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博　士　論　文

Association between worsening renal function severity during hospitalization and low physical function at discharge：a retrospective cohort study of older patients with heart failure and chronic kidney disease from Japan

（入院中の腎機能悪化の重症度と退院時低身体機能との関係：日本の高齢心不全および慢性腎臓病患者を対象とした後方視的コホート研究）

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Abstract

***Background*:** The number of hospitalized older patients with chronic heart failure, chronic kidney disease, and worsening renal function is rising in Japan. This study aimed to clarify the impact of the severity of worsening renal function during hospitalization on low physical function at discharge of these patients.

Methods: We included 573 consecutive heart failure patients who underwent phase I cardiac rehabilitation. Worsening renal function severity was defined according to elevation during hospitalization of baseline serum creatinine on admission: non-worsening renal function, serum creatinine <0.2 mg/dL; worsening renal function Ⅱ/I, serum creatinine ≥0.2 to <0.5 mg/dL; worsening renal function III, serum creatinine ≥0.5 mL/dL. Physical function was measured with the Short Performance Physical Battery. We compared background factors, clinical parameters, pre-hospitalization walking levels, Functional Independence Measure score, and physical function in the three renal function groups. Multiple regression analysis was performed with the Short Performance Physical Battery at discharge as the dependent variable.

Results: The final analysis included 196 patients (mean age 82.7 years, male 51.5%) categorised into three groups based on worsening renal function: worsening renal function grade III group(n=55), worsening renal function grade II/I group (n=36), and non-worsening renal function group (n=105). There is no significant difference in walking levels before hospitalization between the three groups, but physical function at discharge was significantly lower in the worsening renal function III group. Moreover, worsening renal function III was an independent factor for low physical function at discharge.

Conclusions: Worsening of renal function during hospitalization in older patients with heart failure and chronic kidney disease was strongly associated with low physical function at discharge, even after adjusting for other potentially confounding factors such as pre-hospitalization walking levels, walking start day, and Geriatric Nutrition Risk Index at discharge. Notably, worsening renal function of mild or moderate severity (grade II/I) did not show a significant association with low physical function.

Keywords

Older patients with heart failure and chronic kidney disease・Severity of worsening renal function・Indoxyl sulfate・Mitochondrial dysfunction・Sarcopenia・Physical function

Introduction

Japan has the fastest aging population in the world, and the prevalence of heart failure (HF) is also increasing rapidly [1]. Older HF patients are often characterized by rehospitalization, multiple diseases, and frailty due to acute exacerbations [1]. Especially in older patients with chronic HF and chronic kidney disease (CKD) with an estimated glomerular filtration rate of less than 60 mL/min/1.73 m2 who are hospitalized with acute exacerbation of HF, the complication rate (number of complications divided by the number of patients) is as high as 70% [2].

Recently, the concept of the heart-renal connection has been proposed in which the heart and kidneys substantially affect each other [3]. Older patients with HF and advanced CKD have a poor prognosis that can lead to frailty, uremic sarcopenia, and adverse outcomes [2, 4–6]. Similarly, worsening renal function (WRF) with an elevated serum creatinine (sCr) level of 0.3 mg/dL or higher in hospitalized patients with acute HF has also been reported to lead to worse clinical outcomes, including hospital mortality, complications, extended length of hospital stay, CKD progression, increased rates of readmission, and rising medical costs [7–9]. Furthermore, severe WRF as indicated by an increase in sCr level of 0.5 mg/dL or more affects prognosis and adverse outcomes more than that of a sCr level of <0.5 mg/dL [10–12].

Hospitalized patients with HF require treatment with medications and bed rest until hemodynamics are normalized, which can exacerbate their physical condition [13, 14]. In particular, older patients with HF and CKD are prone to marked progression of frailty and sarcopenia at hospitalization that can lead to a decrease in walking ability, activity of daily living (ADL), and physical function (PF) [14]. Therefore, early determination of and countermeasures for predictors of these declines and appropriate cardiac rehabilitation (CR) are necessary.

In older patients with HF, the Short Physical Performance Battery (SPPB) is often used to evaluate PF [5, 13, 15]. Comprehensive evaluation of leg muscle strength, balance function, and walking speed is possible, and as no special procedures or techniques are required, the PF of older patients with complications or frailty can be easily evaluated [5, 13, 15].

Therefore, the SPPB was used for PF evaluation in this study. Our previous study revealed that WRF, defined as an increase in sCr of 0.3 mg/dL or more or a 25% increase in sCr from baseline during hospitalization in older patients with HF, is an independent factor of ADL decline at discharge [16]. However, in older patients with HF and CKD, whether severe WRF with an increase in sCr ≥0.5 mg/dL during hospitalization (classified as WRF III) or even mild-to-moderate WRF with an increase in sCr to 0.2–0.5 mg/dL during hospitalization (classified as WRF I/II) effects PF is not clear.

Therefore, we hypothesized that WRF III would be an independent factor of low PF in older patients with HF and CKD at discharge, even after adjusting for other influencing factors (walking levels before hospitalization, walking start day, and discharge nutritional status).

The purpose of this study was to clarify the impact of WRF III during hospitalization on PF at discharge in older patients with HF and CKD.

Methods

Participants and ethics

This retrospective cohort study enrolled 1170 patients admitted for HF from October 2017 to August 2020 at Yodogawa Christian Hospital Cardiology Department, Osaka, Japan. Inclusion criteria were acute HF and acute exacerbation of chronic HF and undergoing CR. Exclusion criteria were age <65 years, could not walk before hospitalization, refusal of CR, hospitalization within one week, in-hospital death, missing data, sepsis, dialysis, and non-CKD patients (patients in whom it could not be determined whether they met the definition of CKD were classified as having no data) (Figure 1).

This study was approved by the Yodogawa Christian Hospital Ethics Review Board (approval number: 2022-051) and was performed with the written informed consent of each patient.

Investigation

Evaluation items included age, sex, body mass index (BMI), left ventricular ejection fraction, walking levels before hospitalization, medical history/comorbidities, start day of phase I CR, progression of CR, length of stay, PF at discharge, nutritional status, hospital-phase oral and intravenous (iv) medications, duration of furosemide iv medication administration, and laboratory findings. Laboratory data included B-type natriuretic peptide on admission, hemoglobin on admission and discharge, sCr, and estimated glomerular filtration rate (eGFR).

These data were retrospectively investigated by a single physical therapist (PT) from the patient's electronic medical record. Left ventricular ejection fraction was measured echocardiographically by a laboratory technician under the direction of a physician and calculated by the Simpson method.

Definitions

WRF severity was defined based on a previous study according to the elevation during hospitalization of the baseline sCr on admission, with non-WRF defined as sCr <0.2 mg/dL, WRF II/I as sCr ≥0.2 to <0.5 mg/dL, and WRF III as sCr ≥0.5 mL/dL [10]. As recommended by the Japanese Society of Nephrology, eGFR was calculated using the following formula: 194 × sCr – 1.094 × age – 0.28 (× 0.739 for females) [17]. CKD was defined as a decreased eGFR of <60 mL/min/1.73 m2 for at least 3 months [18].

The Geriatric Nutrition Risk Index (GNRI) at admission and at discharge was evaluated as the index of nutritional status. GNRI is calculated by the following formula: GNRI = 14.89 × serum albumin (g/dL) + 41.7 × BMI / 22 [19, 20]. Changes in nutritional status between admission and discharge are indicated by ΔGNRI [19].

Phase I cardiac rehabilitation

We performed Phase I CR in accordance with the "Guidelines for Rehabilitation of Patients with Cardiovascular Diseases" of the Japanese Circulation Society [21]. We confirmed the bed rest instructions ordered by the patient's doctor, evaluated the patient's subjective symptoms and vital signs, and aimed for early mobilization and return to ADL.

We had the patients perform calf raises and squats using their body weight and expanded ADL exercises to those such as walking and climbing stairs in the ward. The patients were then transitioned to a PT and trainer-led group aerobic exercise program when possible. PTs and trainers carried out the program while monitoring the patients' ECG.

Walking start day

From bed rest, the patient advanced from sitting to standing to walking and to early mobilization. Walking start day was defined as the day when the patient started walking for the first time since the day of admission.

Assessment of physical function

The SPPB was used to assess PF indices, which were measured by the PT in charge at the patient's discharge. The SPPB is a comprehensive assessment of PF that

evaluates standing balance ability, 4-meter walking time, and the time required to stand and sit down from a chair five times. Each assessment has a total score of 0–12, and each is scored from 0 (inability to complete task) to 4 (best performance) [5, 13, 15].

Walking levels before hospitalization

Information on walking levels before hospitalization was collected from the patients themselves by the attending PT or from information recorded in electronic medical records obtained from the patients' families and care managers by attending physicians, nurses, and general medical workers.

The walking levels before hospitalization were classified into three categories: (i) a level at which the patient was able to walk outdoors independently without physical or human assistance such as a cane or buggy; (ii) a level at which the patient can walk outdoors alone by using a cane or buggy; and (iii) a level at which the patient can walk without a cane or any walking aids but only indoors [16, 19].

Assessment of ADL

ADL at discharge was measured by a PT using the Functional Independence Measure (FIM). The FIM scale consists of 18 items, which are organized into the motor and cognitive subscales. The motor domain (FIM motor) consists of 13 items such as self-care, excretion control, locomotion, and exercise, and the cognitive domain (FIM cognitive) consists of 5 items covering communication and social cognition.

The FIM seven-point ordinal scale represents caregiver burden, with 1 indicating total assistance, 2 maximum assistance, 3 moderate assistance, 4 minimal contact assistance, 5 supervised, 6 correction independence, and 7 complete independence. The FIM has a maximum total a score of 126 points and a minimum score of 18 points, with higher scores indicating greater functional independence [16, 22].

Duration of furosemide iv administration

The duration of furosemide iv administration was measured as the number of days from the start of furosemide iv administration to the end of its administration.

Statistical methods

Patients were stratified according to their sCr elevation during hospitalization as described above [10]. Data were tested for normality with the Shapiro-Wilk test and are expressed as the mean ± standard deviation (SD) or median (interquartile range) for continuous variables as appropriate.

Categorical variables are presented numerically and as percentages. One-way ANOVA and the Kruskal-Wallis tests were performed, and the three groups were compared using the Tukey-Kramer and Steel-Dwass methods as post-hoc tests. The $\chi 2$ and Fisher's exact tests were used to compare categorical variables.

In addition, SPPB at discharge was used as the dependent variable, and multiple regression analysis was performed using the forced-entry method with adjustment for confounding factors to evaluate the independent factors for the decrease in PF at discharge.

Independent variables were selected based on the following: (1) variables with variance inflation factor <2.78; (2) variables that differed by multiple comparison methods between the three groups; (3) variables with a P value of <0.5 in single correlation with SPPB at discharge; and (4) input variables selected for multiple regression analysis based on previous studies [16, 19].

A P value <0.05 was considered significant. Statistical analysis was performed using R ver. 2.8.1 statistical software (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Flow of included patients

Figure 1 shows a flowchart of the patients included in this study. Out of 573 consecutive heart failure patients who underwent phase I cardiac rehabilitation, 377 were excluded based on the exclusion criteria, leaving 196 patients for inclusion in the final analysis. They were divided to three groups: WRF III group (n = 55), WRF II/I group (n = 36), and non-WRF group (n = 105).

Table 1. Clinical characteristics, comorbidity, medications, and nutritional index

Parameters	sCr≥0.5	sCr≥0.2＜0.5	sCr＜0.2	P value		
	WRF III	WRF II・I	Non-WRF	WRF III vs.	WRF II・I vs.	WRF III vs.
	n=55	n=36	n=105	WRF II・I	Non-WRF	Non-WRF
Age (years)	83 (80-87)	87 (78-89)	83 (77-86)	0.8	0.20	0.80
Male, n (%)	30 (41.8)	21 (58.3)	50 (48.3)	0.77	0.20	0.80
Body mass index on admission, kg/m^2	21.6 (19.6-25.5)	22.9 (21-25)	22.4 (19.7-25)	0.7	0.80	1.00
Body mass index at discharge, kg/m^2	20.1 (18.3-25.6)	20.4 (18.8-24.4)	20.7 (18.3-23)	0.7	0.90	0.80
LVEF (%)	45.8 ± 15.4	45.4 ± 14.6	42.2 ± 15.7	0.7	0.90	0.80
Medical history/Comorbidity, n (%)						
Diabetes mellitus	28 (50.9)	16 (44.4)	42 (40)	0.55	0.64	0.19
Atrial fibrillation	29 (52.7)	18 (50)	51 (48.6)	0.80	0.88	0.62
Hypertension	42 (76.4)	29 (80.6)	76 (72.4)	0.64	0.33	0.59
Orthopedic disease	18 (32.7)	10 (27.8)	33 (31.4)	0.62	0.68	0.87
Respiratory disease	9 (16.4)	10 (27.8)	23 (21.9)	0.19	0.47	0.41
Laboratory data						
CRP (mg/dL) on admission	0.6 (0.3-2.5)	1.4 (0.3-5.0)	0.4 (0.2-1.5)	0.49	0.02	0.18
CRP (mg/dL) at discharge	0.4 (0.1-1.1)	0.4 (0.2-0.8)	0.5 (0.2-1.1)	0.96	0.85	0.96
Hemoglobin (g/dL) on admission	10.4 (9.7-11.5)	10.1 (9-12.1)	11.2 (10-12.9)	0.92	0.17	0.08
Hemoglobin (g/dL) at discharge	10.4 (9.2-11.3)	10.3 (9.5-12.5)	11 (9.9-12.5)	0.38	0.64	0.01
Creatinine (mg/dL) on admission	1.7 (1.1-2.5)	1.2 (1.1-1.5)	1.2 (1.0-1.2)	0.03	0.97	0.007
Creatinine (mg/dL) at discharge	2.0 (1.4-3.0)	1.4 (1.2-1.6)	1.2 (1.0-1.5)	＜0.001	0.01	＜0.001
Δ Creatinine	0.8 (0.6-1.1)	0.3 (0.3-0.4)	0.02 (0.04-0.1)	＜0.001	＜0.001	＜0.001
eGFR on admission (mL/min/1.73 m^2)	25.2 (18-41.5)	40 (31.6-47.1)	37.7 (25.8-49.8)	0.01	0.91	＜0.001
eGFR at discharge (mL/min/1.73 m^2)	22.8 (15.7-32.0)	33.6 (27.1-42.7)	42.6 (30.0-49.2)	＜0.001	0.05	＜0.001
BNP on admission (pg/mL)	810.5 (508.5-991.6)	724.5 (486.9-1060.7)	780.2 (411.7-997.1)	1.0	0.9	0.77
Nutritional index						
GNRI on admission	94.0 ± 11.6	94.3 ± 11.6	94.9 ± 10.2	0.98	0.96	0.87
GNRI at discharge	87.6 ± 10.7	91.1 ± 11.4	91.3± 8.6	0.22	0.99	0.06
ΔGNRI	6.5 ± 8.1	3.3 ± 5.1	3.6 ± 7.0	0.09	0.96	0.045
Albumin on admission	3.4 (3.1-3.8)	3.4 (3.1-3.7)	3.5 (3.3-3.8)	0.76	0.25	0.67
Albumin at discharge	3.3 (2.9-3.6)	3.3 (3.0-3.6)	3.4 (3.1-3.7)	0.74	0.80	0.15

Medications, n (%)						
Loop diuretics	52 (94.5)	34 (94.4)	93 (88.6)	1.0	0.18	0.27
Tolvaptan	17 (30.9)	16 (44.4)	35 (33.3)	0.02	0.002	0.76
Aldosterone antagonist	26 (47.3)	19 (52.8)	38 (36.2)	0.61	0.08	0.17
β blockers	37 (67.3)	18 (50.0)	63 (60.0)	0.01	0.29	0.37
ACE-I/ARB	13 (23.6)	11 (30.6)	34 (32.4)	0.46	0.84	0.25
Intravenous medications, n (%)						
Furosemide, n (%)	48 (87.3)	32 (88.9)	84 (80)	1.0	0.31	0.28
Furosemide period, (days)	3 (1.3-5.0)	2 (1.0-4.3)	2 (1.0-4.0)	0.66	0.4	0.048
hANP, n (%)	11 (20.0)	4 (11.1)	13 (12.4)	0.39	1.0	0.2
Nitrate	15 (27.3)	4 (11.1)	15 (14.3)	0.19	0.78	0.046
Catecholamine	15 (27.3)	3 (8.3)	16 (15.2)	0.032	0.4	0.067

sCr: serum creatinine; WRF: worsening renal function; LVEF: left ventricular ejection fraction; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; BNP: b-type natriuretic peptid; GNRI: Geriatric Nutritional Risk Index; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; hANP: human atrial natriuretic peptide.

Values are expressed as mean ± standard deviation or median (interquartile range).

Patient characteristics

Tables 1 and 2 show the clinical characteristics and CR-related indices of the three groups. In the WRF III group, hemoglobin at discharge and ΔGNRI were significantly lower, and the durations of furosemide iv and nitrate iv administration were longer.

In addition, although there was no difference in walking levels before hospitalization between the three groups, in the WRF III group, progression in CR was significantly slower, FIM at discharge was at a low value, PF at discharge was at a significantly low value, and length of stay was significantly prolonged.

Comparison of WRF severity with discharge SPPB

Figure 2 shows a boxplot comparing the severity of WRF during hospitalization with low PF at discharge. There was a significant difference in PF at discharge between the Non-WRF and WRF Ⅲ groups (Table 2).

Table 2. Physical function, walking levels before hospitalization, FIM, CR progress, and length of stay

Parameters	sCr≥0.5	sCr≥0.2＜0.5	sCr＜0.2	P value		
	WRF III	WRF II・I	Non-WRF	WRF III vs.	WRF II・I vs.	WRF III vs.
	n=55	n=36	n=105	WRF II・I	Non-WRF	Non-WRF
SPPB score at discharge (points)	6.0 (2.3-8.6)	6.5 (4-10)	9 (6-11)	0.50	0.17	0.002
Walking levels before hospitalization (n, %)	16/13/26	11/8/17	40/30/35	0.98	0.33	0.22
(Outdoor independence/Outdoor aid/Indoor)	(29.1/23.6/47.3)	(30.6/22.2/47.2)	(30.1/28.6/33.3)			
FIM score at discharge (points)	103.5 (92-117.3)	104 (94-113)	115 (104-122)	0.96	0.004	＜0.001
Motor FIM score (points)	70 (60-82.5)	72 (63.8-81)	82 (71-88)	0.89	0.007	＜0.001
Cognitive FIM score (points)	33 (28-35)	31.5 (28.3-35)	34 (32-35)	0.88	0.04	0.10
Cardiac rehabilitation progress						
Start day of cardiac rehabilitation (days)	4 (3-5)	3 (2-8)	2 (2-4)	0.37	0.15	0.002
Start day of standing (days)	4 (3-6)	3 (3-5)	3 (2-4)	0.28	0.058	＜0.001
Start day of walking (days)	5 (4-7)	4 (3.8-6.3)	4 (3-6)	0.59	0.08	0.003
Length of stay (days)	22.5 (15-35.3)	22 (16-33)	16 (13-23)	1.0	0.019	0.005

FIM: Functional Independence Measure; CR: cardiac rehabilitation; sCR: serum creatinine; WRF: worsening renal function; SPPB: Short Performance Physical Battery.

Measurements are presented as number (%.)

Values are express as mean ± standard deviation or median (interquartile range).

Bivariate correlation and multiple regression analysis with discharge SPPB as the dependent variable

Table 3 shows the bivariate correlation of factors influencing SPPB at discharge and the results of multiple regression analysis with SPPB at discharge as the dependent variable. When variables that met the selection criteria for independent variables were input into the multiple regression analysis, WRF III (β = -0.122, P = 0.037), GNRI at discharge (β = 0.156, P = 0.038), walking start day (β = -0.113, P = 0.037), and walking level before hospitalization (β = -0.614, P = <0.001) were extracted as independent factors (adjusted R^2 = 0.54) for a decrease in SPPB at discharge.

Table 3. Bivariate correlation and multiple regression analysis of SPPB at discharge

Variables	Bivariate correlation		Multiple regression	
	Spearman *r*	P value	*β*	P value
Presence of WRF				
Non-WRF	Reference		Reference	
WRF II・I (sCr≥0.2<0.5) during hospitalization	-0.054	0.448	-0.075	0.146
WRF III (sCr≥0.5) during hospitalization	-0.221	0.001	-0.122	0.037
Age	-0.390	<0.001	-0.042	0.473
Hemoglobin at discharge	0.220	0.001	-0.033	0.548
sCr on admission	-0.190	0.008	-0.035	0.615
sCr at discharge	-0.196	0.005	-0.062	0.383
GNRI at discharge	0.321	<0.001	0.156	0.038
ΔGNRI during hospitalization	-0.107	0.133	-0.047	0.356
Start day of walking	-0.30	<0.001	-0.133	0.037
Walking levels before hospitalization	-0.698	<0.001	-0.614	<0.001
R: 0.57				
Adjusted R^2: 0.54				

SPPB: Short Performance Physical Battery; WRF: worsening renal function; sCR: serum creatinine; GNRI: Geriatric Nutrition Risk Index.

Discussion

To our knowledge, this is the first study to show a relationship between WRF III and PF in older patients with HF and CKD during hospitalization.

Our findings suggest that WRF III is associated with low FP at discharge. Although there was no difference in walking levels before hospitalization in the three groups in this study, SPPB at discharge and FIM were at significantly low values in the WRF III group. The multiple regression analysis in this study showed that even after adjusting for influencing factors such as walking level before hospitalization, start day of walking, and nutritional status at discharge, WRF III during hospitalization was found to be an independent factor decreasing PF at discharge.

In our previous study of elderly HF patients, WRF (sCr ≥0.3 from baseline or 25% increase in sCr from baseline) during hospitalization was an independent factor for a decrease in ADL and PF at discharge [16, 19]. However, in older HF patients with CKD, WRF III, but not WRF II/I, was an independent factor for low PF at discharge. In a previous study of older patients with HF by Saitoh et al., CKD and anemia (defined as a hemoglobin level of <12 g/dL in males and <11 g/dL in females) were the factors that contributed to a decrease in PF [5]. The present study found that WRF III during hospitalization was independently associated with low FP at discharge. However, WRF III was not associated with a low hemoglobin level at discharge or changes/increases in sCr levels at admission or discharge.

Decreased renal function leads to the accumulation of various uremic toxins that have unfavorable effects on the body [23, 24]. These compounds are considered directly harmful to various tissues and organs and have been extensively studied, especially in the context of cardiovascular disease and kidney damage [25].

Recently, the accumulation of serum indoxyl sulfate (sIS) in CKD patients has been recognized as a potential trigger for cardiovascular events and further progression of CKD [26–28] as well as skeletal muscle loss and dysfunction [29, 30]. A high correlation has also been reported between increased sCr/decreased eGFR and sIS concentration in CKD patients [23, 24]. Furthermore, sIS concentrations remained high not only in patients with CKD but also in those with hospital-acquired acute kidney injury 7 days after diagnosis, which was associated with worse outcome [31]. Thus, sIS concentrations may be elevated in WRF during hospitalization of older patients with HF and CKD.

In the WRF III group, sCr at admission was 1.7 (1.1–2.5) mg/dL, sCr at discharge was 2.0 (1.4–3.0) mg/dL, and ΔsCr was the highest at 0.8 (0.6–1.1) mg/dL. In addition, eGFR in the non-WRF group was 37.7 (25.8–49.8) mL/min/1.73 m^2 at admission but improved to 42.6 (30–49.2) mL/min/1.73 m^2 at discharge. However, in the WRF III and WRF II/I groups, the eGFR at admission was significantly worse at discharge than at

admission. In particular, the eGFR in the WRF III group was as low as 25.2 (18–41.5) mL/min/1.73 m^2 at admission and was the lowest at 22.8 (15.7–32) mL/min/1.73 m^2 at discharge. Thus, patients with WRF III may be considered to have the highest sIS concentration at discharge.

Sato et al. stated that accumulation of sIS in muscle cells induces oxidative stress and metabolic changes, resulting in loss of energy production and disruption of the mitochondrial network. They described the possibility that accumulation of sIS contributes to loss of muscle mass, leading to the progression of sarcopenia due to disruption of the skeletal muscle mitochondrial network [30]. Therefore, it is possible that WRF of classes II and I during hospitalization suppressed an increase in sIS concentration, which resulted in no progression of sarcopenia. In addition, even though the duration of bed rest from immobility was the same between the three groups, patients with WRF III during hospitalization may experience the lowest PF at discharge.

The results of this study showed that the incidence of WRF III during hospitalization in older HF patients with CKD was 28.1%. Previous studies have reported that the cause of WRF III is frequent use of high-dose loop diuretics [10]. It has also been reported that the incidence of WRF in HF patients is due to a decreased diuretic response to furosemide iv for up to 4 days of hospitalization [32]. In addition, 70% of WRF in HF patients occurs within the first week of hospitalization [33].

The administration period of furosemide iv was significantly longer in the WRF III group than WRF II/I group in the present study (Table 1). The weaker kidney function of older HF patients with CKD can result in a poorer diuretic response, which may have prolonged the administration of furosemide iv and led to the development of WRF III.

In recent years, the efficacy of tolvaptan sodium phosphate in patients with HF who were inadequately affected by loop diuretics such as furosemide iv has attracted attention in Japan [34]. Because this new drug can be administered intravenously, it holds promise for renal protection and treatment of congestion in acute HF patients with severe renal dysfunction [34]. Alpha-human atrial natriuretic peptide (hANP) may also provide long- and short-term renal protection in the treatment of acute HF [35]. Furthermore, SGLT2 inhibitors reduced the risk of renal disease progression and hospitalization for HF in both CKD and HF patients, and the positive effects of SGLT2 inhibitors on renal function and HF were consistent across the stages of CKD and independent of the severity of HF [36]. Therefore, to prevent WRF III, it is important to change from administering furosemide iv to administering tolvaptan sodium phosphate iv or hANP or SGLT2 inhibitors according to renal function at admission and WRF severity in the early phase.

A low PF at discharge is particularly concerning in patients with low walking levels before hospitalization, high risk of WRF III during hospitalization, delayed early ambulation, and poor nutritional status. As a countermeasure for these patients, in

addition to medication adjustment in the acute phase by physicians and pharmacists, it is necessary for nurses and registered dietitians to improve dietary intake and devise nutritional supplements [19]. As well, it is important for PTs to quickly request CR prescriptions for patients with low walking level before hospitalization. Further, they need to promote early ambulation and screen PF from an early stage in patients at risk of low PF, such as those with WRF III and malnutrition, and then perform progressive CR according to the individuality of the patient's low PF, such as a low balance ability, muscle strength, or exercise tolerance [37]. In addition, patients with low levels of physical activity during hospitalization are more likely to develop hospital-acquired disability [38]. Therefore, to prevent a low PF at discharge, it is important to increase the amount of physical activity of the patients during times other than CR while also paying attention to symptoms of HF.

Compared with the ADL at discharge in the non-WRF group (FIM score: 115 [104–122] points), those in the WRF III group (103.5 [92–117.3] points) and WRF II/I group (104 [94–113] points) were significantly lower. Patients with decreased ADL at discharge need to apply for long-term care insurance in Japan and change their classification, and it is important to implement continuous home-visit rehabilitation and outpatient rehabilitation. In addition, Kitamura et al. reported that the cutoff value of FIM motor score predicting readmission within 90 days of discharge in older HF patients was 74.5 points [39].

The patients in the WRF III and WRF II/I group had FIM motor scores of 70 (60–82.5) and 72 (63.8–91) points, respectively, suggesting a high risk of re-hospitalization. In previous studies, the causes of rehospitalization in older patients with HF are diverse, including excessive hydration, excessive salt intake, drug neglect, overactivity, lack of weight and blood pressure control, and lack of patient awareness [40]. For this reason, we consider it essential not only to educate patients and their families about prevention of the recurrence of HF but also to introduce home-visit nursing and home-visit rehabilitation, as well as multi-professional collaboration at home, such as with nurses, PTs, care managers, and home helpers.

This study has several limitations. Leg muscle strength, muscle mass, and sIS concentration were not evaluated. Patients with acute HF and those with acute exacerbation of chronic HF were included. Admission sCr and eGFR values in patients with acute decompensated HF on admission may only partially reflect renal dysfunction due to the effects of HF. The time of onset of WRF during hospitalization and furosemide iv dosage were not investigated in detail.

We did not investigate differences between HF with reduced, mid-range, and preserved ejection fraction and transient versus permanent WRF. Treatment with furosemide iv for decongestion results in weight loss at discharge compared to admission, which affects BMI and GNRI. Therefore, it is difficult to simply compare

the nutritional status at admission and at discharge using the GNRI. Detailed examination of multimorbidity, illness severity, and pre-hospital frailty in older patients with HF and CKD is a future task. We consider that the walking level before hospitalization reflects the state of frailty roughly rather than sharply.

WRF III during hospitalization in older patients with HF and CKD was an independent factor for low PF at discharge, even after adjustment for other influencing factors such as walking level before hospitalization, walking start day, and GNRI at discharge; however, WRF II/I was not an influencing factor.

Although our present regression analysis cannot establish causality, our data lend support to the hypothesis that limiting an increase in sCr due to WRF during hospitalization to within 0.5 mL/dL is not only associated with a reduced risk of progression of renal failure, but also improved PF at discharge in older patients with HF and CKD.

Statements and Declarations

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Conflict of interest

All authors declare no conflicts of interest in relation to the work reported in this manuscript.

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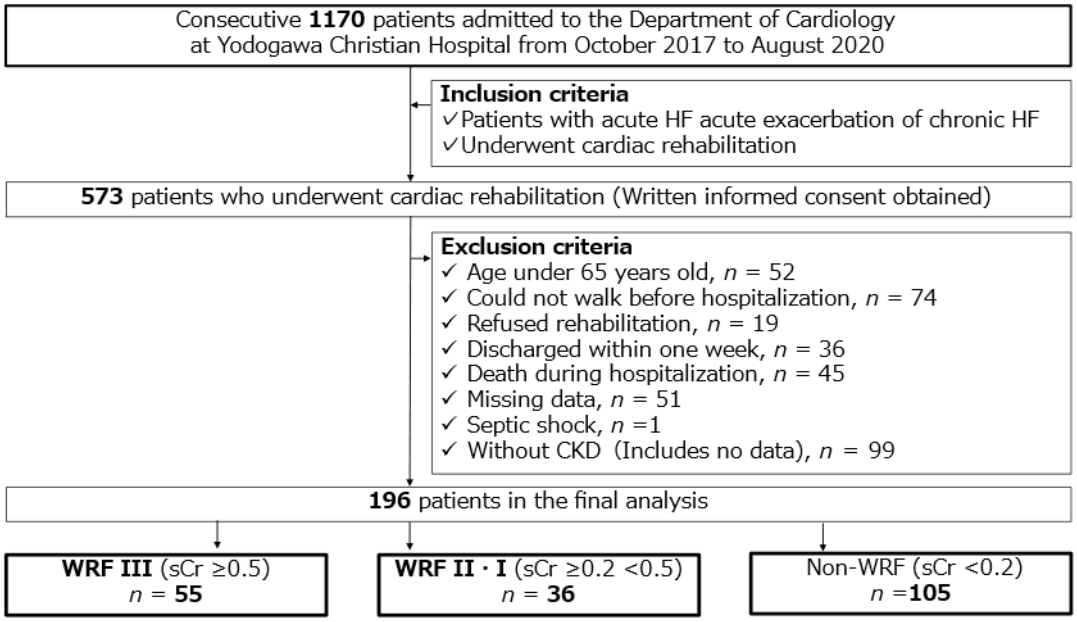


Figure. 1. Flowchart of classification of the elderly HF patients with CKD into the non-WRF, WRF II/I, and WRF III groups. *CKD* chronic kidney disease; *HF* heart failure; *sCr* serum creatinine; *WRF* worsening renal function.

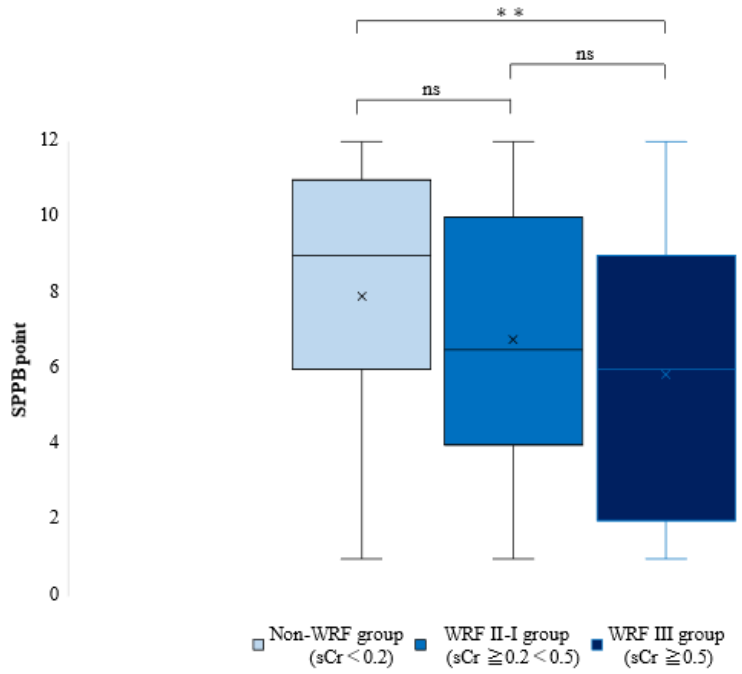


Figure. 2. Boxplots comparing WRF severity with discharge SPPB in the three groups. The y-axis shows the SPPB points, the whisker bars show the maximum and minimum values, and the horizontal line in the rectangle shows the median. *WRF* worsening renal function; *SPPB* Short Physical Performance Battery.