Clinical Investigation

Prognostic Impact of Worsening Renal Function in Hospitalized Heart Failure Patients With Preserved Ejection Fraction: A Report From the JASPER Registry

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ABSTRACT

Background: The characteristics and prognostic impact of persistent worsening renal function (WRF; defined as an increase in serum creatinine of >0.3 mg/dL during hospitalization) on heart failure with preserved ejection fraction have not yet been fully examined.

Methods and Results: This was a post hoc analysis of the Japanese Heart Failure Syndrome with Preserved Ejection Fraction (JASPER) registry. We divided 523 patients with heart failure with preserved ejection fraction: the WRF group (n = 92 [17.6%]) and the non-WRF group (n = 431 [82.4%]). The WRF group showed a higher systolic blood pressure on admission and a higher prevalence of atherosclerotic diseases, respectively. Logistic regression analysis revealed that systolic blood pressure and loop diuretics were associated with WRF development ($P < .05$). The Kaplan-Meier analysis (median, 732 days) showed a higher all-cause death in the WRF group, as well as a higher composite end point of all-cause death or rehospitalization for HF (log-rank $P < .001$). The Cox proportional hazard analysis revealed WRF to be a predictor of both all-cause death (hazard ratio, 2.725; 95% confidence interval, 1.709−4.344; $P < .001$) and the composite end point (hazard ratio, 2.083; 95% confidence interval, 1.488−2.914; $P < .001$).

Conclusions: Persistent WRF was associated with systolic blood pressure, atherosclerotic diseases, diuretics, and poor postdischarge prognosis in patients with heart failure with preserved ejection fraction. (*J Cardiac Fail 2019;25:631−642*)

Key Words: Heart failure with preserved ejection fraction, worsening renal function, creatinine, atherosclerosis, prognosis.

Worsening renal function (WRF), generally defined as increased serum creatinine levels of >0.3 mg/dL (26.5 μmol/L), is a well-known predictor of adverse prognosis in patients with heart failure (HF) with reduced ejection fraction (HFrEF).[1−5] In hospitalized patients with HFrEF, WRF is associated with higher mortality and rehospitalization rates[4,5]; nevertheless, aggressive decongestion, which achieves hemoconcentration, is associated with improved survival, even in patients with WRF.[6] In contrast, compared with HFrEF, HF with preserved ejection fraction (HFpEF) has a different pathophysiology[7,8] and demonstrates different phenotypes, such as higher blood pressure and more comorbidities, such as hypertension and diabetes mellitus.[9,10] In addition, HFpEF has a distinct congestion mechanism from that of HFrEF.[11,12] In brief, patients with decompensated HFpEF demonstrate more interstitial fluid congestion and less intravascular volume expansion.[11,12] The subsequent impaired fluid refilling from the extravascular area to the intravascular space triggers WRF.[12] Thus, it is necessary to investigate (1) the detailed clinical features

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of patients with HFpEF with WRF, (2) the associated factors between HFpEF and WRF (eg, management, signs of congestion/decongestion during hospitalization), and (3) the prognostic impact of WRF in patients with HFpEF. In the present study, we recruited data from a HFpEF-specific multicenter registry, and investigated the differences in detailed phenotypes between patients with WRF and those without WRF. To clarify the sequential change, we focused not only on static values, but also on dynamic values, such as changes in each parameter. Thus, the aims of this present analysis were to clarify (1) the characteristics of patients with HFpEF with WRF, (2) which factors at the time of admission were associated with the WRF development, and (3) prognosis after discharge in hospitalized patients with HFpEF, using the data from the Japanese Heart Failure Syndrome with Preserved Ejection Fraction (JASPER) registry.[13]

Methods

Patient Recruitment

This was a post hoc analysis of the JASPER registry, which is a multicenter, observational, prospective cohort that includes consecutive patients aged ≥20 years who were hospitalized between April 2012 and March 2015 with acute HF, diagnosed according to the Framingham criteria[14] by ≥2 experienced cardiologists.[13] Preserved left ventricular (LV) systolic function was defined as LV ejection fraction ≥50% by the modified Simpson method or LV fractional shortening ≥25% by echocardiography.[13] Patients with acute coronary syndrome or a history of heart transplantation, as well as those receiving hemodialysis, were excluded. The patients' demographic data, including comorbid conditions, laboratory and echocardiographic data, and length of hospital stay were obtained. Laboratory and echocardiographic data were measured both on admission and at discharge, and the differences between the 2 time points were calculated (eg, Δcreatinine equals the serum creatinine levels at discharge minus that on admission). Persistent WRF was defined as Δcreatinine of >0.3 mg/dL.[1–5] The estimated glomerular filtration rate (eGFR) was calculated using the modified Modification of Diet in Renal Disease equation: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine $^{(-1.094)}$ × age $^{(-0.287)}$ × 0.739 (if female).[15] A decrease in eGFR of ≥20% during hospitalization was considered to be another definition criteria of WRF.[1,6,12,16] Chronic kidney disease was defined as eGFR of <60 mL/min/1.73 m^2.[17] Proportional pulse pressure was calculated as a surrogate marker of low cardiac index, and a cutoff value was set at <25%.[18] Scheduled follow-ups were performed at discharge and at 12 and 24 months after discharge. The methods used for follow-up were direct contact with patients or their physicians at their hospital or outpatient clinic; telephone interview of patients or, if deceased, family members; and by mail.[13] The prognosis of some participants was confirmed after completion of the scheduled follow-up. The causes of death and rehospitalization for HF as end points were judged on site by experienced cardiologists. In the current study, because patient information was anonymized and deidentified before analysis, written informed consent was not obtained from each patient, and opt-out methods were adopted as previously reported.[13,19] The study was publicized by posting a summary of the protocol on the National Cerebral and Cardiovascular Center website, where a notice clearly informed all subjects of their right to refuse enrollment. The enrollment procedures were approved by the institutional review board of all hospitals and clinics involved in the study, and registered under the Japanese UMIN Clinical Trials Registration (UMIN000010601).[13]

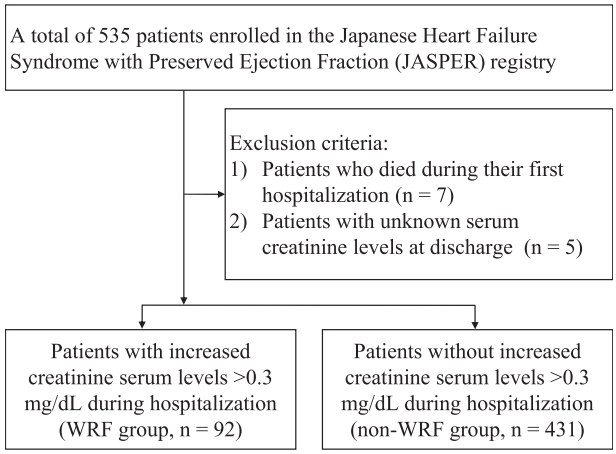

Fig. 1. Patient flow chart. WRF, worsening renal failure.

The patient flow chart of the present study is shown in Fig. 1. Of the 535 patients enrolled in the JASPER registry, 7 who died during the initial hospitalization and 5 whose serum creatinine levels were unknown were excluded. Therefore, the final number of patients enrolled in the present analysis was 523. We divided these patients into 2 groups, according to the presence or absence of persistent WRF; the WRF group (n = 92 [17.6%]) and the non-WRF group (n = 431 [82.4%]). We compared the patients' demographic data, laboratory and echocardiographic data, initial treatments, length of hospital stay, and prognosis after discharge between the 2 groups. This analysis had 2 primary end points: (1) all-cause death and (2) all-cause death or rehospitalization for HF.

Statistical Analysis

Normality was confirmed using the Shapiro-Wilk test in each group. Normally distributed variables were presented as mean ± standard deviation, non-normally distributed variables were presented as median (interquartile range), and categorical variables were expressed as counts and percentages. Normally distributed variables were compared using the Student *t* test, non-normally distributed variables were compared using the Mann−Whitney *U* test, and the χ^2 test was used for comparisons of categorical variables. Logistic regression analysis was used to clarify which parameters obtained on admission were associated with WRF development. Univariable factors that had *P* values of <.05 were entered into a multiple logistic regression model

for the development of WRF. Spearman's correlation analysis was used to assess any correlations with Δcreatinine. Kaplan−Meier analysis was used to assess all-cause death and the composite end point of all-cause death or rehospitalization for HF, and a log-rank test was used for initial comparisons. Each factor was evaluated by a univariable Cox proportional hazard analysis to predict all-cause death and the composite end point. To assess the potential heterogeneity of the associations between WRF and these end points, we also conducted subgroup analyses. The prognostic impact of WRF was evaluated using the univariable Cox proportional hazard analysis in each subgroup. A multiple Cox proportional hazard model including WRF, subgroup factor, and their interaction was fit to obtain the interaction *P* values. The subgroups were based on the presence/absence of possible confounding factors or median of other variables. *P* values of <.05 were considered statistically significant for all analyses, except for subgroup analysis with an interaction *P* value of <.002 in accordance with the Bonferroni correction to avoid type I statistical errors. All analyses were performed using a statistical software package (SPSS ver. 25, IBM, Armonk, NY).

Results

As shown in Fig. 1, of the 523 patients with HFpEF, 92 (17.6%) belonged to the WRF group and 431 (82.4%) belonged to the non-WRF group. Comparisons of the patients' baseline characteristics are shown in Table 1. Age, sex, body weight on admission and at discharge, and change in body weight were comparable between the 2 groups. The prevalence of New York Heart Association functional class Ⅲ or Ⅳ on admission was more frequent in the WRF group (87.6% vs 76.2%; *P* = .018), although the statistical significance did not persist until hospital discharge (5.7% vs 6.4%; *P* = .818). Furthermore, the WRF group showed higher systolic blood pressure (SBP) on admission and greater reduction in SBP through hospitalization (SBP on admission, 151.0 mm Hg vs 145.0 mm Hg; *P* = .005; ΔSBP, −38.0 mm Hg vs −30.0 mm Hg; *P* = .007). The prevalence of proportional pulse pressure of <25% and clinical signs were comparable between the 2 groups, except for a lower prevalence of third heart sound in the WRF group. Regarding past history, the WRF group had a higher prevalence of prior HF admission, diabetes mellitus/impaired glucose tolerance, hyperuricemia, arteriosclerosis obliterans, cerebrovascular accident, and chronic kidney disease (*P* < .05). The use of angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs), calcium channel blockers, and loop diuretics on admission were more common (*P* < .05), and those of *β*-blockers and ACEIs/ARBs were more frequent at discharge (*P* < .05).

Laboratory and echocardiographic data, initial treatments, and length of hospital stay are summarized in Table 2. Absolute serum creatinine levels on admission and at discharge, as well as the degree of change between the 2 time points, were higher in the WRF group (creatinine on admission, 1.29 mg/dL vs 1.01 mg/dL [*P* < .001]; creatinine at discharge, 1.89 mg/dL vs 1.01 mg/dL [*P* < .001]; Δcreatinine, +0.50 mg/dL vs +0.03 mg/dL [*P* < .001]). In addition, the eGFR was lower, the change in eGFR (%), blood urea nitrogen (BUN), and ΔBUN were greater in the WRF group (*P* < .01). Furthermore, the WRF group showed lower hemoglobin levels both on admission (*P* = .003) and at discharge (*P* < .001). Serum sodium levels were comparable between the groups on admission, although a greater decrease was seen in the WRF group at discharge (sodium on admission, 141.0 mEq/L vs 141.0 mEq/L; *P* = .350; sodium at discharge, 138.0 mEq/L vs 140.0 mEq/L, *P* < .001; Δsodium, −3.0 mEq/L vs −0.5 mEq/L, *P* < .001). B-type natriuretic peptide (BNP) tended to be higher on admission in the WRF group and the difference was statistically significant at discharge (BNP on admission, 456.8 pg/mL vs 394.8 pg/mL; *P* = .058; BNP at discharge, 206.4 pg/mL vs 145.2 pg/mL; *P* = .027). Serum uric acid (UA) levels were similar on admission, but at discharge were more increased in the WRF group than in the non-WRF group (UA on admission, 6.9 mg/dL vs 6.5 mg/dL [*P* = .258]; UA at discharge, 8.3 mg/dL vs 6.9 mg/dL [*P* < .001]; ΔUA , +1.4 mg/dL vs +0.4 mg/dL [*P* < .001]). Regarding echocardiographic data, including LV ejection fraction or inferior vena cava diameter, there were no significant differences through hospitalization, except for higher LV outflow tract velocity time integral and tricuspid regurgitation pressure gradient (TR-PG) on admission in the WRF group (LV outflow tract velocity time integral on admission, 21.9 cm vs 19.0 cm [*P* = .041]; TR-PG on admission, 39.0 mm Hg vs 34.0 mm Hg [*P* = .004]). The WRF group was administered vasodilators more frequently than the non-WRF group as initial treatment (71.7% vs 58.2%; *P* = .016). The use of intravenous diuretics, inotropes, and noninvasive positive pressure ventilation was equivalent between the 2 groups. Length of hospital stay was longer in the WRF group (18.0 days vs 15.0 days; *P* = .022).

Table 3 shows the results of the univariable and multivariable logistic regression analyses. Among the data obtained on admission, SBP and the use of loop diuretics were independently associated with WRF development (*P* < .05). Additionally, regarding factors associated with WRF during hospitalization, Spearman's correlation analysis (Supplementary Table 1) revealed that change in heart rate, ΔSBP, and Δsodium showed significant negative correlations with Δcreatinine, whereas ΔBUN and ΔUA demonstrated significant positive correlations. In contrast, there were no statistically significant correlations between Δcreatinine and indices of decongestion/hemoconcentration, such as change in body weight, ΔBNP, change in inferior vena cava diameter, ΔTR-PG, Δhemoglobin, and Δalbumin.

During a median postdischarge follow-up period of 732 days, there were 82 all-cause deaths and 127 rehospitalizations owing to HF. In the Kaplan-Meier analysis (Fig. 2), the WRF group showed higher rates of all-cause death and composite end point (log-rank *P* < .001). In the univariable Cox proportional hazard analysis, WRF was a predictor

Table 1. Baseline Patient Characteristics (n = 523)

Characteristics	Non-WRF (n = 431)	WRF (n = 92)	*P* Value	Missing (%)
Age, y	80.0 (73.0 to 84.0)	80.5 (74.0 to 85.0)	.602	0
Male sex, %	215 (49.9)	45 (48.9)	.866	0
Body weight on admission, kg	56.9 (48.9 to 64.6)	55.9 (47.7 to 65.3)	.592	7 (1.3)
Body weight at discharge, kg	52.3 (45.4 to 61.5)	52.6 (44.7 to 59.8)	.446	9 (1.7)
Change in body weight, kg	-3.5 (-5.9 to -1.8)	-4.1 (-6.3 to -2.1)	.313	14 (2.7)
NYHA functional class Ⅲ or Ⅳ on admission	314 (76.2)	78 (87.6)	.018	22 (4.2)
NYHA functional class Ⅲ or Ⅳ at discharge	25 (6.4)	5 (5.7)	.818	46 (8.8)
Vital signs				
HR on admission, beats/min	80.0 (65.0 to 102.0)	80.0 (72.0 to 98.0)	.463	0
HR at discharge, beats/min	66.0 (60.0 to 74.0)	66.0 (59.5 to 75.0)	.871	3 (0.6)
ΔHR, beats/min	−12.0 (−32.0 to 0.0)	−13.0 (−31.5 to −0.5)	.701	3 (0.6)
SBP on admission, mm Hg	145.0 (122.0 to 171.0)	151.0 (138.5 to 176.5)	.005	0
SBP at discharge, mm Hg	113.0 (103.0 to 124.0)	115.0 (102.0 to 130.0)	.619	2 (0.4)
ΔSBP, mm Hg	−30.0 (−57.0 to −10.0)	−38.0 (−60.5 to −24.0)	.007	2 (0.4)
PPP <25% on admission	16 (3.7)	2 (2.2)	.361	4 (0.8)
PPP <25% at discharge	7 (1.6)	2 (2.2)	.493	3 (0.6)
Clinical signs on admission				
Breathlessness	394 (92.7)	81 (89.0)	.237	7 (1.3)
Neck vein distension	199 (52.6)	37 (45.7)	.255	64 (12.2)
Rales	227 (56.2)	57 (66.3)	.085	33 (6.3)
Cardiomegaly	329 (97.6)	68 (98.6)	.530	117 (22.4)
Acute pulmonary edema	199 (53.2)	48 (58.5)	.381	67 (12.8)
Third heart sound	138 (35.9)	19 (23.5)	.031	58 (11.1)
Lower extremity edema	307 (71.9)	65 (71.4)	.928	5 (1.0)
Pleural effusion	297 (71.7)	66 (72.5)	.880	18 (3.4)
Hepatomegaly	31 (9.4)	5 (7.0)	.534	121 (23.1)
Past history				
Smoking history	182 (43.6)	47 (52.8)	.115	17 (3.3)
Prior HF admission	150 (35.7)	41 (47.7)	.037	17 (3.3)
Prior MI	53 (12.4)	12 (13.2)	.846	6 (1.1)
Atrial fibrillation	270 (63.4)	52 (57.1)	.265	6 (1.1)
DM/IGT	156 (36.4)	46 (50.0)	.016	3 (0.6)
Hypertension	330 (76.9)	76 (82.6)	.233	2 (0.4)
Dyslipidemia	182 (42.5)	40 (43.5)	.867	3 (0.6)
Hyperuricemia	148 (34.7)	50 (54.9)	<.001	6 (1.1)
ASO	18 (4.3)	10 (11.2)	.014	17 (3.3)
CVA	93 (21.9)	28 (31.8)	.046	10 (1.9)
Chronic kidney disease	203 (47.3)	65 (70.7)	<.001	2 (0.4)
COPD	28 (6.6)	10 (11.0)	.150	10 (1.9)
Medications on admission				
β-Blockers	183 (42.5)	47 (51.1)	.130	0
ACEIs/ARBs	237 (55.0)	62 (67.4)	.029	0
Spironolactone	68 (15.8)	17 (18.5)	.524	0
CCBs	214 (49.7)	57 (62.0)	.032	0
Loop diuretics	208 (48.3)	63 (68.5)	<.001	0
Tolvaptan	4 (0.9)	1 (1.1)	.621	0
Digitalis	48 (11.1)	10 (10.9)	.941	0
Nitrates	56 (13.0)	10 (10.9)	.578	0
Medications at discharge				
β-Blockers	270 (62.6)	68 (73.9)	.040	0
ACEIs/ARBs	297 (68.9)	74 (80.4)	.027	0
Spironolactone	120 (27.8)	18 (19.6)	.102	0
CCBs	223 (51.7)	53 (57.6)	.306	0
Loop diuretics	312 (72.4)	75 (81.5)	.070	0
Tolvaptan	16 (3.7)	6 (6.5)	.173	0
Digitalis	26 (6.0)	7 (7.7)	.558	2 (0.4)
Nitrates	47 (10.9)	13 (14.1)	.378	0

Normality was confirmed using the Shapiro-Wilk test: normally distributed variables are presented as mean ± standard deviation and non-normally distributed variables are presented as median (interquartile range).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASO, arteriosclerosis obliterans; CCB, calcium channel blocker. COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; HF, heart failure; HR, heart rate; IGT, impaired glucose tolerance; MI, myocardial infarction; NYHA, New York Heart Association; PPP, proportional pulse pressure; SBP, systolic blood pressure; WRF, worsening renal function.

Table 2. Laboratory and Echocardiographic Data, Initial Treatments, and Length of Hospital Stay (n = 523)

Characteristic	Non-WRF (n = 431)	WRF (n = 92)	*P* value	Missing (%)
Laboratory data				
Creatinine on admission, mg/dL	1.01 (0.74 to 1.39)	1.29 (0.86 to 2.00)	<.001	0
Creatinine at discharge, mg/dL	1.01 (0.80 to 1.33)	1.89 (1.32 to 2.66)	<.001	0
ΔCreatinine, mg/dL	+0.03 (−0.10 to +0.13)	+0.50 (+0.38 to +0.85)	<.001	0
eGFR on admission, mL/min/1.73 m^2	49.0 (33.2 to 65.9)	36.9 (22.6 to 53.8)	<.001	0
eGFR at discharge, mL/min/1.73 m^2	48.3 (35.3 to 61.9)	23.5 (15.9 to 33.1)	<.001	0
Change in eGFR, %	−3.2 (−14.2 to +9.0)	−33.2 (−43.9 to −23.8)	<.001	0
BUN on admission, mg/dL	21.0 (15.7 to 31.0)	25.0 (18.9 to 33.5)	.002	0
BUN at discharge, mg/dL	23.0 (17.6 to 32.0)	42.0 (31.0 to 58.0)	<.001	0
ΔBUN, mg/dL	+1.0 (-3.7 to +7.0)	+15.5 (+6.0 to +26.0)	<.001	0
Hb on admission, g/dL	11.1 (9.8 to 12.8)	10.3 (9.7 to 11.3)	.003	0
Hb at discharge, g/dL	11.5 (10.2 to 12.9)	10.5 (9.8 to 12.0)	<.001	1 (0.2)
ΔHb, g/dL	+0.3 (−0.5 to +1.1)	+0.3 (−0.7 to +1.3)	.986	1 (0.2)
Alb on admission, g/dL	3.7 (3.4 to 4.0)	3.6 (3.2 to 3.9)	.219	31 (5.9)
Alb at discharge, g/dL	3.7 (3.4 to 4.0)	3.5 (3.2 to 4.0)	.051	102 (19.5)
ΔAlb, g/dL	0.0 (−0.3 to +0.2)	0.0 (−0.3 to +0.3)	.752	115 (22.0)
Sodium on admission, mEq/L	141.0 (138.0 to 142.0)	141.0 (138.0 to 142.5)	.350	0
Sodium at discharge, mEq/L	140.0 (137.0 to 142.0)	138.0 (136.0 to 140.0)	<.001	0
ΔSodium, mEq/L	−0.5 (−3.0 to +2.0)	−3.0 (−5.2 to +1.0)	<.001	0
BNP on admission, pg/mL	394.8 (225.3 to 664.9)	456.8 (284.7 to 857.2)	.058	9 (1.7)
BNP at discharge, pg/mL	145.2 (73.9 to 257.5)	206.4 (101.4 to 396.0)	.027	91 (17.4)
ΔBNP, pg/mL	−205.6 (−447.8 to −64.5)	−222.3 (−456.1 to −61.5)	.718	94 (18.0)
UA on admission, mg/L	6.5 (5.2 to 7.9)	6.9 (5.7 to 7.9)	.258	19 (3.6)
UA at discharge, mg/dL	6.9 (5.7 to 8.3)	8.3 (6.9 to 9.9)	<.001	68 (13.0)
ΔUA, mg/dL	+0.4 (−0.6 to +1.4)	+1.4 (+0.4 to +3.1)	<.001	81 (15.5)
Echocardiographic data				
LVEF on admission, %	60.0 (53.9 to 65.0)	60.0 (54.3 to 64.5)	.781	36 (6.9)
LVEF at discharge, %	60.0 (55.0 to 65.0)	60.0 (53.0 to 65.5)	.340	192 (36.7)
Δ LVEF, %	+0.1 (−3.9 to +5.0)	0.0 (−3.4 to +3.0)	.253	207 (39.6)
IVCD on admission, mm	19.5 ± 6.1	18.4 ± 5.8	.133	53 (10.1)
IVCD at discharge, mm	16.5 (12.3 to 20.0)	16.0 (11.0 to 19.5)	.324	187 (35.8)
ΔIVCD, mm	−3.2 (−7.0 to 0.0)	−3.5 (−6.5 to −1.0)	.890	219 (41.9)
LVOT-VTI on admission, cm	19.0 (15.1 to 23.0)	21.9 (16.2 to 26.9)	.041	316 (60.4)
LVOT-VTI at discharge, cm	18.9 (15.6 to 22.9)	20.2 (15.7 to 23.4)	.501	351 (67.1)
Δ LVOT-VTI, cm	−0.7 (−3.3 to +2.4)	−1.2 (−5.9 to +2.0)	.433	404 (77.2)
TR-PG on admission, mm Hg	34.0 (27.0 to 44.0)	39.0 (32.0 to 48.5)	.004	66 (12.6)
TR-PG at discharge, mm Hg	27.0 (21.3 to 34.0)	29.0 (24.0 to 33.0)	.262	214 (40.9)
ΔTR-PG, mm Hg	−9.0 (−15.0 to 0.0)	−8.0 (−16.0 to −2.5)	.469	242 (46.3)
Initial treatments				
Intravenous diuretics	347 (80.5)	76 (82.6)	.642	0
Vasodilators	251 (58.2)	66 (71.7)	.016	0
Inotropes	18 (4.2)	4 (4.3)	.561	0
NIPPV	87 (20.2)	12 (13.0)	.112	0
LOS, days	15.0 (11.0 to 23.0)	18.0 (13.0 to 23.0)	.022	0

Alb, albumin; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IVCD, inferior vena cava diameter; LOS, length of hospital stay; LVEF, left ventricular ejection fraction; LVOT-VTI, left ventricular outflow tract velocity time integral; NIPPV, noninvasive positive pressure ventilation; TR-PG, tricuspid regurgitation pressure gradient; UA, uric acid. Other abbreviation as in Table 1.

Normality was confirmed using the Shapiro-Wilk test. Normally distributed variables are presented as mean ± standard deviation and non-normally distributed variables are presented as median (interquartile range); other variables are number (%).

both of all-cause death (Table 4; hazard ratio, 2.725; 95% confidence interval, 1.709−4.344; $P < .001$) and the composite end point (Table 5; hazard ratio, 2.083; 95% confidence interval, 1.488−2.914; $P < .001$). Regarding the associations between WRF and both all-cause death and the composite end point, there were no interactions in any subgroup analysis (Tables 4 and 5). The prognostic impact of the other factors are summarized in Supplementary Table 2. As well as creatinine serum levels, eGFR on admission and at discharge were associated with both end points. Change in eGFR of ≤−20% was not associated with the composite end point but was associated with all-cause death. The BUN/creatinine ratio at discharge was associated with both end points.

Table 3. Logistic Regression Analysis for the Development of WRF

Characteristic	Univariable		Multivariable	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.003 (0.981−1.025)	.809	–	–
Male sex	0.962 (0.613−1.509)	.866	–	–
Body weight	0.996 (0.980−1.013)	.674	–	–
NYHA functional class Ⅲ or Ⅳ	2.213 (1.132−4.328)	.020	1.246 (0.588−2.643)	.566
Heart rate	0.999 (0.991−1.007)	.884	–	–
Systolic blood pressure	1.009 (1.002−1.015)	.006	1.010 (1.002−1.018)	.011
Smoking history	1.445 (0.913−2.287)	.116	–	–
Prior heart failure admission	1.640 (1.027−2.618)	.038	0.896 (0.488−1.645)	.722
Prior myocardial infarction	1.069 (0.546−2.093)	.846	–	–
Atrial fibrillation	0.770 (0.487−1.220)	.266	–	–
DM/IGT	1.744 (1.108−2.744)	.016	0.957 (0.538−1.701)	.880
Hypertension	1.425 (0.795−2.555)	.235	–	–
Dyslipidemia	1.040 (0.660−1.638)	.867	–	–
Hyperuricemia	2.291 (1.448−3.624)	<.001	1.682 (0.943−3.001)	.078
Arteriosclerosis obliterans	2.806 (1.248−6.306)	.013	2.404 (0.939−6.153)	.067
Cerebrovascular accident	1.666 (1.006−2.758)	.047	1.411 (0.768−2.591)	.268
Chronic kidney disease	2.680 (1.647−4.362)	<.001	1.729 (0.914−3.273)	.092
COPD	1.737 (0.812−3.717)	.155	–	–
B-Blockers	1.415 (0.901−2.222)	.131	–	–
ACEIs/ARBs	1.692 (1.052−2.721)	.030	1.053 (0.591−1.876)	.861
Spironolactone	1.210 (0.673−2.176)	.524	–	–
CCBs	1.651 (1.041−2.619)	.033	1.374 (0.778−2.428)	.274
Loop diuretics	2.329 (1.443−3.759)	.001	1.988 (1.064−3.715)	.031
Tolvaptan	1.173 (0.130−10.62)	.887	–	–
Digitalis	0.973 (0.473−2.003)	.941	–	–
Nitrates	0.817 (0.400−1.668)	.578	–	–
Log BNP	1.870 (1.027−3.406)	.041	1.450 (0.723−2.910)	.296
Intravenous diuretics	1.150 (0.638−2.073)	.642	–	–
Vasodilators	1.820 (1.112−2.979)	.017	1.671 (0.879−3.175)	.117
Inotropes	1.043 (0.345−3.157)	.941	–	–
NIPPV	0.593 (0.309−1.137)	.116	–	–

CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1 and 2.
Variables were measured at admission.

Discussion

To our knowledge, the current study is the first to report (1) the detailed clinical features of patients with HFpEF with WRF, (2) the associated factors of WRF and HFpEF, and (3) the prognostic impact of WRF in patients with HFpEF, not HFrEF. The main findings of this analysis were as follows: (1) hospitalized patients with HFpEF who developed WRF (17.6%) during hospitalization had more preexisting atherosclerotic comorbidities and impaired renal function; (2) signs of hypoperfusion occurred more often in the WRF group during hospitalization (eg, BUN and sodium at discharge, ΔSBP, ΔBUN, and Δsodium); (3) SBP and the use of loop diuretics on admission were

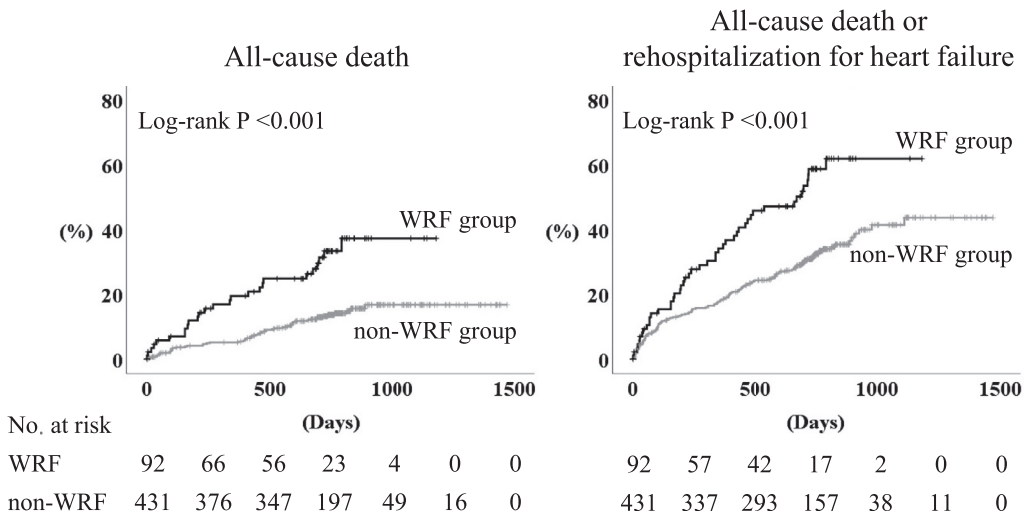

Fig. 2. Kaplan-Meier analysis. WRF, worsening renal failure.

Table 4. Univariable Cox Proportional Hazard Analysis and the Subgroup Analysis for All-Cause Death: The Impact of WRF

Factor and Subgroup	n	HR	95% CI	*P* Value	Interaction *P* Value
Total	523	2.725	1.709−4.344	<.001	—
Age, y					
≥80	272	2.558	1.431−4.571	.002	.898
<80	251	2.786	1.273−6.098	.010	
Sex					
Male	260	3.433	1.860−6.336	<.001	.259
Female	263	2.012	0.973−4.164	.059	
Body weight, kg					
≥52.5	257	3.111	1.403−6.899	.005	.847
<52.5	257	2.747	1.528−4.939	.001	
NYHA functional class at discharge					
Ⅰ or Ⅱ	447	3.789	2.235−6.423	<.001	.643
Ⅲ or Ⅳ	30	2.108	0.447−9.940	.346	
Systolic blood pressure at discharge, mm Hg					
≥113.0	267	3.791	1.971−7.291	<.001	.171
<113.0	254	1.971	0.995−3.904	.052	
Smoking history					
Yes	229	4.333	2.279−8.239	<.001	.032
No	277	1.418	0.656−3.065	.374	
Prior HF admission					
Yes	191	2.303	1.184−4.481	.014	.328
No	315	3.472	1.750−6.889	<.001	
Prior MI					
Yes	65	3.954	1.139−13.732	.030	.664
No	452	2.739	1.649−4.550	<.001	
Atrial fibrillation					
Yes	322	2.616	1.457−4.697	.001	.816
No	195	2.739	1.217−6.164	.015	
DM/IGT					
Yes	202	2.492	1.153−5.384	.020	.662
No	318	3.077	1.706−5.552	<.001	
Hypertension					
Yes	406	2.479	1.437−4.279	.001	.330
No	115	4.141	1.683−10.186	.002	
Dyslipidemia					
Yes	222	2.323	0.959−5.624	.062	.552
No	298	3.114	1.792−5.409	<.001	
Hyperuricemia					
Yes	198	2.047	1.073−3.903	.030	.392
No	319	3.403	1.705−6.790	.001	
ASO					
Yes	28	5.842	1.175−29.048	.031	.233
No	478	2.394	1.428−4.013	.001	
CVA					
Yes	121	2.710	1.227−5.985	.014	.706
No	392	2.297	1.248−4.228	.008	
Chronic kidney disease					
Yes	268	2.363	1.310−4.262	.004	.555
No	253	3.201	1.452−7.057	.004	
Use of β-blockers at discharge					
Yes	338	3.356	1.937−5.813	<.001	.199
No	185	1.596	0.606−4.204	.344	
Use of ACEIs/ARBs at discharge					
Yes	371	3.335	1.920−5.792	<.001	.266
No	152	1.869	0.711−4.909	.205	
Use of loop diuretics at discharge					
Yes	387	2.317	1.366−3.930	.002	.186
No	136	4.872	1.793−13.235	.002	
Creatinine at discharge, mg/dL					
≥1.10	262	2.066	1.201−3.554	.009	.657
<1.10	261	3.138	0.745−13.219	.119	
BUN at discharge, mg/dL					
≥25.0	267	2.313	1.345−3.979	.002	.689
<25.0	256	1.747	0.415−7.351	.446	
Hemoglobin at discharge, g/dL					
≥11.4	261	2.914	1.225−6.932	.016	.663
<11.4	261	2.350	1.343−4.112	.003	
Albumin at discharge, g/dL					
≥3.6	234	4.204	1.999−8.843	<.001	.077
<3.6	187	1.613	0.872−2.983	.128	

(*continued*)

Table 4 (*Continued*)

Factor and Subgroup	n	HR	95% CI	*P* Value	Interaction *P* Value
Sodium at discharge, mEq/L					
≥139.5	263	4.079	1.663−10.007	.002	.134
<139.5	260	1.933	1.119−3.339	.018	
BNP at discharge, pg/mL					
≥154.3	216	3.326	1.811−6.111	<.001	.059
<154.3	216	1.057	0.368−3.038	.918	
UA at discharge, mg/mL					
≥7.2	235	2.205	1.223−3.975	.009	.377
<7.2	220	3.396	1.439−8.015	.005	
LVEF at discharge, %					
≥60.0	202	1.674	0.724−3.874	.229	.139
<60.0	129	4.038	1.774−9.190	.001	
IVCD at discharge, mm					
≥16.0	180	2.495	1.182−5.264	.016	.568
<16.0	156	3.349	1.447−7.751	.005	
LVOT-VTI at discharge, cm					
≥18.9	89	6.290	2.615−15.129	<.001	.214
<18.9	83	2.802	0.991−7.924	.052	
TR-PG at discharge. Mm Hg					
≥28.0	156	2.160	1.003−4.650	.049	.390
<28.0	153	3.454	1.507−7.914	.003	
Length of hospital stay, d					
≥16.0	263	2.012	1.109−3.649	.021	.169
<16.0	260	4.086	1.927−8.663	<.001	

CVA, cerebrovascular accident; HR, hazard ratio; other abbreviations as in Tables 1−3.

associated with WRF; and (4) WRF was a predictor of adverse postdischarge prognosis in hospitalized patients with HFpEF.

WRF is important in terms of its preventability and modifiability, unlike baseline renal function, which is usually not modifiable.[3,20,21] A large body of literature, most of which focused on HFrEF, has explained the underlying mechanism of WRF development in the setting of HF, impaired cardiac output and intravascular volume depletion resulting in neurohormonal activation, elevated central venous pressure, and/or side effects of medical treatment.[1,22−25] In a subanalysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, aggressive decongestion that led to hemoconcentration was associated with lower mortality in hospitalized patients with HFrEF, despite the use of high-dose loop diuretics and an association with WRF.[6,26] However, this result cannot directly be extrapolated to hospitalized patients with HFpEF. In the ESCAPE trial, several participants, who had an SBP of >125 mm Hg and/or serum creatinine levels of >3.5 mg/dL, were excluded.[6,26] In addition, patients with HFpEF might have a different pathophysiology from those of HFrEF.[7,8]

In the present analysis, patients with WRF had more atherosclerotic comorbidities, such as diabetes mellitus/impaired glucose tolerance, hyperuricemia, arteriosclerosis obliterans, and cerebrovascular accidents, suggesting that patients with WRF might have a more active renin−angiotensin−aldosterone system, as well as higher sympathetic nervous activity and more severe inflammation. In addition, the higher SBP observed in the WRF group also indicated poorer elasticity of the arteries.[27,28] Thus, these results suggest that patients with HFpEF with WRF have more abnormal ventricular−vascular coupling than those without WRF.[7,20,28] These patients have a greater dependence on preload, and a reduction in this factor can easily cause a greater decrease in renal perfusion, as well as cardiac output and SBP.[7,20,28,29] Moreover, in patients with HFpEF, extravascular volume overload is reported to be more likely to cause congestion than intravascular fluid retention, when compared with patients with HFrEF.[11] Therefore, diuresis and impaired fluid refilling from the extravascular space to the intravascular area can cause WRF in patients with HFpEF.[12] In the present analysis, findings of compromised perfusion (eg, low proportional pulse pressure, hypotension, and hyponatremia)[1,30] were comparable on admission between the 2 groups, except for renal function, which was impaired in the WRF group. However, the WRF group showed a greater decrease in SBP and sodium, and increase in BUN with a higher use of loop diuretics and vasodilators during hospitalization. There was a significant negative correlation between ΔSBP and Δcreatinine. These results might be associated with emerging arterial underfilling and a decrease in renal perfusion during hospitalization.[31−34] Additionally, we found that Δcreatinine significantly correlated with ΔBUN. Elevated BUN predicts not only renal hypoperfusion and neurohormonal activation, but also adverse postdischarge prognosis.[35,36] Moreover, ACEIs and ARBs, which were prescribed more frequently in the WRF group, may have deteriorated renal function through the disruption of the autoregulation of renal blood flow.[20,37] The correlation between Δcreatinine and ΔUA was likely confounded by several factors, including diabetes mellitus, chronic kidney disease, and the use of loop diuretics.[1,38−41]

Table 5. Univariable Cox Proportional Hazard Analysis and the Subgroup Analysis for All-Cause Death or Rehospitalization for HF: WRF Impact

Factor and Subgroup	*n*	HR	95% CI	*P* Value	Interaction *P* Value
Total	523	2.083	1.488−2.914	<.001	—
Age, y					
≥80	272	1.808	1.168−2.798	.008	.390
<80	251	2.434	1.438−4.120	.001	
Sex					
Male	260	2.800	1.766−4.441	<.001	.080
Female	263	1.517	0.924−2.491	.100	
Body weight at discharge, kg					
≥52.5	257	2.123	1.245−3.618	.006	.900
<52.5	257	2.175	1.403−3.371	.001	
NYHA functional class at discharge					
Ⅰ or Ⅱ	447	2.406	1.679−3.447	<.001	.822
Ⅲ or Ⅳ	30	1.976	0.548−7.122	.298	
Systolic blood pressure at discharge, mm Hg					
≥113.0	267	2.641	1.650−4.228	<.001	.152
<113.0	254	1.690	1.039−2.747	.034	
Smoking history					
Yes	229	3.436	2.152−5.488	<.001	.006
No	277	1.245	0.738−2.098	.412	
Prior HF admission					
Yes	191	1.467	0.914−2.357	.113	.042
No	315	2.971	1.825−4.835	<.001	
Prior MI					
Yes	65	2.349	0.981−5.628	.055	.995
No	452	2.150	1.490−3.102	<.001	
Atrial fibrillation					
Yes	322	1.838	1.205−2.803	.005	.296
No	195	2.677	1.494−4.796	.001	
DM/IGT					
Yes	202	2.331	1.400−3.882	.001	.507
No	318	1.908	1.213−3.002	.005	
Hypertension					
Yes	406	1.947	1.337−2.836	.001	.446
No	115	2.650	1.251−5.610	.011	
Dyslipidemia					
Yes	222	2.323	1.362−3.962	.002	.628
No	298	1.959	1.270−3.024	.002	
Hyperuricemia					
Yes	198	1.676	1.057−2.657	.028	.449
No	319	2.388	1.440−3.960	.001	
ASO					
Yes	28	2.890	1.059−7.885	.038	.432
No	478	1.872	1.290−2.717	.001	
CVA					
Yes	121	2.349	1.308−4.219	.004	.473
No	392	1.797	1.173−2.752	.007	
Chronic kidney disease					
Yes	268	1.777	1.165−2.710	.008	.465
No	253	2.490	1.397−4.440	.002	
Use of β-blockers at discharge					
Yes	338	2.424	1.651−3.558	<.001	.139
No	185	1.262	0.597−2.671	.542	
Use of ACEIs/ARBs at discharge					
Yes	371	2.359	1.600−3.479	<.001	.356
No	152	1.594	0.782−3.248	.199	
Use of loop diuretics at discharge					
Yes	387	1.945	1.340−2.822	<.001	.623
No	136	2.534	1.154−5.562	.021	
Creatinine at discharge, mg/dL					
≥1.10	262	1.774	1.199−2.623	.004	.890
<1.10	261	2.006	0.631−6.377	.238	
BUN at discharge, mg/dL					
≥25.0	267	1.719	1.170−2.526	.006	.849
<25.0	256	1.574	0.573−4.326	.379	
Hemoglobin at discharge, g/dL					
≥11.4	261	2.593	1.507−4.462	.001	.216
<11.4	261	1.621	1.055−2.489	.027	
Albumin at discharge, g/dL					
≥3.6	234	2.728	1.619−4.597	<.001	.108
<3.6	187	1.411	0.874−2.279	.159	

(*continued*)

Table 5 (*Continued*)

Factor and Subgroup	*n*	HR	95% CI	*P* Value	Interaction *P* Value
Sodium at discharge, mEq/L					
≥139.5	263	3.028	1.759−5.212	<.001	.037
<139.5	260	1.501	0.978−2.303	.063	
BNP at discharge, pg/mL					
≥154.3	216	1.738	1.090−2.769	.020	.591
<154.3	216	2.240	1.231−4.074	.008	
Uric acid at discharge, mg/dL					
≥7.2	235	2.181	1.420−3.352	<.001	.491
<7.2	220	1.607	0.822−3.145	.166	
LVEF at discharge, %					
≥60.0	202	1.618	0.913−2.867	.099	.159
<60.0	129	2.847	1.610−5.035	<.001	
IVCD at discharge, mm					
≥16.0	180	1.408	0.795−2.493	.241	.010
<16.0	156	3.854	2.219−6.695	<.001	
LVOT-VTI at discharge, cm					
≥18.9	89	3.014	1.494−6.082	.002	.666
<18.9	83	2.263	1.044−4.904	.039	
TR-PG at discharge, mm Hg					
≥28.0	156	1.409	0.797−2.492	.238	.020
<28.0	153	3.606	2.042−6.366	<.001	
Length of hospital stay, d					
≥16.0	263	1.902	1.229−2.943	.004	.618
<16.0	260	2.298	1.346−3.923	.002	

Abbreviations as in Tables 1−4.

There are pros and cons to UA as a potential factor of impaired renal function.[39,41−43]

WRF occurs not only due to renal hypoperfusion, but also due to other mechanisms. Venous congestion is another leading cause of WRF.[22,44] In the current study, although there were no correlations between Δcreatinine and changes in the parameters of decongestion/hemoconcentration (eg, change in body weight, ΔBNP, and change in inferior vena cava diameter), the WRF group demonstrated higher TR-PG on admission and higher BNP levels at discharge, suggesting the presence of congestion. Nonhemodynamic factors, such as the activation of the renin−angiotensin−aldosterone system and sympathetic nervous system, inflammation, endothelial dysfunction, and anemia, also influence renal dysfunction.[44] In summary, the results of the present study indicate that patients with HFpEF with preexisting atherosclerotic diseases, such as nephrosclerosis, develop WRF through diuresis and subsequent reduction in SBP, in addition to previously hypothesized causes, such as congestion.

Although preventing WRF in hospitalized patients with HFpEF remains challenging, it is essential because the prognostic impact of transient WRF and that of persistent WRF seem to be equivalent.[25] Patients with acute decompensated HFpEF generally have a higher SBP[9,10] and less intravascular volume expansion[11,45,46] relative to those with acute decompensated HFrEF. In such patients with HFpEF, vasodilators, which are recommended in the current HF guidelines,[1,47] are safer than diuretics as an initial treatment because they are not a predictor of WRF development.[25] Concordant with the results of our logistic regression analysis, excessive use of diuretics should be avoided because they can cause intravascular volume depletion, resulting in WRF.[12,48] Unlike in hospitalized patients with HFrEF,[49] the addition of tolvaptan to conventional diuretic therapy has been reported to decrease WRF through the maintenance of renal blood flow in those hospitalized for HFpEF.[21,50] Even though vasodilators are not associated with the development of WRF, they could cause a decrease in SBP,[20,28,29] which was correlated with Δcreatinine in the current study. Careful monitoring to avoid excessive SBP decreases is necessary. For a similar reason, attention must also be paid to avoid excessive SBP-lowering therapy using ACEIs/ARBs after compensation of HFpEF.[16,37]

Study Strengths and Limitations

There were several strengths to the present study. First, the data used were obtained from a HFpEF-specific multicenter registry. Second, we detected parameters that can predict the development of in-hospital WRF at the time of admission. Third, we focused on changes in important parameters and found correlations with Δcreatinine. Fourth, we performed a subgroup analysis to confirm the impact of in-hospital WFR across the relevant variables and signs of congestion, decongestion, and hemoconcentration. To date, there have been few studies investigating in-hospital WRF in patients with HFpEF.[12,21,25,51] We analyzed data from a multicenter registry focusing on HFpEF. Moreover, because the hemodynamics of acute decompensated HF change dramatically,[1,2,47] this analysis was novel because we focused on not only static indicators, but also dynamic ones.

In contrast, the current study also has some limitations. Focusing on WRF, medication dosages (eg, diuretics and ACEIs/ARBs) were not listed in the JASPER registry. The present study included only variables during hospitalization for decompensated HF, and we did not take into

consideration changes in postdischarge treatment. In addition, there are 2 types of WRF: transient WRF (WRF followed by recovery in serum creatinine levels during hospitalization) and persistent WRF (persistent deterioration of creatinine serum levels until discharge).[25,52] Because we defined WRF using only 2 data points, namely, creatinine levels on admission and at discharge, it may be possible to underestimate temporary WRF. The significance and predictors of transient WRF should be examined in the future study. The causal relationships and mechanisms of WRF on worsened prognosis could not be fully explained because this was a prospective, observational study. There are limited data on right-sided cardiac function, although it plays a key role in the development of WRF in patients with HFpEF.[51] There were non-negligible missing data, particularly in the echocardiographic findings. We used the Bonferroni correction for the interaction *P* values, and this strategy increased the possibility of type II errors. Other general limitations of the JASPER registry have been described in previous reports.[13] Therefore, the present results should be viewed as preliminary, and further studies with a larger population are needed.

Conclusions

Patients with decompensated HFpEF who experience persistent WRF have more preexisting atherosclerotic comorbidities, a higher use of diuretics, and are associated with greater decrease in SBP and poor postdischarge prognosis.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.04.009.

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