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Worsening renal function during hospitalization in elderly patients with heart failure: an independent factor of activity of daily living decline

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Abstract

Aims: This study aimed to clarify the effects of worsening renal function (WRF) during hospitalization on ADL at discharge of elderly heart failure (HF) patients.

Methods: We included 323 consecutive patients hospitalized for HF who were prescribed phase I cardiac rehabilitation (CR) from November 2017 to April 2019. WRF was defined as a relative increase from baseline in serum creatinine of 25% or that in serum creatinine ≥ 0.3 mg/dL during hospitalization. The indices of activity of daily living (ADL) and physical function were the Functional Independence Measure (FIM), Short Physical Performance Battery (SPPB) and 10-m comfortable gait speed as assessed at discharge. We compared background factors, clinical parameters, pre-hospitalization walking level, physical function, and FIM in two groups. Multiple regression analysis was performed with FIM at discharge as the dependent variable and items with $P < 0.05$ in bivariate correlation as independent variables.

Results: Ultimately, 160 patients were included and divided into the WRF group ($n = 72$) and non-WRF group ($n = 88$). FIM, SPPB, and 10-m comfortable walking speed were significantly lower in the WRF group. Moreover, even after adjustment for confounding factors (age, Hb, eGFR, CKD, GNRI, start day of standing), eGFR on admission ($\beta = 0.13$), WRF ($\beta = 0.23$) and pre-hospitalization walking level ($\beta = -0.48$) were independent factors of ADL decline at discharge (adjusted $R^2 = 0.42$).

Conclusion: WRF during hospitalization of elderly HF patients was a factor affecting ADL decline at discharge along with pre-hospitalization walking level and renal function at admission.

Keywords

Heart failure, worsening renal function, cardiac rehabilitation progress, oxidative stress, mitochondrial dysfunction, activity of daily living

Introduction

Against the background of an aging society, in the clinical setting, the number of elderly patients with heart failure (HF) who have multiple disorders has increased significantly.¹ Above all, 60–70% of patients admitted for acute exacerbation of chronic heart failure have chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) of $< 60 \text{ mL/min/1.73 m}^2$.¹ The association between the heart and kidney is called cardiorenal syndrome,² and renal dysfunction is considered to be an independent prognostic factor in elderly HF patients.³ Similarly, worsening renal function (WRF) in acute HF that occurs during hospitalization has also been reported to result in a poor prognosis.⁴⁻⁶ WRF during hospitalization for patients with HF has been reported to have significantly worsened clinical outcomes, including hospital mortality, complications, length of stay (LOS), additional renal dysfunction, readmission rates, and rising medical costs.^{5,7,8}

One purpose of cardiac rehabilitation (CR) in patients with HF is the recovery of activity of daily living (ADL).⁹ In patients with HF, because treatment is performed with the patient on bed rest until the circulatory dynamics are corrected, the patient's physical condition tends to be exacerbated.¹⁰ Especially in elderly patients, physical deconditioning progresses remarkably when they are hospitalized, walking ability declines, and difficulty with ADL increases.¹¹ However, the effects of WRF during hospitalization on ADL at discharge remain unclear. In other previous studies, factors that affect ADL, physical function, and exercise tolerance in elderly patients with HF have been reported to be a combination of renal dysfunction and anemia,¹²⁻¹⁴ and

malnutrition.^{15,16} Furthermore, we identified walking level before hospitalization and estimated glomerular filtration rate (eGFR) at admission to be independent factors of delay in early ambulation acquisition in elderly HF patients.¹⁷

Therefore, we hypothesized that walking level before hospitalization, eGFR at admission, and WRF during hospitalization could be causes of ADL decline at discharge. The purpose of this study was to determine the effects of WRF during hospitalization on ADL in elderly patients with HF at hospital discharge.

Methods

Study design and participants

We included in this retrospective cohort study 323 consecutive patients hospitalized for HF who were prescribed CR in the cardiovascular center of Yodogawa Christian Hospital, Osaka, Japan, from October 2017 to April 2019. Exclusion criteria included patients who were aged under 65 years old, could not walk before hospitalization, refused to participate in CR, were discharged within one week of admission, had no data on physical function evaluation or no laboratory data during hospitalization, were in septic shock, and who died during hospitalization. After determining whether the patients met the definition of WRF, we divided them into two groups according to the presence or absence of WRF and investigated and compared various patient characteristics and clinical parameters (Fig. 1).

The protocol of this study was approved by the institutional review board for ethics at Yodogawa Christian Hospital (approval no. 2019-036). Written informed consent was obtained from each patient.

Investigation

Patients' characteristics and clinical parameters evaluated included age, sex, body mass index (BMI), walking level before hospitalization, comorbidities before and during hospitalization, duration of oxygen administration during hospitalization, start day of phase I CR, start day of standing, start day of walking, Short Physical Performance Battery (SPPB), 10-m comfortable gait speed and Functional Independence Measure (FIM) at discharge, LOS, presence of positive pressure ventilation, intubated ventilator management, and hospital-phase oral and intravenous (iv) medications. Laboratory data included B-type natriuretic peptidase at admission, and hemoglobin, C-reactive protein, and serum creatinine levels, and eGFR at discharge. The Geriatric Nutritional Risk Index (GNRI) at discharge was adopted as the index of nutritional status. Under the direction of a doctor, a laboratory technician used echocardiography to measure the left ventricular ejection fraction (LVEF) and inferior vena cava diameter at admission in a physiology laboratory. Each test was performed using a standard protocol, and the LVEF was calculated using a modified Simpson method. All survey items were retrospectively investigated by one physical therapist (PT) from the patients' electronic medical records.

Definition of WRF

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.^{6,7}

Phase I cardiac rehabilitation

Patients in this study participated in phase I CR in accordance with the Japanese Circulation Society guidelines for rehabilitation in patients with cardiovascular disease.⁹ After confirming the attending physician's orders for each patient's rest and assessing the patient's subjective symptoms and vital signs, we initiated early mobilization exercises consisting of getting out of bed (sitting on the edge of the bed), standing at bedside, and walking around the bed. If patients were able to walk in the ward corridor, resistance training such as sit-to-stand exercise and calf raises was conducted by a PT using the patient's own weight, and then the patients participated in an aerobic exercise program assisted by PTs, nurses, and trainers. During the aerobic exercise, the patient was monitored with an ECG monitor.

Assessment of ADL

ADL at discharge was measured by FIM by seven PTs in charge. The FIM is divided into two domains of exercise and cognition. The motor domain (motor FIM) includes 13 items consisting of self-care, excretion control, transfer, and movement. The cognitive domain (cognitive FIM) consists of five items covering communication and social cognition. The 7-point ordinal scale of the FIM indicates the burden of care, with 1 point indicating total assistance; 2 points, maximal assistance; 3 points, moderate assistance; 4 points, minimal contact assistance; 5 points, supervision; 6 points, modified independence; and 7 points, complete independence. The FIM score ranges from a minimum of 18 points to a maximum of 126 points, whereas the minimum scores for the motor FIM and cognitive FIM were 13 points and 5 points, and maximum

scores were 91 points and 35 points, respectively.¹⁸

Assessment of physical function

The SPPB and 10-m comfortable gait speed were used as indices of physical function. All physical function assessments were measured by a PT in charge at discharge. The SPPB is a test of physical ability that assesses the ability to balance, 4-m walking time, and time required to stand-up over 5 repetitions. Test scores range from 0 points (inability to complete the task) to 4 points (highest level of performance), and the sum of the scores (0-12 points) was measured.¹⁹ The 10-m comfortable gait speed was measured by placing a 10-m line on a flat floor, and a PT using a stopwatch measured the time required for the patient to walk from the beginning to the end of the line. Two trials were performed. We calculated walking speed as 10 m/ s, with the highest value measured considered the walking speed (m/s).²⁰

eGFR and GNRI

eGFR was determined by a laboratory technician at admission and discharge, and GNRI at discharge. The eGFR was calculated using the following formula: $194 \times \text{serum creatine} - 1.094 \times \text{age} - 0.28 (\times 0.739 \text{ for females})$, as recommended by the Japanese Society of Nephrology.²¹ The GNRI includes serum albumin level and the ratio of body weight (BW) to ideal BW = $22 \times \text{square of height in meters}$. $\text{GNRI} = 14.89 \times \text{serum albumin concentration in g/dL} + 41.7 \times (\text{BW in kg/ideal BW})$.²²

Walking level before hospitalization

The cut-off criteria for pre-hospitalization walking levels were (1) independent outdoor

walking, in which the subject could walk outdoors independently without any support; (2) assisted outdoor walking, in which the subject could walk outdoors using a cane or buggy, etc.; and (3) indoor walking, in which the subject could walk indoors with the aid of a cane or walking aid. Information on walking levels was initially obtained by the primary doctor or nurse, by a medical social worker, who obtained it from the patient's family, or by the care manager, who obtained it from the patient's electronic medical record. Alternatively, the PT in charge collected this information directly from the patient, family, nurse or care manager.¹⁷

Arterial oxygen saturation, duration of oxygen administration and ventilation

Oxygen therapy was administered via nasal cannula or oxygen mask to maintain an oxygen saturation above 95%.²³ The duration of oxygen administration during hospitalization included that administered by cannula or mask along with noninvasive positive pressure ventilation and intubated ventilator management. Oxygen therapy was terminated when the patient's arterial oxygen saturation remained at or above 95% throughout a 24-hour period.

Statistical methods

We performed statistical analysis after using the Shapiro-Wilk test to determine whether the data were normally distributed. To evaluate patient characteristics and clinical parameters in the WRF group and Non-WRF group, we performed the Mann-Whitney U test, *t*-test, Chi-square test, and Fisher's exact test, as appropriate, on the data of the two groups. In addition, stepwise multiple regression analysis was performed to

evaluate the effects of WRF during hospitalization on ADL at discharge. In the multiple regression analysis, discharge FIM was used as the dependent variable, the independent variables were selected on the basis of previous studies^{12–17}, and the items with bivariate correlation with discharge FIM of $P < 0.05$ were input into the multiple regression analysis as independent variables. Bivariate correlation analysis was performed by a two-sided test using Pearson's product moment correlation when following a normal distribution and Spearman's rank correlation when not. Data are expressed as the mean $\pm$ standard deviation. 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

A flowchart of the patients included in this study is shown in Fig. 1. Among the 323 consecutive patients with HF who were prescribed Phase I CR, we excluded 163 patients who met the exclusion criteria. Therefore, 160 patients were ultimately included in the final analysis and were divided into the WRF group ($n = 72$) and non-WRF group ($n = 88$).

Patient characteristics

The clinical characteristics of the patients can be compared in Tables 1 and 2. Compared to the Non-WRF group, the WRF group had significantly higher serum creatinine values at discharge, lower eGFR values at discharge, and higher rates of iv furosemide

iv administration and aldosterone antagonist oral administration. In addition, FIM motor and cognitive scores at discharge were significantly lower. Furthermore, the times from disease initiation to the start of CR, to the start day of standing, and to the start day of walking exercise, and the LOS and duration of oxygen administration were significantly prolonged.

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

The results of bivariate correlation of influential factors in the discharge FIM and the results of multiple regression analysis with discharge FIM as the dependent variable and the influential factors as the independent variables are shown in Table 3. The bivariate correlations of the influential factors in the FIM showed significant correlations between age, hemoglobin at discharge, eGFR at admission, eGFR at discharge, WRF during hospitalization, CKD before admission, GNRI at discharge, and walking level before hospitalization. When these variables were input into the multiple regression analysis, eGFR at admission ($\beta = 0.12$, $P = 0.02$), WRF during hospitalization ($\beta = -6.42$, $P = <0.001$), GNRI at discharge ($\beta = 0.34$, $P = 0.001$), and walking level before hospitalization ($\beta = -0.66$, $P < 0.001$) were extracted as independent factors (adjusted $R^2 = 0.46$) for ADL decline at discharge.

Discussion

The results of the present study showed that even after adjusting for influencing factors such as nutritional status, eGFR at admission and discharge, hemoglobin level at

discharge, start day of standing, and walking level before hospitalization, WRF during hospitalization was an independent factor of ADL decline at discharge.

In our previous study, we clarified that the factors that delay early ambulation in elderly HF patients are their walking level before hospitalization and eGFR at baseline.^{13,17} However, in the present study, independent factors that reduced ADL at discharge for elderly patients with HF were pre-hospital walking level and eGFR at admission as well as WRF during hospitalization. The reason why baseline eGFR and WRF during hospitalization were the factors that decreased ADL at discharge, and not eGFR at discharge, was that the decrease in walking level before hospitalization was affected by progression of the CKD stage,²⁴ and we thought that the influence of the baseline eGFR might be great. In addition, WRF during hospitalization may have a significant impact on delayed rehabilitation. However, we suspect that there may be patients in whom the eGFR at discharge was transiently reduced.

Previous studies have reported that nutritional status is a strong influencing factor of ADL and physical function decline.^{15,16} The results of the multiple regression analysis showed WRF to be an independent factor in ADL decline even after adjusting for nutritional status as a confounding factor. A recent study by Beldhuis et al. showed that the trajectory of altered renal function in patients with acute HF had no prognostic effect.²⁵ However, we consider that the cause of the ADL decline at discharge in elderly patients with HF may be a result not only of a significant decline in ADL due to WRF during hospitalization but also to the interaction with walking level before hospitalization, baseline renal function, and

nutritional status.

Mechanisms of ADL and physical function decline at discharge

The pre-hospital walking level in the WRF group did not differ from that in the non-WRF group, but SPPB, 10-m comfortable gait speed, and motor FIM at discharge were significantly lower and LOS was prolonged. Further, the start day of walking and that of standing were significantly extended to 4.3 ± 2.8 and 3.0 ± 1.9 days in the non-WRF group and 7.0 ± 6.5 days and 5.2 ± 4.0 days in the WRF group, respectively (Table 2). Muscle weakness due to bed rest decreases by about 1–4% per day.²⁶ In the WRF group, the period of bed rest was significantly longer, and delays in the start date of walking caused a decrease in disused muscle strength, resulting in decreased physical function as indicated by the SPPB, walking speed at discharge, and decreased motor FIM, and these factors were thought to have led to extension of the LOS.

Interestingly, WRF itself can cause muscle weakness and muscle atrophy. In a recent report, oxidative stress and mitochondrial dysfunction were shown to play a major role in all stages of disease development during uremia followed by acute kidney injury, CKD, and their comorbidities.²⁷ In addition, excessive oxidative stress causes various types of cell damage and mitochondrial dysfunction.²⁸ Furthermore, mitochondrial dysfunction causes rapid muscle weakness and muscle atrophy.²⁹ Therefore, we believe that the significant decrease in the FIM movement and physical function scores in the WRF group was caused by muscular weakness and muscle atrophy due to oxidative stress and mitochondrial dysfunction caused by WRF. Thus, patients with WRF may experience more changes from disuse, such as muscle weakness

and muscle atrophy, than do non-WRF patients during the same period of immobility.

When considering the reason for the delay in the progress of CR such as the start of walking in the WRF group, previous studies have reported that diminished diuretic response during hospitalization in patients with acute HF causes WRF and decreased relief from dyspnea.^{30,31} In addition, 70% of WRF in HF patients occurred within one week after admission,³² and the duration of oxygen administration was significantly extended in the WRF group. Therefore, the delays in the start days of walking and standing may have been affected by the decreased relief of dyspnea with oxygen administration. Besides, patients with poor diuretic response often have not only a nasal cannula for oxygen delivery, but also a urinary catheter for urine volume measurement, which may limit ADL at the bedside other than that performed during CR.

Furthermore, FIM cognition at discharge was significantly reduced in the WRF group. In previous studies, immobility and environmental stress due to acute HF treatment caused delirium, sleeping disorder, and cognitive decline,³³ and ADL decline is an independent predictor of mild cognitive impairment in patients with heart disease.³⁴ It is also possible that the cognitive function of the patients in the WRF group was lower than that before admission.

Therefore, cognitive decline due to hospital treatment for acute HF may have caused a further decline in ADL.

Causes and countermeasures of WRF complications in elderly HF patients

The rate of WRF in the present study was 49.2%, whereas that reported in previous studies at other institutions in Japan was 39.2%⁶ and is 10% lower than that in the

present study. This may be due to the fact that the present patients were 81.7 ± 7.3 years old whereas those in the previous study were younger at 73.1 ± 14.5 years.

Previous studies have reported the cause of WRF in patients with HF to be decreased diuretic response to iv furosemide by day 4 of hospitalization.²⁸ The present study found that the rates of administration of iv furosemide and oral aldosterone antagonists were significantly higher in the WRF group. During treatment with iv furosemide in the early stage of hospitalization, a decrease in diuretic response may lead to a further increase in the amount and duration of iv furosemide administration, with WRF resulting as a side effect of the diuretic's administration. In addition, spironolactone is also used to improve diuretic response when it is reduced, and in elderly patients with HF complicated with CKD, administration at or above the standard dose may cause acute kidney injury.³⁵ In addition, tolvaptan is used for fluid diuresis, and diuresis can be performed in some patients with severe renal impairment.³⁶ Moreover, hANP may offer long- and short-term renal protection in the treatment of heart failure.³⁷ Therefore, it is important to pay attention to the adjustment of diuretics, the use of tolvaptan and hANP, and changes in renal function in patients at risk for WRF in the early stages of hospitalization.

It is also important to prevent the occurrence of WRF and to implement appropriate early mobilization,^{17,23} mental support, and improvement of exercise tolerance and ADL training to prevent the decline of ADL in elderly HF patients at discharge. Therefore, the physician needs to coordinate with a pharmacist in regard to diuretics administered from the beginning of hospitalization and to check the patient's nutritional status with a

registered dietitian to implement appropriate nutrition therapy. In addition to early mobilization, it is necessary to expand the scope of patient activities such as the use of portable toilets and toilet guidance in collaboration with ward nurses. Furthermore, because pre-hospital walking level is the factor that most affects ADL decline at discharge, to improve physical function and walking ability of HF patients at home,³⁸ as an important future task, a system is needed that can provide CR continuously at home to help prevent hospitalization.

Clinical implications

To our knowledge, this is the first study to determine the impact of hospitalization on ADL at discharge in elderly HF patients with WRF. Older HF patients with WRF may be more deconditioned due to immobility than non-WRF patients. It is important to perform early mobilization in elderly hospitalized HF patients with WRF while taking into account the control of their HF. Continuation of CR at home is important to maintain the ADL present at the time of hospital discharge.

Limitations

This cohort study has several limitations. We did not evaluate leg muscle strength, muscle mass, mitochondrial dysfunction, and oxidative stress. Both acute HF patients and patients with acute exacerbation of chronic HF were included. In the clinical setting of acute decompensated HF, serum creatinine levels and eGFR at admission might only partially reflect renal dysfunction due to the effects of HF. We did not investigate the timing of WRF onset during hospitalization in detail,

nor did we consider sex or age differences in physical function. We also did not perform specific dose assessments of drug therapy. Two patients received HOT in the WRF group and 1 received it in the Non-WRF group. We did not exclude these 3 patients receiving HOT. The differences between HFrEF, HEmrEF, HFpEF, and WRF severity and transient or permanent WRF were not investigated. Previous studies on the factors and prognosis of WRF in patients with HF produced different results depending on these differences. These differences may affect ADL and physical function and investigating them will be a future task.

Conclusion

WRF during hospitalization of elderly HF patients was a factor affecting ADL decline at discharge in addition to pre-hospital walking level and renal function at admission. In older HF patients, it is important to prevent WRF during hospitalization in the acute phase so that patient ADL does not decrease at discharge. Further investigation is necessary because WRF may affect physical function, ADL, and a decline in exercise tolerance in all patients with cardiovascular disease, not just elderly patients with HF.

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Author Contributions

Conceptualization, I.K. and K.P.I.; formal analysis, I.K.; investigation, I.K., N.K., M.R., and H.A.; data curation, I.K.; writing—original draft preparation, I.K., A.O., and M.K.; writing—review and editing, K.P.I., H.M., and D.M.; supervision, K.P.I. and H.M.;

project administration, K.P.I. and D.M.; funding acquisition, K.P.I. All authors approved the manuscript for submission.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

Abbreviations

ADL: activity of daily living

BMI: body mass index

CKD: chronic kidney disease

CR: cardiac rehabilitation

eGFR: estimated glomerular filtration rate

FIM: Functional Independence Measure

GNRI: Geriatric Nutrition Risk Index

HF: heart failure

LVEF: left ventricular ejection fraction

SPPB: Short Performance Physical Battery

WRF: worsening renal function

References

1. Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, Yokota T, Goto D, Yokoshiki H, Kato N, Takeshita A, Tsutui H (2009) Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (J CARE-CARD). *Circ J* 73:1893–1900.
2. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R (2008) Cardiorenal syndrome. *J Am Coll Cardiol* 52:1527-1539.
3. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurry JJ, Yusuf S, Granger CB, Michelson EL, Ostergren J, Comel JH, de Zeeuw D, Pocock S, van Veldhuisen DJ (2006) Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 133: 671-678.
4. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL (2014) Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 35: 455-469.
5. Palmer JB, Friedman HS, Waltman Johnson K, Navaratnam P, Gottlieb SS (2015) Association of persistent and transient worsening renal function with mortality risk, readmissions risk, length of stay, and costs in patients hospitalized with acute heart failure. *Clinicoecon Outcomes Res* 7: 357–367.
6. Okabe T, Yakushiji T, Kido T, Oyama Y, Igawa W, Ono M, Ebara S, Yamashita K, Yamamoto MH, Saito S, Amemiya K, Isomura N, Araki H, Ochiai M (2017) Relationship between worsening renal function and long-term cardiovascular mortality in heart failure patients. *Int J Cardiol* 230: 47-52.

7. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlib SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM (2004) Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol.* 43(1):61-67
8. Breidthardt T, Socrates T, Noveanu M, Klima T, Heinisch C, Reichlin T, Potocki M, Nowak A, Tschung C, Arenja N, Binqisser R, Mueller C (2011) Effect and clinical prediction of worsening renal function in acute decompensated heart failure. *Am J Cardiol* 107: 730-735.
9. JCS Joint Working Group (2014) Guidelines for rehabilitation in patients with cardiovascular disease (JCS 2012). *Circ J* 78: 2022-2093.
10. Saltin B, Blomqvist G, Hitchell JH, Johnson RL Jr, Wildenthal K, Chapman CB (1968) Response to exercise after bed rest and after training. *Circulation* 38(5 Suppl): VII1-VII78.
11. Gill TM, Allore HG, Gahbauer EA, Murphy TE (2010) Change in disability after hospitalization or restricted activity in older persons. *JAMA* 304:1919-1928.
12. Saitoh M, Ozawa T, Shiotani Y (2014) Effects of ventricular systolic dysfunction and cardio-renal anemia syndrome on walking ability and activities of daily living in patients with heart failure. *Rigaku ryōhōgaku* [Japanese with English abstract] 40:10-15.
13. Kitamura M, Saitoh K, Mizutani M, Yokoi T, Yaekura M, Miura Y, Nagashima H (2016) Recovery process of mobility and prognosis of walking independence in elderly patients with heart failure. *Rigaku ryōhōgaku* [Japanese with English abstract] 43:47-55.

14. Hotta C, Hiraki K, Watanabe S, Izawa KP, Yasuda T, Osada N (2011)
Determination of exercise capacity in chronic heart failure patients with chronic kidney disease. *Rigaku ryōhōgaku* [Japanese with English abstract] 38:436-441.
15. Izawa KP, Watanabe S, Oka K, Mogamiya T, Tada M, Nakata S, Yoshizawa K, Hirano Y, Osada N, Omiya K, Shimizu H (2015) Differences in physical performance based on the Geriatric Nutritional Risk Index in elderly female cardiac patients. *Aging Clin Exp Res* 27:195-200.
16. Izawa KP, Watanabe S, Oka K (2015) Relationship of thresholds of physical performance to nutritional status in older hospitalized male cardiac patients. *Geriatr Gerontol Int* 15:189-195.
17. Kubo I, Izawa KP, Kajisa N, Ogura A, Kanai M, Matsumoto D (2019) Factors delaying progress of early rehabilitation of elderly Japanese patients with heart failure. *Aging Clin Exp Res* 32(3):399-406.
18. Ottenbacher KJ, Hsu Y, Granger CV, Fiedler RC (1996) The reliability of the functional independence measure: a quantitative review. *Arch Phys Med Rehabil* 77:1226-1232.
19. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB (1994) A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 49:M85-M94.
20. Iida S, Aoki C (2017) Reliability of 10-meter walking test [part 1]: Influence of different measurement orders on the fast walking and normal walking. *Rigaku ryōhōgaku* [Japanese with English abstract] 32: 81–84.

21. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata H, Hishida A (2009) Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 53:982-992.
22. Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, Benazeth S, Cynober L, Aussel C (2005) Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. *Am J Clin Nutr* 82:777-783.
23. JCS Joint Working Group. (2013) Guidelines for treatment of acute heart failure (JCS 2011) *Circ J* 77:2157-2201.
24. Hiraki K, Yasuda T, Hotta C, Izawa PK, Morio Y, Watanabe S, Sakurada T, Shibagaki Y, Kimura K (2012) Decreased physical function in pre-dialysis patients with chronic kidney disease. *Clin Exp Nephrol* 17:225-231.
25. Beldhuis IE, Streng KW, van der Meer P, Ter Maaten JM, O'Connor CM, Metra M, Dittrich HC, Ponikowski P, Cotter G, Cleland JGF, Davison BA, Givertz MM, Teerlink JR, Bloomfield DM, Voors AA, Damman K. (2019) Trajectories of changes in renal function in patients with acute heart failure. *J Card Fail* 25(11):866-874.
26. Müller EA. (1970) Influence of training and of inactivity on muscle strength. *Arch Phys Med Rehabil* 51:449-462.
27. Popkov VA, Silachev DN, Zalevsky AO, Zorov DB, Plotnikov E Y (2019) Mitochondria as a source and a target for uremic toxins. *Int J Mol Sci* 20: E3094.
28. Tsutsui H, Ide T, Hayashidani S, Suematsu N, Shiomi T, Wen J, Nakamura K, Ichikawa K, Utsumi H, Takeshita A (2001) Enhanced generation of reactive oxygen species in the limb skeletal muscle a murine infarct model of heart failure.

Circulation 104:134-136.

29. Sudevan S, Takiura M, Kubota Y, Higashitani N, Cooke M, Ellwood RA, Etheridge T, Szewczyk NJ, Higashitani A (2019) Mitochondrial dysfunction causes Ca²⁺ overload and ECM degradation-mediated muscle damage in *C. elegans*. *FASEB J* 33:9540-9550.
30. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, Ponikowski JR, Cotter G, Davison B, Cleland JG, Givertz MM, Bloomfield DM, Fiuzat M, Dittrich HC, Hillege HL (2014) Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur Heart J* 35:1284-1293.
31. Voors AA, Davison BA, Teerlink JR, Felker GM, Cotter G, Filippatos G, Greenberg BH, Pang PS, Levin B, Hua TA, Severin T, Ponikowski P, Metra M (2014) Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome--an analysis from RELAX-AHF. *Eur J Heart Fail* 16:1230-1240.
32. Cowie MR, Komajda M, Murray-Thomas T, Underwood J, Ticho B (2006) Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective outcomes study in heart failure (POSH). *Eur Heart J* 27:1216-1222.
33. Krumholz HM. (2013) Post-hospital syndrome--an acquired, transient condition of generalized risk. *N Engl J Med* 368:100-102.
34. Ishihara K, Izawa KP, Kitamura M, Shimogai T, Kanejima Y, Morisawa T, Shimizu I (2019) Influence of mild cognitive impairment on activities of daily living in patients with cardiovascular disease. *Heart Vessels* 34:1944-1951.

35. Witham MD, Gillespie ND, Struthers AD (2004) Tolerability of spironolactone in patients with chronic heart failure -- a cautionary message. *Br J Clin Pharmacol* 58:554-557.
36. Vaduganathan M, Gheorghiade M, Pang PS, Konstam MA, Zannad F, Swedberg K, Grinfeld L, Burnett JC Jr, Krasa HB, Zimmer C, Blair J, Ouyang J, Maggioni AP; EVEREST investigators (2012) Efficacy of oral tolvaptan in acute heart failure patients with hypotension and renal impairment. *J Cardiovasc Med (Hagerstown)* 13(7):415-22.
37. Sasaoka T, Seya M, Hatano Y, Tao S, Sasaki T, Yoshikawa S, Maejima Y, Kawabata M, Goya M, Ashikaga T, Hirao K, Isobe M (2014) Low dose carperitide (alpha-hANP) administration is effective for preventing worsening renal function (WRF) and long-term renal protection. *J Card Fail* 20(8):S96.
38. Chien CL, Lee CM, Wu YW, Wu YT (2011) Home-based exercise improves the quality of life and physical function but not the psychological status of people with chronic heart failure: a randomized trial. *J Physiother* 57: 157–163.

Figure Legend

Figure 1. Diagram of the process to select elderly heart failure patients for the worsening renal failure (WRF) group and Non-WRF group.

Consecutive patients admitted to Yodogawa Christian Hospital with acute heart failure and acute exacerbation of chronic heart failure from October 2017 to April 2019

323 patients in whom cardiac rehabilitation was prescribed

Exclusion criteria

- ✓ Age under 65 years old, $n = 31$
- ✓ Could not walk before hospitalization, $n = 45$
- ✓ Refused rehabilitation, $n = 14$
- ✓ Discharge within one week, $n = 30$
- ✓ Death during hospitalization, $n = 15$
- ✓ Missing data, $n = 27$
- ✓ Septic shock, $n = 1$

160 patients in the final analysis

Non-WRF group, $n = 88$

WRF group, $n = 72$

Figure 1

Table 1. Patients' clinical characteristics

	WRF N = 72	Non-WRF N = 88	t or χ^2 value	p-Value
Age, (years)	83.0 $\pm$ 7.1	80.6 $\pm$ 7.3		0.08
Male, n (%)	34 (44.1)	40 (45.4)	0.04	0.82
Body mass index, kg/m ²	21.1 $\pm$ 4.1	20.4 $\pm$ 3.5	1.07*	0.28
LVEF at admission, (%)	46.1 $\pm$ 16.2	44.5 $\pm$ 15.8		0.56
Comorbidity/Medical history				
Diabetes mellitus, n (%)	27 (37.5)	26 (29.5)	1.13	0.28
Chronic kidney disease, n (%)	38 (52.7)	42 (47.7)	0.40	0.52
Hypertension, n (%)	57 (79.1)	56 (63.6)	4.60	0.03
Orthopedic disease, n (%)	24 (33.3)	26 (29.5)	0.26	0.82
Laboratory data (at discharge)				
CRP (mg/dL)	1.1 $\pm$ 1.9	0.9 $\pm$ 1.4		0.86
BNP (pg/dL) on admission	862.7 $\pm$ 631.6	804.5 $\pm$ 592.1		0.55
Creatinine (mg/dL)				
On admission	1.5 $\pm$ 1.1	1.2 $\pm$ 0.5		0.59
At discharge	1.8 $\pm$ 1.6	1.1 $\pm$ 0.4		<0.001
eGFR (mL/min/1.73 m ²)				
On admission	45.4 $\pm$ 26.0	46.7 $\pm$ 17.8		0.08
At discharge	36.4 $\pm$ 20.4	48.6 $\pm$ 17.3		<0.001
Hemoglobin (g/dL)				
On admission	11.3 $\pm$ 2.0	11.9 $\pm$ 1.8	1.65*	0.10
At discharge	11.1 $\pm$ 1.7	11.6 $\pm$ 1.9	1.58*	0.11
GNRI at discharge	89.7 $\pm$ 12.3	88.5 $\pm$ 9.4	-0.12*	0.90
Oxygen administration period (days)	4.5 $\pm$ 4.2	7.0 $\pm$ 7.2		0.03
Positive pressure ventilation, n (%)	12 (16.6)	9 (10.2)	2.69*	0.10
Intubation ventilation, n (%)	3 (4.1)	1 (1.1)		0.23
Oral medications, n (%)				

Loop diuretics, n (%)	67 (93.1)	75 (85.2)	2.43	0.11
Tolvaptan, n (%)	24 (33.3)	26 (29.5)	0.26	0.60
Aldosterone antagonist, n (%)	43 (59.7)	35 (39.7)	6.30	0.01
ACE-I or ARB, n (%)	19 (26.4)	28 (31.8)	0.56	0.45
Intravenous medications, n (%)				
Furosemide, n (%)	66 (91.6)	70 (79.5)	4.56	0.03
hANP, n (%)	17 (23.6)	11 (12.5)	3.38	0.06

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

All measurements are presented as number (%). Values are mean $\pm$ standard deviation unless otherwise noted. *t Value.

Table 2. Physical function, FIM, and length of stay

	WRF N = 72	Non-WRF N = 88	t or χ^2 value	p-Value
SPPB (points)	6.9 ± 3.4	8.5 ± 3.4		0.003
Ten-meter comfortable gait speed (m/s)	0.6 ± 0.2	0.8 ± 0.2		0.01
FIM at discharge (points)	102.4 ± 19.9	111.9 ± 14.4		<0.001
Motor FIM score	71.6 ± 16.4	78.8 ± 11.9		0.025
Cognitive FIM score	30.8 ± 5.4	33.1 ± 3.3		<0.001
Walking level before hospitalization (n, %)	27/18/27	40/18/30	1.09	0.57
(Outdoor independence/ Outdoor with aid/Indoor)	(37.5%/25%/37.5%)	(45.4%/20.4%/34%)		
CR Start day (days)	3.0 ± 2.5	1.7 ± 1.6		<0.001
Start day of standing (day)	5.2 ± 4.0	3.0 ± 1.9		<0.001
Start day of walking (day)	7.0 ± 6.5	4.3 ± 2.8		<0.001
Length of stay (days)	27.9 ± 17.2	18.9 ± 11.8		<0.001

FIM: Functional Independence Measure; SPPB: Short Performance Physical Battery; CR: cardiac rehabilitation; HF: heart failure.

All measurements are presented as number (%). Values are mean ± standard deviation unless otherwise noted.

*t value.

Table 3. Bivariate correlation and multiple regression analysis with FIM at discharge as the dependent variable

	Bivariate correlation		Stepwise multiple regression	
	Pearson r (Spearman r)	p-Value	β	p-Value
Age	-0.40	<0.001		
Hemoglobin on admission	0.20	0.01		
Hemoglobin at discharge	0.34	<0.001		
eGFR at admission	0.26	<0.001	0.12	0.02
eGFR at discharge	0.38	<0.001		
WRF during hospitalization		<0.001	-6.42	0.008
CKD before hospitalization		<0.001		
Start day of standing	-0.18	0.01	-0.71	0.04
Walking level before hospitalization	-0.66	<0.001	-10.00	<0.001
GNRI	0.30	<0.001	0.34	0.001
R		0.69		
Adjusted R ²		0.46		

FIM: Functional Independence Measure; eGFR: estimated glomerular filtration rate; WRF: worsening renal function; CKD: chronic kidney disease; GNRI: Geriatric Nutrition Risk Index.