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Pump failure death and sudden cardiac death in patients with cardiac dysfunction: A search for prognostic predictive factors—A long-term follow-up study

Hiroki Usuku (MD) [a],[*], Masafumi Nakayama (MD, PhD) [a],
Hitoshi Sumida (MD, PhD) [a], Megumi Yamamuro (MD, PhD) [a],
Yasuhiro Izumiya (MD, PhD) [a], Satoru Suzuki (MD, PhD) [a],
Kenichi Kusuhara (MD) [a], Hirofumi Ueno (MD) [a],
Seigo Sugiyama (MD, PhD) [a], Michihiro Yoshimura (MD, PhD, FJCC) [b],
Hisao Ogawa (MD, PhD, FJCC) [a]

[a] Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto City 860-8556, Japan
[b] Division of Cardiology, Department of Internal Medicine, The Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo 105-8471, Japan

Summary
Background: There have been few reports that have analyzed the predictive factors for heart failure death, which is sub-divided into pump failure death and sudden cardiac death, in the long term.
Methods and results: We followed 186 consecutive patients with myocardial infarction (MI) and 115 consecutive patients with non-ischemic heart failure (NIHF) during 73 ± 3 months. In the MI group, 26 died from pump failure and 12 died from sudden cardiac death. In the NIHF group, 21 died from pump failure and 9 died from sudden cardiac death. Multivariate analysis revealed that the log B-type natriuretic peptide (BNP) was an independent predictor for pump failure death in both groups. In the MI group, the estimated glomerular filtration rate (eGFR) was an independent predictor for sudden cardiac death. Kaplan—Meier analysis revealed that a high BNP level was a risk factor for pump failure death in either MI or NIHF patients. On the other hand, the sudden cardiac death rate was significantly higher in the MI patients with low eGFR than in those with high eGFR.

* Corresponding author. Tel.: +81 96 373 5175; fax: +81 96 362 3256.
  E-mail address: uhuhuhuh@kumamoto-u.ac.jp (H. Usuku).

Conclusions: The plasma BNP level is an independent predictor for pump failure death in both MI and NIHF patients. The eGFR is an independent predictor for sudden cardiac death in MI patients.

Introduction

Heart failure is an important leading cause of morbidity and mortality [1]. Because many patients who die due to heart failure have myocardial dysfunction, such as myocardial infarction (MI) or non-ischemic heart failure (NIHF), prognostic factors for these diseases have been the subject of numerous investigations worldwide. Recently, B-type natriuretic peptide (BNP) has been recognized as a diagnostic marker in patients with myocardial dysfunction.

We previously reported that BNP is mainly secreted from the heart in patients with heart failure [2–4]; furthermore, that BNP secretion levels from the heart increase in proportion to the severity of heart failure [2–4]. Secretion of BNP from the heart is induced by mechanical stress on cardiomyocytes [5]. Cytokines, including interleukin-1β, cardiotrophine I, and leukemia inhibitory factor (LIF), also induce BNP secretion [6–8]. Further, oxidative stress induces the secretion of BNP, via the re-expression of fatal gene programs and the apoptosis process in cardiomyocytes [9].

Plasma levels of BNP are able to be used as a marker of the degree of myocardial dysfunction in patients with acute myocardial infarction (AMI) [3,10,11]. We previously reported that plasma BNP levels rapidly and markedly increase after the onset of AMI. Plasma BNP levels decrease within 48 h from the onset of AMI, and thereafter the plasma BNP levels increase again after several days in AMI patients with severe anterior MI [10]. The time course of the plasma BNP levels shows a distinct pattern with two peaks. The mechanism for the formation of the first peak is considered to be an acute-phase reactant in response to acute tissue injuries, including mechanical stress, cytokines, and oxidative stress. The mechanisms for the formation of the second peak are considered to be myocardial expansion and subsequent ventricular remodeling. Many MI patients with high plasma BNP levels at the second peak have large infarct sizes, and so they also have high plasma BNP levels in the chronic phase [10]. We previously reported that plasma BNP level in the chronic phase is an independent predictor for cardiac death in patients with AMI [12].

It has been reported that the plasma BNP levels in the stable phase are more useful as predictive factors for morbidity and mortality in patients with heart failure than the plasma BNP levels in the acute phase [13]; however, there have been few long-term follow-up studies done to investigate prognostic values, including evaluating the plasma BNP levels at the stable phase in patients with heart failure. We began to measure plasma BNP levels from 1990 after the initial discovery of BNP, and a novel antibody for BNP was created by our research group shortly thereafter [4,14]. Besides plasma BNP levels, many other variables including anemia, renal dysfunction, low blood pressure, low body mass index, and male sex have been reported to be prognostic predictive factors for cardiac death in heart failure patients [15–18].

The aim of this study was to investigate the long-term prognostic predictive factors, including the clinical characteristics and plasma BNP levels, in patients with MI or in those with NIHF.

Methods

Study patients

The study recruitment began in January 1990 and ended in December 2004. The final follow-up date was November 1, 2007. During this period, there were 942 admitted patients with MI or NIHF. In these patients, we were ultimately able to follow up 301 patients for whom highly reliable information was available about their prognoses from their affiliated hospitals. The present study included 186 patients with MI and 115 patients with NIHF.

Inclusion criteria for patients with MI were as follows: (1) clinical symptoms, including ST changes or a new left bundle branch block, and an elevation of serum creatine kinase-MB isoenzyme level to more than twice the normal upper level; (2) development of pathological Q waves with or without symptoms; or, (3) region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause. Inclusion criteria for patients with NIHF were as follows: (A) negative findings for coronary artery disease utilizing coronary arteriography; (B) negative findings for primary valvular heart disease utilizing echocardiography; (C) global left ventricular dysfunction with an ejection fraction of less than 60% and (D) history of heart failure (New York Heart Association class II to IV).

All clinical causes of myocardial dysfunction were obtained from the hospital charts. End points of this study were defined as cardiac death, including pump failure or sudden cardiac death. Deaths resulting from a deterioration of congestive heart failure, with progression of congestive symptoms, were classified as pump failure. Sudden cardiac death was defined as witnessed cardiac arrest or death within 1 h after the onset of acute symptoms or as an unexpected, unwitnessed death (i.e. during sleep). Noncardiac death was defined as survivors, including patients, who died from other causes. The protocol was in agreement with our institutional review boards and as published in the University Hospital Medical Information Network (UMIN: 000000923).

Data collection

In the present study, we obtained blood samples and performed physical examinations, including body mass index,

mean blood pressure, and heart rate at the stable phase (3—4 weeks after admission).

Measurement of plasma BNP levels

The plasma BNP concentration levels were measured utilizing a specific radioimmunoassay for human BNP from 1990 to 1993. A specific immunoradiometric assay for human BNP was utilized from 1993 (Shionoria BNP; Shionogi Inc., Osaka, Japan). There were no significant differences in the BNP values obtained by the radioimmunoassay and immunoradiometric assay methods [19].

Measurement of estimated glomerular filtration rate

Measuring estimated glomerular filtration rate (eGFR) is considered the most suitable method for quantifying renal function [20]. The eGFR was assessed using the 4 component Modification of Diet in Renal Disease Equation, incorporating age, race, gender, and serum creatinine level. The Japan Chronic Kidney Disease Initiative has found an equation for accurate GFR estimation in Japanese people: eGFR in Japanese (in ml/min/1.73 m^2) = $0.741 \times 175 \times$ [serum creatinine level (in mg/dl)]$^{-1.154} \times$ [age (in year)]$^{-0.203}$ [20]. The Japanese Society of Nephrology has recommended using this equation to measure GFR in Japanese [20]. Because all of the study patients were Japanese, we used this equation to measure eGFR.

Statistical analysis

Continuous values are expressed as the mean $\pm$ SD. A Cox proportional hazards regression analysis was performed to identify independent predictors for pump failure death and sudden cardiac death including the following variables: age, gender body mass index, current smoking, history of hypertension, history of diabetes mellitus, history of dyslipidemia, atrial fibrillation, mean blood pressure, heart rate, log BNP, eGFR and the following clinical laboratory data: white blood cell count, hemoglobin levels, serum uric acid levels, serum sodium, and serum potassium levels. The plasma BNP level was not normally distributed, so we selected normally distributed log BNP for analysis. When we evaluated the prognosis for pump failure death, we excluded the sudden cardiac death patients. When we evaluated the prognosis for sudden cardiac death, we excluded the pump failure death patients. We set out a cut-off point to determine a patient group with a low risk of cardiac death. Kaplan—Meier survival curves were used for survival comparisons between the patient groups stratified according to this cut-off point. Statistical significance was defined as a probability value <0.05.

Results

Follow-up periods

For all study patients, the mean follow-up period was 74 months (range 1—215 months), with a mean follow-up period of 51 ± 6 months (range 1—191 months) for the cardiac death group and 80 ± 4 months (range 1—215 months) for the non-cardiac death group.

Clinical characteristics

The clinical characteristics in the MI, NIHF, and total groups are shown in Table 1. The mean ages in the MI, NIHF, and total groups were 67.8 ± 10.7, 56.2 ± 14.3, and 63.4 ± 13.4 years, respectively. The MI patients were significantly older than the NIHF patients ($p < 0.05$). The mean levels of left ventricular ejection fraction (LVEF) in the MI, NIHF, and total groups were 51.4 ± 17.0, $34.5 \pm 13.3\%$, and $49.9 \pm 17.7\%$, respectively. The LVEF was significantly higher in the MI group than in the NIHF group ($p < 0.05$). The incidence of diabetes mellitus and dyslipidemia was significantly higher in the MI group than in the NIHF group. The incidence of atrial fibrillation was significantly lower in the MI group than in the NIHF group. The prescription rates of angiotensin-converting enzyme inhibitors, digitalis, furosemide, and spironolactone were significantly lower in the MI group than in the NIHF group ($p < 0.003$). On the other hand, calcium-channel blockers and statins were prescribed more often in the MI group than in the NIHF group ($p < 0.005$). There were no significant differences in prescription rates of angiotensin II receptor blockers and β-blockers between the MI group and the NIHF group.

Prognosis of patients and causes of death

In the MI group, 136 survived and 50 died during the study period. Out of the 50 patients who died, 26 (52%) died from pump failure, 12 (24%) died from sudden cardiac death, and 12 (24%) died from other causes: 7 (14%) with malignant disease, 3 (6%) with pneumonia, 1 (2%) with sepsis and 1 (2%) with senility.

In the NIHF group, 76 survived and 39 died during the study period. Out of the 39 patients who died, 21 (68%) died from pump failure, 9 (23%) died from sudden cardiac death, and 9 (24%) died from other causes: 1 (3%) with malignant disease, 4 (10%) with pneumonia, 2 (5%) with cerebral infarction, 1 (3%) with cerebral hemorrhage and, 1 (3%) with liver dysfunction.

Univariate and multivariate analysis for predictors of cardiac death

MI group

The results of univariate and multivariate analyses in the MI group are shown in Table 2.

According to the univariate analysis, eGFR, serum uric acid levels, serum potassium levels, and log BNP were significant predictive factors for cardiac death in the MI group. Subsequently, we examined multivariate analysis using age, heart rate, eGFR, serum uric acid levels, serum potassium levels, and log BNP, for which p-values were less than 0.1. Multivariate analysis revealed that log BNP was an independent predictor for cardiac death in the MI group [HR 4.01 (1.62—9.92), $p = 0.0060$]. The univariate analysis revealed that hemoglobin level, eGFR, serum uric acid level, and log BNP were significant predictive factors for pump failure

Table 1   Clinical characteristics.

	MI group (n = 186)	NIHF group (n = 115)	Total group (n = 301)
Age (years)	67.8 ± 10.7	56.2 ± 14.3[*]	63.4 ± 13.4
Male	67% (124/186)	69% (79/115)	67% (203/301)
LVEF (%)	51.4 ± 17.0	34.5 ± 13.3[*]	44.9 ± 17.7
Current smoking	52% (97/186)	44% (51/115)	49% (148/301)
Hypertension	42% (78/186)	31% (35/114)	38% (113/300)
Diabetes mellitus	39% (72/186)	18% (20/114)[*]	31% (92/300)
Dyslipidemia	47% (87/186)	25% (28/114)[*]	38% (115/300)
Atrial fibrillation	5% (10/186)	22% (25/115)[*]	12% (35/301)
ICD	1% (2/186)	1% (1/115)	1% (3/301)
Dialysis	1% (1/186)	1% (1/115)	1% (2/301)
Pharmacotherapy			
ACEI	51% (95/185)	85% (98/115)[*]	64% (193/300)
ARB	13% (24/185)	19% (22/115)	15% (46/300)
Digitalis	3% (5/185)	20% (23/115)[*]	9% (28/300)
Furosemide	27% (50/185)	48% (55/115)[*]	35% (105/300)
Spironolactone	11% (20/185)	24% (28/115)[*]	16% (48/300)
Calcium-channel blockers	75% (139/185)	9% (10/115)[**]	50% (149/300)
Nitrate	53% (98/185)	6% (7/115)	35% (105/300)
β-Blockers	26% (48/185)	28% (32/115)	27% (80/300)
Statins	32% (59/185)	17% (19/115)	26% (78/300)

MI, myocardial infarction; NIHF, non-ischemic heart failure; LVEF, left ventricular ejection fraction; ICD, implanted cardiac defibrillator; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

[*] p < 0.05 vs MI group.
[**] p < 0.01 vs MI group.

Table 2   Predictive factors in myocardial infarction patients.

	Cardiac death (pump failure death + sudden cardiac death)				Pump failure death				Sudden cardiac death			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	P-value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age (per year)	1.03 (1.00−1.07)	0.0971	1.01 (0.96−1.06)	0.7701	1.02 (0.98−1.06)	0.3098			1.05 (0.99−1.12)	0.1238		
Male (+)	0.72 (0.35−1.48)	0.3669			0.99 (0.44−2.22)	0.9728			0.18 (0.02−1.41)	0.1021		
BMI (per 1 kg/m²)	1.04 (0.93−1.16)	0.4659			1.03 (0.90−1.17)	0.6702			1.08 (0.89−1.32)	0.4386		
Current smoking (+)	0.96 (0.51−1.83)	0.9056			0.97 (0.45−2.11)	0.9459			0.84 (0.27−2.65)	0.7656		
Hypertension (+)	1.28 (0.65−2.51)	0.4771			1.50 (0.65−3.46)	0.3456			0.96 (0.30−3.07)	0.9462		
Mean blood pressure (per 1 mmHg)	0.99 (0.97−1.02)	0.5429			0.98 (0.96−1.01)	0.2168			1.02 (0.98−1.06)	0.3673		
Diabetes mellitus (+)	0.82 (0.43−1.56)	0.5405			0.79 (0.36−1.72)	0.5486			0.88 (0.28−2.79)	0.8298		
Dyslipidemia (+)	1.20 (0.63−2.28)	0.5841			1.23 (0.56−2.68)	0.6047			1.27 (0.40−4.01)	0.6812		
Heart rate (per 1 beat/min)	1.02 (1.00−1.04)	0.051	1.01 (0.96−1.06)	0.5961	1.02 (1.00−1.04)	0.1419			1.02 (0.99−1.06)	0.1681		
Atrial fibrillation (+)	0.67 (0.16−2.85)	0.5912			0.49 (0.11−2.14)	0.3450			...	...		
WBC (per 1 count/μl)	1 (1.00−1.00)	0.5616			1 (1.00−1.00)	0.2205			1.00 (1.00−1.00)	0.4188		
Hemoglobin level (per 1 g/dl)	0.89 (0.76−1.04)	0.1435			0.82 (0.68−0.98)	0.0296	0.87 (0.69−1.10)	0.2493	1.14 (0.80−1.62)	0.4732		
eGFR (per 1 ml/min/1.73 m²)	0.96 (0.95−0.98)	<0.0001	0.98 (0.96−1.01)	0.1800	0.96 (0.94−0.98)	0.0005	0.99 (0.96−1.02)	0.4592	0.95 (0.93−0.99)	0.0034	0.96 (0.93−0.99)	0.0211
Serum uric acid level (per 1 mg/dl)	1.45 (1.17−1.80)	0.0007	1.16 (0.90−1.51)	0.2550	1.49 (1.16−1.91)	0.0019	1.31 (0.94−1.81)	0.1103	1.39 (0.93−2.10)	0.1128		
Serum sodium level (per 1 mequiv./l)	0.95 (0.85−1.06)	0.3542			0.92 (0.81−1.05)	0.2336			1.02 (0.83−1.25)	0.8697		
Serum potassium level (per 1 mequiv./l)	2.03 (1.02−4.05)	0.0453	0.81 (0.36−1.82)	0.6164	2.06 (0.90−4.74)	0.0872	0.78 (0.29−2.11)	0.6310	2.20 (0.68−7.15)	0.1887		
Log BNP [per 1 log (pg/ml)]	5.70 (2.65−12.24)	<0.0001	4.01 (1.62−9.92)	0.0060	8.98 (3.36−23.99)	<0.0001	3.64 (1.11−11.95)	0.0335	3.03 (0.92−9.97)	0.0678	1.66 (0.56−4.99)	0.3633

HR, hazard ratio; CI, confidence interval; BMI, body mass index; WBC, white blood cell; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide.

Table 3 Predictive factors in non-ischemic heart failure patients.

	Cardiac death (pump failure death + sudden cardiac death)				Pump failure death				Sudden cardiac death	
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age (per year)	1.01 (0.98—1.04)	0.4825			1.01 (0.98—1.04)	0.4663			1.01 (0.96—1.06)	0.7456
Male (+)	1.27 (0.60—2.68)	0.526			1.44 (0.59—3.47)	0.4225			1.02 (0.25—4.09)	0.9814
BMI (per 1 kg/m^2)	0.93 (0.84—1.03)	0.1615			0.86 (0.75—0.97)	0.0167	1.05 (0.86—1.29)	0.6134	1.05 (0.91—1.21)	0.5078
Current smoking (+)	1.33 (0.63—2.81)	0.4542			1.33 (0.55—3.23)	0.5296			1.46 (0.37—5.87)	0.5905
Hypertension (+)	1.84 (0.70—4.84)	0.2178			2.31 (0.67—7.93)	0.1825			1.44 (0.30—7.02)	0.6505
Mean blood pressure (per 1 mmHg)	0.97 (0.95—0.995)	0.015	0.98 (0.95—1.004)	0.0984	0.96 (0.93—0.99)	0.0048	0.97 (0.93—1.00)	0.0645	0.99 (0.96—1.03)	0.657
Diabetes mellitus (+)	0.94 (0.32—2.73)	0.9084			1.34 (0.31—5.82)	0.6995			0.58 (0.12—2.88)	0.5066
Dyslipidemia (+)	1.59 (0.55—4.60)	0.3886			2.37 (0.55—10.26)	0.2475			0.93 (0.19—4.57)	0.9314
Heart rate (per 1 beat/min)	0.99 (0.98—1.01)	0.3538			0.99 (0.97—1.01)	0.2521			1.00 (0.98—1.03)	0.9995
Atrial fibrillation (+)	1.34 (0.55—3.28)	0.5246			1.49 (0.48—4.27)	0.5233			1.19 (0.25—5.75)	0.827
WBC (per 1 count/μl)	1.00 (1.00—1.00)	0.5099			1.00 (1.00—1.00)	0.1588			1.00 (0.999—1.00)	0.3029
Hemoglobin level (per 1 g/dl)	0.90 (0.77—1.05)	0.1832			0.78 (0.65—0.93)	0.0045	0.82 (0.62—1.08)	0.154	1.36 (0.95—1.94)	0.0951
eGFR (per 1 ml/min/1.73 m^2)	0.98 (0.97—0.999)	0.0435	0.99 (0.97—1.006)	0.1737	0.98 (0.96—1.00)	0.048	0.99 (0.96—1.02)	0.702	0.99 (0.96—1.01)	0.3038
Serum uric acid level (per 1 mg/dl)	1.05 (0.88—1.26)	0.5838			1.12 (0.91—1.37)	0.2837			0.88 (0.60—1.30)	0.5149
Serum sodium level (per 1 mequiv./l)	0.95 (0.86—1.05)	0.3463			0.93 (0.83—1.04)	0.2061			1.02 (0.81—1.29)	0.8406
Serum potassium level (per 1 mequiv./l)	0.92 (0.44—1.90)	0.8131			1.31 (0.56—3.06)	0.5287			0.37 (0.09—1.42)	0.1468
Log BNP [per 1 log (pg/ml)]	3.68 (1.83—7.39)	0.0003	4.77 (1.98—11.49)	0.0005	5.26 (2.24—12.34)	0.0001	7.65 (1.98—29.56)	0.0032	2.14 (0.68—6.79)	0.1947

HR, hazard ratio; CI, confidence interval; BMI, body mass index; WBC, white blood cell; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide.

death in the MI group. Subsequently, we examined multivariate analysis using hemoglobin level, eGFR, serum uric acid level, serum potassium level, and log BNP, for which p-values were less than 0.1. Multivariate analysis revealed that log BNP was an independent predictor for pump failure death in the MI group [HR 3.64 (1.11—11.95), p = 0.0335]. The univariate analysis revealed that eGFR was a significant predictive factor for sudden cardiac death in the MI group. Subsequently, we examined multivariate analysis using eGFR and log BNP, for which p-values were less than 0.1. Multivariate analysis revealed that eGFR was an independent predictor for sudden cardiac death in the MI group [HR 0.96 (0.93—0.99), p = 0.0211].

NIHF group

The results of univariate and multivariate analyses in the NIHF group are shown in Table 3. According to the univariate analysis, mean blood pressure, eGFR, and log BNP were significant predictive factors for cardiac death in the NIHF group. Subsequently, we examined multivariate analysis using mean blood pressure, eGFR and log BNP, for which p-values were less than 0.1. Multivariate analysis revealed that log BNP was an independent predictor for cardiac death in the NIHF group [HR 4.77 (1.98—11.49), p = 0.0005]. The univariate analysis revealed that body mass index, mean blood pressure, hemoglobin level, eGFR, and log BNP were significant predictive factors for pump failure death in the NIHF group. Subsequently, we examined multivariate analysis using mean blood pressure, hemoglobin level, eGFR,

and log BNP, for which p-values were less than 0.1. Multivariate analysis revealed that log BNP was an independent predictor for pump failure death in the NIHF group [HR 7.65 (1.98—29.56), p = 0.0032]. There were no significant predictive factors found utilizing both univariate and multivariate analyses for sudden cardiac death in the NIHF group.

Receiver operating characteristic analysis

We examined the sensitivity and specificity of various cut-off values of independent predictive factors for predicting survival and created receiver operating characteristic (ROC) curves. In the MI group, the cut-off values determined by ROC curve analysis were 2.36 of log BNP, equivalent to a BNP level of 230 pg/ml for cardiac death (Fig. 1a), 2.36 of log BNP, equivalent to a BNP level of 230 pg/ml for pump failure death (Fig. 1b), and 54.2 ml/min/1.73 m^2 of eGFR for sudden cardiac death (Fig. 1c). In the NIHF group, the cut-off values determined by ROC curve analysis were 2.28 of log BNP, equivalent to a BNP level of 191 pg/ml for cardiac death (Fig. 2a) and 2.28 of log BNP, equivalent to a BNP level of 191 pg/ml for pump failure death (Fig. 2b).

Kaplan—Meier survival analysis

We separated each group into two sub-groups based on their cut-off values which were determined by ROC curve analysis, and examined the Kaplan—Meier survival analysis.
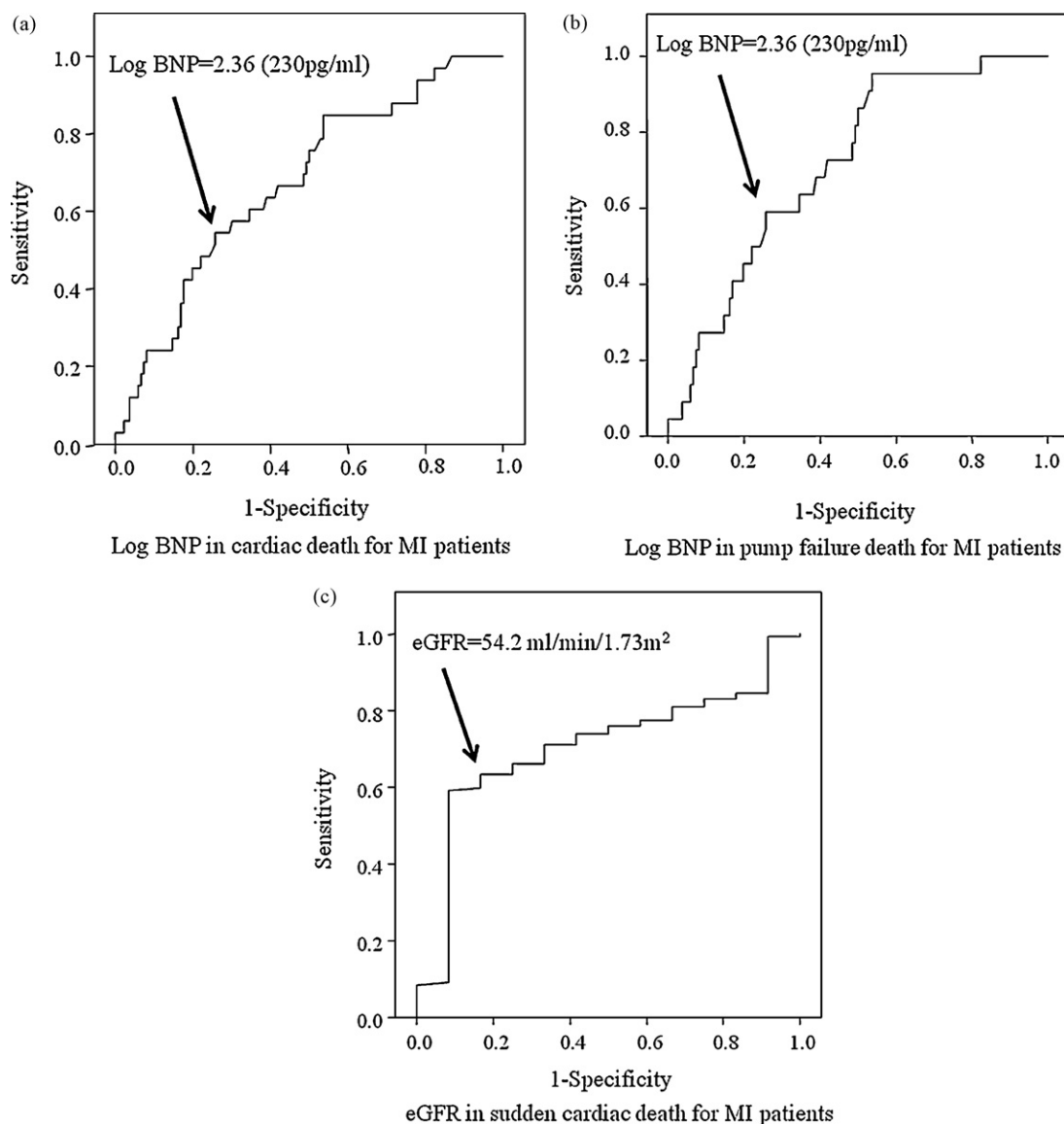
Figure 1   The receiver operating characteristics (ROC) curves of predictive factors for myocardial infarction (MI) patients. (a) ROC curve of log B-type natriuretic peptide (BNP) for MI patients with cardiac death. Area under the curve (AUC) was 67.3%, sensitivity was 54.5% and specificity was 74.3%. The cut-off value of log BNP was 2.36, equivalent to a BNP level of 230 pg/ml. (b) ROC curve of log BNP for MI patients with pump failure death. AUC was 71.7%, sensitivity was 59.1% and specificity was 74.3%. The cut-off value of log BNP was 2.36, equivalent to a BNP level of 230 pg/ml. (c) ROC curve of estimated glomerular filtration rate (eGFR) for MI patients with sudden cardiac death. AUC was 70.4%, sensitivity was 63.4% and specificity was 83.3%. The cut-off value of eGFR was 54.2 ml/min/1.73 m^2.

In the MI patients, the occurrence of cardiac death was significantly higher in the patients with high BNP levels than in those with low BNP levels ($p < 0.0001$) (Fig. 3a). The occurrence of pump failure death was significantly higher in the patients with high BNP levels than in those with low BNP levels ($p < 0.0001$) (Fig. 3b). The occurrence of sudden cardiac death was significantly higher in the patients with low eGFR levels than in those with high eGFR levels ($p < 0.0001$) (Fig. 3c).

In the NIHF patients, the occurrence of cardiac death was significantly higher in the patients with high BNP levels than in those with low BNP levels ($p = 0.0002$) (Fig. 4a). The occurrence of pump failure death was significantly higher in the patients with high BNP levels than in those with low BNP levels ($p < 0.0001$) (Fig. 4b).

Discussion

Although the diagnostic value of measuring plasma BNP levels has been established in patients with cardiac dysfunction, there have been few reports investigating the prognostic value of it in the long term; furthermore, there have been few reports analyzing the predictive factors for heart failure death, which is sub-divided into pump failure death and sudden cardiac death. In the present study, we sub-divided the heart failure patients who died into two groups:
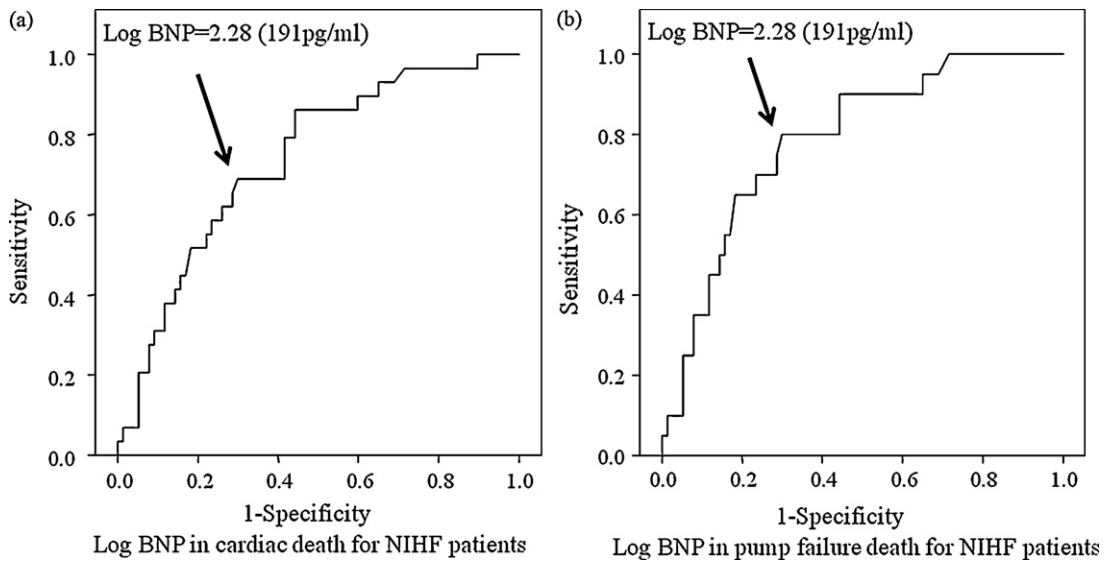
Figure 2 The receiver operating characteristics (ROC) curves of predictive factors for non-ischemic heart failure (NIHF) patients. (a) ROC curve of log B-type natriuretic peptide (BNP) for NIHF patients with cardiac death. Area under the curve (AUC) was 73.7%, sensitivity was 69.0% and specificity was 70.1%. The cut-off value of log BNP was 2.28, equivalent to a BNP level of 191 pg/ml. (b) ROC curve of log BNP for NIHF patients with pump failure death. AUC was 78.7%, sensitivity was 80.0% and specificity was 70.1%. The cut-off value of log BNP was 2.28, equivalent to a BNP level of 191 pg/ml.
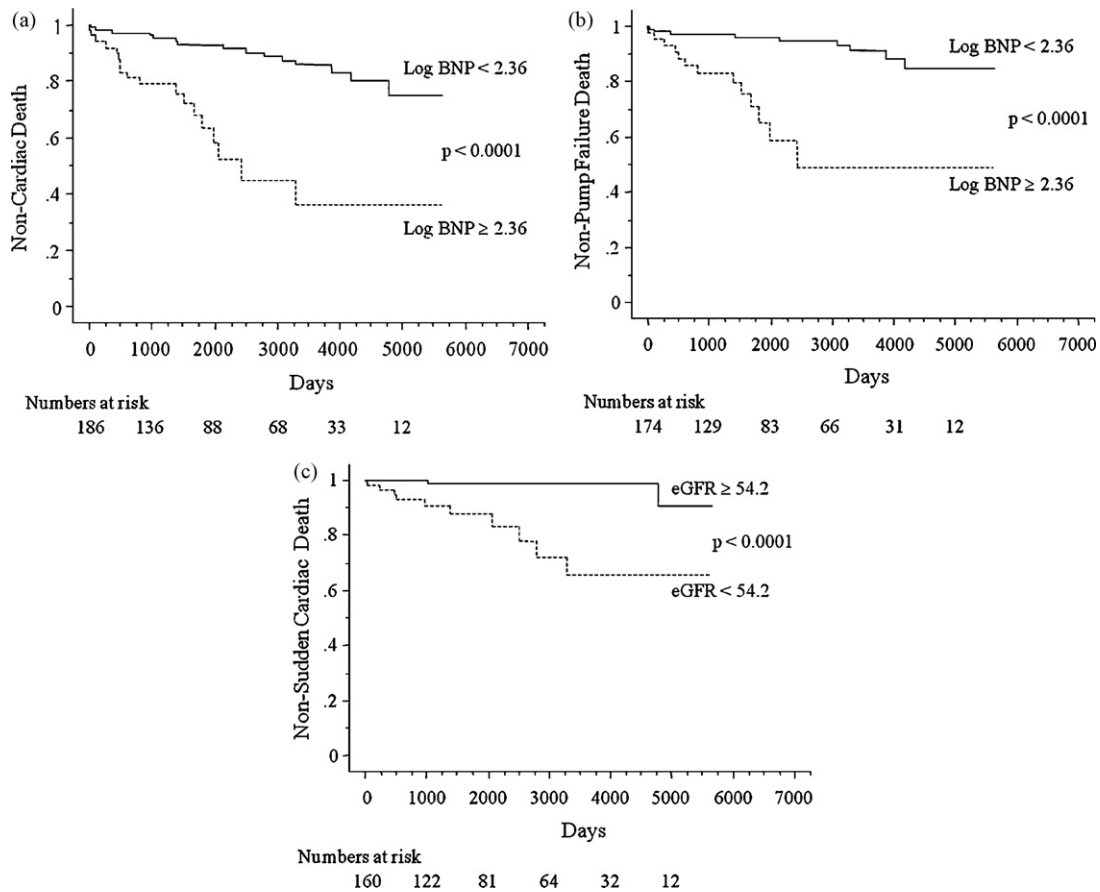

Figure 3 Kaplan—Meier survival curves of cumulative survival rates in patients with myocardial infarction (MI). (a) Kaplan—Meier survival curves of cumulative non-cardiac death rates in patients with MI divided into two sub-groups according to their log B-type natriuretic peptide (BNP) values. (b) Kaplan—Meier survival curves of cumulative non-pump failure death rates in patients with MI divided into two sub-groups according to their log BNP values. (c) Kaplan—Meier survival curves of cumulative non-sudden cardiac death rates in patients with MI divided into two sub-groups according to their estimated glomerular filtration rate (eGFR) values.
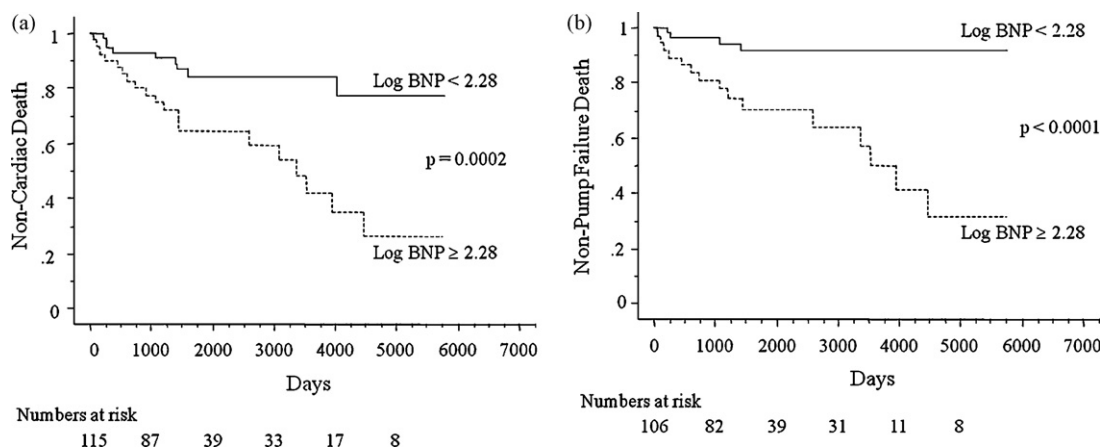
Figure 4 Kaplan–Meier survival curves of cumulative survival rates in patients with non-ischemic heart failure (NIHF). (a) Kaplan–Meier survival curves of cumulative non-cardiac death rates in patients with NIHF divided into two sub-groups according to their log B-type natriuretic peptide (BNP) values. (a) Kaplan–Meier survival curves of cumulative non-pump failure death rates in patients with NIHF divided into two sub-groups according to their log BNP values.

those with pump failure death and those with sudden cardiac death. Herein we investigated the prognostic predictive factors for pump failure death and sudden cardiac death, in the MI patients and in the NIHF patients: furthermore, we determined cut-off values which can be used for prognostic predictive factors.

In the MI group, a plasma BNP level was the only independent prognostic predictive factor for pump failure death. We determined that the best cut-off value of plasma BNP level for predicting morbidity and mortality was 230 pg/ml. This plasma BNP level dovetails neatly with previous reports [12,21]. Out of 38 cardiac death patients, 12 patients died from sudden cardiac death in the MI group, eGFR was the only independent predictive factor for sudden cardiac death. We decided that the best cut-off value of eGFR was 54.2 ml/min/1.73 m^2. Recent studies have shown an association between progressive chronic kidney disease and cardiovascular morbidity and mortality [16,22]. The occurrence of malignant arrhythmia, including ventricular tachycardia and ventricular fibrillation, is high in end-stage renal failure patients because of cardiac hypertrophy and/or cardiac fibrosis [23,24]. Components of autonomic dysfunction and altered electrolyte metabolism have also been suggested to contribute to a risk of malignant arrhythmia [25,26]. Previous studies have shown a significant association between sudden cardiac death and renal dysfunction in MI patients with severe cardiac dysfunction (left ventricular ejection fraction ≤30%) [27]. In the present long-term follow-up study, we found that mild to severe renal dysfunction was a significant prognostic predictive factor for sudden cardiac death in consecutive MI patients who had mild to severe cardiac dysfunction; therefore, we recommend that patients with MI and renal dysfunction (eGFR <54.2 ml/min/1.73 m^2) should be treated much more carefully by clinicians.

Up until now, there have been no long-term follow-up studies to investigate plasma BNP levels in patients with NIHF. In the NIHF patients, the plasma BNP level was the only significant independent predictor for pump failure death. We decided that the best cut-off value for plasma BNP level

in the pump failure death patients was 191 pg/ml. The cut-off value of log BNP for predicting morbidity and mortality was higher in patients with MI than in those with NIHF. Secretion levels of BNP from cardiomyocytes are induced by hypertrophy, mechanical stress, cytokines, and/or oxidative stress. In a heart undergoing MI, myocardial hypertrophy is induced in the non-infarct myocytes, especially in the myocytes around the infarction site [28]. The myocytes also sustain mechanical stress. Around the infarction site, we can see abundant inflammatory cells which produce abundant cytokines and oxidative stress. These above results possibly show the reason why the plasma BNP levels in MI patients are higher than in NIHF patients and why the cut-off value of log BNP for predicting morbidity and mortality was higher in patients with MI than in those with NIHF. We recommend that an effort should be made to control the plasma BNP level in MI patients but more rigorously in NIHF patients.

There were no significant predictive factors for sudden cardiac death in the NIHF group among the variables that we utilized in this study. Almost all NIHF patients in the present study presented with dilated cardiomyopathy (DCM).

DCM is recognized as a heritable disorder, especially in patients with malignant arrhythmia [29]. Mutations in genes related to cytoskeletal [30], contractile [31], nuclear membrane [32], and other [33] proteins have been identified in patients with familial or sporadic DCM. There are possibly genetic factors which predispose the patients to cardiac sudden death due to their malignant arrhythmia. Further research, using a larger and genetic clinical study, is necessary to clarify the significant predictive factors for cardiac sudden death in NIHF patients.

Conclusion

A plasma BNP level is a significant independent predictive factor for pump failure death in MI and NIHF patients. eGFR is a significant independent predictive factor for sudden cardiac death in MI patients.

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