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ORIGINAL ARTICLE
Heart Failure

Sex Differences in Time-Dependent Changes in B-Type Natriuretic Peptide in Hypertrophic Cardiomyopathy

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Background: Female sex is reported to be associated with poor prognosis in hypertrophic cardiomyopathy (HCM). The plasma B-type natriuretic peptide (BNP) concentration is a prognostic predictor in HCM. However, the effect of sex on BNP concentrations remains unclear among HCM patients.

Methods and Results: Patient records in the Clinical Personal Records of HCM national database of the Japanese Ministry of Health, Labour and Welfare from 2009 to 2014 were analyzed. Of 3,570 HCM patients, 611 in whom BNP concentrations were assessed at both baseline and the 2-year follow-up were included in this analysis. The mean age was 60.4 years and 254 (41.6%) patients were female. Median (interquartile range) BNP concentrations were higher in females than males at both baseline (320.3 [159.0–583.1] vs. 182.8 [86.1–363.9] pg/mL; P<0.001) and the 2-year follow-up (299.2 [147.0–535.3] vs. 161.0 [76.2–310.0] pg/mL; P<0.001). Female sex was associated with higher natural log-transformed BNP at the 2-year follow-up regardless of clinical characteristics, including echocardiographic findings and BNP concentrations at baseline (coefficient 0.31; 95% confidence interval 0.13–0.48; P<0.001). Cubic spline analysis showed that, among patients with high BNP concentrations at baseline, females had higher BNP concentrations at the 2-year follow-up than males.

Conclusions: In HCM, female sex was associated with higher BNP concentrations than male sex, independent of clinical characteristics, including BNP concentrations at baseline.

Key Words: B-type natriuretic peptide; Hypertrophic cardiomyopathy; Sex difference

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac disorder, with an estimated prevalence of 1 : 500.[1] Gene mutations are detectable in 75% of HCM patients, the most common of which are in the cardiac myosin-binding protein C (*MYBPC3*) and β-myosin heavy chain (*MYH7*) genes.[2,3] Although the mode of inheritance is autosomal dominant, male patients had a 3 : 2 predominance,[4–7] suggesting the existence of sex differences in this disease. Indeed, there are several reports regarding sex differences in clinical features, cardiac morphology, and prognosis in HCM.[4,6,8–13] In general, female HCM patients are known to be under-represented, older, and more symptomatic, as well as having a higher risk of heart failure (HF) with an outflow obstructive phenotype, than males.[4] Importantly, female sex is reported to be associated with poor prognosis.[4,6,10,14] Recently, therapeutic options for HCM have been developed, including implantable defibrillator, myectomy, and alcohol septal ablation to avert lethal ventricular arrhythmia and HF death and morbidity. In order for better stratification in HCM, it is clinically relevant to clarify sex differences not only for mortality, but also for surrogate outcomes.

B-type natriuretic peptide (BNP) is useful in predicting prognosis in several cardiovascular diseases.[15–18] In HCM, elevated BNP concentrations are associated with sudden death[19] and progression to end-stage disease.[20] In addition, BNP is reported to be a prognostic predictor, independent of left ventricular (LV) mass and fibrosis.[21] Furthermore, persistent elevation of BNP concentrations has been shown to be predictive of long-term major adverse cardiovascular events.[22] However, sex differences in BNP concentrations, particularly time-dependent changes in BNP, among HCM

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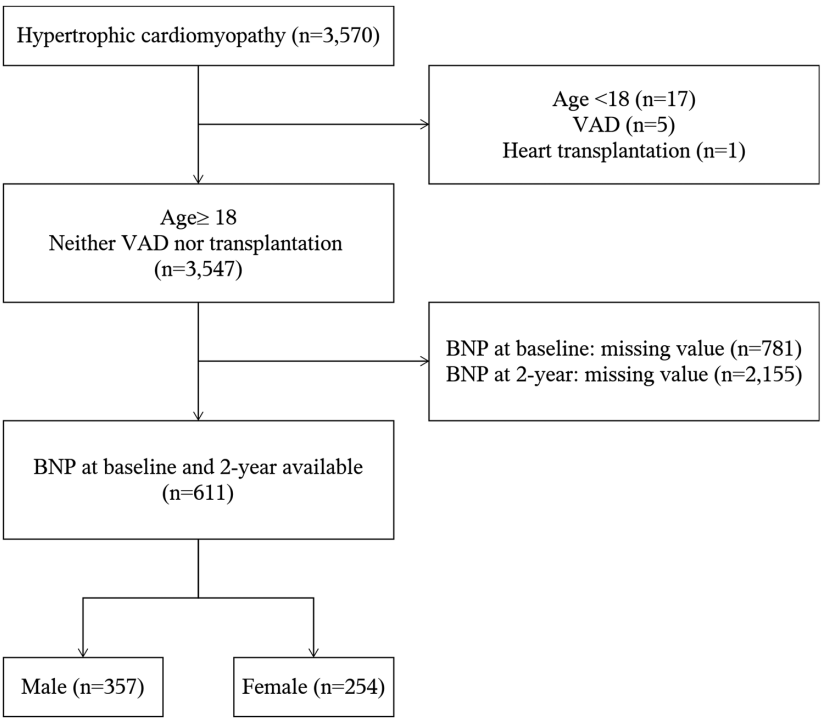

Figure 1. Patient Selection. BNP, B-type natriuretic peptide; VAD, ventricular assist device.

patients remain unclear.

The Clinical Personal Record is a nationwide administrative database of public expenditure for refractory disease of the Japanese Ministry of Health, Labour and Welfare in which intractable diseases throughout Japan, including cardiomyopathy, are registered and certified. This database is useful for investigating the clinical features of and routine practice regarding HCM patients in Japan.[23] The aim of this study was to clarify sex differences in BNP levels among HCM patients by using the nationwide Clinical Personal Record registry.

Methods

Clinical Personal Record

The Clinical Personal Record of HCM, a nationwide administrative database of public expenditure for refractory disease, prospectively and annually collects the following: (1) demographic data (age, sex, HF duration, and New York Heart Association [NYHA] functional class); (2) vital signs; (3) comorbidities; (4) electrocardiographic data; (5) echocardiographic data; (6) laboratory data; and (7) medication use. This database does not collect information about clinical outcomes, such as cardiovascular death and all-cause death. HCM was diagnosed as asymmetric or diffuse LV hypertrophy with reduced diastolic function in the absence of any specific cardiac or systemic diseases, such as hypertensive heart disease, valvular heart disease, congenital heart disease, coronary artery disease, alcoholic cardiomyopathy, cardiomyopathy caused by toxins/medications, amyloidosis, sarcoidosis, connective tissue disease, and dystrophy, or metabolic diseases such as Pompe disease or Fabry disease. All database entries were registered after being reviewed by certified cardiologists. In this study, we analyzed this nationwide database for the period 2009–2014.

Study Population

Patients aged >18 years were identified in the Clinical Personal Record of HCM. Patients who received an LV assist device (LVAD) or underwent heart transplantation during the follow-up period or those whose BNP concentrations were not assessed at baseline or the 2-year follow-up were excluded from the study.

BNP Measurement

BNP was measured at each participating hospital. Plasma BNP concentrations at baseline and the 2-year follow-up were analyzed according to sex.

Statistical Analysis

Patient characteristics, including age, sex, NYHA functional class, HF duration, vital signs, electrocardiographic findings, echocardiographic findings, comorbidities, laboratory data, and medications, were compared using Pearson's χ^2 test for categorical variables or Student's t-test or the Wilcoxon rank-sum test for continuous variables and are presented as the mean±SD or as the median with interquartile range (IQR).

Changes in BNP concentrations from baseline to the 2-year follow-up were examined by paired t-test after log transformation of BNP data. The coefficient for natural log-transformed BNP at the 2-year follow-up was estimated using analysis of covariance (ANCOVA) including female sex, natural log-transformed BNP at baseline, and other covariates, as listed below, and is reported with 95% confidence intervals (CI) and P values. We examined the outcomes using several ANCOVA models, including

covariates as follows:

Model 1: demographics and vital signs (age, HCM duration, NYHA functional class, systolic blood pressure, and heart rate)
Model 2: Model 1 + comorbidities (hypertension and stroke)
Model 3: Model 2 + electrocardiographic findings and devices (atrial fibrillation, pacemaker, implantable cardioverter defibrillator, and cardiac resynchronization therapy)
Model 4: Model 3 + echocardiographic findings (LV ejection fraction [LVEF], interventricular septal wall [IVS] thickness, LV posterior wall [LVPW] thickness, left atrial diameter, mitral regurgitation, and LV obstruction)
Model 5: Model 4 + laboratory data (albumin and estimated glomerular filtration rate)
Model 6: Model 5 + medication (β-blockers, angiotensin-converting enzyme inhibitors [ACEI]/angiotensin II receptor blockers [ARB], and mineralocorticoid receptor antagonists).

Table 1. Patient Characteristics

	Males (n=357)	Females (n=254)	P value
Demographics			
Age (years)	60.0±13.5	60.9±15.5	0.47
Disease duration (years)	8 [3–16]	8 [3–15]	0.88
NYHA functional class III–IV	33 (9.8)	27 (11.6)	0.48
Family history			
Hypertrophic cardiomyopathy	87 (24.4)	82 (32.3)	0.031
Sudden cardiac death	28 (7.8)	25 (9.8)	0.39
Vital signs			
Systolic blood pressure (mmHg)	119.9±17.6	119.9±19.1	1.00
Diastolic blood pressure (mmHg)	70.1±12.6	69.0±13.5	0.34
Heart rate (beats/min)	68.0±15.7	66.3±12.9	0.16
Comorbidities			
Hypertension	66 (29.1)	45 (27.1)	0.67
CKD stage 3–5	124 (35.6)	119 (47.4)	0.004
Stroke	9 (2.5)	3 (1.2)	0.24
Electrocardiographic findings			
Atrial fibrillation	120 (33.6)	51 (20.1)	<0.001
Ventricular fibrillation or tachycardia	122 (34.2)	50 (19.7)	<0.001
Pacemaker	15 (4.2)	22 (8.7)	0.023
Implantable cardioverter defibrillator	17 (4.8)	10 (3.9)	0.62
Cardiac resynchronization therapy	2 (0.6)	1 (0.4)	0.77
Right bundle branch block	25 (11.0)	16 (9.6)	0.66
Left bundle branch block	9 (4.0)	4 (2.4)	0.39
Echocardiographic findings			
LVEF (%)	61.4±16.0	64.7±14.5	0.012
LVDd (mm)	48.0±8.0	43.4±7.8	<0.001
LVDs (mm)	31.2±9.0	27.3±8.9	<0.001
IVS (mm)	16.4±5.5	15.6±4.8	0.062
LVPW (mm)	11.9±3.8	11.2±3.0	0.011
Left atrial diameter (mm)	45.8±10.1	41.8±8.8	<0.001
E wave (cm/s)	67.5±24.1	74.8±30.0	0.006
A wave (cm/s)	64.5±33.4	74.0±38.3	0.010
e' (cm/s)	5.5±2.8	5.5±3.0	0.93
E/A	1.2±0.7	1.2±0.6	0.55
E/e'	14.3±7.0	16.9±7.6	0.012
Deceleration time (ms)	216.4±73.7	242.4±87.1	0.002
TR velocity (m/s)	2.7±0.5	2.7±0.5	0.77
MR III–IV	22 (7.9)	23 (11.2)	0.21
Left ventricular obstruction	96 (26.9)	112 (44.1)	<0.001
LVOT obstruction	73 (20.4)	87 (34.3)	<0.001
LVOT gradient >50 mmHg	55 (15.4)	67 (26.4)	0.001
LV mid obstruction	26 (7.3)	30 (11.8)	0.056
Pericardial effusion	15 (4.2)	19 (7.5)	0.081

(**Table 1** continued the next page.)

	Males (n=357)	Females (n=254)	P value
Laboratory data			
Hemoglobin (g/dL)	14.5±1.6	12.9±1.3	<0.001
Albumin (g/dL)	4.2±0.4	4.1±0.5	0.079
BUN (mg/dL)	18.4±13.3	18.0±12.6	0.65
Creatinine (mg/dL)	0.91 [0.82–1.09]	0.74 [0.64–0.89]	<0.001
eGFR (mL/min/1.73 m^2)	65.5±18.0	63.1±20.4	0.15
Uric acid (mg/dL)	6.5±1.4	5.5±1.5	<0.001
Sodium (mEq/L)	140.6±2.7	141.0±2.6	0.077
Potassium (mEq/L)	4.3±0.5	4.3±0.5	0.68
BNP (pg/mL)	182.8 [86.1–363.9]	320.3 [159.0–583.1]	<0.001
ln[BNP]	5.2±1.1	5.7±1.1	<0.001
Medication			
β-blockers	218 (61.1)	138 (55.0)	0.13
ACEI or ARB	221 (61.9)	123 (48.4)	0.001
MRA	74 (20.7)	61 (24.0)	0.33
Dihydropyridine CCB	54 (15.1)	25 (9.8)	0.055
Verapamil	23 (6.4)	21 (8.3)	0.39
Diltiazem	19 (5.3)	14 (5.5)	0.92
Loop diuretics	100 (28.0)	72 (28.3)	0.93
Thiazides	18 (5.0)	10 (3.9)	0.52
Digitalis	11 (3.1)	10 (3.9)	0.57
Amiodarone	57 (16.0)	23 (9.1)	0.013
Disopyramide	12 (3.4)	22 (8.7)	0.005
Cibenzoline	43 (12.1)	65 (25.7)	<0.001
Oral inotropes	5 (2.5)	2 (1.4)	0.48

Unless specified otherwise, data are shown as n (%), the mean±SD, or median [interquartile range]. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CCB, calcium channel blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IVS, interventricular septal thickness; ln, natural log; LV, left ventricular; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVDs, left ventricular systolic diameter; LVOT, left ventricular outflow tract; LVPW, left ventricular posterior wall thickness; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; TR, tricuspid regurgitation.

We examined outcomes in patients with or without LV obstruction separately using Model 1. We also performed a multivariate analysis, including covariates that were significant on univariate analysis for natural log-transformed BNP at the 2-year follow-up. Outcomes were also analyzed using a combination of multiple imputation and multivariate analysis to assess the effects of missing data. For all missing data at baseline, multiple imputation was performed (10 imputed datasets) by predictive mean matching for continuous variables and using a logistic regression model for binary variables. The multivariate analysis included covariates used in multiple imputations. Coefficients for natural log-transformed BNP concentrations at the 2-year follow-up from 10 iterations were combined using Rubin's rule. To model the effects of sex on changes in BNP, a cubic spline analysis adjusted for age and LVEF was performed. To assess the effects of selection bias, we compared baseline characteristics of eligible patients with those who were excluded because their BNP was not assessed at the 2-year follow-up.

All tests were 2-tailed and P<0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethics Statement

The study protocol complied with the Declaration of Helsinki. The original study protocol was approved by the Institutional Review Board at Kyushu University. An "opt-out" approach was applied to consent because this study analyzed a nationwide administrative database.

Results

Baseline Characteristics

From 2009 to 2014, 3,570 consecutive patients with HCM were screened and 3,547 patients aged >18 years who did not receive an LVAD and did not undergo heart transplantation during the follow-up period were identified (**Figure 1**). Of these patients, 611 who had BNP assessed at both baseline and the 2-year follow-up were included in the present analysis. There was a predominance of males (n=357; 58.4%) compared with females (n=254; 41.6%). Comparing female and male HCM patients, there were no significant differences in age (60.9±15.5 vs. 60.0±13.5 years, respectively; P=0.47) or disease duration (8 [3–15] vs. 8 [3–16] years, respectively; P=0.88; **Table 1**). We also compared eligible patients with those patients who did not have BNP assessed at the 2-year follow-up. Although the latter group was older (62.2±15.0 vs. 60.4±14.4 years; standardized mean difference [SMD] 0.123; P=0.010), the echocardiographic findings and BNP concentrations at baseline (245.9 [104.6–530.0] vs. 233.1 [114.6–465.0] pg/mL; SMD

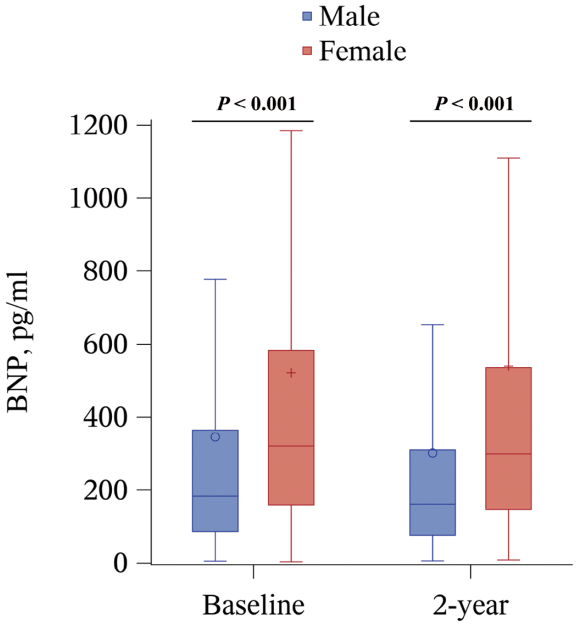

Figure 2. B-Type natriuretic peptide (BNP) at baseline and the 2-year follow-up according to sex. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range.

0.053; P=0.40) were similar between the 2 groups (**Supplementary Table 1**).

Echocardiography

Compared with males, females with HCM had a greater LVEF (64.7±14.5% vs. 61.4±16.0%; P=0.012), smaller LV diastolic diameter (43.4±7.8 vs. 48.0±8.0 mm; P<0.001), smaller LV systolic diameter (27.3±8.9 vs. 31.2±9.0 mm; P<0.001), smaller left atrial transverse dimensions (41.8±8.8 vs. 45.8±10.1 mm; P<0.001), slightly lower IVS thickness (15.6±4.8 vs. 16.4±5.5 mm; P=0.061), lower LVPW thickness (11.2±3.0 vs. 11.9±3.8 mm; P=0.011), a higher E/e' ratio (16.9±7.6 vs. 14.3±7.0; P=0.012), and longer deceleration time (242.4±87.1 vs. 216.4±73.7 ms; P=0.001; **Table 1**). Females had a higher prevalence of LV outflow obstruction (34.3% vs. 20.5%; P<0.001) and any LV obstruction, including outflow obstruction and mid-ventricular obstruction (44.1% vs. 26.9%; P<0.001; **Table 1**).

Plasma BNP Concentrations

Median (IQR) BNP concentrations at both baseline (320.3 [159.0–583.1] vs. 182.8 [86.1–363.9] pg/mL; P<0.001) and the 2-year follow-up (299.2 [147.0–535.3] vs. 161.0 [76.2–310.0] pg/mL; P<0.001) were higher in females than males (**Figure 2**). Natural log-transformed BNP at the 2-year follow-up was higher in female patients in multivariate models 1 (Model 1: coefficient 0.31, 95% CI 0.13–0.48; P<0.001; **Table 2**). The same results were confirmed in multivariate Models 2–6 (**Table 2**). Furthermore, multiple imputation analysis also demonstrated that BNP at the 2-year follow-up was higher in female patients (coefficient 0.63, 95% CI 0.44–0.82; P<0.001; **Table 2**). Natural log-transformed BNP at the 2-year follow-up was higher in female patients with or without LV obstruction (coefficients 0.33 [95% CI 0.02–0.63; P=0.034] and 0.29 [95% CI 0.08–0.50; P=0.007], respectively; **Supplementary Table 2**). Multivariate analysis (including covariates significant on univariate analysis) also showed that natural log-transformed BNP at the 2-year follow-up was higher in female patients (coefficient 0.36, 95% CI 0.05–0.67; P=0.024; **Table 3**). After adjusting for age and LVEF, cubic spline analysis also demonstrated that females had higher BNP concentrations at the 2-year follow-up than males (**Figure 3**).

Outcomes

De novo HF hospitalization was numerically more frequent in females, but the difference did not reach statistical significance (15.3% vs. 9.3%; odds ratio 1.75, 95% CI 0.98–3.13; P=0.059; **Table 4**). There was no significant difference in new-onset atrial fibrillation, lethal ventricular arrhythmia, and stroke between males and females (**Table 4**).

Discussion

The major finding of this study was that BNP concentrations at the 2-year follow-up were higher in females than males after adjusting for baseline covariates, including

Table 2. Analysis of Covariance for Natural Log-Transformed BNP at the 2-Year Follow-up

Analysis	Coefficient for female sex (95% CI)	P value
Complete case analysis		
Model 1 (demographics, vital signs)	0.31 (0.13–0.48)	<0.001
Model 2 (Model 1+comorbidities)	0.41 (0.18–0.64)	<0.001
Model 3 (Model 2+ECG findings)	0.42 (0.19–0.65)	<0.001
Model 4 (Model 3+UCG findings)	0.47 (0.16–0.78)	0.003
Model 5 (Model 4+laboratory data)	0.38 (0.04–0.72)	0.030
Model 6 (Model 5+medication)	0.36 (0.01–0.70)	0.043
Multiple imputation analysis	0.63 (0.44–0.82)	<0.001

Model 1: Analysis of covariance including female sex, natural log-transformed BNP at baseline, age, hypertrophic cardiomyopathy duration, NYHA functional class, systolic blood pressure, and heart rate. Model 2: Model 1+hypertension and stroke. Model 3: Model 2+atrial fibrillation, pacemaker, implantable cardioverter defibrillator, and cardiac resynchronization therapy. Model 4: Model 3+LVEF, IVS, LVPW, left atrial diameter, MR, and left ventricular obstruction. Model 5: Model 4+albumin and estimated glomerular filtration rate. Model 6: Model 5+β-blockers, ACEI/ARB, and MRA. CI, confidence interval; ECG, electrocardiogram; UCG, ultrasound cardiogram. Other abbreviations as in Table 1.

Table 3. Univariate and Multivariate Analysis for Natural Log-Transformed BNP at the 2-Year Follow-up

Variables	Univariate analysis		Multivariate analysis	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Female sex	0.65 (0.48, 0.83)	<0.001	0.36 (0.05, 0.67)	0.024
Age	0.07 (0.00, 0.13)	0.036	0.01 (0.00, 0.03)	0.008
Disease duration	0.02 (0.01, 0.03)	<0.001	0.02 (0.00, 0.03)	0.038
NYHA functional class	0.26 (−0.05, 0.57)	0.10		
Systolic blood pressure	−0.14 (−0.19, −0.09)	<0.001	−0.01 (−0.02, 0.00)	0.014
Heart rate	−0.08 (−0.14, −0.01)	0.026	−0.01 (−0.02, 0.00)	0.01
Hypertension	−0.31 (−0.57, −0.05)	0.018	0.06 (−0.25, 0.36)	0.71
Stroke	−0.19 (−0.85, 0.48)	0.58		
Atrial fibrillation	0.25 (0.04, 0.45)	0.018	0.08 (−0.24, 0.41)	0.62
Ventricular arrhythmia	0.01 (−0.20, 0.21)	0.93		
Pacemaker	0.24 (−0.14, 0.63)	0.22		
Implantable cardioverter defibrillator	0.22 (−0.23, 0.67)	0.33		
Cardiac resynchronization therapy	1.16 (−0.15, 2.48)	0.083		
Right bundle branch block	0.10 (−0.29, 0.48)	0.61		
Left bundle branch block	0.26 (−0.40, 0.92)	0.44		
LVEF	−0.05 (−0.11, 0.01)	0.13		
LVDd	−0.23 (−0.34, −0.12)	<0.001	−0.02 (−0.04, 0.00)	0.024
LVDs	−0.05 (−0.16, 0.05)	0.32		
IVS	0.02 (0.00, 0.04)	0.016	0.01 (−0.02, 0.04)	0.45
LVPW	0.00 (−0.03, 0.03)	0.91		
Left atrial diameter	0.15 (0.05, 0.25)	0.004	0.01 (0.00, 0.02)	0.12
MR	0.46 (0.10, 0.82)	0.013	0.19 (−0.26, 0.63)	0.41
LV obstruction	0.26 (0.07, 0.45)	0.009	0.01 (−0.28, 0.31)	0.93
Systolic anterior movement	0.20 (−0.82, 1.22)	0.70		
Pericardial effusion	0.74 (0.34, 1.13)	<0.001	0.58 (0.15, 1.00)	0.008
Apical hypertrophy	0.00 (−0.94, 0.93)	>0.99		
Hemoglobin	−0.13 (−0.19, −0.08)	<0.001	0.02 (−0.07, 0.11)	0.68
Albumin	−0.10 (−0.36, 0.16)	0.44		
eGFR	−0.09 (−0.14, −0.04)	<0.001	0.00 (0.00, 0.01)	0.37
Uric acid	0.00 (−0.06, 0.07)	0.89		
Sodium	−0.24 (−0.60, 0.12)	0.19		
Potassium	0.11 (−0.10, 0.31)	0.31		
ln[BNP]	0.67 (0.61, 0.73)	<0.001	0.59 (0.47, 0.71)	<0.001
β-blockers	0.02 (−0.17, 0.21)	0.84		
ACEI or ARB	−0.15 (−0.34, 0.03)	0.11		
MRA	0.37 (0.15, 0.59)	0.001	0.21 (−0.12, 0.54)	0.20
Loop diuretics	0.33 (0.13, 0.53)	0.001	0.11 (−0.22, 0.44)	0.52
Thiazide	−0.17 (−0.61, 0.27)	0.44		
Digitalis	0.52 (0.01, 1.02)	0.045	−1.28 (−2.22, −0.33)	0.008
Amiodarone	0.02 (−0.26, 0.29)	0.90		
Oral inotrope	0.30 (−0.60, 1.19)	0.52		

Abbreviations as in Tables 1,2.

LVEF, wall thickness, LV outflow obstruction, and baseline BNP concentration. This is the first report assessing the effect of sex on time-dependent changes in BNP among patients with HCM.

Several sex differences in clinical features of HCM have been reported. A Mayo Clinic study analyzing the largest database of HCM showed that females with HCM had worse outcomes than males.[6] The Tufts Institute study showed that females developed advanced HF symptoms more frequently than males.[13] Other studies showed that female sex was associated with progression to severe HF and death.[4,9,10] The results of the present study, namely that females have higher BNP concentrations not only at baseline but also at the 2-year follow-up, provide evidence supporting the sex difference in HF progression in patients with HCM. Indeed, female sex was more likely associated with a higher rate of de novo HF hospitalization (P=0.059; **Table 4**). However, it is still unclear whether higher BNP concentrations in female HCM patients affect prognosis because we were not able to collect information regarding mortality, cardiovascular events, or rehospitalization due to HF. Further investigations are needed to elucidate the relationship between sex differences in BNP and prognosis in HCM patients.

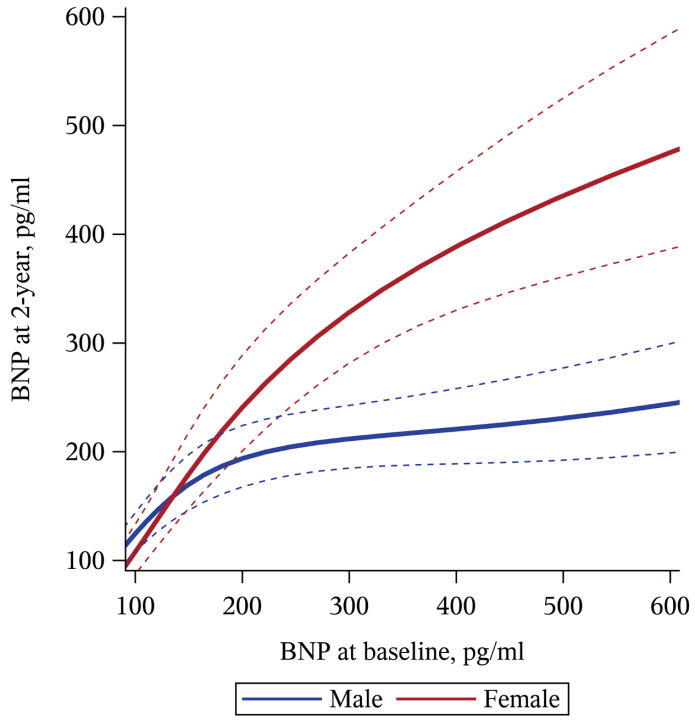

Figure 3. Cubic spline analysis of B-type natriuretic peptide (BNP) at the 2-year follow-up according to sex. Solid lines represents estimated BNP at the 2-year follow-up, with dotted lines indicating the 95% confidence interval.

Table 4. Secondary Outcomes

Outcomes	Males	Females	Odds ratio (95% CI)	P value
De novo HF hospitalization	25 (9.3)	27 (15.3)	1.75 (0.98–3.13)	0.059
New-onset atrial fibrillation	10 (4.2)	5 (2.5)	0.57 (0.19–1.71)	0.32
New-onset ventricular arrhythmia	22 (9.4)	14 (6.9)	0.71 (0.35–1.43)	0.34
New-onset stroke	5 (1.4)	4 (1.6)	1.11 (0.30–4.18)	0.88

CI, confidence interval; HF, heart failure.

It is generally known that women have higher BNP concentrations.[24] Thus, there is a possibility that what is generally said is also true in HCM patients. However, in the present study in HCM patients, we demonstrated that females had higher BNP concentrations at the 2-year follow-up than males after adjusting for baseline BNP. This finding indicates that the sex difference in BNP in HCM patients is not only a reflection of the BNP concentration at baseline.

LV diastolic dysfunction and LV mass are associated with BNP concentrations. Female patients with HCM are reported to have greater diastolic dysfunction than males.[12,25] Although E and A waves and the E/e' ratio were higher and deceleration time was longer in females than in males (**Table 1**), these factors could not be analyzed because almost half of them had missing values in the present study. Conversely, LV wall thickness and left atrial diameter, an indicator of diastolic dysfunction, were smaller in females despite their higher BNP concentrations (**Table 1**), and the BNP concentrations at the 2-year follow-up were higher in females independent of these factors (**Table 3**). Body surface area (BSA) should be considered in the evaluation of wall thickness and chamber size. However, unfortunately, the database used in this study did not have information about height, body weight, and BSA. In general, BSA is smaller in females than males.[26] Thus, LV wall thickness and left atrial diameter indexed for BSA may not be that much smaller in females than in males. To elucidate the association between these factors and sex differences in BNP, further investigations are needed.

Females are known to have a higher prevalence of the obstructive phenotype, possibly due to smaller hearts than males,[4,6,9] which could lead to more severe HF symptoms.[4,6] In the present study, the obstructive phenotype was more frequent in females (**Table 1**). However, female sex was independently associated with higher BNP concentrations at the 2-year follow-up, even after adjusting for the obstructive phenotype (**Table 2**), indicating that the obstructive phenotype does not explain sex differences in BNP concentrations.

The present study demonstrated a predominance of males in the HCM cohort (**Table 1**), which is consistent with previous studies.[4–7] Rowin et al reported that the less frequent HCM diagnosis in females was associated with a

delay in clinical recognition.[13] In addition, more severe cellular remodeling has been detected in females than males because of a more advanced disease stage at the time of treatment.[27] Therefore, disease duration is important for the evaluation of BNP concentrations. In fact, the present study demonstrated that disease duration was associated with BNP concentrations at the 2-year follow-up (**Table 3**). Nevertheless, there were no significant sex differences in the age at registration or that at the time of HCM diagnosis (**Table 1**), suggesting that the male predominance was not necessarily explained by under-recognition of HCM in females. Furthermore, although age and cardiac function affect higher BNP concentrations in females, multivariate analysis showed that females had higher BNP at the 2-year follow-up than males independent of age and LVEF (**Table 2**).

Medical treatment should also be considered because it can affect BNP. Beta-blockers are effective in HCM with LV outflow tract obstruction,[28] and ACEI/ARB lower the risk of new-onset atrial fibrillation[29] and decrease LV mass.[30] These drugs could have decreased the BNP concentrations in the present study. However, sex affected BNP concentrations at the 2-year follow-up independent of these medications (**Table 2**). Intriguingly, cubic spline analysis demonstrated that females with high BNP concentrations at baseline did not tend to have lower BNP concentrations at the 2-year follow-up compared with males. There is a possibility that females with HCM may be refractory to therapy. Although most previous studies analyzed sex differences in BNP cross-sectionally, this study provides a novel finding regarding the association of sex with longitudinal changes in BNP.

A previous study showed that the ratio of the more compliant N2BA/stiffer N2B titin isoforms was higher and interstitial fibrosis was greater in females than males.[12] The N2BA/N2B ratio has been shown to be associated with myocardial stiffness.[31–33] The switch to longer titin isoforms may be an attempt to compensate for the diastolic dysfunction. In an animal diabetic model, female rats had higher levels of compliant titin isoforms, and female sex hormones modulated titin isoform expression and collagen deposition.[34] These differences in microstructure may be related to sex differences in BNP concentrations.

The role of sex hormones in the pathogenesis of HF is also the subject of debate.[35,36] The drop in estrogen during the menopausal transition may have affected the results. Age-adjusted mortality is reduced by 2% with each increasing year of age at menopause,[37] indicating that later menopause is associated with a decreased cardiovascular risk. Interestingly, estrogenic compounds recapitulated the fibrotic, proapoptotic, and negative hemodynamic effects in male HCM mice.[38] Sex hormones are potentially involved in sex differences in BNP concentrations among HCM patients.

When the relationship between sex differences in BNP and cardiac dysfunction or prognosis among HCM patients is revealed, it may be possible to identify high-risk patients and preventive strategies for the transition to dilated phase according to sex.

Study Limitations

Several potential limitations must be acknowledged in the present study. First, we did not have information regarding mortality, cardiovascular events, or rehospitalization due to HF because the Clinical Personal Record did not contain these data. We were only able to evaluate de novo HF hospitalization, new-onset atrial fibrillation and ventricular arrhythmia, and new-onset stroke. We could not determine whether this sex difference is only a reflection of that in the general cohort or not. Further investigations are needed to elucidate the relationship between sex differences in BNP and prognosis in HCM patients.

Second, there is a difference between Europe and Japan in the diagnostic criteria for HCM. According to the 2014 European Society of Cardiology Guidelines on the Diagnosis and Management of Hypertrophic Cardiomyopathy,[39] HCM is defined by a wall thickness ≥15 mm in ≥1 LV myocardial segments that is not explained solely by loading conditions. Conversely, in the 2012 HCM Japanese guidelines, HCM is defined as an asymmetric or diffuse LV hypertrophy with reduced diastolic function in the absence of any specific cardiac or systemic diseases. In the Clinical Personal Record, certified cardiologists diagnosed HCM according to this definition, guaranteeing the accuracy of diagnosis before registration. In comparison with data in other county, the differences in diagnostic criteria should be considered.

Third, genetic testing results were lacking for most of the patients. The *MYH7*-R403Q mutation is associated with a shorter life expectancy,[40] but mutations in *MYBPC* have been shown to be associated with a later onset and milder disease characteristics,[41–43] which may affect the results of the present study. Fourth, three-quarters of patients in the Clinical Personal Record database were excluded from this study because they did not have their BNP assessed at the 2-year follow-up, which could have led to potential selection bias. The excluded patients were slightly older than those included in the study, but there were no differences in other variables, including BNP at baseline (**Supplementary Table 1**). In addition, in this cohort, BNP concentrations were higher in females than in males (median [IQR] 182.8 [86.1–363.9] vs. 320.3 [159.0–583.1] pg/mL). These findings indicate that there are no critical differences in background between the 2 groups and support our result of sex differences in BNP.

Finally, the present study is an observational study. Thus, we cannot completely exclude other unmeasured factors that may have affected outcomes, despite validation of sex differences in BNP concentrations by several sensitivity analyses.

Despite the limitations described above, we analyzed clinical characteristics and time-dependent changes in BNP concentrations using a large-scale database of HCM. This study provides important insights for better stratification and therapeutic strategies for HCM.

Conclusions

Female sex is associated with higher BNP concentrations in HCM than male sex, independent of cardiac systolic function, morphology, medical treatment, and BNP concentrations at baseline.

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Disclosures

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IRB Information

The original study protocol was approved by the Institutional Review Board at Kyushu University (No. 29-48).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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