

[ORIGINAL ARTICLE]

Combined Assessment of the Red Cell Distribution Width and B-type Natriuretic Peptide: A More Useful Prognostic Marker of Cardiovascular Mortality in Heart Failure Patients

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Abstract:

Objective An increased red cell distribution width (RDW) has been reported to be associated with adverse outcomes in patients with heart failure (HF). This study aimed to evaluate the prognostic power of the combined measurement of RDW and B-type natriuretic peptide (BNP) concentrations in patients with HF.

Methods and Results We retrospectively studied 116 patients (mean age, 63.7±14.3 years) who were admitted for the treatment of HF. Data including demographic information, vital signs, and laboratory and echocardiographic measurements at admission were collected from medical records. The observational period was defined as the number of days from hospitalization, and the study endpoint was defined as cardiovascular death. The mean RDW and BNP concentration at admission were 14.5±2.0% and 626±593 pg/mL, respectively. During a median observation period of 1,046 days, 22 patients died of cardiovascular disease. A univariate Cox proportional hazard analysis revealed that both RDW [hazard ratio (HR) 1.252, $p = 0.0391$] and BNP (HR 1.001, $p = 0.0445$) were significant prognostic indices for cardiovascular death. A receiver operating characteristic curve analysis revealed that the optimal cut-off RDW and BNP values for cardiovascular death were 14.9% and 686 pg/mL, respectively. The Kaplan-Meier survival curve revealed that the survival rate of patients with both RDW $\geq 14.9\%$ and BNP ≥ 686 pg/mL showed the poorest prognosis in comparison to the patients in the other groups.

Conclusion The combined assessment of the RDW and BNP concentrations may be useful for predicting mortality in patients with HF.

Key words: heart failure, prognosis, B-type natriuretic peptide, red cell distribution width

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Introduction

Heart failure (HF), which is among the most common cardiovascular disorders, is associated with high rates of morbidity and mortality. The accurate prediction of the outcome of HF is critically important and many approaches have been suggested. Although various parameters can be used to predict the prognosis of HF, most are costly to evaluate. Thus, there is a need for prognostic parameters that can be measured simply and inexpensively.

B-type natriuretic peptide (BNP) is a polypeptide secreted

by the ventricles in response to the excessive stretching of ventricular cardiomyocytes (1). BNP is a sensitive biochemical marker that reflects the ventricle load (2). Many studies have demonstrated the usefulness of the serum BNP concentration in the diagnosis of HF (2-5). Furthermore, several studies have reported that the serum BNP concentration has prognostic value in HF patients (6-8); thus, BNP is considered to be the gold standard for predicting the outcome of HF.

The red cell distribution width (RDW) is a measurement of the variation in the size of circulating red blood cells. This parameter is a widely investigated, and in routine labo-

ratory tests, it is reported as a component of the complete blood cell count. It is calculated as the percentage of the standard deviation of the red blood cell size divided by the mean corpuscular volume. RDW elevation has been traditionally used as a surrogate for ineffective erythropoiesis (9), in the investigation of the etiology of anemia (10). Recently, many studies have reported an association between the RDW and adverse cardiovascular outcomes. The RDW is a novel prognostic marker in patients with HF (11-14), stroke (15), myocardial infarction (16), and pulmonary hypertension (17).

The RDW and BNP are independent prognostic predictors in HF patients. However, the impact of the combined assessment of the RDW and BNP levels as a prognostic marker in HF is unknown. This study aimed to assess the prognostic value of the combination of the RDW and BNP in predicting the cardiovascular outcomes of HF patients.

Materials and Methods

Study population

This study was a single-center, retrospective cohort study. We enrolled 123 patients who were admitted to the Kagoshima University Hospital with a clinical diagnosis of HF from April 2008 to February 2011. Demographic information, medical history, vital signs and drug utilization data were routinely collected on admission. There were no patients with end-stage renal disease requiring hemodialysis, severe liver function abnormality (total bilirubin >3.0 mg/dL), recent transfusion (within the past 3 months), or a condition associated with an increased RDW (*i.e.*, hemolytic anemia), evident neoplastic metastasis to bone marrow, pregnancy, severe arthritis, or inflammatory bowel disease.

The study conformed to the Declaration of Helsinki and was approved by the institutional ethics committee of Kagoshima University Hospital.

Laboratory measurements and echocardiographic findings

Blood samples were collected from all patients on admission, and routine biochemical parameters were measured by standard techniques. Hematologic variables, such as the hemoglobin concentration, hematocrit, and RDW, were determined using a hematology analyzer (Sysmex XE-5000™ Automated Hematology System, Sysmex Corporation, Kobe, Japan). The reference range of normal RDW values was 12.0-16.0%. The BNP level was measured using a completely automated sample selective analyzer with a commercially available assay (Lumipulse® G1200, Fujirebio, Tokyo, Japan).

On admission, the diameter of the left atrium (LAD), the diameter of the left ventricle (LVDd), and the left ventricular ejection fraction (LVEF) were evaluated by two-dimensional echocardiography. The left ventricular inflow velocity pattern and estimated systolic pressure of the right

ventricle were evaluated using pulse and continuous wave Doppler echocardiography, and the peak early diastolic velocity of the mitral annulus in the septum was evaluated using tissue Doppler echocardiography.

Follow-up and the clinical endpoints

The study endpoint was defined as cardiovascular death, and all study participants were followed up from the time that they were identified by our department. The mortality data were obtained from hospital medical records and/or by contacting the patient or relatives.

Statistical analysis

Continuous variables, including age, body mass index, RDW, and BNP, were expressed as the mean±SD. Categorical variables, including sex, etiology of HF, and history of underlying disease, were shown as the number of subjects and proportions (percentages). The optimal cut-off RDW and BNP values were considered to be those that yielded the highest sensitivity and specificity for predicting cardiovascular mortality in a receiver operating characteristics (ROC) curve analysis. Cumulative hazard curves were constructed to assess the association between the rates of cardiovascular death and the RDW or/and BNP level. Differences in the survival rate were evaluated using a log-rank test. The effects of variables on cardiovascular death were calculated by a Cox univariate proportional hazard regression analysis. The hazard ratio (HR) with 95% confidence interval demonstrated the risk of cardiovascular mortality. All statistical analyses were performed using the JMP Pro software program (version 11 for Windows, SAS Institute Inc, Cary, USA). *p* values of < 0.05 were considered to indicate statistical significance.

Results

The baseline characteristics and clinical outcomes

One hundred sixteen patients (94.3%) were followed up and twenty-four deaths occurred during the median observational period of 1,046 days, of which 22 were cardiovascular deaths (HF, *n*=15; sudden death, *n*=5; rupture of aortic aneurysm, *n*=1; stroke, *n*=1).

The clinical characteristics of the HF patients on admission are summarized in Table 1. The mean age was 63.7±14.3 years, and 80 patients (69.0%) were men. Sixty patients (51.7%) had a New York Heart Association (NYHA) functional class III or IV. The mean systolic blood pressure, LVDd, and LVEF were 109±20 mmHg, 62±9 mm and 32±12%, respectively. The mean hemoglobin concentration, corpuscular volume, and corpuscular hemoglobin concentration were 13.3±2.2 g/dL, 91.8±5.5 μm³, and 33.2±2.9 g/dL, respectively; all values were within the normal range. The mean RDW and BNP were 14.5±2.0% and 626±593 pg/mL, respectively. The etiology of HF was dilated cardiomyopathy in 50.0% of the patients and ischemic cardiomyopathy in

Table 1. Baseline Patients Characteristics.

	All	RDW<14.9% BNP<686 pg/mL	RDW ≥ 14.9% BNP<686 pg/mL	RDW<14.9% BNP≥686 pg/mL	RDW ≥ 14.9% BNP≥686 pg/mL
	n=116	n=63	n=19	n=16	n=18
Demographics					
Age (years)	63.7±14.3	63.4±13.2	63.2±18.6	62.0±13.2	66.2±14.4
Male (%)	80 (69.0)	48 (76.2)	9 (47.4)	11 (68.8)	12 (66.7)
BMI (kg/m ²)	21.9±3.3	22.3±2.9	22.2±3.5	21.4±5.1	20.8±2.4
Clinical variables					
SBP (mmHg)	109±20	112±17	118±27	97±14	100±17
DBP (mmHg)	67±14	69±12	71±19	64±16	62±11
Heart rate (beats/min)	76±15	74±13	78±21	79±19	78±11
NYHA I (%)	9 (7.8)	7 (11.1)	1 (5.3)	0 (0.0)	1 (5.6)
NYHA II (%)	47 (40.5)	33 (52.4)	6 (31.6)	6 (37.5)	2 (11.1)
NYHA III (%)	54 (46.6)	23 (36.5)	10 (52.6)	10 (62.5)	11 (61.1)
NYHA IV (%)	6 (5.1)	0 (0.0)	2 (10.5)	0 (0.0)	4 (22.2)
Current smoker (%)	21 (18.1)	12 (19.1)	2 (10.5)	5 (31.3)	2 (11.1)
Etiology					
DCM (%)	58 (50.0)	32 (55.2)	7 (12.1)	10 (17.2)	9 (15.5)
Ischemic (%)	34 (29.3)	15 (44.1)	7 (20.6)	5 (14.7)	7 (20.6)
Valvular or Congenital (%)	8 (6.9)	5 (62.5)	1 (12.5)	0 (0.0)	2 (25.0)
Hypertensive (%)	5 (4.3)	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)
Others (%)	11 (9.5)	7 (63.6)	3 (27.3)	1 (9.1)	0 (0.0)
History of underlying disease					
Hypertension (%)	31 (26.7)	16 (51.6)	10 (32.2)	2 (6.5)	3 (9.7)
Diabetes mellitus (%)	27 (23.3)	14 (51.9)	2 (7.4)	6 (22.2)	5 (18.5)
Dyslipidemia (%)	51 (44.0)	27 (52.9)	13 (25.5)	9 (17.6)	2 (3.6)
Atrial fibrillation (%)	40 (34.5)	22 (55.0)	8 (20.0)	2 (5.0)	8 (20.0)
Laboratory (blood cell count)					
WBC (×10 ³ /μL)	6.0±1.9	5.8±1.8	6.1±1.9	7.1±2.6	5.4±1.3
RBC (×10 ⁶ /μL)	4.3±0.7	4.4±0.7	4.3±0.8	4.2±0.8	4.3±0.7
Hemoglobin (g/dL)	13.3±2.2	13.8±2.2	12.5±1.8	13.3±2.4	12.7±1.8
Hematocrit (%)	39.8±6.2	40.8±6.2	38.3±6.1	39.4±7.1	38.5±5.0
MCV (μm ³)	91.8±5.5	92.4±4.5	89.8±6.6	95.0±3.1	89.3±7.3
MCH (pg/cell)	30.7±2.2	31.1±1.7	29.4±2.4	32.0±1.4	29.4±2.8
MCHC (g/dL)	33.2±2.9	33.2±3.8	32.8±0.9	33.7±0.8	32.9±1.3
RDW (%)	14.5±2.0	13.4±0.7	16.6±1.7	13.5±0.8	16.8±1.3
PLT (×10 ⁴ /μL)	19.9±7.4	20.6±8.0	19.1±5.8	21.2±8.6	16.9±4.8
Laboratory (chemistry)					
Albumin (g/dL)	4.1±0.9	4.1±0.4	4.4±0.5	3.8±0.4	3.8±0.5
Triglyceride (mg/dL)	103±65	114±80	103±44	80±26	80±35
HDL-C (mg/dL)	54±18	57±20	49±12	50±13	49±18
LDL-C (mg/dL)	108±36	111±37	106±38	108±26	99±42
BS (mg/dL)	107±36	110±43	92±18	117±34	103±16
HbA1c (%)	6.0±1.4	6.2±1.8	5.5±0.5	5.9±0.7	6.2±0.6
Uric acid (mg/dL)	6.8±2.2	6.5±1.9	6.8±2.3	7.5±2.9	7.1±2.2
Total bilirubin (mg/dL)	1.0±0.6	0.9±0.1	1.2±1.0	1.0±0.7	1.2±0.5
BUN (mg/dL)	24.8±11.6	22.3±9.0	26.2±14.2	30.4±14.2	27.3±12.9
Creatinine (mg/dL)	1.1±0.5	1.0±0.4	1.1±0.5	1.2±0.5	1.2±0.6
eGFR (mL/min/1.73m ²)	75.6±39.2	80.8±41.7	75.5±43.6	67.2±35.6	64.4±26.2
Sodium (mEq/L)	139±4	139±4	140±4	138±3	136±6
CRP (mg/dL)	0.9±2.3	0.6±1.6	0.6±1.0	2.5±4.6	0.6±1.7
BNP (pg/mL)	626±593	315±162	371±156	1,393±680	1,303±616

Table 1. Baseline Patients Characteristics. (continued).

	All	RDW<14.9% BNP<686 pg/mL	RDW ≥ 14.9% BNP<686 pg/mL	RDW<14.9% BNP≥686 pg/mL	RDW ≥ 14.9% BNP≥686 pg/mL
	n=116	n=63	n=19	n=16	n=18
Echocardiographic findings					
LVDd (mm)	62±9	62±9	57±8	65±9	63±8
LVDs (mm)	52±11	51±11	47±9	57±13	54±8
LVEF (%)	32±12	35±12	36±14	25±10	25±6
LAD (mm)	46±10	44±8	47±8	45±8	52±7
E/A	1.7±1.3	1.4±1.2	2.1±1.4	1.8±1.1	2.6±1.4
E/E'	20±13	16±9	21±15	22±9	27±17
RVSP (mmHg)	39±12	36±11	39±11	39±13	44±10
Medication					
ACE-I (%)	57 (49.1)	28 (44.4)	8 (42.1)	9 (56.3)	12 (66.7)
ARB (%)	54 (46.6)	34 (54.0)	10 (52.6)	7 (43.8)	3 (16.7)
Beta blocker (%)	104 (89.7)	53 (84.1)	18 (94.7)	15 (93.8)	18 (100.0)
Loop diuretics (%)	106 (91.4)	55 (87.3)	18 (94.7)	16 (100.0)	17 (94.4)
Aldosterone antagonist (%)	86 (74.1)	42 (66.7)	15 (79.0)	14 (87.5)	15 (83.3)
CCB (%)	20 (17.2)	15 (23.8)	4 (21.1)	0 (0.0)	1 (5.6)
Digitalis (%)	20 (17.2)	10 (15.9)	5 (26.3)	2 (12.5)	3 (16.7)
Pimobendan (%)	26 (22.4)	6 (9.5)	5 (26.3)	4 (25.0)	11 (61.1)
Aspirin (%)	59 (50.9)	32 (50.8)	9 (47.4)	9 (56.3)	9 (50.0)
Statin (%)	46 (39.7)	26 (41.3)	7 (36.8)	7 (43.8)	6 (33.3)

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, NYHA: New York Heart Association, DCM: dilated cardiomyopathy, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, BS: blood sugar, HbA1c: glycosylated hemoglobin, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, CRP: C reactive protein, BNP: B-type natriuretic peptide, WBC: white blood cell count, RBC: red blood cell count, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width, PLT: platelet count, LVDd: diastolic diameter of left ventricle, LVDs: systolic diameter of left ventricle, LVEF: left ventricular ejection fraction, LAD: diameter of left atrium, E/A: ratio of peak early diastolic mitral inflow to peak late diastolic mitral inflow, E/E': ratio of peak early diastolic mitral inflow to annular velocity, RVSP: systolic pressure of right ventricle, ACE-I: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB: calcium channel blocker

29.3% of the patients. The baseline electrocardiogram revealed atrial fibrillation in 40 patients (34.5%). At discharge, 111 patients (95.7%) were taking angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and 104 patients (89.7%) were taking beta-blockers.

The association between cardiovascular death and RDW, BNP, and other variables

The results of a Cox proportional hazard analysis to investigate the factors that predict cardiovascular death are shown in Table 2. The univariate analyses revealed that age, history of prior chronic heart failure (CHF), NYHA class, RDW, BNP, and ratio of the early transmitral flow velocity to the early mitral annular velocity (E/Eka') were significant prognostic indices for survival, but that LVDd and LVEF were not. Furthermore, an age-adjusted bivariate analysis revealed that both the RDW and BNP on admission were significant predictors of cardiovascular mortality (RDW: HR 1.303, $p = 0.0185$; BNP: HR 1.001, $p = 0.0051$). In addition, the RDW remained a significant predictor after adjustment for BNP (HR 1.243, 95% CI 1.006-1.496, $p = 0.0441$). An ROC curve analysis was performed to assess the power of RDW and BNP for predicting cardiovascular death (Fig. 1). At RDW = 14.9%, the area under the curve

(AUC) was 0.59, and the sensitivity and specificity were 50.0% and 73.1%, respectively. In addition, when BNP was 686 pg/mL, the AUC was 0.58 and the sensitivity and specificity were 45.5% and 75.3%, respectively (Table 3).

Survival curves of RDW and BNP in predicting cardiovascular death

The Kaplan-Meier survival curve was assessed using a cut-off RDW of 14.9% and a cut-off BNP value of 686 pg/mL. Fig. 2A shows the Kaplan-Meier survival curves for patients with an RDW of $\geq 14.9\%$ and those with an RDW of $< 14.9\%$. The survival rate of patients with a high RDW was significantly greater than that of patients with a low RDW ($p = 0.0037$). In addition, patients with BNP values of ≥ 686 pg/mL had significantly higher rates of cardiovascular mortality than those with BNP values of < 686 pg/mL (Fig. 2B, $p = 0.0101$). Furthermore, patients with both a high RDW and a high BNP levels (RDW $\geq 14.9\%$ and BNP ≥ 686 pg/mL) showed the highest rate of mortality among the groups (Fig. 2C, $p = 0.0003$).

Discussion

In the present study, we demonstrated that the RDW and

Table 2. Cox Proportional Hazard Analysis Investigating the Predicting Factors for Cardiovascular Death.

Variables	Univariate			Adjusted by age		
	χ^2	Hazard ratio (95%CI)	p value	χ^2	Hazard ratio (95%CI)	p value
Age, years	5.441	1.043 (1.006-1.088)	0.0197			
History of prior CHF	6.476	3.546 (1.311-12.341)	0.0109	8.384	1.887 (1.223-2.983)	0.0048
NYHA class	6.313	2.237 (1.306-3.186)	0.0110	2.068	1.512 (1.116-1.908)	0.0317
BNP, pg/mL	7.861	1.001 (1.000-1.002)	0.0050	7.841	1.001 (1.000-1.002)	0.0051
RDW, %	5.996	1.289 (1.057-1.534)	0.0143	5.551	1.303 (1.049-1.579)	0.0185
LVEF, %	0.099	0.994 (0.956-1.028)	0.7522	0.722	0.985 (0.946-1.019)	0.3954
LVDd, mm	0.008	0.999 (0.952-1.044)	0.9281	0.208	1.011 (0.963-1.061)	0.6480
E/E'	3.941	1.026 (1.001-1.046)	0.0471	1.801	1.010 (0.995-1.024)	0.1796

CHF: congestive heart failure, NYHA: New York Heart Association, BNP: B-type natriuretic peptide, RDW: red cell distribution width, LVEF: left ventricular ejection fraction, LVDd: diastolic diameter of left ventricle, E/E': ratio of peak early diastolic mitral inflow to annular velocity

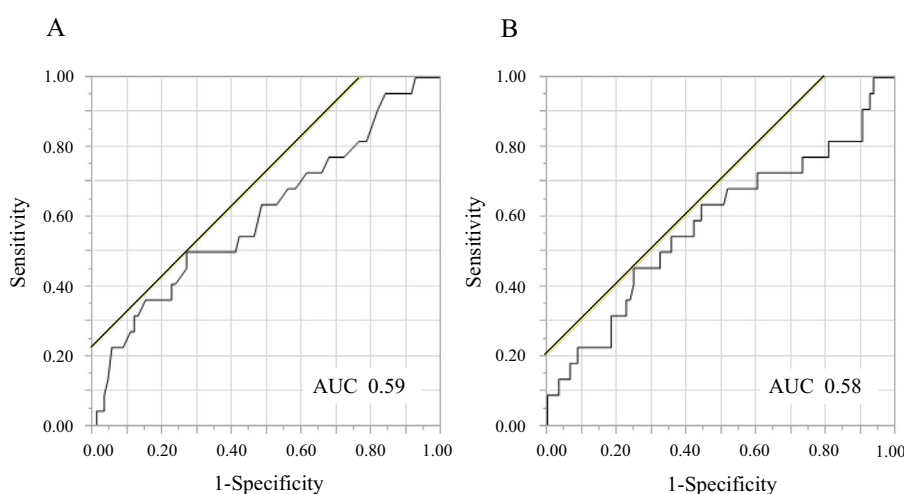


Figure 1. The receiver operating characteristic curves between RDW or BNP and cardiovascular death in patients with heart failure. (A) Cardiovascular death and RDW. (B) Cardiovascular death and BNP. AUC: area under the curve, RDW: red cell distribution width, BNP: B-type natriuretic peptide

Table 3. Diagnostic Information for the Prediction of Cardiovascular Death by RDW and BNP.

Variables	Optimal cut-off point	Sensitivity% (95%CI)	Specificity% (95%CI)	PPV% (95%CI)	NPV% (95%CI)
RDW	14.9%	50.0 (32.4-67.2)	73.1 (69.0-77.2)	30.6 (19.8-41.1)	86.1 (81.2-90.9)
BNP	686 pg/mL	45.5 (28.5-62.9)	75.3 (71.3-79.4)	30.3 (19.0-41.9)	84.5 (80.8-90.0)

RDW: red cell distribution width, BNP: B-type natriuretic peptide

BNP level on admission can individually predict cardiovascular mortality in HF patients. Moreover, the combined assessment of the RDW and BNP was more useful for predicting cardiovascular mortality in comparison to the RDW or BNP alone.

The clinical usefulness of the RDW is noteworthy because the RDW is routinely available with every complete blood count test and is relatively inexpensive to perform and minimally invasive. Several reports have demonstrated the value of the RDW for predicting adverse outcomes in HF patients (14, 18, 19). The RDW is a useful prognostic

marker not only for HF but also for atherosclerotic diseases, such as coronary artery disease (20-22) or carotid artery disease (23). Various mechanisms have been suggested to underlie the association between the RDW and poor outcomes in patients with HF. Several studies have suggested that the RDW is related to the degree of inflammation, the inadequate production of erythropoietin, the renal function, or the nutritional status (24-26). In this study, there were no significant differences in the serum albumin (4.0 ± 0.4 vs. 3.8 ± 0.6 g/dL, $p = 0.1207$), total cholesterol (183 ± 39 vs. 169 ± 43 mg/dL, $p = 0.0925$), blood urea nitrogen (23.9 ± 10.6 vs.

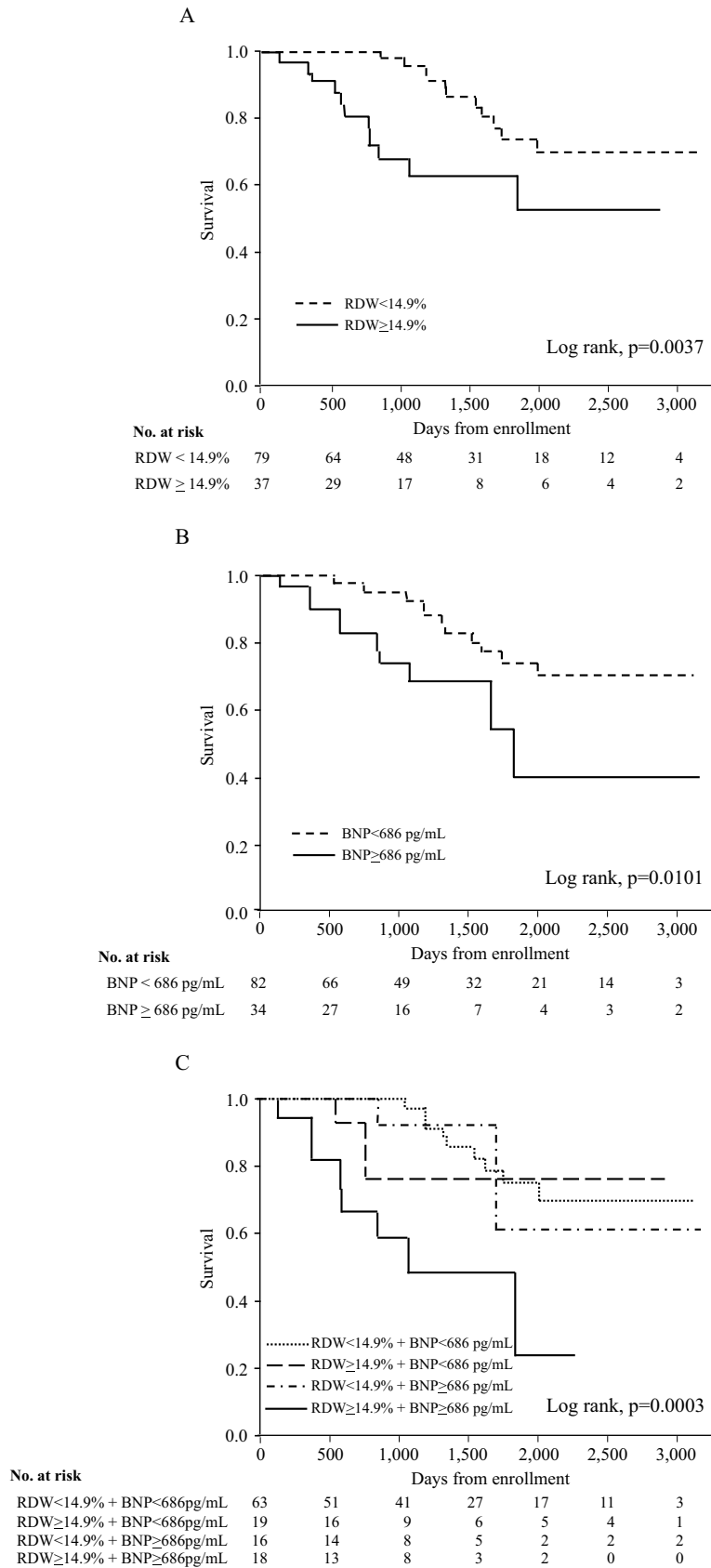


Figure 2. Kaplan-Meier survival curves for RDW and BNP. Kaplan-Meier survival curves demonstrating cardiovascular mortality when the patients were divided into two groups according to a cut-off RDW of 14.9% (A), a cut-off BNP of 686 pg/mL (B), and when the patients were divided into four groups according to both the RDW and BNP (C). RDW: red cell distribution width, BNP: B-type natriuretic peptide

26.8±13.6 mg/dL, $p = 0.1876$), or creatinine (1.0 ± 0.4 vs. 1.2 ± 0.6 mg/dL, $p = 0.0938$) values of the low RDW (< 14.9%) and high RDW (> 14.9%) groups; however, both the renal function and the nutritional status tended to be worse in the high RDW group. We think that this is because the number of participants was too small to detect significant differences in these factors. Natriuretic peptides are principally produced within the heart and released into the circulation in response to elevated intra-cardiac filling pressure and myocardial wall stress (27). Traditionally, BNP has been an important prognostic predictor in HF patients (7, 28, 29). In the present study, patients with high RDW or BNP levels showed a significantly poorer prognosis than patients with low RDW or BNP levels. Moreover, the combination of RDW and BNP provided further prognostic value in HF patients. The combination of RDW and BNP appears to be a more powerful prognostic indicator for the clinical outcome of HF than either RDW or BNP alone, and the risk stratification of patients according to combination of RDW and BNP levels may be useful in the clinical setting.

Previous studies have demonstrated that both RDW and BNP were independent prognostic factors in HF patients. An increased RDW level in HF patients is associated with inflammation, which is a principal pathophysiologic finding in with endothelial dysfunction or HF (30, 31). BNP is influenced by renal dysfunction (32, 33). Although BNP is a widely accepted measure of severe HF, most geriatric patients who with HF have concomitant chronic kidney disease, and the severity of HF may be overestimated by BNP in these patients. Both RDW and BNP represent a different aspect of HF severity. Thus, the combined assessment of RDW and BNP for the prediction of mortality in HF patients may be worthy of consideration.

The present study is associated with several limitations. First, it was a single-center study with a relatively small number of patients. Because of the small sample size, the relationship between well-known predictors may either be insignificant or only marginally significant. In addition, we could not perform a multivariate analysis that included more than three items as explanatory variables because of the small study population. Consequently, we could not show the independence of RDW in the present study. Thus, a large prospective study is necessary to validate the results of the present study. Second, we examined the predictive power of variables at a single time point and did not explore the possibility that the variables may change over time, which might have affected the outcome. Finally, we lacked data regarding the erythropoietin, folate, vitamin B12, iron, and inflammatory cytokine levels, which might have contributed to the mechanism underlying the association between the RDW and the outcome.

In conclusion, the combined assessment of RDW and BNP concentrations may be useful for predicting mortality in patients with HF.

The authors state that they have no Conflict of Interest (COI).

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