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**Activities of daily living at different levels of renal function in elderly
hospitalized heart failure patients**

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26 **ABSTRACT**

27 *Background* Renal function (RF) and activities of daily living (ADL) are risk factors for
28 heart failure (HF) patients.

29 *Aims* We evaluated differences in motor and cognitive ADL in relation to RF in elderly
30 hospitalized HF patients.

31 *Methods:* Participants were selected from 414 consecutive hospitalized HF patients based on
32 certain criteria. We investigated patient characteristics including functional independence
33 measure (FIM) and estimated glomerular filtration rate (eGFR). Subjects were divided into
34 three groups by RF level and analyzed with one-way ANOVA and chi-square tests and two-
35 way ANCOVA and multiple comparison tests.

36 *Results* Of the 414 patients, 165 met the inclusion criteria (high RF: 41, moderate RF: 84,
37 low RF: 40). There were significant differences between the three groups in age, eGFR,
38 hemoglobin level, mobility, cognitive function, and length of hospital stay ($p < 0.05$). Motor
39 FIM showed an interaction between term and group, and cognitive FIM showed a main effect
40 on the group ($p < 0.05$). In the multiple comparisons, motor FIM of all groups indicated
41 significant recovery, but it was significantly lower after one week in the low RF versus
42 moderate/high RF groups ($p < 0.05$). Cognitive FIM showed no significant recovery in the
43 low RF group; the FIM score after two weeks was significantly lower than that in the
44 moderate/high RF groups ($p < 0.05$).

45 *Conclusions* In elderly hospitalized HF patients, the motor ADL recovery process in the low
46 RF group was delayed compared to the high RF group. Cognitive ADL in hospitalized HF
47 patients is difficult to recover, especially in those with low RF.

48

49 **Keywords** Activities of daily living, Estimated glomerular filtration rate, Elderly, Heart
50 failure, Hospitalized, Renal function

Introduction

Heart failure (HF) is highly prevalent, affecting about 1% of people in their 50s and rising progressively with age to afflict 10% of those in their 80s [1]. Moreover, the incidence and prevalence of HF are high among the elderly worldwide [2]. In an epidemiological study of Japanese patients with HF, the elderly patients had increased comorbidities, length of hospital stay, and medical costs [3]. One of the purposes of rehabilitation in HF patients is recovery of the activities of daily living (ADL) [4]. Age and comorbidities are risk factors for ADL [5] that may affect the length of hospital stay and medical costs in elderly hospitalized HF patients. In addition, low renal function (RF) is an important risk factor for cardiovascular disease and mortality in HF patients with comorbidities [6]. Levey et al. previously reported that an estimated glomerular filtration rate (eGFR) ≤ 60 is related to an increase in cardiovascular events [7]. With the trend toward an increased incidence of chronic kidney disease (CKD) [8], patients with low RF will increase as the elderly population increases because RF is known to decrease with aging [9].

With regard to the relationship between RF and physical function, two previous studies reported that the exercise capacity of HF patients with low RF was independently related to knee extensor muscle strength and eGFR [10], and low RF was independently associated with a low Short Physical Performance Battery score in HF patients [11]. Moreover, Wang et al. suggested that RF and cognitive function are related in elderly hypertensive patients [12].

Elias et al. also suggested that cognitive function decreases in non-dialysis CKD patients [13].

However, it is unclear whether RF in elderly hospitalized HF patients through each term of measurement, such as the weekly interval from admission, can affect motor and cognitive ADL. In previous studies, ADL evaluation was performed at one time point, discharge, or at two time points, admission and discharge, but evaluation of the detailed recovery process of motor and cognitive ADL at three or more time points during hospitalization has not been performed in HF patients with low RF [14, 15]. Thus, we believe that any differences in RF in relation to motor and cognitive ADL in elderly hospitalized HF patients require the investigation of both the relation between RF and ADL at each term and the relation between ADL recovery and the level of RF.

In the present study, we hypothesized that a low RF might be related to the decline in motor and cognitive ADL seen in HF patients. Therefore, the purposes of the present study were to evaluate the differences in motor and cognitive ADL in relation to RF in three groups of elderly hospitalized HF patients and to evaluate these differences in terms of the recovery process in these patients.

Methods

Study design and participants

Participants for this prospective cohort study were selected from 414 consecutive elderly Japanese patients with HF who underwent rehabilitation at one acute-care hospital from May 2013 to July 2015. Of these patients, those aged ≥ 65 years old who could walk with assistance before hospitalization were included. Patients whose assessment was difficult at the three points of measurement (admission and at one and two weeks thereafter), who had severe psychiatric disease, who underwent dialysis before hospitalization, and who died during hospitalization in the study were excluded. The Kokura Rehabilitation College Institutional Review Committee on Human Research approved this study (approval no. 25-0517), and informed consent was obtained from each patient.

Investigation

Patient characteristics and clinical parameters investigated by retrospective review of medical records included age, sex, body mass index (BMI), New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), brain natriuretic peptide (BNP) concentration, eGFR at admission and discharge, hemoglobin level, acute management, comorbidities, medications on admission, Rivermead Mobility Index (RMI) [16] and Karasawa Dementia Scale (KDS) at discharge [17], initiation of walking exercise, and length of hospital stay. The LVEF was calculated with the Simpson method for echocardiography and served as the index of left ventricular systolic function. NYHA class and BNP were also evaluated as indices of

the severity of HF. The hemoglobin level was evaluated as an index of anemia. NYHA class was determined in all patients by a cardiologist, and BNP and hemoglobin levels were measured by means of blood sampling at admission.

Acute management was evaluated when the patients received catecholamines, intra-aortic balloon pump, percutaneous cardiopulmonary support, respirator, or continuous hemodiafiltration. RMI was evaluated as an indicator of mobility, and KDS was evaluated as an indicator of cognitive function.

The eGFR was evaluated as the index of RF and was calculated using the following formula recommended by the Japanese Society of Nephrology: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ ($\times 0.739$ for females) [18]. We then divided the patients into three groups according to eGFR as reported in previous studies [19, 20]: high RF group (≥ 60 ml/min/1.73 m²), moderate RF group (≤ 30 to < 60 ml/min/1.73 m²), and low RF group (< 30 ml/min/1.73 m²).

We also used the Functional Independence Measure (FIM) to evaluate ADL [21]. FIM, which was developed to assess rehabilitative aspects of patients with disabilities, consists of two domains: motor and cognitive. The motor domain (motor FIM) consists of 13 items: eating, grooming, bathing, dressing upper body, dressing lower body, toileting, bladder and bowel management, transfer to bed, chair, or wheelchair, transfer to toilet, transfer to tub or shower, walking/wheelchair, and stairs. The cognitive domain (cognitive FIM) consists of 5

items: comprehension, expression, social interaction, problem solving, and memory. Scores are measured on a scale from 1 to 7 points (1 point: 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 minimum total FIM score is 18 points and the maximum total FIM score is 126 points, whereas minimum/maximum scores for motor FIM and cognitive FIM were 13/91 points and 5/13 points, respectively. This measurement performed by two physical therapists was carried out at the time of admission and then at weekly intervals.

Statistical Analysis

Patient characteristics and clinical parameters are reported using percentages for categorical variables and mean $\pm$ SD for continuous variables. One-way analysis of variance and chi-square test were used to compare patient characteristics and clinical parameters between the three groups. Two-way analysis of covariance (ANCOVA) with a within-groups factor (term: admission, after one week, and after two weeks) and between-groups factor (group: high RF, moderate RF, and low RF) was conducted to analyze motor and cognitive ADL recovery and differences in RF and was also used to adjust the FIM score and the significant difference of patient characteristics between the three groups. Bonferroni multiple comparison study was used to analyze both the within-groups and between-groups relations between motor ADL

and RF and those between cognitive ADL and RF. A p value <0.05 indicated statistical significance. Statistical analyses were performed with IBM SPSS 23.0 J statistical software (IBM SPSS Japan, Inc., Tokyo, Japan).

Results

Participant flow in the study was as shown in Figure 1. Of the 414 patients, 165 met the inclusion criteria and were divided into the high RF group (n = 41), moderate RF group (n = 85), and low RF group (n = 40).

The clinical characteristics of the elderly hospitalized HF patients at the three different levels of RF can be compared in Table 1. There were no significant differences in patient characteristics and clinical parameters between the three groups except for those of age, eGFR at admission and discharge, hemoglobin level, RMI, KDS, and length of hospital stay (p <0.05). The results of two-way ANCOVA showed a significant group and term main effect and interaction effect for the motor FIM score (p <0.05). There was no significant interaction effect or main effect of term for the cognitive FIM score. There was a significant main effect of group (Table 2).

Table 3 shows motor and cognitive FIM scores for the three different RF classifications at each term and in each group. In the within-groups comparison of the difference in motor FIM scores by RF group, the motor FIM score in all three groups showed significant recovery

at the one-week interval ($p < 0.05$). In the between-groups comparison of motor FIM at each term, the motor FIM scores after one week and after two weeks in the low RF group were significantly lower than those in the moderate and high RF groups ($p < 0.05$), and these scores after two weeks in the moderate RF group were significantly lower than those in the high RF group ($p < 0.05$). In the within-groups comparison of the difference in cognitive FIM scores by RF group, the cognitive FIM scores in the moderate RF and high RF groups showed significant recovery ($p < 0.05$), but the cognitive FIM score in the low RF group did not. In the between-groups comparison of cognitive FIM scores at each term, the cognitive FIM score after two weeks in the low RF group was a significantly lower than those in the moderate and high RF groups ($p < 0.05$).

Discussion

To our knowledge, this is the first study to assess the effect of differences in RF on motor and cognitive ADL recovery processes in elderly hospitalized Japanese HF patients. The results of this study show that the motor ADL recovery process in the patients with low RF appeared to be delayed compared with that in the patients with good RF. Also, the cognitive ADL recovery process in these patients was poor compared with that in the patients with good RF.

Comparison of patient characteristics

The elderly patients in the low RF group had a lower hemoglobin level, eGFR, and mobility and cognitive function at discharge, and longer hospital stay than those in the high RF group. In addition, compared to the other two groups, the low RF group tended to have a higher BNP, more atrial fibrillation, and lower doses of angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB). Davies and Shock found that aging reduces RF [9], and Astor et al. reported that erythropoietin production decreases as RF decreases and is known to cause anemia [22].

Go et al. reported that the prevalence of atrial fibrillation increases in an age-dependent manner, from <0.1% in adults younger than 55 years to 8% in those aged 80 years or older [23], Damman et al. showed a strong association between the worsening of RF and mortality in HF patients [24], and Adhiyaman et al. reported that ACEI administration in elderly patients with low RF could cause worsening of their RF [25]. In terms of changes in the eGFR of hospitalized HF patients, Reid et al. reported that the rates of improved, stable, and worsening eGFR in hospitalized HF patients were 19%, 64%, and 17%, respectively and that the rate of stable eGFR was high [26]. Wang et al. reported the association of RF with cognitive function in elderly patients with heart disease [12], and Palmer et al. suggested that hospitalized HF patients with low RF have low mobility and experience a long hospital stay [27]. Thus, the elderly HF patients in the low RF group might be on lower doses of ACEI/ARB, have a longer hospital stay, low mobility, low cognitive function, low eGFR at

203 discharge, and have lower cardiac function, as indicated by a high BNP, the presence of atrial
204 fibrillation, and anemia, than patients with better levels of RF.

205

206 **Effect of RF on motor ADL**

207 There was a significant interaction between the group and term for the motor FIM scores.

208 Thus, the motor ADL recovery process might be different depending on the level of RF. The

209 within-groups comparison showed significant recovery of the motor FIM scores in all three

210 RF groups at the one-week interval. Saltin et al. showed that exercise is effective for de-

211 conditioning caused by bed rest in cardiovascular disease [28], and the Japanese guidelines

212 based on those findings recommend early rehabilitation to prevent a decrease in ADL and

213 physical function in hospitalized HF patients [29]. Other previous studies reported that early

214 rehabilitation is likely to be able to prevent a decrease in physical function in intensive care

215 patients [30, 31] and improve the mobility of hospitalized HF patients [32]. Therefore,

216 regardless of the differences in RF, we believe that the motor ADL recovery obtained at the

217 one-week interval in the hospitalized HF patients was likely due to rehabilitation.

218 The motor FIM score after one week and two weeks in the low RF group was low

219 compared with that in the moderate and high RF groups. However, significant differences in

220 motor FIM score at admission were not recognized. Thus, we estimated that compared with

221 that in the moderate and high RF groups, the delay in motor ADL recovery seen in the low

222 RF group was due to low RF.

223 ADL at discharge in hospitalized HF patients with low RF is low [14]. Compared to
224 those in non-CKD patients, physical function, mobility, and ADL in CKD patients are poor
225 [33]. Physical function and ADL in non-dialysis patients with low RF are poor due to the
226 decrease in RF, and the decline of physical function in CKD patients is associated with a
227 reduction in RF and anemia [34]. In addition, ADL in the elderly is known to correlate with
228 the hemoglobin level [35]. The elderly patients in the low RF group had a low e-GFR,
229 hemoglobin level, and mobility. These factors associated with decreased RF are related to
230 physical function in HF patients, and we speculate that they affect ADL recovery.

231 Furthermore, the length of hospital stay in the low RF group was about 3 weeks. If a
232 certain degree of rehabilitation of ADL is provided in hospital for HF patients with low RF,
233 they might recover and their prognosis may improve. However, in the current health care
234 system, shortening of the length of hospital stay and suppression of medical costs are
235 recommended [3]. Cardiovascular disease patients with renal failure have longer lengths of
236 stay and higher hospital charges than those without renal failure [36]. Because our patients in
237 the low RF group had low heart function and could not be treated with medications such as
238 ACEI/ARB, these might be reasons why a treatment effect was difficult to obtain and the
239 length of stay was longer compared to the other two groups. It is also possible that ADL
240 deteriorated in the wake of admission in the HF patients with low RF, which suggests the

241 importance of maintaining good RF and ADL in community-dwelling HF patients.

242

243 **Effect of RF on cognitive ADL**

244 In terms of the cognitive FIM score, although there was no interaction between the group and
245 term and no main effect was shown for the term, a main effect for the group was seen. Such a
246 result indicates that differences in RF might have affected cognitive ADL in the hospitalized
247 HF patients.

248 In the within-groups comparison, the cognitive FIM score of the low RF group showed
249 no significant recovery at the one-week interval. As one cause of the poor recovery process of
250 cognitive ADL, it is possible that a low hemoglobin level and atrial fibrillation associated
251 with the low RF can influence the oxygen transport system of the brain. Previous studies
252 showed that although early intervention for cognitive function is safe, it is not clear whether
253 recovery of cognitive function and cognitive ADL can be obtained [37–40]. Thus, in
254 hospitalized HF patients with low RF, it is necessary to clarify the relationship between RF,
255 cognitive function, and cognition in ADL.

256 In the between-groups comparison, the cognitive FIM score in the HF patients with low
257 RF was low after two weeks compared with that in the high and moderate RF groups. In
258 addition, their cognitive function at discharge was also significantly lower. Several previous
259 studies in HF patients reported a strong relation between renal function and cognitive

function [12, 13, 41] and showed that poor cognitive function is a risk factor for ADL [15].

Also, Pulignano et al. reported that cognitive impairment was diagnosed in 38.9% of community-dwelling HF patients, in 85.7% of the patients with CKD (GFR <60 ml/min/1.73 m²), and in 42.6% with anemia (hemoglobin <12 g/dl) and that it was an independent predictor of hospitalization for HF [42].

Compared with that in the other two groups, the cognitive ADL recovery process of the HF patients in the low RF group was poor. One possible reason is that cognitive decline caused by low RF and anemia might affect poor cognition in ADL. These results also suggest the importance of interventions for RF and cognitive function in community-dwelling elderly HF patients.

Strengths and limitations

The strengths of the present study are that it showed both the characteristics of elderly hospitalized HF patients with low RF and the within-group and between-group features of motor and cognitive ADL according to different levels of RF in these patients.

There are several limitations in the present study. This was a single-center study with a small sample population, and sex-related differences could not be evaluated. Therefore, our results may have limited generalizability. We divided the RF group by eGFR only and could not use the Kidney Disease: Improving Global Outcomes (KDIGO) RF classifications based

on disease cause and albuminuria [7]. Thus, some patients with severe RF might have been included in the moderate RF group in the present study. We could not investigate other factors related to FIM and physical function such as gait speed, muscle mass, muscle strength, frailty, and cognitive function such as that measured by the Mini-Mental State Examination or perform a comprehensive geriatric assessment of our patients, including their quality of life and social circumstances. In other words, we could not elucidate the causes of physical and cognitive function related to ADL decline and a poor recovery process. We need to clarify these causes to seek an intervention-specific method of ADL improvement. These factors might be related in elderly cardiac patients with renal dysfunction. Thus, future studies in longitudinal settings performed for longer periods and with long-term follow-up will be needed to evaluate the effect of the improvement of ADL by increasing the physical and cognitive function of these patients.

Conclusions

Although motor ADL in elderly hospitalized Japanese patients with HF showed recovery regardless of the level of RF, the ADL recovery process in the HF patients with low RF was delayed compared with that in the patients with moderate and high RF. In contrast, cognitive ADL in the hospitalized HF patients was difficult to recover; especially, the ADL recovery process in the patients with low RF was poor in comparison with that in the other two groups.

298 A future intervention study of ADL in community-dwelling HF patients should be undertaken
299 to investigate the relation between physical function and cognitive function in ADL.
300

301 **Acknowledgments**

302 **Compliance with ethical standards** The participants received oral explanations of the
303 research procedures from the researchers.
304

305 **Conflict of interest** There are no conflicts of interest to report in relation to this study.
306

307 **Ethical approval** This study was approved by the Kokura Rehabilitation College
308 Institutional Committee.
309

310 **Informed consent** Informed consent was obtained from each patient.
311

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443 **Figure Legends**

444

445 **Fig. 1** Patient flow during the study

Consecutive heart failure patients who underwent rehabilitation at one acute-care hospital from May 2013 to July 2015 (N = 414)

Inclusion criteria:

- Age $\geq$ 65 years old
- Ability to walk with assistance before hospitalization

Heart failure patients meeting inclusion criteria (N = 233)

Exclusion criteria:

- Three-point measurement difficult (N = 39)
- Severe and psychiatric disease (N = 9)
- Underwent dialysis before hospitalization (N = 5)
- Died during hospitalization (N = 15)

HF patients after exclusion criteria applied (N = 165)

Table 1 Patient characteristics

	High RF n=41	Moderate RF n=84	Low RF n=40	For χ^2 value	p Value
Age, yrs	78.5±7.8	82.8±6.6*	84.9±7.0*	8.98 ^a	<0.001
Sex, male, %	48.8	45.2	35.0	1.74	0.42
BMI, kg/m ²	20.9±4.8	21.3±4.9	19.6±6.6	1.46 ^a	0.24
Clinical parameters					
NYHA class	2/20/44/34	1/22/44/33	0/3/42/55	10.86	0.09
I/II/III/IV, %					
LVEF, %	45.2±14.8	44.2±16.3	52.0±14.9	2.56 ^a	0.08
BNP, pg/mL	670.6±530.8	879.4±814.5	1124.8±1103.3	2.85 ^a	0.06
Hemoglobin, g/dL	13.0±1.8	12.1±2.5	8.8±2.7*†	36.10 ^a	<0.001
eGFR at admission, ml/min/1.73 m ²	75.5±13.7	45.4±7.5*	17.0±7.4*†	394.3 ^a	<0.001
eGFR at discharge, ml/min/1.73 m ²	61.2±16.0	45.2±23.6*	23.4±12.2*†	38.1 ^a	<0.001
Acute management, %	22.0	22.9	25.6	0.17	0.92
Comorbidity, %					
Hypertension	90.2	89.2	79.5	2.69	0.26
Diabetes	41.5	31.3	35.9	1.26	0.53
Ischemic heart disease	57.5	41.0	53.8	3.62	0.16

Valvular disease	32.5	38.6	33.3	0.57	0.75
Atrial fibrillation	37.5	57.8	41.0	5.70	0.06
Orthopedic disease	31.7	43.4	41.0	1.59	0.45
Neurological disease	17.1	15.7	17.9	0.11	0.95
Respiratory disease	24.4	14.5	15.4	2.02	0.64
Medication					
Diuretic	94.7	97.5	97.1	0.65	0.72
β-Blockers	76.3	66.3	54.3	3.95	0.14
ACEI/ARB	56.1	51.2	32.5	5.27	0.07
Mobility					
RMI at discharge	9.0±2.3	7.7±2.4	6.5±1.6	12.9 ^a	<0.001
Cognitive function					
KDS at discharge, normal/I/II/III/IV, %	66/25/7/2/0	57/20/16/7/0	30/35/18/15/2	17.0	0.03
Rehabilitation					
progress (days)					
Initiation of walking exercise	4.6±3.0	6.7±6.8	7.5±6.7	2.64 ^a	0.08
Length of hospital stay	16.6±5.7	19.1±9.4	21.6±8.4*	3.56 ^a	0.03

Values are mean ± SD or %.

ACEI angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BMI* body mass index, *BNP* brain natriuretic peptide, *eGFR* estimated glomerular filtration rate, *KDS* Karasawa Dementia Scale, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *RF* renal function, *RMI* = Rivermead Mobility Index

^a F value. $p \leq 0.05$: * vs high RF, † vs moderate RF.

Table 2 Two-way ANCOVA adjusted for age

	Mean square	f Value	p Value
Motor FIM			
Term	1917.7	14.6	<0.01
Group	3827.0	6.2	<0.01
Interaction	339.3	2.6	0.04
Cognitive FIM			
Term	55.0	2.7	0.07
Group	467.6	16.2	<0.01
Interaction	11.7	0.6	0.62

ANCOVA analysis of covariance, *FIM* Functional Independence Measure

Table 3 Motor and cognitive FIM in difference of renal function

	Admission	One week	Two weeks
Motor FIM score			
High RF	35.6±15.9	55.8±18.7*	73.0±17.6*
Moderate RF	34.9±15.4	52.5±18.1*	64.0±17.1*†
Low RF	29.1±15.7	43.3±18.4*†‡	57.2±17.3*†‡
Cognitive FIM score			
High RF	27.0±9.1	29.7±7.3*	31.0±6.5*
Moderate RF	27.5±8.8	29.4±7.1*	30.8±6.3*
Low RF	24.7±9.1	26.1±7.3	26.9±6.6†‡

Values are mean ± SD.

p ≤0.05: * Recovery at one-week intervals; † vs high RF; ‡ vs moderate RF.

FIM Functional Independence Measure, *RF* renal function