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ORIGINAL RESEARCH ARTICLE

The prognostic value of brain natriuretic peptide in patients with heart failure and left ventricular ejection fraction higher than 60%: a sub-analysis of the J-MELODIC study

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Abstract

Aims Cardiac function varies in the population of patients with heart failure (HF) with preserved left ventricular ejection fraction (LVEF; HFpEF). This study investigated the heterogeneity of clinical features associated with HF and the prognostic value of BNP levels in patients with HFpEF.

Methods and results The study enrolled 288 patients with stable HF and serum creatinine <1.5 mg/dL who were part of the original J-MELODIC study cohort. They were categorized as having HF with reduced LVEF (HFrEF; EF $\leq 40\%$, $n = 83$) or as having HFpEF (EF $> 40\%$, $n = 205$). Patients with HFpEF were further categorized as having relatively low LVEF (HFrlEF; EF 40–60%, $n = 107$) or as having relatively high LVEF (HFrhEF; EF $\geq 60\%$, $n = 98$). We defined cardiovascular death and hospitalization for HF as adverse events and evaluated the prognostic value of the BNP levels in each group. There was no significant difference in event-free survival between HFpEF and HFrEF patients or between HFrhEF and HFrlEF patients. A multivariate Cox proportional hazards model revealed that the BNP level was an independent predictor of adverse events in HFrEF patients (hazard ratio: 4.088, 95% confidence interval: 1.178–14.179, $P = 0.027$) and in HFrlEF patients (hazard ratio: 14.888, 95% confidence interval: 4.969–44.608, $P < 0.001$) but not in HFrhEF patients ($P = 0.767$).

Conclusions The BNP level has prognostic value in HFrlEF but not in HFrhEF. This indicates that HFrhEF and HFrlEF are distinct entities that may require different approaches for the management of HF.

Keywords BNP; Heart failure; Preserved LVEF; Prognosis

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Introduction

Almost half of all patients with clinical features of heart failure (HF) have preserved left ventricular ejection fraction (LVEF), and the prognosis of these patients is similar to that of patients with HF and reduced LVEF (HFrEF). Although the morbidity and mortality of patients with HFrEF have improved recently, they remain unchanged in patients with HF with preserved LVEF (HFpEF).[1,2] HFpEF patients are generally categorized according to their HF symptoms and according to LVEF $\geq 50\%$, which represents an impairment of LV diastolic function even when systolic function is normal. However, several studies in patients with HFpEF have performed detailed examinations using echocardiography and/or cardiac magnetic resonance imaging. The results demonstrated that LV systolic function is impaired in patients with much higher LVEF levels than LVEF 50%.[3–5] In addition, we previously reported loss of inertia force of late systolic aortic flow (IFLAF), which was obtained by using a catheter-tipped micromanometer in cardiac catheterization, as a predictor of development of HF in patients with preserved LVEF.[6] The existence of IFLAF is strongly dependent on LV systolic

function and through which LV relaxation is speeded.[7] Our previous findings demonstrated that the patients having less than 58% of LVEF could lose IFLAF even though they had preserved LVEF (>50%).[8] Thus, we hypothesized that patients who are commonly categorized into HFpEF may not be uniform in the clinical features associated with HF as well as in their cardiac function.

Brain natriuretic peptide (BNP) is secreted primarily from cardiac myocytes in response to changes in LV wall stress, and it acts to promote myocyte stretch. BNP levels are associated with HF severity and are a reliable predictor of prognosis throughout the stages of HF.[9–11] In addition, recent reports show that elevated BNP levels are associated with poor prognosis in patients with HFpEF as well as in those with HFrEF.[12,13] Accordingly, the current study investigated the heterogeneity of clinical features associated with HF and the prognostic value of BNP levels in patients with HFpEF. The study patients were derived from the cohort of the Japanese Multicenter Evaluation of LOng- vs. short-acting Diuretics In Congestive heart failure (J-MELODIC) trial. In addition, the correlations between the BNP levels and measured values of IFLAF were evaluated in another cohort as a supplemental analysis.

Methods

Study population and data collection

The J-MELODIC study was a multicentre, prospective, randomized, open, and blinded endpoint trial in Japan that compared the effect of long-term administration of azosemide, a long-acting loop diuretic, to that of furosemide, a short-acting diuretic, on the prognosis of patients with chronic HF. The trial design and main findings were published previously.[14,15] The study, which ran from June 2006 to August 2008, enrolled 320 patients using the following inclusion and exclusion criteria. The inclusion criteria were age 20 years or older, a clinical diagnosis of HF based on a slight modification of the Framingham criteria[16] within 6 months before study entry, New York Heart Association functional class II or III symptoms, loop diuretic(s) use, and no changes in baseline drug therapy or in HF symptoms within 1 month prior to enrolment. The exclusion criteria were uncontrolled diabetes mellitus or hypertension, serum creatinine (sCr) $>$ 2.5 mg/dL, acute coronary syndrome, an implantable cardiac defibrillator, haemodynamically significant LV outflow tract obstruction, acute myocardial infarction within the past 3 months, percutaneous coronary intervention or open heart surgery within the past 3 months, any changes in cardiovascular drug therapy within a month prior to randomization (such as the requirement of intravenous inotropes), and/or any serious non-cardiovascular disease, including malignancy. We analysed 288 patients from the J-MELODIC study cohort after excluding 32 patients who had severe renal dysfunction with sCr $\geq$ 1.5 mg/dL. We used the demographic, laboratory, and echocardiographic data at enrolment and the outcome data from the J-MELODIC study. The study endpoint was a composite of unplanned hospital admission due to acute decompensated HF and cardiovascular death. Cardiovascular death was defined in the J-MEDOLIC study as death from worsening of congestive HF, coronary artery disease, cardiac arrest, cardiac arrhythmia, myocardial infarction, stroke, or sudden death.

Study design

In this study, the patient population was divided into two groups: patients with HFrEF (LVEF $\leq$ 40%; the HFrEF group) and patients with HFpEF (LVEF $>$ 40%; the HFpEF group). Patients with HFpEF were further divided into two subgroups using 60% LVEF as a cut-off value. This is because we found previously that LVEF $\geq$ 60% was associated with the maintenance of IFLAF in patients with HFpEF. The IFLAF is a notable systolic functional parameter with predictive value for adverse events in HFpEF and is calculated from the LV pressure and the dP/dt relationship.[6–8] One subgroup consisted of patients with HF with relatively high LVEF (LVEF $\geq$ 60%; the HFrhEF group), and the other subgroup consisted of patients with relatively low LVEF (40% $<$ LVEF $<$ 60%; the HFrlEF group). This study compared the clinical backgrounds and outcomes in the HFrEF, HFrhEF, and HFrlEF groups. It also compared the impact of BNP levels on the prognosis of the patients in each study group.

This sub-analysis of the J-MELODIC study was conducted in full accordance with the Declaration of Helsinki, and it received approval from the Institutional Review Boards and Ethics Committees at all sites. The supplemental study was also performed in full accordance with the Declaration of Helsinki, and it received approval from the Institutional Review Boards of Nagoya City University Hospital, Japan.

Supplemental analysis

We conducted a supplemental analysis to clarify the pathophysiological background of the difference in the impact of BNP levels on the prognosis of patients with HFpEF between the HFrhEF and HFrlEF groups. A total of 428 patients, who received a catheterization study using a catheter-tipped micromanometer to evaluate a coronary artery disease and demonstrated LVEF $>$ 40% in left ventriculography in our institution (Nagoya City University Hospital, Japan) from April 2001 to December 2010, were enrolled in this analysis. We analysed the data of patients' clinical backgrounds including BNP and LVEF levels. In addition, from the recorded LV pressure waves, we computed the IFLAF from the LV pressure and

dP/dt relationship (phase loop) based on the theoretical basis, which was previously reported by Sugawara *et al.*[7] We devided the study patients into two subgroups; patients with rhEF (LVEF $\geq$ 60%) and those with rlEF (40% $<$ LVEF $<$ 60%). The correlations between the BNP levels and measured values of IFLAF were evaluated in the whole study patients and in these two subgroups.

Statistical analysis

Continuous data are presented as means ± standard deviation or medians (with 25th and 75th percentiles). To compare variables, the Student's unpaired *t*-test or Mann–Whitney *U* test was used between two groups and one-way analysis of variance with Tukey test or Kruskal–Wallis test was used among three groups. Categorical variables are summarized as frequencies and percentages and were compared using Pearson's χ^2 test or Fisher's exact test. A *P*-value $<$ 0.05 was considered statistically significant. A Cox proportional hazards model was used to evaluate the contributions of the clinical variables and log BNP levels to the relative hazard of experiencing the composite terminal adverse events. The model was adjusted for age, sex, azosemide use, and for selected variables that showed a significant association ($P < 0.1$) with adverse events in the univariate analysis. For the prognosis analysis, the observation period was the time from enrolment to the occurrence of a terminal adverse event or to the last censoring time point at which the patients had survived without adverse events during the follow-up period. Cumulative event-free survival was calculated with Kaplan–Meier product limit estimators. Survival curves were compared among the groups using a log-rank test. The Pearson correlation coefficient is used to measure the strength of a linear association between the BNP levels and measured values of IFLAF. The tightness

Table 1 Characteristics of patients ($n = 288$) with heart failure

	HFrEF	HFpEF		
		Total	HFrlEF	HFrhEF
	($n = 83$)	($n = 205$)	($n = 107$)	($n = 98$)
Age, years	67.1 ± 11.9	72.4 ± 10.1[a]	70.1 ± 11.0[a]	75.0 ± 8.3[a, b]
Female, *n* (%)	18 (21.7)	113 (55.1)[a]	39 (36.4)[a]	53 (54.1)[a, b]
BMI, kg/m^2	22.7 ± 3.7	23.6 ± 4.6	24.0 ± 4.6	23.2 ± 4.7
Systolic BP, mmHg	117 ± 19	128 ± 16[a]	126 ± 15[a]	130 ± 16[a]
Heart rate, beats/min	71 ± 14	71 ± 13	71 ± 13	71 ± 14
Ischaemic heart disease, *n* (%)	39 (47.0)	52 (25.4)[a]	37 (34.6)[a]	15 (15.3)[a, b]
NYHA class II/III, *n* (%)	72/11 (86.7/13.3)	186/19 (90.8/9.2)	98/9 (91.6/8.4)	88/10 (89.8/10.2)
Sodium, mmol/L	139.6 ± 2.4	140.4 ± 2.8[a]	140.3 ± 2.9	140.5 ± 2.8
Potassium, mmol/L	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.5	4.3 ± 0.4
Haemoglobin, g/dL	13.2 ± 1.6	12.7 ± 2.0[a]	13.0 ± 1.9	12.3 ± 2.0[a, b]
eGFR, mL/min/1.73m^2	60.5 ± 18.0	55.5 ± 15.7[a]	56.5 ± 17.0	54.4 ± 14.1[a]
BNP, pg/mL	137.0 (68.0, 348.5)	105.4 (47.7, 237.6)[a]	109.0 (52.7, 266.9)	100.0 (47.5, 212.0)[a]
Log BNP, pg/mL	2.152 ± 0.540	1.985 ± 0.511[a]	2.000 ± 0.550	1.970 ± 0.467
Comorbidities, *n* (%)				
Atrial fibrillation/flutter	15 (18.1)	87 (42.4)[a]	41 (38.3)[a]	46 (46.9)[a]
Hypertension	44 (53.0)	138 (67.3)[a]	69 (64.5)	69 (70.4)
Diabetes	25 (30.1)	65 (31.7)	33 (30.8)	32 (32.7)
Myocardial infarction	42 (50.6)	45 (22.0)[a]	35 (32.7)[a]	10 (10.2)[a, b]
Stroke	6 (7.2)	32 (15.6)	13 (12.1)	19 (19.4)
Echocardiographic findings				
LVEF, %	32.9 ± 6.1	58.8 ± 10.4[a]	50.4 ± 5.5[a]	67.9 ± 5.7[a, b]
LVEDD, mm	60.6 ± 8.1	51.7 ± 7.8[a]	54.5 ± 7.8[a]	48.6 ± 6.5[a, b]
IVST, mm	8.7 ± 2.1	10.2 ± 2.3[a]	9.9 ± 2.3[a]	10.5 ± 2.4[a]
LAD, mm	43.0 ± 8.1	45.4 ± 8.6[a]	45.1 ± 8.3	45.6 ± 8.9
IVC, mm	13.8 ± 4.0	15.7 ± 4.5[a]	15.2 ± 4.4	16.1 ± 4.7[a]
E/A	1.15 ± 0.88	0.91 ± 0.64	0.97 ± 0.75	0.84 ± 0.43
Medication for HF, *n* (%)				
ACE-I and/or ARB	66 (79.5)	142 (69.3)	79 (73.8)	63 (64.3)
Beta-blocker	65 (78.3)	84 (41.0)[a]	55 (51.4)[a]	29 (29.6)[a, b]
Aldsterone blocker	45 (54.2)	74 (36.1)[a]	43 (40.2)	31 (31.6)[a]
Azosemid	42 (50.6)	98 (47.8)	55 (51.4)	43 (43.9)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI , body mass index; BNP, brain natriuretic peptide; BP, blood pressure; eGFR, estimated glomerular filtration rate; E/A, ratio of E to A wave velocity of transmitral flow; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFrhEF, heart failure with relatively high ejection fraction; HFrlEF, heart failure with relatively low ejection fraction; IVC, inferior vena cava; IVST, interventricular septal thickness; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NYHA class, New York Heart Association classification of cardiac performance.
[a]Significant difference compared with the HFrEF group.
[b]Significant difference between the HFrlEF and HFrhEF groups.

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of association between the rhEF and rlEF groups was compared using Fisher's *z*-test for Pearson correlations in the supplemental analysis. All statistical analyses were performed with SPSS version 23.0 software (SPSS Japan Inc., Tokyo).

Results

Patient characteristics

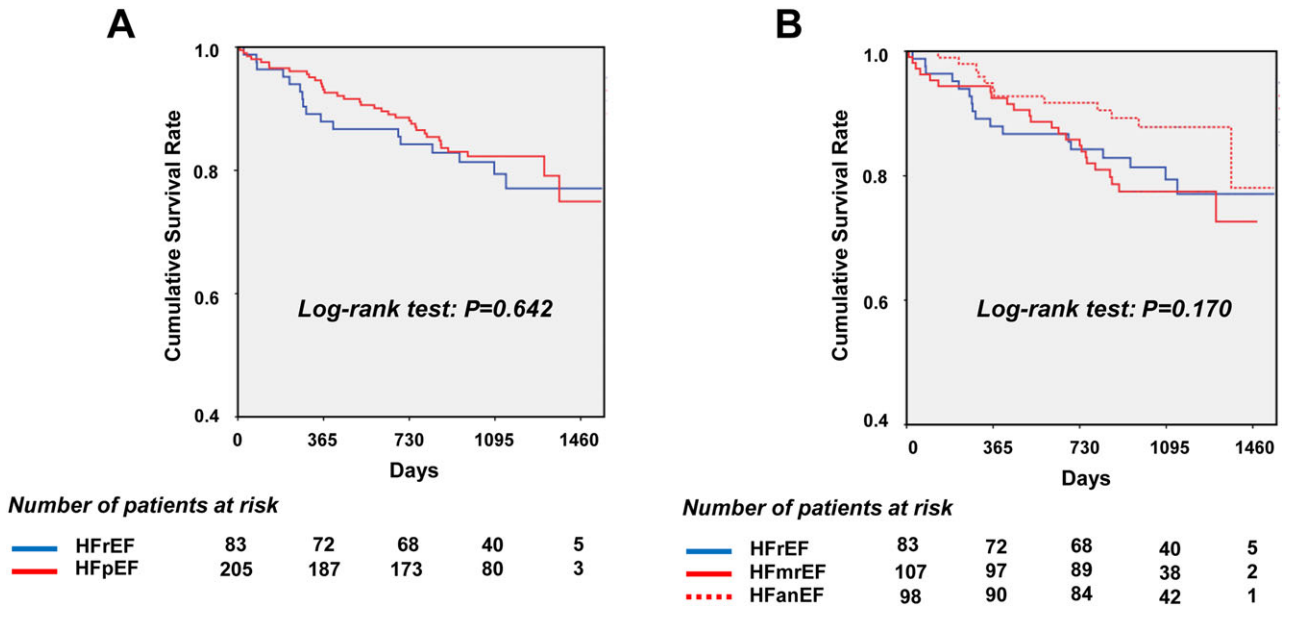
Of a total of 320 patients in the J-MELODIC study, 288 patients were enrolled in the current study, including 83 patients with HFrEF (28.8%) and 205 patients with HFpEF (71.2%). About half of the patients with HFpEF were patients with HFrlEF (n = 107, 52.2%), and the rest were patients with HFrhEF (n = 98, 47.8%). The patient characteristics at the time of enrolment are summarized in *Table 1*. Compared with patients in the HFrEF groups, those in the HFpEF group were older, more frequently female, and more frequently had atrial fibrillation and/or flutter and hypertension; these patients less frequently had ischaemic heart disease as the aetiology of HF. The BNP levels of the HFpEF group were significantly lower than those of the HFrEF group. Comparisons of the clinical backgrounds of the HFrhEF and HFrlEF groups demonstrated that patients in the HFrhEF group were older and more frequently female but that they less frequently had ischaemic heart disease as the aetiology of HF and less frequently used β-blockers. The BNP levels did not differ significantly between the HFrhEF and HFrlEF groups; however, the haemoglobin level was significantly lower in the HFrhEF group than in the HFrlEF group (12.3 ± 2.0 vs. 13.9 ± 1.9 g/dL, $P < 0.05$).

Event-free survival

There were 11 cardiovascular deaths and 42 hospitalisations for HF during the follow-up period [median follow-up period: 1045.5 days (25th and 75th percentiles: 797.5 and 1230.0, respectively)]. There were 2 cardiovascular deaths and 15 hospitalisations for HF in the HFrEF groups [median follow-up period: 1092.0 days (25th and 75th percentiles: 784.0 and 1297.5, respectively)], and there were 9 cardiovascular deaths and 27 hospitalisations in the HFpEF group [median follow-up period: 1016.0 days (25th and 75th percentiles: 802.0 and 1194.0, respectively)].

We compared the cumulative adverse event-free survival curves between the HFrEF and the HFpEF groups. There was no significant difference in event-free survival between the two groups (P = 0.642; *Figure 1A*). Furthermore, the HFrlEF group had 5 cardiovascular deaths and 19 hospitalisations for HF [median follow-up period: 985.0 days (25th and 75th percentiles: 781.5 and 1194.0, respectively)] and the HFrhEF group had 4 cardiovascular deaths and 8 hospitalisations for HF [median follow-up period: 1054.0 days

Figure 1 (A) Comparison of adverse event-free survival curves of patients with heart failure with reduced ejection fraction (HFrEF; blue line) vs. patients with heart failure with preserved ejection fraction (HFpEF; red line). Event-free survival was not significantly different in the two groups. (B) Comparison of adverse event-free survival curves in patients with HFrEF (blue line), with heart failure and relatively low ejection fraction (HFrlEF; red line), and with heart failure and relatively high ejection fraction (HFrhEF; dashed red line). Event-free survival was not significantly different in these three groups.



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(25th and 75th percentiles: 838.5 and 1191.3, respectively)]. We also compared the cumulative adverse event-free survival curves among the HFrEF, the HFrlEF, and the HFrhEF groups. There were no significant differences in event-free survival among the three groups (P = 0.170; *Figure 1B*). However, the HFrhEF group showed a tendency to have better adverse event-free survival than the HFrlEF group (P = 0.067).

Prognostic value of BNP

Table 2 shows the prognostic value of the BNP levels in each group. In the HFrEF group, a multivariate Cox proportional hazards model revealed that the log BNP level was a significant independent predictor of adverse events [hazard ratio (HR): 4.088, 95% confidence interval (CI): 1.178 to 14.179, P = 0.027) after adjusting for age, sex, azosemide use, and selected variables with significance in the univariate analysis, such as haemoglobin level, LVEF, and estimated glomerular filtration rate. Similarly, in the HFpEF group, a multivariate Cox proportional hazards model revealed that the log BNP level was a significant independent predictor of adverse events (HR: 4.632, 95% CI: 2.154 to 9.961, $P < 0.001$) after adjusting for age, sex, and selected variables with significance in the univariate analysis, such as LVEF, estimated glomerular filtration rate, and azosemide use. Furthermore, in the HFrlEF group, a multivariate Cox proportional hazards model revealed that the log BNP level was a significant independent predictor of adverse events (HR: 14.888, 95% CI: 4.969 to 44.608, $P < 0.001$) after adjusting for age, sex, LVEF, and selected variables with significance in the univariate analysis, such as azosemide use.

In contrast, in the HFrhEF group, a univariate Cox proportional hazards model revealed that age and serum sodium concentration were significantly associated with terminal adverse events, but the BNP level was not (P = 0.668). A multivariate Cox proportional hazards model revealed that serum sodium concentration was a significant independent predictor of adverse events after adjusting for age, sex, LVEF, azosemide use, and log BNP level (HR: 0.701, 95% CI: 0.572 to 0.859, P = 0.001).

Correlation between the BNP levels and measured values of inertia force of late systolic aortic flow

The patient characteristics of the supplemental analysis were shown in *Table 3*. Compared with the patients with rhEF, the patients with rlEF were significantly younger, less frequently of female sex, had significantly lower systolic blood pressure, higher BNP levels, and lower measured values of IFLAF. In addition, hyperlipidaemia was less frequently seen, and past histories of both myocardial infarction and HF were more frequently seen in the patients with rlEF. A significant negative correlation between the BNP levels and measured values of IFLAF was observed ($r = -0.319$, $P < 0.001$) in whole study patients (*Figure 2*). The tightness of such a correlation was significantly lower in the patients with rhEF ($r = -0.228$, $P < 0.001$) than in those with rlEF ($r = -0.345$, $P < 0.001$) (Fisher's z-test for Pearson correlation, $P < 0.001$) (*Figure 3*).

Discussion

There were four main findings from this study. (i) Half of the patients with HFpEF showed LVEF $\geq$ 60%. These patients were older and more frequently female, but they less frequently had ischaemic heart disease as the aetiology for HF compared with patients with HFpEF and LVEF $<$ 60%. (ii) There was no significant difference in event-free survival between patients with HFrhEF and those with HFrlEF. (iii) The BNP levels demonstrated significant prognostic value for adverse events in patients with HFrlEF but not in patients with HFrhEF. (iv) Low serum sodium levels were related to adverse events in patients with HFrhEF.

Ageing, female sex, hypertension, and atrial fibrillation are risk factors for readmission and for disease pathogenesis in HFpEF. In addition, myocardial infarction is reported to be less associated with disease pathogenesis in HFpEF than in HFrEF.[17,18] In the current study, a comparison of the characteristics of the patients in the HFpEF and HFrEF groups revealed a tendency that was in accordance with previous reports. Specifically, we found that the characteristics of patients in the HFrhEF and HFrEF groups were less similar than the characteristics of the HFrlEF and HFrEF groups. Ueda *et al.*[19] demonstrated that patients with HFpEF and LVEF $>$55% were significantly less likely to have ischaemic heart disease as an aetiology of HF compared with those with HF and 50% $<$ LVEF $\leq$ 55%. This is consistent with the results in our study. In addition, Ueda *et al.*[19] concluded that LVEF-55% in patients with HFpEF (LVEF $>$ 50%) was significantly associated with a decrease in LVEF to below 50% during a mean follow-up period of 31.5 ± 17.0 months. They suggested that patients with HF and preserved but relatively low LVEF (50% $<$ LVEF $\leq$ 55%) were distinct (in terms of HF) from those with HF and relatively high LVEF (LVEF $>$ 55%) in a group of patients with HFpEF based on the aetiology of HFpEF. In contrast, we demonstrated that patients with HF and preserved but relatively low LVEF (40% $<$ LVEF $<$ 60%) were pathophysiologically dissimilar to those with HF and relatively high LVEF (LVEF $\geq$ 60%) based on the aforementioned findings indicating that the LVEF 60% was a crucial value to determine the importance of BNP level as a predictor of future HFpEF.

We reported previously that a loss of IFLAF, which was calculated from the LV pressure and dP/dt relationship as derived from LV pressure waves obtained with a catheter-tipped micromanometer,[7] was significantly associated with adverse events in HF among patients with preserved LVEF (LVEF $\geq$ 50%).[6,8] The loss of IFLAF is highly associated with

Table 2 Baseline clinical characteristics associated with adverse events in patients (n = 288) with heart failure

	HFrEF			HFpEF			HFrlEF			HFrhEF		
	Univariate	Multivariate		Univariate	Multivariate		Univariate	Multivariate		Univariate	Multivariate	
	P value	HR (95% CI)	*P* value	*P* value	HR (95% CI)	*P* value	*P* value	HR (95% CI)	*P* value	*P* value	HR (95% CI)	*P* value
Log BNP, pg/mL	0.002	4.088 (1.178–14.179)	0.027	<0.001	4.632 (2.154–9.961)	<0.001	<0.001	14.888 (4.969–44.608)	<0.001	0.668		0.767
Age, years	0.010		0.864	0.165		0.867	0.369		0.711	0.015	1.164 (1.034–1.310)	0.012
Female sex	0.574		0.215	0.252		0.196	0.720		0.861	0.347		0.377
BMI	0.189			0.325			0.455			0.358		
Systolic BP, mmHg	0.368			0.154			0.619			0.217		
HR, beats/min	0.637			0.442			0.948			0.196		
Hb, mg/dL	0.004		0.098	0.209			0.349			0.158		
Na, mmol/mL	0.646			0.152			0.397			0.001	0.701 (0.572–0.859)	0.001
LVEF, %	0.036		0.119	0.051	0.959 (0.925–0.993)	0.020	0.530		0.585	0.613		0.421
eGFR, mL/min/1.72m^2	0.002	0.929 (0.876–0.985)	0.014	0.055		0.118	0.146			0.150		
Beta-blocker	0.351			0.126			0.126			0.791		
ACE-I/ARB	0.856			0.984			0.261			0.106		
Azosemide	0.684		0.164	0.058	0.479 (0.233–0.986)	0.046	0.060	0.371 (0.142–0.966)	0.042	0.392		0.149

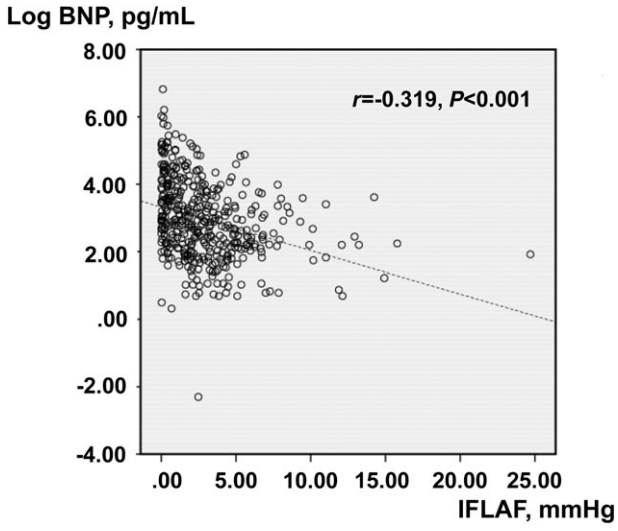
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HR, hazard ratio; HR, heart rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFrhEF, heart failure with relatively high ejection fraction; HFrlEF, heart failure with relatively low ejection fraction; LVEF, left ventricular ejection fraction; Na, sodium.

Table 3 Patients characteristics of supplemental analysis

	Whole (n = 428)	LVEF ≤ 60% (n = 117)	LVEF > 60% (n = 311)	P-value
Age, years	66.8 ± 9.4	64.1 ± 10.2	67.8 ± 8.9	<0.001
Female	108 (25.2)	20 (17.1)	88 (28.3)	0.018
BSA, m^2	1.67 ± 0.18	1.70 ± 0.17	1.66 ± 0.18	0.057
Systolic BP, mmHg	128 ± 19	122 ± 17	130 ± 18	<0.001
Heart rate, beats/min	68 ± 12	69 ± 12	67 ± 12	0.517
Haemoglobin, g/dL	13.4 ± 1.5	13.4 ± 1.5	13.4 ± 1.6	0.989
Creatine, mg/dL	0.83 ± 0.19	0.86 ± 0.20	0.82 ± 0.19	0.089
BNP, pg/mL (IQR)	17.8 (8.7, 41.3)	37.6 (16.8, 91.6)	13.5 (7.6, 28.7)	
Log BNP, pg/mL	2.95 ± 1.17	3.61 ± 1.24	2.70 ± 1.05	<0.001
IFLAF, mmHg	2.91 ± 2.91	1.29 ± 1.31	3.51 ± 3.11	<0.001
LVEF, %	66.1 ± 10.9	51.7 ± 5.4	71.5 ± 6.6	<0.001
Comorbidities, n (%)				
Hypertension	250 (58.4)	62 (53.0)	188 (60.5)	0.187
Diabetes	153 (35.7)	46 (39.3)	107 (34.4)	0.366
Hyperlipidaemia	240 (56.1)	55 (47.0)	185 (59.5)	0.022
Past history of MI	183 (42.8)	86 (73.5)	97 (31.2)	<0.001
Past history of HF	30 (7.0)	19 (16.2)	11 (3.5)	<0.001

BNP, brain natriuretic peptide; BP, blood pressure; BSA, body surface area; IFLAF, inertia force of late systolic aortic flow; IQR, interquartile range; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Figure 2 Correlation between BNP levels and measured values of inertia force of late systolic aortic flow (IFLAF) in patients with preserved left ventricular ejection fraction (n = 248, left ventricular ejection fraction > 40%).

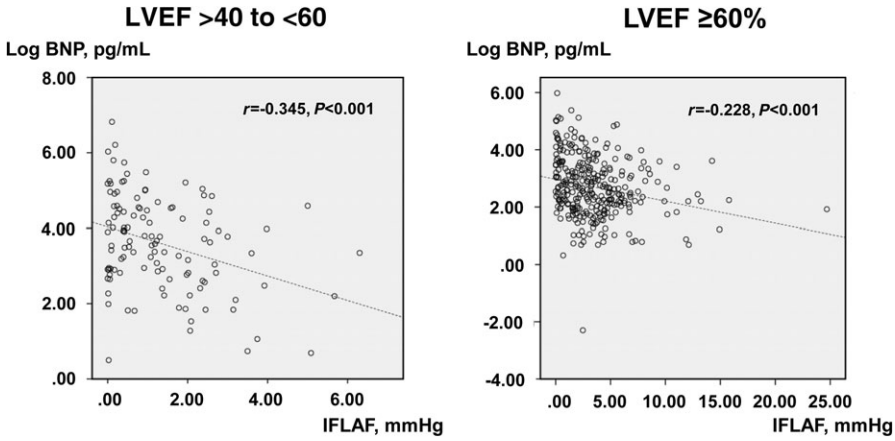


the impairment of LV relaxation because of a lack of elastic recoil at the very early phase of diastole.[7,17,20] We also demonstrated previously that LVEF < 58% could significantly predict the loss of inertia force in patients with preserved LVEF.[8] In addition, several other studies that used Doppler echocardiography or cardiac magnetic resonance have reported the impairment of systolic function in patients with LVEF levels that are much higher than 50% (up to around 60%) of LVEF in patients with preserved LVEF.[4–6,8] Therefore, in this study, we divided the patients with HFpEF into two subgroups using 60% of LVEF as a cut-off value in order to investigate differences in clinical features associated with HF in these two subgroups.

Previous data indicated that HFpEF morbidity and mortality were similar to HFrEF morbidity and mortality. Whereas survival in HFrEF has improved over the last decade, it remains unchanged, or has even worsened, in HFpEF. In addition, there are no medical treatments that convincingly improve the outcome in HFpEF.[1,21,22] In the current study, the adverse event-free survival of patients with HFpEF was similar to that of patients with HFrEF. That is consistent with previous reports. Furthermore, we found that there was a tendency for event-free survival to be better in patients with HFrhEF compared with those with HFrlEF among patients with HFpEF; however, this trend did not reach statistical significance (P = 0.067). Good systolic function of LV is observed in patients with high LVEF and should speed LV relaxation, which overcomes a substantial risk of development of HF associated with LV diastolic dysfunction.[6,7,20] This result suggests that maintaining higher LVEF in HF might improve prognosis.[23]

Plasma BNP level is reported to be a reliable predictor of poor outcome not only in HFrEF but also in HFpEF.[12,13] BNP is secreted primarily by cardiac myocytes in response to increase in LV wall stress, resulting in myocyte stretch, and the BNP level shows good correlation with LV end-diastolic pressure. BNP levels are associated with HF severity across the spectrum of HF stages.[9–11] In the current study, the BNP levels showed a significantly independent predictive value for poor prognosis in patients with HFrEF, HFpEF, and HFrlEF. In contrast, the BNP levels of patients with HFrhEF were not significantly associated with adverse events. This suggests that the BNP level loses its prognostic value in HFrhEF while maintaining prognostic value in HFrlEF. It further suggests that HFrhEF and HFrlEF are, to some extent, distinct entities in HFpEF that require different approaches to evaluate the HF status.

Figure 3 Correlation between BNP levels and measured values of inertia force of late systolic aortic flow (IFLAF) in patients with relatively low ejection fraction [n = 117, 40 < left ventricular ejection fraction (LVEF) < 60%] (left) and in patients with relatively high ejection fraction (n = 311, LVEF ≥ 60%) (right).



Our supplemental analysis demonstrated a significant negative correlation between BNP levels and measured values of IFLAF ($r = -0.319$, $P < 0.001$) in patients with preserved LVEF. Goto *et al*. reported the importance of IFLAF as a prognostic indicator in patients with preserved LVEF.[8] Furthermore, when the tightness of correlation was compared between patients with rlEF and those with rhEF, such a correlation would become significantly lower in the patients with rhEF ($r = -0.228$, $P < 0.001$) compared with those with rlEF ($r = -0.345$, $P < 0.001$). The attenuation of tightness of correlation between BNP levels and measured values of IFLAF in patients with LVEF ≥ 60% compared with those LVEF < 60% may be associated with a decrease in prognostic value of BNP levels in patients with HFrhEF.

Notably, a multivariate Cox proportional hazards model revealed that hyponatraemia was significantly associated with adverse events in patients with HFrhEF. In a recent report, Kusaka *et al*.[24] demonstrated that the serum sodium level was independently correlated with future HF-related events in HFpEF. The authors concluded that pathophysiological conditions were different in HF patients with vs. without hyponatraemia. Here, we found that hyponatraemia was associated with adverse events in patients with HFrhEF, which is consistent with the report of Kusaka *et al*.[24] Hyponatraemia is an electrolyte abnormality that is commonly observed in patients with HF and that indicates poor prognosis in HF.[25,26] Fluctuations in the serum sodium concentration are regulated through the secretion of antidiuretic hormone (ADH), and the increased ADH secretion in HF induces water retention in renal tubules, resulting in hypervolemic hyponatraemia.[27,28] Activation of the ADH axis, which is a predominant neurohormonal activation in the pathogenesis of HF,[29] is observed in patients with HFpEF as well as in those with HFrEF.[30] Hyponatraemia may be associated with worsening of HFrhEF through the mechanism that causes increased ADH secretion in HF.[31]

This study had several limitations. First, our study was a retrospective analysis of data from the J-MELODIC study. The J-MELODIC study cohort showed stable HF, and the participants received loop diuretic therapy. Therefore, we only analysed patients who required loop diuretic therapy for their HF symptoms. Second, we investigated a small cohort that had a limited number of adverse events. To strengthen our conclusion, a prospective study is needed that has a larger study cohort and that includes patients with HF who are not receiving loop diuretics therapy for HF. Finally, we did not address any changes in LVEF during the course of each patient's illness, and we did not investigate the association between changes in LVEF and prognosis.

In conclusion, the differences in clinical characteristics and in the relationships between the BNP levels and prognostic value for adverse events indicate that HFrhEF (LVEF ≥ 60%) and HFrlEF (40% <LVEF < 60%) have some distinct clinical and pathophysiological characteristics even though both are categorized as HFpEF.

Conflict of interest

None declared.

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