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Relationship between worsening renal function and long-term cardiovascular mortality in heart failure patients

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ABSTRACT

Background: Recently several studies showed that worsening renal function (WRF) during hospitalization might be a strong independent predictor of poor prognosis in decompensated heart failure (HF) patients. However, these studies had a relatively short follow-up duration and their data were limited to in-hospital outcomes. Our purpose was to assess the relationship between WRF and long-term cardiovascular mortality in HF patients.
Methods: We enrolled decompensated HF patients who were admitted to our hospital between April 2010 and March 2015. WRF was defined as a relative increase in serum creatinine of at least 25% or an absolute increase in serum creatinine ≥0.3 mg/dL from the baseline. We assessed the cardiovascular mortality and all-cause mortality in HF patients with WRF (WRF group) and without WRF (no WRF group).
Results: Among 301 patients enrolled, WRF developed in 118 patients (39.2%). During a median follow-up period of 537 days [interquartile range, 304.3 to 1025.8 days], cardiovascular mortality and all-cause mortality were significantly higher in the WRF group than in the no WRF group (23.2% vs. 6.1%, $P < 0.001$; 30.3% vs. 14.7%, $P < 0.001$, respectively). In the multivariate Cox proportional hazards model, age and serum B-type natriuretic peptide (BNP) level were associated with both cardiovascular death and all-cause death. However, WRF was not the independent predictor of cardiovascular death ($P = 0.19$) nor all-cause death ($P = 0.57$).
Conclusions: WRF was associated with cardiovascular death in patients with HF. Although not an independent predictor, WRF might be one of useful markers to identify patients who should be followed carefully after discharge.

1. Introduction

Renal dysfunction is highly prevalent in patients with heart failure (HF). According to previous studies of HF patients, the prevalence of renal dysfunction ranged from 20% to 67% and renal dysfunction on admission is a strong independent predictor of prognosis in HF patients [1–4]. Recently, several studies showed that worsening renal function (WRF) during hospitalization might be a strong independent predictor in acute decompensated HF patients. However, their data were limited to either in-hospital or up to 6-month outcomes [5–8]. Whereas, Testani et al. reported that aggressive decongestion might improve prognosis of HF regardless the occurrence of WRF [9]. Thus, the association of WRF during the treatment of decompensated HF and cardiovascular outcomes is still controversial. Our purpose was to assess the relationship between WRF and long-term outcome including all-cause and cardiovascular mortality in HF patients.

2. Methods

We obtained medical records of acute decompensated HF patients who admitted to Showa University Northern Yokohama hospital between March 2010 and March 2015. Patients 20 years of age and older were eligible for the study and the diagnosis of HF was based on the criteria of the Framingham study. We excluded the HF patients with acute coronary syndrome, pulmonary embolism, hemodialysis, or bradycardia that required pacemaker implantation. Patients with serum B-type natriuretic peptide (BNP) level < 100 pg/mL on admission were also excluded because non-cardiovascular factors might be the main cause of symptoms. The dose of loop diuretic was calculated as furosemide equivalent for patients who did not receive furosemide. The formula used to convert other loop diuretics to furosemide equivalents was as follows: furosemide 20 mg = azosemide 30 mg [10].

According to a previous study that investigated the relationship between WRF and HF, WRF was defined as a relative increase in serum creatinine of at least 25% or an absolute increase in serum creatinine ≥0.3 mg/dL from the baseline [11]. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2. The eGFR was calculated from serum creatinine with the Japanese coefficient for the abbreviated Modification of Diet in Renal Disease Study equation [12]. Medical records were reviewed by experienced cardiologists and clinical data including history, heart rate, systolic and diastolic blood pressure, medication, results of echocardiography, and laboratory values on admission and during hospitalization were collected. We assessed that the relationship between serum BNP level at discharge and the occurrence of WRF. The primary outcome in the present study was cardiovascular mortality and the secondary

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Table 1
Patient characteristics at baseline.

	All $n = 301$	WRF $n = 118$	No WRF $n = 183$	*P* value
Age, years	73.1 ± 14.5	75.7 ± 14.5	71.4 ± 14.3	0.01
Male gender, n (%)	184 (61.1)	68 (57.6)	116 (63.4)	0.32
NYHA class	3.4 ± 0.6	3.5 ± 0.7	3.3 ± 0.6	0.12
Heart rate, bpm	98.1 ± 26.7	98.9 ± 24.9	97.6 ± 27.8	0.67
SBP, mm Hg	140.7 ± 33.5	144.5 ± 35.9	138.3 ± 31.7	0.11
DBP, mm Hg	84.6 ± 23.8	87.1 ± 25.1	82.9 ± 23.0	0.13
Rehospitalization, n (%)	60 (19.9)	29 (24.6)	31 (16.9)	0.11
Mechanical ventilation, n (%)	58 (19.3)	29 (24.6)	29 (15.9)	0.06
Coarse crackles, n (%)	205 (68.1)	88 (74.6)	117 (63.9)	0.05
Gallop rhythm, n (%)	35 (11.6)	14 (11.9)	21 (11.5)	0.92
Edema, n (%)	209 (69.4)	85 (72.0)	124 (67.8)	0.43
LV diastolic diameter, mm	55.0 ± 9.1	54.7 ± 9.1	55.2 ± 9.1	0.63
LV systolic diameter, mm	43.2 ± 10.8	42.8 ± 10.9	43.5 ± 10.8	0.56
Ejection fraction, %	42.3 ± 15.5	43.3 ± 15.3	41.7 ± 15.6	0.41
Ejection fraction >50%, n (%)	99 (32.9)	40 (35.7)	59 (33.5)	0.70
Ischemic heart disease, n (%)	90 (29.9)	38 (32.2)	52 (28.4)	0.48
Medical history				
Atrial fibrillation, n (%)	171 (56.8)	95 (33.1)	76 (41.5)	0.14
Hypertension, n (%)	213 (70.7)	90 (76.3)	123 (67.1)	0.09
Hyperlipidemia, n (%)	124 (41.2)	54 (45.8)	70 (38.3)	0.20
Diabetes, n (%)	105 (34.9)	42 (35.6)	63 (34.4)	0.84
CKD, n (%)	160 (53.2)	69 (59.0)	91 (49.7)	0.12
Prescribed medications prior to admission				
Beta blocker, n (%)	84 (27.9)	31 (26.7)	53 (29.0)	0.67
ACEI/ARB, n (%)	119 (39.5)	47 (40.5)	72 (39.3)	0.84
Loop diuretics, n (%)	115 (38.2)	54 (46.6)	61 (33.3)	0.02
Furosemide equivalent dose, mg	31.1 ± 25.5	32.1 ± 26.9	30.2 ± 24.3	0.68
Aldosterone antagonist, n (%)	47 (15.6)	24 (20.7)	23 (12.6)	0.06
Thiazide diuretics, n (%)	7 (2.3)	1 (0.9)	6 (3.3)	0.15
In-hospital treatment				
Inotropic agents, n (%)	41 (13.6)	27 (22.9)	14 (7.7)	<0.001
Vasodilators, n (%)	223 (74.1)	90 (76.3)	133 (72.7)	0.49
IV furosemide, n (%)	217 (72.1)	92 (77.9)	125 (68.3)	0.07
IV furosemide dose, mg/day	22.6 ± 14.4	25.7 ± 18.3	20.4 ± 10.1	0.007
Tolvaptan, n (%)	67 (22.3)	38 (32.2)	29 (15.9)	0.001

Abbreviations: ACEI; angiotensin converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; IV, intravenous; LV, left ventricular; NYHA, New York Heart Association; SBP, systolic blood pressure.

outcome was all-cause mortality. The cardiovascular mortality was defined as death from HF, arrhythmia, or ischemic heart disease. Clinical follow-up was performed by periodic clinical visits or telephone calls to patients, their physicians or their relatives. We compared HF patients with WRF (WRF group) to HF patients without WRF (no WRF group). We assessed the association between all-cause and cardiovascular mortality and WRF. The present study complied with the Declaration of Helsinki and the study protocols were approved by the institutional review board. Waiving the requirement for obtaining written informed consents was allowed by the institutional review board since this study was a retrospective and observational study.

3. Statistical analysis

Data were analyzed using JMP 11 (SAS Institute, Inc., Cary, NC, USA). Continuous variables were reported as mean ± standard deviation or median ± interquartile range (IQR) which represents the 25th to 75th percentiles of the distribution of data. Categorical variables were presented as percentage and compared by chi-square test or Fisher's exact test, as appropriate. Comparisons between the WRF group and the no WRF group were performed by unpaired *t*-test or Wilcoxon rank sum test. The Kaplan-Meier method was used to estimate the cumulative survival and statistical significance was tested using the log rank test. Univariate and multivariate Cox proportional hazards models were used to estimate the hazard ratios and 95% confidence intervals (CI) for the association between WRF and all-cause or cardiovascular mortality. Variables with *P* value <0.10 were entered into the multiple regression analysis. We forced age and sex in the model. Variables usually reported in the literature to be associated with prognosis were also

Table 2
Laboratory data on admission.

	All $n = 301$	WRF $n = 118$	No WRF $n = 183$	*P* value
Hemoglobin, g/dL	12.3 ± 2.6	11.8 ± 2.7	12.6 ± 2.5	0.01
Albumin, g/L	3.46 ± 0.50	3.44 ± 0.55	3.48 ± 0.48	0.61
Uric acid, mg/dL	7.0 ± 2.3	6.9 ± 2.4	7.0 ± 2.2	0.58
BUN, mg/dL	24.7 ± 15.3	25.8 ± 15.2	24.0 ± 15.4	0.34
Creatinine, mg/dL	1.17 ± 0.69	1.28 ± 0.84	1.11 ± 0.59	0.05
eGFR, mL/min/1.73 m^2	53.7 ± 22.1	51.0 ± 23.2	55.3 ± 21.4	0.11
Plasma glucose, mg/dL	144.0 ± 88.2	155.9 ± 122.5	136.6 ± 57.5	0.19
Hemoglobin A1c, %	6.3 ± 1.3	6.4 ± 1.4	6.3 ± 1.2	0.62
Sodium, mEq/L	139.4 ± 4.3	139.2 ± 0.4	139.6 ± 4.4	0.41
Potassium, mEq/L	4.2 ± 0.6	4.2 ± 0.6	4.2 ± 0.6	0.81
Chloride, mEq/L	105.1 ± 4.8	104.9 ± 4.7	105.1 ± 4.9	0.73
BNP, pg/mL	785.8 ± 603.5	811.2 ± 664.2	770.7 ± 566.8	0.64

Abbreviations: BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

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