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ORIGINAL ARTICLE
Population Science

Importance of B-Type Natriuretic Peptide in the Detection of Patients With Structural Heart Disease in a Primary Care Setting

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Background: Early detection and intervention for preclinical heart failure (HF) are crucial for restraining the potential increase in patients with HF. Thus, we designed and conducted a single-center retrospective cohort study to confirm the efficacy of B-type natriuretic peptide (BNP) for the early detection of preclinical HF in a primary care setting.

Methods and Results: We investigated 477 patients with no prior diagnosis of HF who were under the care of general practitioners. These patients were categorized into 4 groups based on BNP concentrations: Category 1, 0 pg/mL≤BNP≤35 pg/mL; Category 2, 35 pg/mL<BNP≤100 pg/mL; Category 3, 100 pg/mL<BNP≤200 pg/mL; and Category 4, BNP >200 pg/mL. There was a marked and statistically significant increase in the prevalence of preclinical HF with increasing BNP categories: 19.9%, 57.9%, 87.5%, and 96.0% in Categories 1, 2, 3, and 4, respectively. Compared with Category 1, the odds ratio of preclinical HF in Categories 2, 3, and 4 was determined to be 5.56 (95% confidence interval [CI] 3.57–8.67), 23.70 (95% CI 8.91–63.11), and 171.77 (95% CI 10.31–2,861.93), respectively.

Conclusions: Measuring BNP is a valuable tool for the early detection of preclinical HF in primary care settings. Proactive testing in patients at high risk of HF could play a crucial role in addressing the impending HF pandemic.

Key Words: B-type natriuretic peptide; Preclinical heart failure; Structural heart disease

Heart failure (HF) has become a global pandemic, with increasing prevalence, affecting an estimated 26 million people worldwide.[1,2] The overall prevalence of HF is expected to increase 2.3-fold by 2040 and 3-fold by 2060.[3] Furthermore, the mortality rate of patients with HF is 13.5% at 1 year and 43.3% at 5 years.[4] Clinical HF in particular has poor outcomes, with 5-year survival rates of 75% and 20% for Stage C and D HF, respectively.[5] The number of patients with HF is expected to increase further as the population ages.[6,7] Although the prognosis of individuals experiencing symptomatic HF is unfavorable, that of patients with structural heart disease (SHD) who lack signs or symptoms of HF is more favorable.[5] Hence, early detection and intervention in patients with HF in the asymptomatic phase, often referred to as preclinical HF, is imperative to delay progression to clinical HF. Nonetheless, patients in the preclinical stage of HF are commonly managed by general practitioners, necessitating the identification of HF in primary care settings.

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Echocardiography plays a pivotal role in identifying structural anomalies of the left ventricle (LV). Echocardiography can detect not only valvular heart disease and LV systolic dysfunction, but also LV hypertrophy, left atrial (LA) enlargement, and impaired LV systolic and diastolic performance beyond the LV ejection fraction (LVEF) owing to global longitudinal strain (GLS).[8] Thus, echocardiography is an excellent tool for detecting pre-

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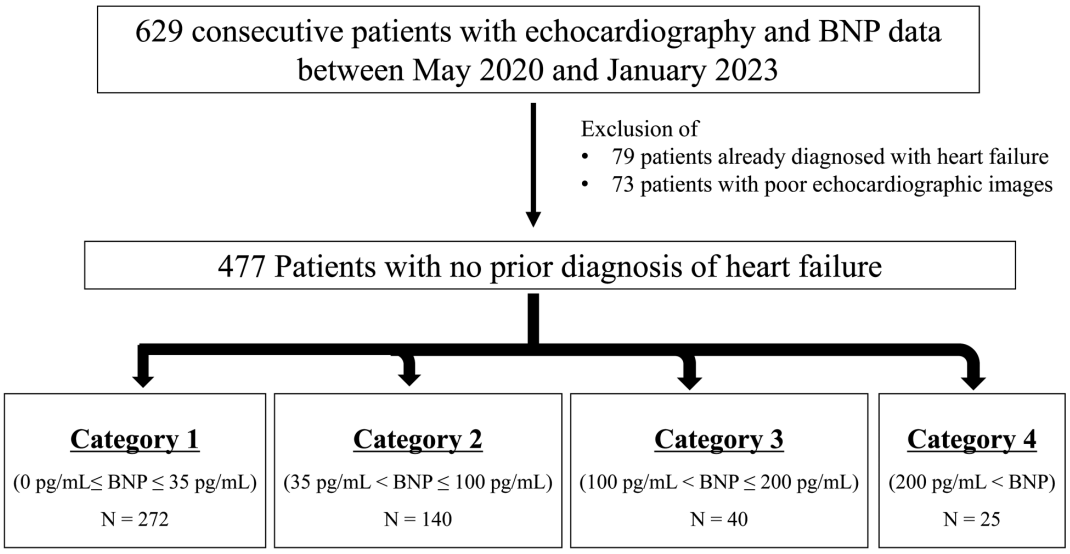

Figure 1. Flowchart of patient recruitment to this study. BNP, B-type natriuretic peptide.

clinical HF. Nonetheless, for all patients at high risk, conducting echocardiography to identify those who are at the preclinical HF stage is neither economically nor logically feasible. Echocardiography is a highly specialized procedure and performing it with high precision is often challenging for non-specialist cardiovascular practitioners.

A B-type natriuretic peptide (BNP) assay is commonly used to determine the presence and severity of HF. The measurement of BNP concentrations is easy for non-specialist cardiovascular practitioners. Along with US and European guidelines,[9,10] the Japanese Heart Failure Society has endorsed the use of BNP for the early diagnosis of HF.[11] However, evidence demonstrating the contribution of BNP to the early detection of preclinical HF in primary care settings in Japan is lacking. Therefore, we conducted a single-center retrospective cohort study to confirm the efficacy of BNP for the early detection of preclinical HF among patients in a primary care setting.

Methods

Study Population

In all, 629 consecutive patients with suspected cardiac disease who underwent simultaneous echocardiography and measurement of BNP concentrations at the Okamoto Cardiology Clinic between May 2020 and January 2023 were retrospectively enrolled in this study (**Figure 1**). Of these 629 patients, 73 were excluded owing to poor echocardiographic images and a further 79 were excluded because they had already been diagnosed with HF. Therefore, the final enrolment included 477 patients without a prior diagnosis of HF.

This study was approved by the Ethics Review Board of the Awaji Medical Center (No. 23-45) and was conducted in accordance with the Declaration of Helsinki.

Echocardiographic Examination

Echocardiography was performed using commercially available ultrasound systems (EPIQ System; Philips Medical Systems, Andover, MA, USA), and standard echocardiographic measurements were obtained in accordance with the American Society of Echocardiography.[12] Specifically, the early diastolic velocity (E) was measured by means of pulsed wave Doppler recording from the apical 4-chamber view. Spectral pulsed-wave Doppler-derived early diastolic velocity (e′) was obtained by averaging the septal and lateral mitral annulus, and the E/e′ ratio was then calculated to obtain an estimate of LV filling pressure. LV mass was estimated from the formula proposed by Devereux et al, and the LV mass index (LVMI) was calculated for each subject by dividing LV mass by body surface area. LA volume was calculated with the biplane modified Simpson's method using apical 2- and 4-chamber views at ventricular end-systole. GLS was assessed using 2-dimensional speckle-tracking longitudinal strain from 3 standard apical views with the aid of a single dedicated software program (AutoSTRAIN; Philips Medical Systems) and was expressed as an absolute value in accordance with the aforementioned current guidelines.

Measurement and Classification of Plasma BNP Concentrations

Venous blood samples were collected using a tube containing edetic acid as an anticoagulant and aprotinin to prevent the degradation of natriuretic hormones. Blood samples were collected by clinicians under standard clinical conditions. BNP was subsequently assayed using an immunochromatographic method (Rapid tip; SEKISUI, Japan).

All patients were categorized into 4 groups based on BNP concentrations. Specifically, 272 patients (57.0%) had BNP concentrations ranging from 0 to 35 pg/mL (Category 1); 140 patients (29.4%) had concentrations exceeding 35 but not 100 pg/mL (Category 2); 40 patients (8.4%) had BNP concentrations above 100 but not 200 pg/mL (Category 3); and 25 patients (5.2%) had BNP concentrations exceeding 200 pg/mL (Category 4).

Table 1. Baseline Characteristics of Patients According to BNP Category

	Category 1 (n=272)	Category 2 (n=140)	Category 3 (n=40)	Category 4 (n=25)	P value
BNP range (pg/mL)	0, ≤35	>35, ≤100	>100, ≤200	>200	
Clinical characteristics					
Age (years)	58.8±16.0	72.6±11.5*	77.3±8.7*	76.0±8.3*	<0.001
Female sex	124 (45.6)	76 (54.3)	20 (50.0)	10 (40.0)	0.317
BMI (km/m^2)	24.3±3.8	23.6±3.8	24.1±12.7	24.1±3.2	0.366
Symptom					
Shortness of breath	22 (8.1)	12 (8.6)	4 (10.0)	4 (16.0)	0.603
Edema	11 (4.0)	11 (7.9)	1 (2.5)	1 (4.0)	0.324
Hemodynamics					
Systolic BP (mmHg)	129.1±19.5	133.9±21.7	135.8±18.4	142.0±24.2*	0.003
Diastolic BP (mmHg)	70.9±13.5	68.0±13.0	67.9±12.9	77.9±19.1†,‡	0.005
Comorbidities					
Hypertension	151 (55.5)	98 (70.0)*	35 (87.5)*	21 (84.0)*	<0.001
Diabetes	40 (14.7)	23 (16.4)	9 (22.5)	3 (12.0)	0.593
Dyslipidemia	101 (37.1)	61 (43.6)	22 (55.0)	13 (52.0)	0.089
Atrial fibrillation	10 (3.7)	16 (11.4)*	13 (32.5)*,†	18 (72.0)*,†,‡	<0.001
Coronary intervention	24 (8.8)	19 (13.6)	10 (25.0)*	6 (24.0)	0.006
Obesity	21 (7.7)	7 (5.0)	2 (5.0)	1 (4.0)	0.664
Atherosclerosis	8 (2.9)	4 (2.9)	2 (5.0)	0 (0.0)	0.717
Sleep apnea syndrome	4 (1.5)	2 (1.4)	0 (0.0)	0 (0.0)	0.812
Laboratory data					
Hemoglobin (g/dL)	13.8±1.6	13.2±1.6*	13.1±1.9	13.5±1.8	<0.001
BUN (mg/dL)	14.8±4.8	17.7±5.3*	19.5±7.8*	16.8±4.0	<0.001
Creatinine (mg/dL)	0.8±0.5	0.9±0.2	1.0±0.8	0.9±0.2	0.166
Medication					
β-blocker	29 (10.7)	34 (24.3)*	10 (25.0)	11 (44.0)*	<0.001
ACEi/ARB	90 (33.1)	52 (37.1)	19 (47.5)	15 (60.0)	0.017
MRA	9 (3.3)	8 (5.7)	3 (7.5)	0 (0.0)	0.320
SGLT2i	24 (8.8)	18 (12.9)	3 (7.5)	3 (12.0)	0.562
Ca antagonist	58 (21.3)	36 (25.7)	14 (35.0)	7 (28.0)	0.247
Other diabetes drugs	28 (10.3)	18 (12.9)	6 (15.0)	2 (8.0)	0.701
Insulin	6 (2.2)	2 (1.4)	0 (0.0)	0 (0.0)	0.656

Unless indicated otherwise, data are given as the mean±SD or n (%). *P<0.05 compared with Category 1; †P<0.05 compared with Category 2; ‡P<0.05 compared with Category 3. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; MRA, mineralocorticoid receptor antagonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

Definitions of Preclinical HF and Comorbidities

Although numerous reports have addressed preclinical HF,[13] a consistent definition of preclinical HF is yet to be established.[14] In the present study, preclinical HF was defined based on the evidence of SHD. We expanded the spectrum of SHD to include not only overt conditions such as LV systolic dysfunction and valvular heart disease, but also subtle structural alterations that contribute to HF progression. These include heightened LV myocardial mass and LA enlargement, an elevated E/e′ ratio indicative of increased LA pressure, and diminished GLS as an early marker of left heart dysfunction. Finally, the definition of SHD included the following criteria: LAVI ≥34 mL/m^2 in sinus rhythm or ≥40 mL/m^2 in atrial fibrillation (AF);[13] LVMI ≥149 g/m^2 in men or ≥122 g/m^2 in women;[13] LVEF <50%; GLS <16%;[13] E/e′ ≥15;[13] or significant valvular heart disease (defined as more than moderate in severity). Obesity was operationally defined as a body mass index (BMI) ≥30 kg/m^2. Atherosclerosis was defined as a medical history indicative of treatment of a peripheral artery or aortic condition.

Statistical Analysis

Continuous variables are presented as the mean±SD or median with interquartile range (IQR) and were compared using one-way analysis of variance followed by Scheffé's post hoc analysis for normally distributed data, or the Kruskal-Wallis test followed by a Conover post hoc analysis for non-normally distributed data. Categorical variables are presented as numbers or frequencies (%) and were compared using the χ^2 test or Fisher's exact test. Associations between clinical parameters and SHD were analyzed using linear logistic regression models for univariate and multivariate analyses. To select independent variables for entry into the multivariate model, Pearson's correlation analyses between independent variables were performed in advance to avoid multicollinearity. If ≥2 variables were used to measure the pathophysiological parameters (BMI and obesity), more clinically relevant parameters were added to the model. Variables with a univariate value of P<0.05 were incorporated into the multivariate analysis. Statistical significance was set at P<0.05. All statistical analyses were conducted using MedCalc version 19.0.7

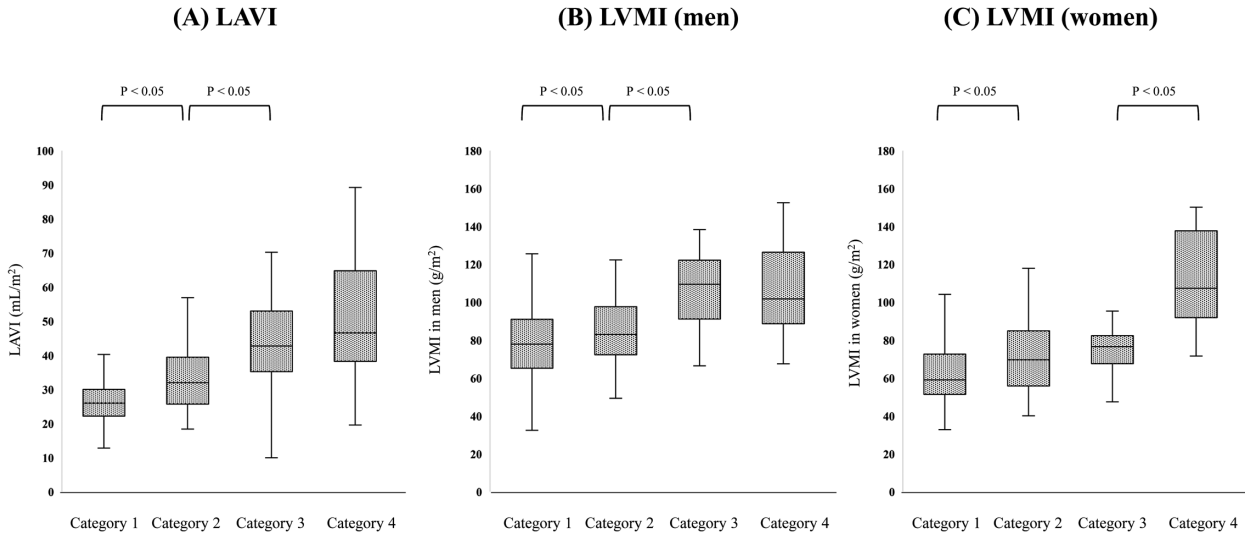

Figure 2. Box plots showing the association of B-type natriuretic peptide (BNP) categories with (**A**) left atrial volume index (LAVI), (**B**) left ventricular mass index (LVMI) in men, and (**C**) LVMI in women. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range. Category 1: 0 pg/mL≤BNP≤35 pg/mL; Category 2: 35 pg/mL<BNP≤100 pg/mL; Category 3: 100 pg/mL<BNP≤200 pg/mL; Category 4: 200 pg/mL<BNP.

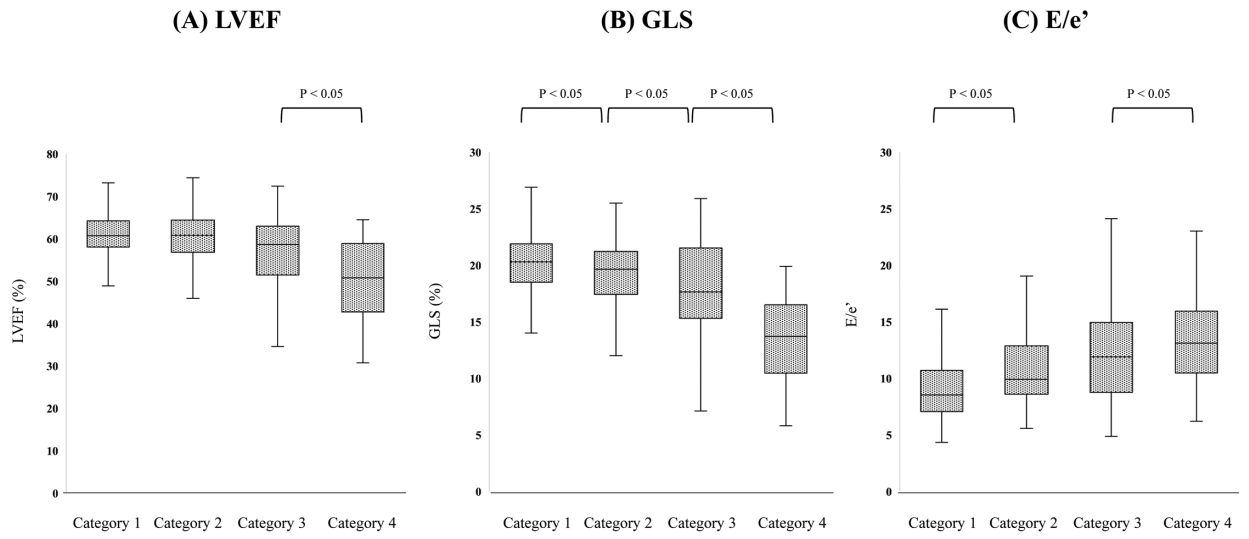

Figure 3. Box plots showing the association of B-type natriuretic peptide (BNP) categories with (**A**) left ventricular ejection fraction (LVEF), (**B**) global longitudinal strain (GLS), and (**C**) early transmitral flow velocity and early diastolic mitral annular velocity ratio (E/e′). The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range. Category 1: 0 pg/mL≤BNP≤35 pg/mL; Category 2: 35 pg/mL<BNP≤100 pg/mL; Category 3: 100 pg/mL<BNP≤200 pg/mL; Category 4: 200 pg/mL<BNP.

(MedCalc Software, Mariakerke, Belgium).

Results

Patient Characteristics

The mean age of the overall population was 65.3±15.9 years, and 48.2% of participants were women. The baseline characteristics of the 477 patients are summarized in **Table 1**. Patients in Category 1 were the youngest among all categories. The prevalence of hypertension was lowest in Category 1, and systolic blood pressure was highest in Category 4. Furthermore, an increase in the prevalence of AF was observed in patients with high BNP concentrations.

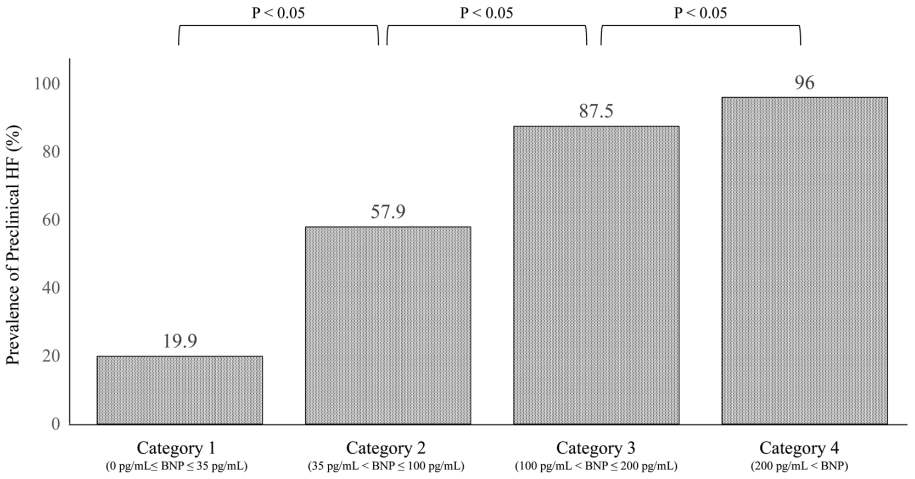

Figure 4. Prevalence of preclinical heart failure (HF) according to B-type natriuretic peptide (BNP) category.

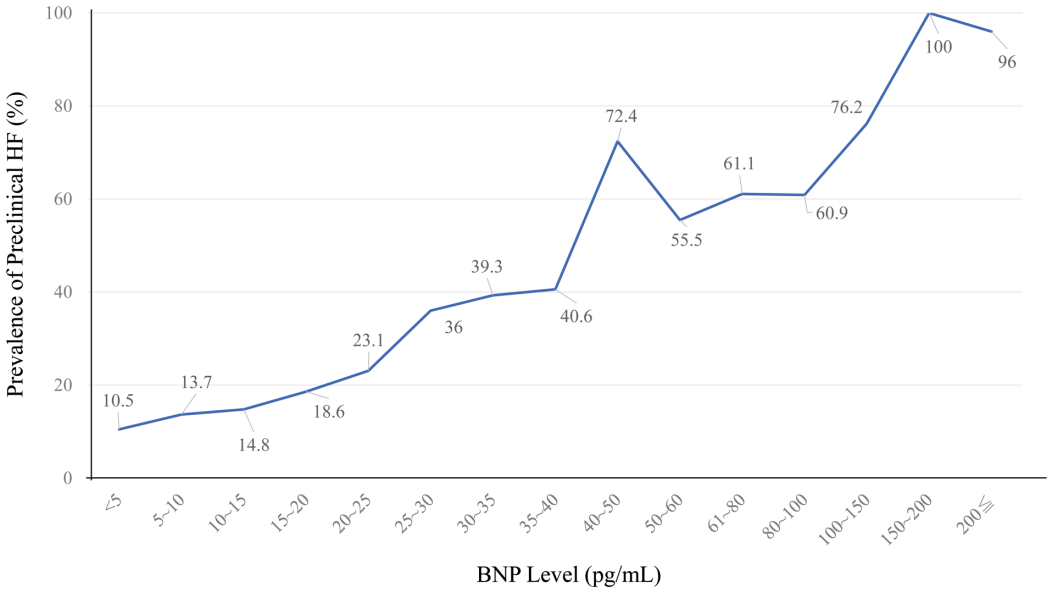

Figure 5. Prevalence of preclinical heart failure (HF) according to B-type natriuretic peptide (BNP) concentrations.

Associations of Echocardiographic Parameters With BNP Category

The associations BNP categories and both LAVI and LVMI are shown in **Figure 2**. This increase was statistically significant in comparisons between Categories 1 and 2 (P<0.01) and between Categories 2 and 3 (P<0.01; **Figure 2A**). Similarly, LVMI increased with increasing BNP concentrations, regardless of sex (**Figure 2B**,**C**). It was of note that LVMI was lowest in Category 1.

The associations between BNP category and LVEF, GLS, and E/e′ are shown in **Figure 3**. LVEF tended to decrease as BNP concentrations increased, reaching its lowest value in Category 4 (**Figure 3A**). Furthermore, GLS decreased significantly as BNP concentrations increased (**Figure 3B**). The E/e′ ratio exhibited a pattern of increasing with higher BNP categories. Category 1 consistently had the lowest E/e′ values (**Figure 3C**).

Prevalence of Preclinical HF According to BNP Category

Figure 4 shows the prevalence of preclinical HF in relation to the BNP categories. There was a marked and statistically significant increase in the prevalence of preclinical HF with increasing BNP category (19.9%, 57.9%, 87.5%, and 96.0% in Categories 1, 2, 3, and 4, respectively). We conducted a more detailed examination of this association by assessing finer increments in BNP values to further

Table 2. Univariate and Multivariate Logistic Regression Analysis for Predicting Structural Heart Disease

Covariate	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.06	1.05–1.08	<0.01	1.03	1.00–1.05	0.04
Female sex	0.77	0.53–1.11	0.16			
BMI	1.09	1.03–1.14	<0.01	1.18	1.10–1.27	<0.01
Hypertension	4.26	2.76–6.58	<0.01	1.85	0.97–3.54	0.06
Diabetes	1.73	1.05–2.83	0.03	0.77	0.34–1.71	0.52
Atrial fibrillation	5.47	2.90–10.33	<0.01	1.23	0.51–2.95	0.65
Coronary intervention	3.95	2.19–7.11	<0.01	2.44	1.08–5.51	0.03
Obesity	1.22	0.59–2.53	0.60			
Atherosclerosis	1.10	0.37–3.21	0.87			
Sleep apnea syndrome	0.73	0.13–4.01	0.71			
Hemoglobin	0.88	0.78–0.98	0.02	0.88	0.75–1.04	0.13
BUN	1.08	1.04–1.12	<0.01	0.97	0.93–1.03	0.32
Creatinine	1.71	0.93–3.17	0.09			
Log[BNP]	17.51	9.95–30.83	<0.01	15.39	7.37–32.16	<0.01
β-blocker	3.06	1.87–4.98	<0.01	1.00	0.51–1.96	0.99
ACEi/ARB	2.68	1.83–3.94	<0.01	1.29	0.71–2.33	0.40
MRA	2.83	1.11–7.23	0.03	2.63	0.74–9.32	0.13
SGLT2i	2.44	1.33–4.50	<0.01	1.84	0.72–4.67	0.20
Insulin	1.47	0.36–5.94	0.59			

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

validate the prevalence of preclinical HF (**Figure 5**). The findings demonstrated a consistent increase in the prevalence of preclinical HF as the BNP concentration increased, surpassing the 40% threshold at a BNP concentration of ≥35 pg/mL.

Predictors of SHD

Odds ratios (ORs) and 95% confidence intervals (CIs) for each variable in the univariate and multivariate logistic regression analyses for predicting SHD are listed in **Table 2**. In multivariate analysis, variables including age, BMI, history of coronary intervention, and Log[BNP] emerged as statistically significant predictors of SHD. In addition, compared with Category 1, the ORs of SHD for Categories 2, 3, and 4 were determined to be 5.56 (95% CI 3.57–8.67), 23.70 (95% CI 8.91–63.11), and 171.77 (95% CI 10.31–2,861.93), respectively.

Discussion

In this study we demonstrated that the prevalence of preclinical HF markedly and significantly increased in with increasing BNP concentrations. Furthermore, an increase in BNP category emerged as a statistically significant predictor of the development of preclinical HF.

Utility of BNP for Detecting Preclinical HF

BNP is well established as an effective tool for the early diagnosis of HF, a recommendation supported by numerous guidelines.[9–11] The Japanese Heart Failure Society recently recommended that in cases where BNP concentrations are measured during the initial diagnosis of suspected HF, further close examination should be performed if the value is ≥35 pg/mL.[15] In a meta-analysis focusing on the diagnosis of HF in an acute care setting, BNP <100 pg/mL had a sensitivity of 95% and a negative predictive value of 94%.[16] In primary care settings, the utility of measuring BNP concentrations as a rule-out test for HF in patients managed by general practitioners has been established.[17–19] Nonetheless, a substantial portion of the evidence emphasizing the utility of BNP in the primary care setting has primarily focused on its diagnostic value for patients presenting with symptoms such as shortness of breath, rather than its role in detecting SHD in asymptomatic patients, often referred to as preclinical HF.

Young et al assessed the rate of progression of preclinical HF in a study involving 413 patients with Stage B HF over a 4-year follow-up period.[20] Among the patients with Stage B HF, 6% experienced progression to clinical HF. The early detection of SHD in asymptomatic individuals is crucial to prevent eventual progression to clinical HF. One of the strengths of the present study is the inclusion of 86.2% of patients without HF-like symptoms, such as shortness of breath or edema (**Supplementary Table A**). In addition, an increase was observed in the prevalence of SHD with higher BNP concentrations. These results suggest that BNP is exceptionally valuable for detecting asymptomatic SHD in preclinical HF to prevent its progression to clinical HF.

Association of SHD in Stage B HF With Cardiovascular Events

Based on the guidelines, SHD in Stage B HF is defined as abnormal LV morphology (including LA enlargement and LV hypertrophy), LV systolic dysfunction (including low LVEF and GLS), and LV diastolic dysfunction.

For LA enlargement, LAVI >34 mL/m^2 independently predicted cardiovascular events, including cardiovascular death and HF hospitalization, in patients without AF or significant valvular heart disease.[13,21–23] In addition, LAVI ≥40 mL/m^2 in patients with AF was determined as a key factor in the diagnosis of HF with preserved ejection frac-

tion (HFpEF) according to the Heart Failure Association of the European Society of Cardiology.[13] In the present study, LAVI increased significantly as BNP concentrations increased, and the prevalence of LAVI ≥34 mL/m^2 in sinus rhythm or ≥40 mL/m^2 in AF was 11.4%, 41.4%, 77.5%, and 80.0% in Categories 1, 2, 3, and 4, respectively (**Supplementary Figure 1A**).

For LV hypertrophy, the relative risk of death was 1.22 for each 50-g/m^2 increase in LVMI in patients with HF.[24,25] Cardiovascular morbidity has also been reported to increase with LVMI in patients with hypertension.[26,27] Moreover, a cut-off value of LVMI ≥149 g/m^2 in men and ≥122 g/m^2 in women has been identified as an important factor in the diagnosis of HFpEF.[13] In the present study, the prevalence of LVMI ≥149 g/m^2 in men or ≥122 g/m^2 in women was 0.0%, 2.1%, 7.5%, and 16.0% in Categories 1, 2, 3, and 4, respectively (**Supplementary Figure 1B**).

For LV systolic dysfunction, GLS has been reported to be a more accurate and sensitive parameter than conventional cardiac functional parameters; abnormal GLS has been associated with the occurrence of cardiovascular events. Wang et al showed that GLS <16% was associated with a higher risk of developing clinical HF in 290 patients with Stage B HF.[8] In the present study, the prevalence of GLS <16% was 6.6%, 14.3%, 30.0%, and 72.0% in Categories 1, 2, 3, and 4, respectively (**Supplementary Figure 1C**).

For LV diastolic dysfunction, E/e′ reflects the mean pulmonary capillary wedge pressure,[28,29] and E/e′ >15 has also been reported as a worsening prognostic factor in patients with HFpEF.[21] Prognostic stratification by E/e′ is possible in patients with AF.[30] In the present study, the prevalence of E/e′ >15 was 5.1%, 12.9%, 22.5%, and 32.0% in Categories 1, 2, 3, and 4, respectively (**Supplementary Figure 1D**).

Clinical Implications

Identifying patients with SHD who have no prior HF diagnosis in primary care settings may play a crucial role in mitigating the increasing number of patients with clinical HF. However, screening patients for SHD in primary care settings remains challenging. In the present study, the prevalence of preclinical HF increased significantly in direct proportion to increasing BNP values. Furthermore, the ascending BNP category emerged as a statistically significant predictor of SHD in multivariate logistic regression analyses. Therefore, BNP assessment is an easy-to-use method for predicting SHD in primary care settings and could be a step towards mitigating the HF pandemic.

Study Limitations

This study has several limitations. First, it was a single-center retrospective study conducted among cardiologists, which may have introduced selection bias. An additional limitation of this study is the potential that the selected patients may not exclusively represent individuals in a pure pre-HF state. The basis for patient selection rested on suspicion of some cardiovascular disease, introducing the possibility of including individuals with mild HF symptoms. The inherent challenge arose from the absence of a definitive criterion to conclusively determine whether symptoms such as shortness of breath and swelling are unequivocally linked to cardiac issues. As a result, the categorization of asymptomatic individuals as experiencing HF became a complex and nuanced undertaking. Further studies should include similar research targeting the general population and other cohorts to validate our findings.

Another limitation of this study is the lack of a general consensus on the definition of SHD in Stage B HF. Although various studies have investigated preclinical HF, its definition varies among studies.[14] When applying the definition of Stage B HF according to the HF guidelines provided by the American Heart Association/American College of Cardiology/Heart Failure Society of America,[9] a staggering 82.0% of our study patients met the criteria for SHD, even among patients in Category 1 (**Supplementary Figure 2**; **Supplementary Table B**). This raises concerns regarding the suitability of using this definition for screening for preclinical HF in the Japanese population. Although we used the already established cut-off value for the definition of SHD in the present study, the appropriateness of the applied definition of SHD as a cut-off value for predicting the onset of symptomatic HF in the Japanese population requires further verification in separate studies.

Conclusions

BNP measurement is a valuable tool for the early detection of preclinical HF in primary care settings. Proactive testing in patients at a high risk of HF could play a crucial role in addressing the impending HF pandemic.

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Disclosures

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IRB Information

This study was approved by the Ethics Review Board of Awaji Medical Center Clinical and Translational Research Center (Reference no. 23-45).

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Supplementary Files

Please find supplementary file(s);
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