



Factors Associated With Elevated N-Terminal Pro B-Type Natriuretic Peptide Concentrations at the Convalescent Stage and 1-Year Outcomes in Patients With Heart Failure With Preserved Ejection Fraction

Bolrathanak Oeun, MD; Daisaku Nakatani, MD, PhD; Shungo Hikoso, MD, PhD; Takayuki Kojima, MD; Tomoharu Dohi, MD, PhD; Tetsuhisa Kitamura, MD; Katsuki Okada, MD, PhD; Akihiro Sunaga, MD; Hirota Kida; Takahisa Yamada, MD, PhD; Masaaki Uematsu, MD, PhD; Yoshio Yasumura, MD, PhD; Yoshiharu Higuchi, MD, PhD; Toshiaki Mano, MD, PhD; Yoshiyuki Nagai, MD, PhD; Hisakazu Fuji, MD, PhD; Hiroya Mizuno, MD, PhD; Yasushi Sakata, MD, PhD for the Osaka CardioVascular Conference (OCVC) Heart Failure Investigators

Background: Little is known about factors associated with elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) at the convalescent stage and their effects on 1-year outcomes in patients with heart failure with preserved ejection fraction (HFpEF).

Methods and Results: This study included 469 patients with HFpEF. Elevated NT-proBNP was defined as the highest quartile. The first 3 quartiles (Q1–Q3) were combined together for comparison with the fourth quartile (Q4). Median NT-proBNP concentrations in Q1–Q3 and Q4 were 669 and 3,504 pg/mL, respectively. Multivariate logistic regression analysis revealed that low albumin (odds ratio [OR] 2.44; 95% confidence interval [CI] 1.35–4.39; $P=0.003$), low estimated glomerular filtration rate (OR 5.83; 95% CI 3.46–9.83; $P<0.001$), high C-reactive protein (OR 2.09; 95% CI 1.21–3.63; $P=0.009$), and atrial fibrillation at discharge (OR 2.33; 95% CI 1.40–3.89; $P=0.001$) were associated with elevated NT-proBNP. Cumulative rates of all-cause mortality and heart failure rehospitalization were significantly higher in Q4 than in Q1–Q3 ($P=0.001$ and $P<0.001$, respectively). Incidence and hazard ratios of these adverse events increased when the number of associated factors for elevated NT-proBNP clustered together ($P<0.001$ and $P=0.002$, respectively).

Conclusions: In addition to atrial fibrillation, extracardiac factors (malnutrition, renal impairment and inflammation) were associated with elevated NT-proBNP at the convalescent stage, and led to poor prognosis in patients with HFpEF.

Key Words: Heart failure with preserved ejection fraction (HFpEF); N-terminal pro B-type natriuretic peptide (NT-proBNP); Prognosis

N-terminal pro B-type natriuretic peptide (NT-proBNP), a hormone secreted by cardiomyocytes in response to cardiac wall stress and volume overload, has been widely used to establish the presence and severity of heart failure (HF).^{1,2} HF with preserved ejection fraction (HFpEF) accounts for almost half of all HF patients and has a poor prognosis, as does HF with reduced ejection fraction (HFrEF).^{3–5} To date, unlike in the case of

HFrEF, no definitive therapeutic strategies have been shown to be effective in reducing morbidity or mortality in patients with HFpEF.^{2,6} Previous studies have shown that elevated NT-proBNP or an increase in NT-proBNP concentrations from baseline have prognostic significance and can predict cardiovascular mortality and rehospitalization for HF.^{7–9} A recent study in the general working Japanese population indicated that plasma concentrations

Received May 20, 2020; accepted May 20, 2020; J-STAGE Advance Publication released online July 7, 2020 Time for primary review: 1 day

Department of Cardiovascular Medicine (B.O., D.N., S.H., T. Kojima, T.D., K.O., A.S., H.K., H.M., Y.S.), Department of Environmental Medicine and Population Sciences (T. Kitamura), Osaka University Graduate School of Medicine, Suita; Division of Cardiology, Osaka General Medical Center, Osaka (T.Y.); Division of Cardiology, National Hospital Organization, Osaka National Hospital, Osaka (M.U.); Division of Cardiology, Amagasaki Chuo Hospital, Amagasaki (Y.Y.); Division of Cardiology, Osaka Police Hospital, Osaka (Y.H.); Division of Cardiology, Kansai Rosai Hospital, Amagasaki (T.M.); Division of Cardiology, Rinku General Medical Center, Izumisano (Y.N.); and Division of Cardiology, Kobe Ekisaikai Hospital, Kobe (H.F.), Japan
The Osaka CardioVascular Conference (OCVC) Heart Failure Investigators are listed in the **Appendix**.

Mailing address: Daisaku Nakatani, MD, PhD, Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita 565-0871, Japan. E-mail: nakatani@cardiology.med.osaka-u.ac.jp

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cr@j-circ.or.jp

ISSN-2434-0790



of NT-proBNP were positively associated with age, female sex, systolic blood pressure, pulse pressure, hypertension, proteinuria, and high-density lipoprotein cholesterol.¹⁰ Indeed, in some patients admitted with acute decompensated HF NT-proBNP concentrations remain remarkably elevated even at the convalescent stage. The higher the NT-proBNP concentration at discharge, the worse the prognosis.^{11,12} A reduction in NT-proBNP of <30% during hospitalization was shown to be associated with a higher mortality rate than a reduction of ≥30%.¹¹ In addition, the 2017 American College of Cardiology and American Heart Association recommend measurement of B-type natriuretic peptide (BNP) or NT-proBNP concentrations to establish prognosis in patients with HF.² To date, however, we are unaware of any study that has determined factors associated with elevated NT-proBNP at discharge and their prognostic value, particularly in patients with HFpEF. It is therefore clinically important to identify these factors, hereinafter referred to as “risk factors”, when aiming to clarify appropriate interventions to improve prognosis in patients with HFpEF.

The PURSUIT-HFpEF registry is a Prospective multicenter observational study of patients with Heart Failure with preserved Ejection Fraction in the Kansai region of Japan that collects demographic, therapeutic, and outcome data for patients with HFpEF. Using this database, the aim of the present study was to investigate the factors associated with elevated NT-proBNP at discharge and their effects on 1-year clinical outcomes in real-world patients admitted to hospital with acute decompensated HFpEF (ADHFpEF).

Methods

PURSUIT-HFpEF Registry

The PURSUIT-HFpEF study is a prospective multicenter observational study of patients with HFpEF. It is a large-scale registry conducted through a collaboration between Osaka University Hospital and 31 other hospitals in the Kansai region of Japan (UMIN Clinical Trials Registry ID: UMIN00021831).¹³ The aim of the PURSUIT-HFpEF Registry is to collect and analyze data on patient characteristics, including demographics, echocardiography, blood samples, and therapeutic procedures, as well as clinical outcomes to identify the pathophysiology, prognostic factors, and prognosis of patients with HFpEF. Research cardiologists and trained research nurses in each participating hospital are encouraged to input data of patients admitted due to ADHFpEF into an electronic data collection system. The data collected are then transferred to the data center of Osaka University Hospital, Suita, Japan, for processing and analysis. Patients enrolled in the Registry are followed-up annually for 5 years after discharge. If patients do not have a follow-up visit after discharge, the primary physician at each hospital attempts to call the patient to collect follow-up data. In cases where contact cannot be established, personal data is transferred to the secretariat office at Osaka University Hospital in order to confirm whether the patient is alive. The secretariat at Osaka University Hospital attempts to check the Annual Mortality in Japan database provided by Ministry of Health, Labour and Welfare of Japan. If a patient has died, the date and cause of death can be obtained from the Annual Mortality in Japan database.

Informed consent to have patient information entered

into the registry for use in research studies was obtained from each participant or his or her relatives. The protocol of the present study was reviewed and approved by the institutional review board of each participating institution.

The diagnosis of ADHFpEF was based on the Framingham Heart Failure criteria, namely: (1) left ventricular ejection fraction (LVEF) ≥50% by echocardiography on admission; and (2) NT-proBNP ≥400 pg/mL or BNP ≥100 pg/mL on admission.

Of note, all data, including laboratory and echocardiographic data, in this analysis were obtained during the recovery stage and were measured just before patient discharge.

Study Population

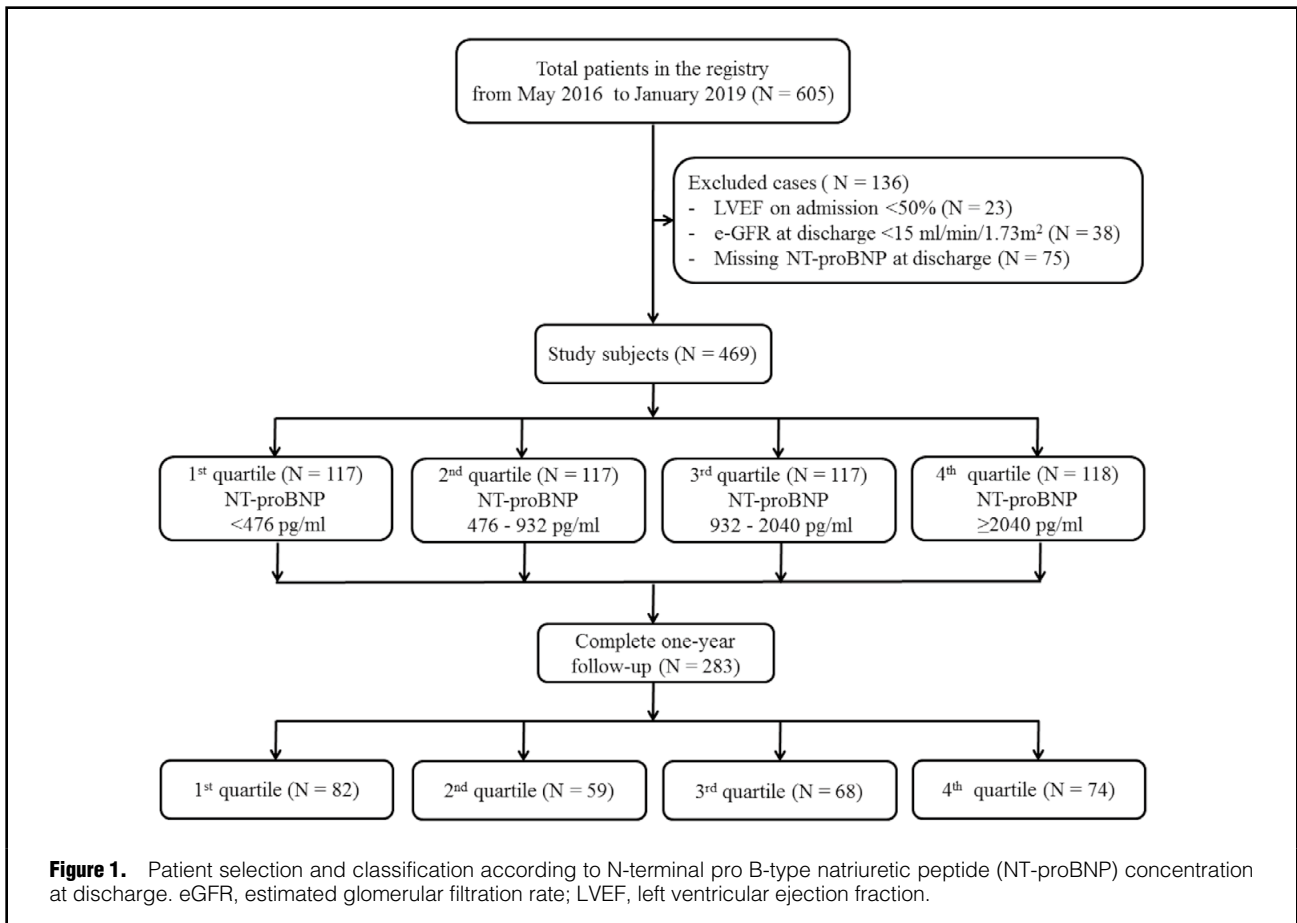
In all, 605 consecutive patients were enrolled in the Registry between May 2016 and January 2019. Those patients with LVEF on admission <50%, severe renal impairment with estimated glomerular filtration rate (eGFR) at discharge <15 mL/min/1.73 m², and those without NT-proBNP data at discharge were excluded from this study. Patients were grouped into quartiles according to NT-proBNP concentration measured just before discharge. The first 3 quartiles were then grouped together (Q1–Q3) to allow comparison with the fourth quartile (Q4), which was defined as elevated NT-proBNP at the recovery stage.

Statistical Analysis

Continuous variables are expressed as the median with interquartile range (IQR) and were compared using non-parametric Mann-Whitney U-tests. Chi-squared tests were used to compare categorical variables, which are expressed as absolute values and percentages. NT-proBNP concentrations in each group are presented as the median with IQR because of a skewed distribution.

To explore factors associated with elevated NT-proBNP, univariate and multivariate logistic regression analyses were performed using the stepwise backward elimination method with a probability for entry of 0.05 and a probability for removal of 0.10. Variables included in the multivariate model included variables with $P < 0.10$ on univariate analysis, and factors of clinical importance in the elevation of NT-proBNP. Because of the limited number of subjects in the study, we eventually decided to choose the following variables as covariates: age, female sex, body mass index (BMI; <19 kg/m², dichotomized by the lowest quartile), hemoglobin (<10 g/dL, dichotomized by the lowest quartile), eGFR (<33 mL/min/1.73 m², dichotomized by the lowest quartile), serum albumin (<3.1 g/dL, dichotomized by the lowest quartile), C-reactive protein (CRP; ≥0.78 mg/dL, dichotomized by the highest quartile), proteinuria, atrial fibrillation (AF) at discharge, and New York Heart Association (NYHA) functional class ≥2 at discharge.

Kaplan-Meier survival curves were constructed for the cumulative event rates of all-cause mortality and HF rehospitalization during the 1-year follow-up stratified by the highest quartile (Q4) of NT-proBNP vs. the combined first, second, and third quartiles (Q1–Q3) of NT-proBNP, as well as by the number of risk factors for elevated NT-proBNP. Log-rank tests were performed to detect statistically significant differences. Because only a very small number of patients had all 4 identified risk factors for elevated NT-proBNP, these patients were grouped with those with 3 risk factors. Multivariate Cox regression analysis was performed to clarify whether the factors



associated with elevated NT-proBNP were associated with an increased risk of all-cause death and HF readmission. Furthermore, hazard ratios (HR) and 95% confidence intervals (CI) of clinical outcomes were calculated according to the number of identified risk factors clustered together, taking patients without the risk factor as the reference group with an HR of 1. The relationship between the number of risk factors and outcomes was examined using non-parametric correlation.

Two-sided $P < 0.05$ was considered significant. All analyses were performed using SPSS statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Of 605 consecutive patients enrolled in the PURSUIT-HFpEF Registry, 469 met the inclusion criteria for this study. Median (IQR) NT-proBNP concentrations in Q1 ($n=117$), Q2 ($n=117$), Q3 ($n=117$), and Q4 ($n=118$) were 282 (177–365), 699 (589–818), 1,362 (1,192–1,665), and 3,504 (2,660–5,731) pg/mL, respectively (**Figure 1**). After the first 3 quartiles were grouped, the median (IQR) NT-proBNP for 351 patients in Q1–Q3 was 669 (369–1,191) pg/mL.

Baseline characteristics for patients in Q1–Q3 vs. those in Q4 of NT-proBNP concentrations are given in **Table 1**. Patients in Q4 were more likely to be older and had a significantly higher prevalence of prior HF hospitalization, chronic kidney disease, AF at discharge, proteinuria, and

NYHA Class ≥ 2 than patients in Q1–Q3. In contrast, the proportion of patients with hypertension, diabetes, and dyslipidemia was comparable between the 2 groups. Patients in Q4 had significantly lower hemoglobin, eGFR, and albumin levels, but significantly higher CRP levels. Patients with elevated NT-proBNP were more likely to stay longer in hospital than patients without elevated NT-proBNP. Echocardiographic data revealed that left atrial diameter, left atrial volume index, and indices of wall thickness, including interventricular septal thickness at end-diastole, left ventricular posterior wall thickness at end-diastole, and left ventricular mass index, were significantly higher in patients with elevated NT-proBNP. With regard to medications used at discharge, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and calcium channel blockers were less frequently prescribed for patients in Q4 of NT-proBNP. In contrast, β -blockers and diuretics were prescribed more frequently for patients in Q4 (**Table 1**).

Univariate logistic regression analyses of factors associated with elevated NT-proBNP concentrations measured just before discharge revealed that age, low hemoglobin, low eGFR, low albumin, elevated CRP, proteinuria, AF at discharge, and NYHA Class ≥ 2 at discharge were individual predictors of elevated NT-proBNP (**Table 2**). Multivariate logistic regression analysis revealed that low eGFR, low albumin level, elevated CRP, and the presence of AF at discharge were independently associated with elevated NT-proBNP concentrations during the recovery stage in patients admitted with ADHFpEF (**Table 2**).

	NT-proBNP quartiles			P-value
	Q1–Q3 (n=351)	Q4 (n=118)	Total (n=469)	
NT-proBNP (pg/mL)	669 [369–1,191]	3,504 [2,660–5,731]	932 [476–2,040]	
Age (years)	82 [76–86]	84 [77–89]	82 [76–87]	0.007
Female sex	193 (55.0)	62 (52.5)	255 (54.4)	0.645
Body mass index (kg/m²)	21.7 [18.8–24.4]	20.8 [19.0–23.4]	21.5 [18.8–24.1]	0.104
SBP (mmHg)	118 [107–130]	117 [101–130]	118 [106–130]	0.173
DBP (mmHg)	64 [57–72]	65 [58–72]	64 [57–72]	0.455
Heart rate (beats/min)	68 [61–78]	72 [62–80]	69 [61–79]	0.074
Medical history				
Prior HF hospitalization	74 (21.4)	50 (44.6)	124 (27.1)	<0.001
Hypertension	295 (84.3)	97 (82.2)	392 (83.8)	0.596
Diabetes	115 (33.2)	39 (33.1)	154 (33.2)	0.970
Dyslipidemia	147 (42.5)	42 (35.6)	189 (40.7)	0.188
Prior MI	23 (6.6)	11 (9.5)	34 (7.3)	0.308
CKD	103 (29.5)	70 (59.8)	173 (37.1)	<0.001
AF				
At admission	145 (41.3)	58 (49.2)	203 (43.3)	0.137
At discharge	120 (34.2)	56 (47.5)	176 (37.5)	0.010
Blood test results at discharge				
White blood cells (×10 ⁹ /μL)	5.4 [4.5–6.8]	5.6 [4.5–7.2]	5.5 [4.5–6.9]	0.289
Hemoglobin (g/dL)	11.5 [10.2–13.0]	11.0 [9.6–12.4]	11.3 [10.1–12.8]	0.019
eGFR (mL/min/1.73 m ²)	45.4 [35.9–58.7]	33.3 [23.6–44.4]	43.7 [33.0–55.4]	<0.001
Albumin (g/dL)	3.5 [3.2–3.8]	3.3 [2.9–3.6]	3.4 [3.1–3.8]	<0.001
AST (U/L)	23 [18–31]	23 [17–31]	23 [18–31]	0.826
ALT (U/L)	17 [11–26]	15 [10–22]	16 [11–24]	0.041
HbA1c (%)	5.9 [5.6–6.5]	5.9 [5.6–6.7]	5.9 [5.6–6.5]	0.817
CRP (mg/dL)	0.22 [0.10–0.60]	0.42 [0.16–1.39]	0.27 [0.10–0.79]	0.001
Proteinuria	114 (33.8)	55 (50.0)	169 (37.8)	0.002
NYHA Class ≥2	210 (60.2)	83 (70.9)	293 (62.9)	0.037
Length of stay (days)	16 [12–21]	18 [14–25]	16 [13–22]	0.004
Echocardiographic parameters at discharge				
LAD (mm)	43.0 [38.0–48.0]	44.0 [40.8–50.0]	44.0 [39.0–49.0]	0.039
LAVI (mL/m ²)	39.0 [30.0–52.0]	44.0 [37.0–59.0]	41.0 [32.0–53.0]	0.001
Mean E/e'	12.0 [9.6–15.6]	13.5 [9.9–18.3]	12.2 [9.6–16.3]	0.067
LVDd (mm)	45.0 [41.0–49.9]	44.0 [39.7–49.0]	45.0 [40.2–49.7]	0.115
IVSTd (mm)	9.7 [8.4–11.0]	10.0 [9.0–12.0]	10.0 [8.5–11.0]	0.019
LVPWTd (mm)	9.5 [8.3–11.0]	10.0 [9.0–11.1]	9.7 [8.4–11.0]	0.033
LVMI (g/m ²)	98.4 [79.4–119.1]	103.2 [88.3–129.4]	100 [82.4–120.2]	0.029
LVEF (%)	66 [60–70]	63 [57–71]	65 [59–70]	0.187
Medications at discharge				
ACEI/ARBs	212 (60.4)	45 (38.1)	257 (54.8)	<0.001
Calcium channel blockers	177 (50.4)	45 (38.1)	222 (47.3)	0.021
β-blockers	170 (48.4)	82 (69.5)	252 (53.7)	<0.001
Diuretics	285 (81.2)	107 (90.7)	392 (83.6)	0.016
Statins	111 (31.6)	42 (35.6)	153 (32.6)	0.426

Patients were stratified according to NT-proBNP concentrations at discharge; those in the first three quartiles (Q1–Q3) were combined and compared with those in the fourth quartile (Q4). Unless indicated otherwise, data are given as n (%) or as the median [interquartile range]. ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ALT, alanine aminotransferase; ARBs, angiotensin II receptor blockers; AST, aspartate aminotransferase; CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; IVSTd, interventricular septal thickness at end-diastole; LAD, left atrial diameter; LAVI, left atrial volume index; LVDd, left ventricular diameter at end-diastole; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LVPWTd, left ventricular posterior wall thickness at end-diastole; MI, myocardial infarction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro B-type natriuretic peptide; SBP, systolic blood pressure.

Of the entire study population, 283 patients completed the 1-year follow-up. All adverse clinical outcomes, including rehospitalization for HF, all-cause death, cardiac death, and non-cardiac death, were more frequent in patients in Q4 than in those in Q1–Q3 of NT-proBNP (Table 3).

Kaplan-Meier curves showed that the cumulative rates of all-cause mortality and rehospitalization for HF were significantly higher in patients with than without elevated NT-proBNP (log-rank test, $P=0.001$ and $P<0.001$, respectively; Figure 2). Multivariate Cox regression analyses

Table 2. Factors Associated With Elevated NT-proBNP as Determined by Univariate and Multivariate Logistic Regression Analysis

	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.04	1.01–1.06	0.007	–	–	–
Female sex	0.91	0.60–1.38	0.645	–	–	–
Body mass index <19 kg/m ²	0.91	0.56–1.47	0.701	–	–	–
Hemoglobin <10 g/dL	1.67	1.05–2.67	0.032	–	–	–
eGFR <33 mL/min/1.73 m ²	4.75	2.99–7.53	<0.001	5.83	3.46–9.83	<0.001
Albumin <3.1 g/dL	2.86	1.76–4.64	<0.001	2.44	1.35–4.39	0.003
CRP ≥0.78 mg/dL	2.35	1.50–3.70	<0.001	2.09	1.21–3.63	0.009
Proteinuria	1.96	1.26–3.03	0.003	–	–	–
AF	1.74	1.14–2.66	0.010	2.33	1.40–3.89	0.001
NHYA Class ≥2	1.62	1.03–2.54	0.038	–	–	–

Body mass index <19 kg/m², hemoglobin <10 g/dL, eGFR <33 mL/min/1.73 m², and serum albumin <3.1 g/dL were dichotomized using their lowest quartiles, whereas CRP ≥0.78 mg/dL was dichotomized using its highest quartile. All data were obtained just before discharge. CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

Table 3. Clinical Outcomes at 1-Year

	NT-proBNP quartiles			P-value ^A
	Q1–Q3 (n=209)	Q4 (n=74)	Total (n=283)	
HF rehospitalization	17 (8.1)	20 (27.0)	37 (13.1)	<0.001
All-cause death	14 (6.7)	15 (20.3)	29 (10.2)	0.001
Cardiac death	6 (2.9)	8 (10.8)	14 (4.9)	0.005
Non-cardiac death	8 (3.8)	7 (9.5)	15 (5.3)	0.046

Patients were stratified according to NT-proBNP concentrations at discharge; those in the first three quartiles (Q1–Q3) were combined and compared with those in the fourth quartile (Q4). Unless indicated otherwise, data show the number of patients in each group, with percentages in parentheses. ^ALog-rank test. Abbreviations as in Table 1.

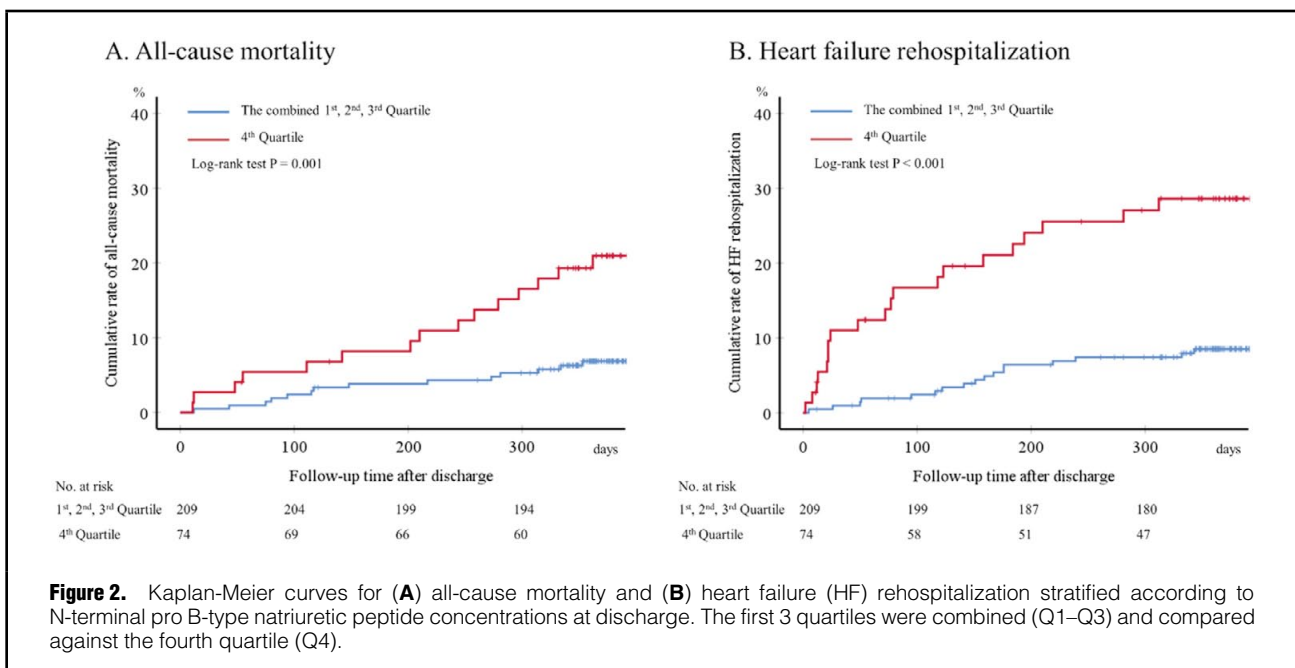


Figure 2. Kaplan-Meier curves for (A) all-cause mortality and (B) heart failure (HF) rehospitalization stratified according to N-terminal pro B-type natriuretic peptide concentrations at discharge. The first 3 quartiles were combined (Q1–Q3) and compared against the fourth quartile (Q4).

showed that albumin at discharge <3.1 g/dL was an independent predictor for all-cause death, but not for HF hospitalization, when variables related to elevated NT-proBNP and log-transformed NT-proBNP were included in the model (Table 4).

Using patients without risk factors for elevated NT-proBNP as the reference (HR=1), the frequency and HRs of 1-year clinical outcomes, including all-cause mortality (log-rank test, P<0.001; Figure 3A) and rehospitalization for HF (log-rank test, P=0.002; Figure 3B), increased

	All-cause death			HF rehospitalization		
	HR	95% CI	P-value	HR	95% CI	P-value
AF at discharge	1.12	0.49–2.56	0.793	0.96	0.48–1.94	0.914
eGFR at discharge <33 mL/min/1.73 m ²	0.94	0.36–2.45	0.896	0.99	0.43–2.27	0.987
Albumin at discharge <3.1 g/dL	2.68	1.16–6.18	0.021	0.93	0.41–2.13	0.864
CRP at discharge ≥0.78 mg/dL	1.88	0.85–4.18	0.122	1.65	0.80–3.39	0.172
Log NT-proBNP	2.91	1.15–7.32	0.024	7.02	3.09–15.93	<0.001

Cut-off values are the same as given in Table 2. All data were obtained just before discharge. HR, hazard ratio. Other abbreviations as in Tables 1,2.

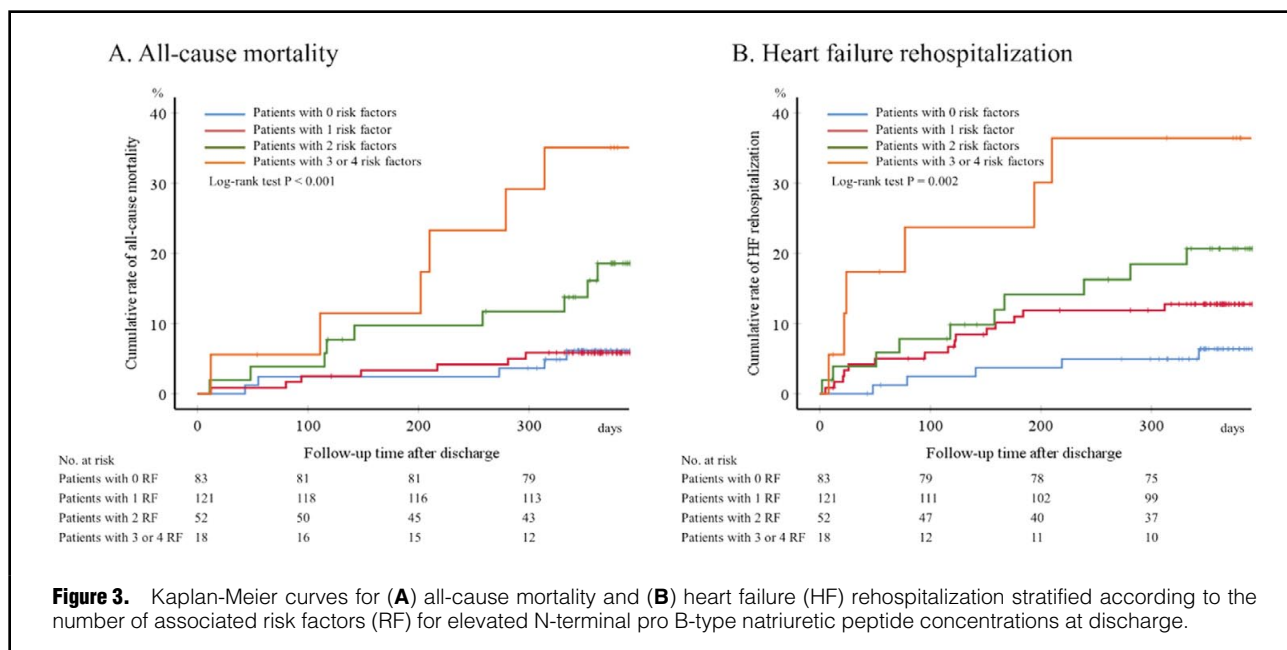


Figure 3. Kaplan-Meier curves for (A) all-cause mortality and (B) heart failure (HF) rehospitalization stratified according to the number of associated risk factors (RF) for elevated N-terminal pro B-type natriuretic peptide concentrations at discharge.

	No. risk factors				P-value
	0 (n=83)	1 (n=121)	2 (n=52)	3 or 4 (n=18)	
All-cause mortality					
No. patients (%)	5 (6.0)	7 (5.8)	9 (17.3)	6 (33.3)	<0.001 ^A
HR	1.00 (Ref.)	0.96	1.75	1.90	
95% CI	–	0.31–3.04	1.01–3.02	1.28–2.82	
P-value	–	0.950	0.045	0.002	<0.001 ^B
HF rehospitalization					
No. patients (%)	5 (6.0)	15 (12.4)	10 (19.2)	6 (33.3)	0.002 ^A
HR	1.00 (Ref.)	2.17	1.89	1.96	
95% CI	–	0.79–5.97	1.11–3.24	1.32–2.91	
P-value	–	0.134	0.020	0.001	<0.001 ^B

^ALog-rank test. ^BP_{trend}. Abbreviations as in Tables 1,2,4.

significantly in a linear manner the number of associated risk factors for elevated NT-proBNP clustered together (P_{trend}<0.001 for both; Table 5).

Discussion

In this study we investigated factors associated with elevated

NT-proBNP concentrations at the convalescent stage and their clinical effect on 1-year outcomes in patients with HFpEF from the real-world population of the PURSUIT-HFpEF Registry. The main findings of this study were that, in addition to the cardiac factor of AF at discharge, another 3 extracardiac factors were independently associated with elevated NT-proBNP concentrations at discharge,

namely low albumin, low eGFR, and elevated CRP. High NT-proBNP concentrations carried a risk of subsequent mortality and rehospitalization for HF during the 1-year follow-up period. In addition, the risk of adverse outcomes increased with number of identified risk factors for elevated NT-proBNP.

Not surprisingly, the presence of AF and low eGFR were associated with elevated NT-proBNP; these 2 factors are known as prognostic factors of adverse outcomes in HF patients.^{10,14-17} AF and HFpEF are age-related conditions and have complex links with each other. A previous report showed that the prevalence of AF in HFpEF ranged from 21% to 33%.¹⁸ In the present study, stable HFpEF patients with AF accounted for 37.5% of the study population, which is relatively high. This inconsistency may be attributable to the advanced age of the subjects in the present study. Moreover, AF is thought to reduce ventricular filling and impair diastolic function, resulting in fluid overload, increased myocardial stretching, and elevated NT-proBNP.¹⁸ Similarly, NT-proBNP increased in patients with AF due to local atrial inflammation and a high frequency of atrial myocyte contraction.¹⁹ In addition, NT-proBNP has been shown to have similar prognostic value in patients with HFpEF and HFrEF.^{9,20} This supports the findings of the present study, which revealed that elevated NT-proBNP reflected the severity of HF and resulted in a poor clinical outcome. In contrast, in patients with chronic kidney disease, decreased eGFR was independently associated with elevated NT-proBNP because plasma NT-proBNP is cleared by kidneys, and has a negative linear relationship with eGFR.^{1,16,21}

In the present study, low albumin, a parameter that reflects nutritional status and inflammation and is considered to be an extracardiac factor, was associated with elevated NT-proBNP. Although the causal mechanisms underlying this association are currently unclear, several possible explanations may be considered. First, the association may be related to hepatic and gastrointestinal congestion in HF patients, which leads to a decrease in albumin synthesis in the liver as well as protein-losing enteropathy and disturbances in food and nutrient absorption in the gastrointestinal tract.^{22,23} In this regard, Liu et al reported that hypoalbuminemia (defined as albumin ≤ 3.4 g/dL) was common and associated with an increased risk of death in patients with HFpEF.²³ Second, hemodilution may be present in patients with HF due to plasma volume expansion, especially in those with severe HF. This may present as low serum albumin and low hemoglobin at baseline in those with elevated NT-proBNP concentrations.^{23,24} Third, hormonal factors that facilitate catabolism are upregulated in HF, including norepinephrine, epinephrine, tumor necrosis factor (TNF)- α , cortisol, and human growth hormone.^{25,26} In contrast, there is an inadequate anabolic response and downregulation of dehydroepiandrosterone, insulin, and aldosterone concentrations.²⁵ These various findings demonstrate an anabolic and catabolic imbalance in cachectic HF patients. This may subsequently result in malnutrition manifested by low serum albumin, and simultaneously worsen the severity of HF, as demonstrated by increased NT-proBNP.^{25,26} Inclusive, the combined results of the present study suggest that hypoalbuminemia at discharge is not only correlated with elevated NT-proBNP (according to multivariable logistic regression analysis), but is also a predictor for all-cause mortality based on multivariable Cox regression analysis after

adjusting for low eGFR, high CRP, the presence of AF, and log-transformed NT-proBNP itself. Hypoalbuminemia may play a role in all-cause mortality through malnutrition, inflammation, and cachexia, in addition to facilitating cardiopulmonary edema and worsening the severity of HF by increasing vascular permeability, volume expansion, diuretic resistance, oxidative stress, and myocardial edema.^{27,28}

With regard to inflammatory biomarkers, CRP was also identified as an independent predictor of elevated NT-proBNP in the present study, indicating an association between the severity of HF and the increase in CRP concentrations. Similar to the present study, DuBrock et al found that high CRP concentrations (>3 mg/L) was present in approximately 60% of patients with HFpEF, suggesting the presence of comorbidity-driven systemic microvascular inflammation in HFpEF.²⁹ High CRP showed a significant association with increased NT-proBNP and other factors in neurohormonal activation, including aldosterone and endothelin-1 in patients with HFpEF.^{29,30} Koller et al found that CRP was not only a strong and independent predictor of mortality in HFpEF, but also an additive prognostic biomarker to NT-proBNP in predicting long-term mortality in HFpEF patients referred for coronary angiography.³⁰ Similarly, it has been reported that CRP in combination with NT-proBNP and other biomarkers of inflammation and neurohormonal activation, including growth differentiation factor-15 and soluble source of tumorigenicity 2, has prognostic utility in patients with HF.³¹ Although we cannot determine whether higher CRP is a cause or consequence of elevated NT-proBNP in the present study, several possibilities may be considered. The systemic inflammatory pathway in HF is widely known, and may be explained by the fact that systemic volume overload in HF results in gut edema, and the translocation and systemic spread of gut bacteria.²² In addition, a cascade of immunological activation results in the release of inflammatory mediators such as TNF- α , interleukin-1, and interleukin-6 in chronic HF.³² CRP, an acute phase reactant produced primarily by hepatocytes, is released by the stimulation of these inflammatory mediators. These findings may reflect the immunological process in HFpEF, and indicate that conditions that upregulate CRP also contribute to an increase in cardiac stress, which, in turn, upregulates NT-proBNP in the heart.

In the present study cohort, the rates of all-cause mortality and HF rehospitalization within the 1-year follow-up period were associated with the number of identified risk factors (both pre-existing cardiac factors and extracardiac factors) for elevated NT-proBNP at discharge. NT-proBNP concentrations at discharge and 1-year adverse outcomes increased significantly with an increase in the number of risk factors. To our knowledge, the present study is the first to examine factors associated with elevated NT-proBNP concentrations at the recovery stage in patients admitted with ADHFpEF. This study highlights the importance of appropriate interventions not only for cardiac factors, but also extracardiac factors, specifically malnutrition and inflammation, which were manifested by low serum albumin and high CRP.

The present study has several limitations. First, the study was a prospective observational study, meaning that a degree of selection bias and missing data cannot be avoided. Notably, we did not obtain comprehensive information regarding nutritional factors, such as the total muscle volume or fat tissue, or inflammation status, including several kinds of cytokines in addition to CRP. Second,

because of the ongoing status of this Registry and its limited clinical outcomes data, the relatively small sample size, and low event rates, we could not adjust for potential covariates when assessing the relationship between the HRs of the number of risk factors for elevated NT-proBNP and adverse outcomes. These results therefore need to be interpreted with caution.

In conclusion, in addition to AF and poor renal function, which are well-known contributors to increases in NT-proBNP, we found that extracardiac factors, including malnutrition and inflammation, were independently associated with elevated NT-proBNP concentrations at the convalescent stage in patients with HFpEF. Further, the number of factors was associated with increased 1-year mortality and HF rehospitalization. Therefore, physicians may need to pay attention not only to cardiac factors, but also to extracardiac factors in HFpEF patients in the clinical practice setting. Interventions in these factors may reduce NT-proBNP concentrations, which may, in turn, improve outcomes in HFpEF patients with high NT-proBNP concentrations at the convalescent stage. These high-risk patients may also require a degree of special care, including close follow-up or therapeutic titration.

Acknowledgments

The authors thank Sugako Mitsuoka, Masako Terui, Nagisa Yoshioka, Satomi Kishimoto, Kyoko Tatsumi, and Noriko Murakami for their assistance with data collection, data management and secretarial work.

Sources of Funding

This work was supported by grants from Japan Society for the Promotion of Science KAKENHI (No. JP 17K09496) and Japan Agency for Medical Research and Development (No. JP16lk1010013) and was funded by Roche Diagnostics K.K. and Fuji Film Toyama Chemical.

Disclosures

D.N. has received honoraria from Roche Diagnostics K.K.; S.H. and Y.S. have received grant support from Roche Diagnostics K.K. and Fuji Film Toyama Chemical. The other authors have no conflicts of interest to declare.

IRB Information

This study was approved by Osaka University Hospital Ethical Review Committee (Reference no. 15471-7).

References

- Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail* 2004; **6**: 257–260.
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017; **136**: e137–e161.
- Andersson C, Vasan RS. Epidemiology of heart failure with preserved ejection fraction. *Heart Fail Clin* 2014; **10**: 377–388.
- Tribouilloy C, Rusinaru D, Mahjoub H, Soulière V, Lévy F, Peltier M, et al. Prognosis of heart failure with preserved ejection fraction: A 5 year prospective population-based study. *Eur Heart J* 2008; **29**: 339–347.
- Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006; **355**: 260–269.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
- Jhund PS, Anand IS, Komajda M, Claggett BL, McKelvie RS, Zile MR, et al. Changes in N-terminal pro-B-type natriuretic peptide levels and outcomes in heart failure with preserved ejection fraction: An analysis of the I-Preserve study. *Eur J Heart Fail* 2015; **17**: 809–817.
- Anand IS, Rector TS, Cleland JG, Kuskowski M, McKelvie RS, Persson H, et al. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: Findings from the I-PRESERVE trial. *Circ Heart Fail* 2011; **4**: 569–577.
- Salah K, Stienen S, Pinto YM, Eurling LW, Metra M, Genis AB, et al. Prognosis and NT-proBNP in heart failure patients with preserved versus reduced ejection fraction. *Heart* 2019; **105**: 1182–1189.
- Tanaka A, Yoshida H, Kawaguchi A, Oyama J, Kotooka N, Toyoda S, et al. N-terminal pro-brain natriuretic peptide and associated factors in the general working population: A baseline survey of the Uranosaki cohort study. *Sci Rep* 2017; **7**: 5810.
- Salah K, Kok WE, Eurlings LW, Bettencourt P, Pimenta JM, Metra M, et al. A novel discharge risk model for patients hospitalised for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: A European coLlaboration on Acute decompensated Heart Failure: ELAN-HF score. *Heart* 2014; **100**: 115–125.
- Lam CSP, Li YH, Bayes-Genis A, Ariyachaipanich A, Huan DQ, Sato N, et al. The role of N-terminal pro-B-type natriuretic peptide in prognostic evaluation of heart failure. *J Chin Med Assoc* 2019; **82**: 447–451.
- Hoshida S, Watanabe T, Shinoda Y, Ikeoka K, Minamisaka T, Fukuoka H, et al. Sex-related differences in left ventricular diastolic function and arterial elastance during admission in patients with heart failure with preserved ejection fraction: The PURSUIT HFpEF study. *Clin Cardiol* 2018; **41**: 1529–1536.
- Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Harst PVD, Hillege HL, et al. Incidence of atrial fibrillation and mortality with cardiovascular events, heart failure, and mortality: A community-based study from the Netherlands. *J Am Coll Cardiol* 2015; **66**: 1000–1007.
- Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail* 2009; **11**: 676–683.
- Anwaruddin S, Lloyd-Jones DM, Baggish A, Chen A, Krauser D, Tung R, et al. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: Results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. *J Am Coll Cardiol* 2006; **47**: 91–97.
- Shiba N, Shimokawa H. Chronic kidney disease and heart failure: Bidirectional close link and common therapeutic goal. *J Cardiol* 2011; **57**: 8–17.
- Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart failure with preserved ejection fraction and atrial fibrillation: Vicious twins. *J Am Coll Cardiol* 2016; **68**: 2217–2228.
- Thejus J, Francis J. N-terminal pro-brain natriuretic peptide and atrial fibrillation. *Indian Pacing and Electrophysiol J* 2009; **9**: 1–4.
- Kang SH, Park JJ, Choi DJ, Yoon CH, Oh IY, Kang SM, et al. Prognostic value of NT-proBNP in heart failure with preserved versus reduced EF. *Heart* 2015; **101**: 1881–1888.
- Spanaus KS, Kronenberg F, Ritz E, Schlaapbach R, Fliser D, Hersberger M, et al. B-Type natriuretic peptide concentrations predict the progression of nondiabetic chronic kidney disease: The Mild-to-Moderate Kidney Disease Study. *Clin Chem* 2007; **53**: 1264–1272.
- Sundaram V, Fang JC. Gastrointestinal and liver issues in heart failure. *Circulation* 2016; **133**: 1696–1703.
- Liu M, Chan CP, Yan BP, Zhang Q, Lam YY, Li RJ, et al. Albumin levels predict survival in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail* 2012; **14**: 39–44.
- Abramov D, Cohen RS, Katz SD, Mancini D, Maurer MS. Comparison of blood volume characteristics in anemic patients with low versus preserved left ventricular ejection fractions. *Am J Cardiol* 2008; **102**: 1069–1072.
- Anker SD, Chua TP, Ponikowski P, Harrington D, Swan JW, Kox WJ, et al. Hormonal changes and catabolic/anabolic imbalance

- in chronic heart failure and their importance for cardiac cachexia. *Circulation* 1997; **96**: 526–534.
26. Anker SD, Coats AJ. Cardiac cachexia: A syndrome with impaired survival and immune and neuroendocrine activation. *Chest* 1999; **115**: 836–847.
 27. Arques S. Human serum albumin in cardiovascular diseases. *Eur J Intern Med* 2018; **52**: 8–12.
 28. Bonilla-Palomas JL, Gámez-López AL, Moreno-Conde M, López-Ibáñez MC, Anguita-Sánchez M, de la Sacristana AG, et al. Hypoalbuminemia in acute heart failure patients: Causes and its impact on hospital and long-term mortality. *J Card Fail* 2014; **20**: 350–358.
 29. DuBrock HM, AbouEzzeddine OF, Redfield MM. High-sensitivity C-reactive protein in heart failure with preserved ejection fraction. *PLoS One* 2018; **13**: e0201836.
 30. Koller L, Kleber M, Goliash G, Sulzgruber P, Scharnagl H, Silbernagel G, et al. C-reactive protein predicts mortality in patients referred for coronary angiography and symptoms of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2014; **16**: 758–766.
 31. Sinning C, Kempf T, Schwarzl M, Lanfermann S, Ojeda F, Schnabel RB, et al. Biomarkers for characterization of heart failure: Distinction of heart failure with preserved and reduced ejection fraction. *Int J Cardiol* 2017; **227**: 272–277.
 32. Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation* 2000; **102**: 3060–3067.
- Daisaku Masuda, Yoshihiro Takeda, Yoshiyuki Nagai, and Shizuya Yamashita (Rinku General Medical Center, Izumisano, Japan)
 Masami Sairyo, Yusuke Nakagawa and Shuichi Nozaki (Kawanishi City Hospital, Kawanishi, Japan)
 Haruhiko Abe, Yasunori Ueda, Masaaki Uematsu, and Yukihiko Koretsune (National Hospital Organization Osaka National Hospital, Osaka, Japan)
 Kunihiko Nagai (Ikeda Municipal Hospital, Ikeda, Japan)
 Masamichi Yano, Masami Nishino, and Jun Tanouchi (Osaka Rosai Hospital, Sakai, Japan)
 Yoh Arita and Shinji Hasegawa (Japan Community Health Care Organization Osaka Hospital, Osaka, Japan)
 Takamaru Ishizu, Minoru Ichikawa and Yuzuru Takano (Higashiosaka City Medical Center, Higashiosaka, Japan)
 Eisai Rin (Kawachi General Hospital, Higashiosaka, Japan)
 Tetsuya Watanabe and Shiro Hoshida (Yao Municipal Hospital, Yao, Japan)
 Masahiro Izumi (Kinki Central Hospital, Itami, Japan)
 Hiroyoshi Yamamoto and Hiroyasu Kato (Japan Community Health Care Organization, Osaka Minato Central Hospital, Osaka, Japan)
 Kazuhiro Nakatani and Hisatoyo Hiraoka (Sumitomo Hospital, Osaka, Japan)
 Mayu Nishio and Keiji Hirooka (Saiseikai Senri Hospital, Suita, Japan)
 Takahiro Yoshimura and Yoshinori Yasuoka (National Hospital Organization Osaka Minami Medical Center, Kawachinagano, Japan)
 Akihiro Tani (Kano General Hospital, Osaka, Japan)
 Yasushi Okumoto and Hideharu Akagi (Kinan Hospital, Tanabe, Japan)
 Yasunaka Makino (Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Japan)
 Toshinari Ohnishi and Katsuomi Iwakura (Sakurabashi Watanabe Hospital, Osaka, Japan)
 Nagahiro Nishikawa and Yoshiyuki Kijima (Japan Community Health Care Organization, Hoshigaoka Medical Center, Hirakata, Japan)
 Takashi Kitao and Hideyuki Kanai (Minoh City Hospital, Minoh, Japan)
 Wataru Shioyama and Masashi Fujita (Osaka International Cancer Institute, Osaka, Japan)
 Koichiro Harada (Suita Municipal Hospital, Suita, Japan)
 Masahiro Kumada and Osamu Nakagawa (Toyonaka Municipal Hospital, Toyonaka, Japan)
 Ryo Araki and Takayuki Yamada (Otemae Hospital, Osaka, Japan)
 Akito Nakagawa and Yoshio Yasumura (Amagasaki Chuo Hospital, Amagasaki, Japan)
 Fusako Sera, Kei Nakamoto, Hidetaka Kioka, Tomohito Ohtani, Katsuki Okada, Hiroya Mizuno, Tomoharu Dohi, Takayuki Kojima, Hirota Kida, Akihiro Sunaga, Bolrathanak Oeun, Shinichiro Suna, Daisaku Nakatani, Shungo Hikoso, Toshihiro Takeda, Yasushi Matsumura, and Yasushi Sakata (Osaka University Graduate School of Medicine, Suita, Japan)

Appendix

The Osaka Cardiovascular Conference (OCVC) Heart Failure Investigators are listed below:

Chair:

Yasushi Sakata (Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan)

Secretariat:

Shungo Hikoso (Chief), Daisaku Nakatani, Shinichiro Suna, Katsuki Okada, Tomoharu Dohi, Takayuki Kojima, Hirota Kida, Bolrathanak Oeun and Sugako Mitsuka (Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan)

Investigators:

Shunsuke Tamaki, Masatake Fukunami, and Takahisa Yamada (Osaka General Medical Center, Osaka, Japan)
 Takaharu Hayashi and Yoshiharu Higuchi (Osaka Police Hospital, Osaka, Japan)
 Masaharu Masuda, Mitsutoshi Asai, and Toshiaki Mano (Kansai Rosai Hospital, Amagasaki, Japan)
 Hisakazu Fuji (Kobe Ekisaikai Hospital, Kobe, Japan)