up of 587 ± 300 days, the composite endpoint of all-cause death or first hospitalization for HF occurred in 91 patients (31.4%). Although neither LVMI nor QRS voltage was not significantly related to clinical outcomes independently, a high value of the LVMI-to-QRS-voltage ratio as a continuous value or a quintile (comparison between Q5 and Q1) was significantly associated with higher incidence of the composite endpoint even after adjustment for differences in patient background (age, sex, history of coronary artery disease, atrial fibrillation, and prior pacemaker implant, and laboratory values on sodium, and blood urea nitrogen) (*Table 2* and *Figure 3*). We also examined the optimal cut-off point of predicting outcomes by using receiver operating curve and identified 70.5 g/m^2/mV as the optimal cut-off point (area under the curve = 0.63) (*Table 2* and Supporting Information, *Figure S1*). We further examined whether the effect of the highest quintile value of the LVMI-to-QRS-voltage ratio (comparison between Q5 and others) on the composite endpoint was modified by age, sex, LV geometry,

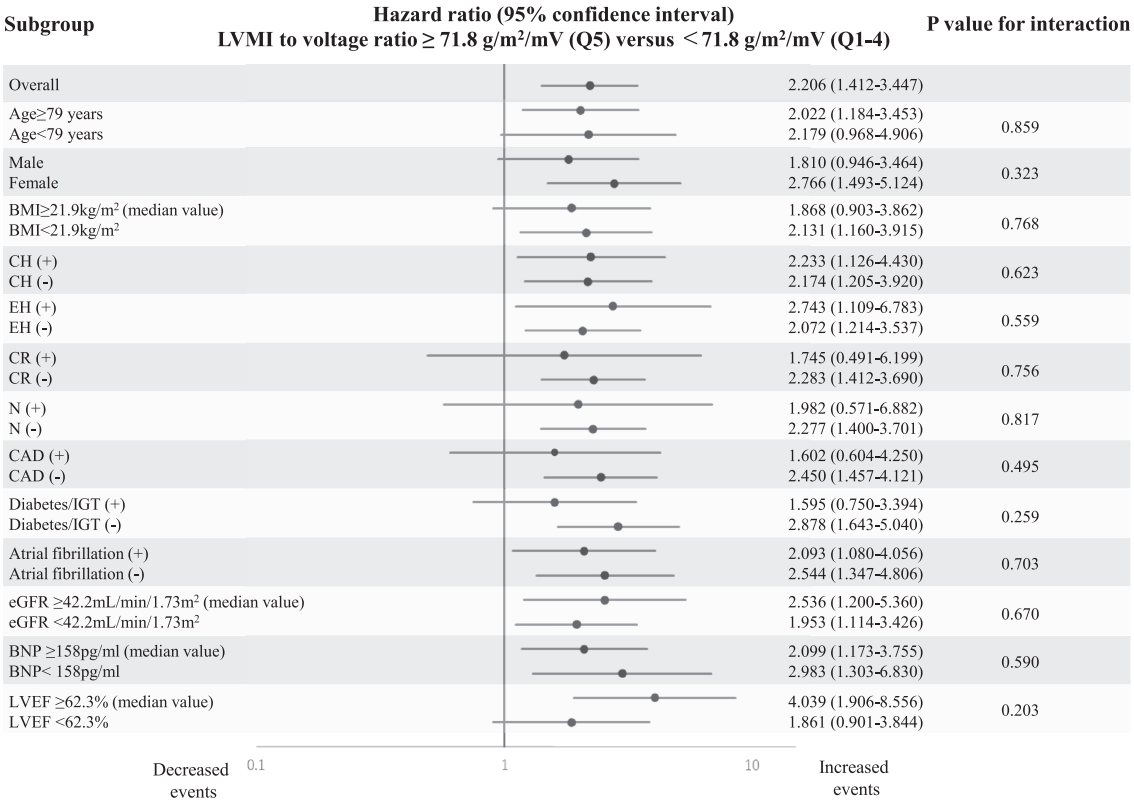
Figure 3 Kaplan–Meier curve for the composite endpoint of all-cause death or hospitalization for HF among the five groups according to quintile value of the LVMI-to-QRS-voltage ratio, with adjustment for differences in the patient background.* HF, heart failure; LVMI, left ventricular mass index; Q1, first quintile; Q2, second quintile; Q3, third quintile; Q4, fourth quintile; Q5, fifth quintile. *Adjusted for age, sex, coronary artery disease, atrial fibrillation, prior pacemaker implant, sodium, and blood urea nitrogen.



Number at risk

Q1	53	47	43	33	10	1	0	0
Q2	55	49	41	35	7	3	0	0
Q3	56	46	43	38	13	6	0	0
Q4	57	50	47	44	10	4	2	1
Q5	56	39	36	28	4	0	0	0

Figure 4 Effect of a high LVMI-to-QRS-voltage ratio on the composite endpoint of all-cause death or hospitalization for HF in the subgroups. BMI, body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; CH, concentric hypertrophy; CR, concentric remodelling; eGFR, estimated glomerular filtration rate; EH, eccentric hypertrophy; HF, heart failure; IGT, impaired glucose intolerance; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; N; normal geometry.



co-morbidities, or laboratory values (*Figure 4*). We found no significant interaction across the subgroups.

Discussion

This is the first study to show that a high ratio of LVMI to QRS voltage, reflecting increased LVM disproportionate to electrocardiographic QRS voltage, is associated with poor prognosis in patients with HFpEF.

The presence of low QRS voltage despite the presence of LVH is helpful for diagnosing infiltrative diseases such as cardiac amyloidosis, and a high LVMI-to-QRS-voltage ratio is associated with poor prognosis in patients with cardiac amyloidosis.[9] A recent study showed that 13–19% of patients hospitalized with HFpEF had ATTR cardiac amyloidosis when evaluated by 99mTc-pyrophosphate (PYP) or 99mTc-3,3-diphosphono-1,2-propano-dicarboxylic acid (DPD) pyrophosphate myocardial scintigraphy or cardiac biopsy.[5–7] The current study found that the top 20% of patients with a high LVMI-to-QRS-voltage ratio more often had a 'red flag' sign of cardiac amyloidosis, such as previous history of atrial fibrillation or conduction disturbance requiring a pacemaker.[8] Thus, the reason for the poor prognosis of HFpEF patients with a high LVMI-to-QRS-voltage ratio may be partially explained by the presence of amyloid infiltration, which contributes to a high risk of mortality and HF rehospitalization in HFpEF.[14] Another reason may be that this index also reflects myocardial fibrosis. Previous studies have reported that, in patients with hypertrophic cardiomyopathy, low QRS voltage is associated with cardiac fibrosis as assessed by magnetic resonance imaging.[11,12] Taken together, a high LVMI-to-QRS-voltage ratio is not simply a marker of identifying cardiac amyloidosis, but comprehensive marker of myocardial structural changes due to myocardial fibrosis and infiltration into the myocardium, which is helpful for risk stratification and understanding pathophysiology in heterogeneous patients with HFpEF.

In the highest quintile group of the LVMI-to-QRS-voltage ratio (Q5), 81% of patients had LVH, consisting of CH in 46.6% and EH in 34.5%. Although CH and CR are common LV geometry in patients with HFpEF,[4,15] EH, which is a common LV geometry in HF with reduced ejection fraction (HFrEF), is also seen in 12–16% of patients with HFpEF.[4,15] It has been reported that, compared with CH, HFpEF with

EH has a lower EF and a pressure–volume loop to mimic that of HFrEF, suggesting that CH and EH are distinct phenotypes of HFpEF.[4] Both CH and EH have been reported to be associated with poor prognosis in patients with HFpEF.[4] Although in this study evaluation of LVH alone was not useful for predicting prognosis, we confirmed that adding ECG potential information to LVMI can identify patients with LVH who have a worse prognosis (*Table 2*). The association between a high LVMI-to-QRS-voltage ratio and poor prognosis did not interact with any of the four LV geometry categories (N, CR, CH, and EH) in the subgroup analysis (*Figure 4*). Thus, this index is useful for predicting prognosis regardless of the type of LV geometry.

There are several limitations to this study. This registry did not evaluate the details of aetiology and phenotypes of HFpEF. Low QRS voltage is affected not only by myocardial function but also by pericardial effusion, ascites, and peripheral oedema. In this study, we could not exclude patients with these findings that might interfere with QRS voltage. In this study protocol, QRS voltage was assessed only by the Sokolow–Lyon criterion, and other criteria could not be validated due to retrospective analysis. Previous anterior or anteroseptal myocardial infarction may affect the QRS voltage in precordial lead. However, there were no significant differences in prevalence of previous anterior or anteroseptal myocardial infarction among the quintile values of LVMI-to-QRS-voltage ratio. In addition, even after adjustment for the prevalence of anterior or anteroseptal myocardial function, the effect of LVMI-to-QRS-voltage ratio on prognosis was not changed (data not shown). Thus, the effect of previous myocardial infarction on LVMI-to-QRS-voltage ratio and prognosis is small, even if it exists. A previous study has reported that low QRS voltage as assessed with the Cornel criterion was the most sensitive in predicting prognosis in cardiac amyloidosis[9]; thus, it is necessary to validate the optimal ECG criteria for assessing QRS voltage in patients with HFpEF. Finally, we could not validate the prognostic significance of the index in another cohort. HFpEF is heterogeneous population, and phenotype of HFpEF may be different among race and countries.[10] Further investigations are necessary to clarify the clinical significance of this index in HFpEF cohort of various race and countries.

In conclusion, a high LVMI-to-QRS-voltage ratio, which reflects increased LVM disproportionate to electrocardiographic QRS voltage, is associated with poor prognosis in patients with HFpEF. This index is easy to assess in routine clinical practice and is useful for risk stratification and understanding pathophysiology in patients with HFpEF.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Kaplan–Meier curve for the composite endpoint of all-cause death or hospitalization for HF based on the optimal cut-off point of LVMI-to-QRS-voltage ratio, with adjustment for differences in the patient background. **Adjusted for age, sex, coronary artery disease, atrial fibrillation, prior pacemaker implant, sodium, and blood urea nitrogen.

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