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ORIGINAL ARTICLE

Cognitive function in post-cardiac intensive care: patient characteristics and impact of multidisciplinary cardiac rehabilitation

Hitoshi Sumida[1] · Yuichi Yasunaga[1] · Kensei Takasawa[1] · Aya Tanaka[1] · Seiko Ida[1] · Tadaoki Saito[1] · Seigo Sugiyama[2] · Kunihiko Matsui[3] · Koichi Nakao[4] · Kenichi Tsujita[5] · Yuji Tohya[1]

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Abstract

New/worsening cognitive and physical impairments following critical care pose significant problems. Multidisciplinary cardiac rehabilitation (CR) can improve physical function after cardiac intensive care (CIC). This observational study aimed to evaluate cognitive function in patients participating in multidisciplinary CR and to identify correlates of impaired cognitive function after CIC. We analyzed 111 consecutive patients admitted to our comprehensive care ward at least 7 days after CIC and assessed factors associated with cognitive function using the Functional Independence Measure (FIM). Patients were stratified into two groups based on the median FIM-Cognitive scores: impaired ($n=56$) and preserved cognition ($n=55$) groups. Multiple logistic regression analysis identified age [odds ratio (OR) 1.06; 95% confidence interval (CI) 1.00–1.13; $p=0.042$], Mini-Nutrition Assessment-Short Form (MNA-SF; OR 0.73; 95% CI 0.56–0.95; $p=0.017$), and FIM-Physical scores (OR: 0.94; 95% CI 0.90–0.99; $p=0.012$) as significant and independent factors associated with impaired cognition. The median length of hospital stay was 28 (interquartile range: 18, 43) days. The FIM-Cognitive and FIM-Physical scores significantly increased from admission to discharge [32.0 (27.0, 35.0) vs. 34.0 (29.0, 35.0) points; $p<0.001$; 67.0 (53.0, 75.0) vs. 85.0 (73.5, 89.0) points; $p<0.001$, respectively]. On subgroup analysis within the impaired cognition group, increased FIM-Cognitive scores positively and significantly correlated with increased FIM-Physical scores ($\rho=0.450$; $p=0.001$). Multiple linear regression analysis identified atrial fibrillation (AF; $\beta=-0.29$; $p=0.016$), ln(glycated hemoglobin; HbA1c) ($\beta=0.29$; $p=0.018$), and ln(high-sensitivity C-reactive protein; hs-CRP) ($\beta=-0.26$; $p=0.034$) as significant and independent factors correlated with increased FIM-Cognitive scores. In conclusion, advanced age, low MNA-SF score, and FIM-Physical score were independent factors associated with impaired cognition in post-CIC patients. Multidisciplinary CR improved both physical and cognitive functions, and AF, HbA1c, and hs-CRP were independent factors correlated with increased FIM-Cognitive score.

Keywords Post-intensive care syndrome · Cognitive function · Cardiac rehabilitation · Physical activity · Nutrition assessment

Introduction

Cognitive function is central to the performance of basic activities of daily living (ADL), including the ability to recognize and describe cardiac symptoms; to adhere to self-care, including adherence to complex medication regimens and daily self-weighing; and self-management, including dietary regimens and compliance with advance care planning in patients with heart disease [1, 2]. New or worsening cognitive and physical function impairment in survivors of critical illness is frequent and noteworthy problems that give rise to the concept of post-intensive care syndrome [3]. This condition may be associated with months to years of disability affecting the performance of ADL. There are numerous reports concerning post-intensive care syndrome that have described associated severe sepsis or acute respiratory failure requiring prolonged mechanical ventilation [4, 5]; nevertheless, little is known about acute episodes of cardiac intensive care (CIC) such as myocardial infarction, heart failure, and cardiac surgery. Early rehabilitation plays an important role in the recovery of physical and cognitive functions in patients with post-intensive care syndrome [6].

✉ Hitoshi Sumida
hitsumida@me.com

Extended author information available on the last page of the article

Multidisciplinary cardiac rehabilitation (CR) with exercise training and nutritional support can improve functional status, health-related quality of life (QOL), and prognosis of post-CIC patients [7, 8]. Nevertheless, little is known about the factors associated with cognitive function in post-CIC patients or the effects of multidisciplinary CR on the recovery of cognitive function.

The Functional Independence Measure (FIM) is one of the most widely used and reliable methods of assessing the performance of tasks broadly categorized as ADL [9]. It indicates a patient's level of disability and any changes in physical status in response to CR or medical interventions [10, 11]. The FIM comprises 5 items related to cognition and 13 related to physical function. Each item is scored from 1 to 7, with 7 indicating complete independence or normal function and 1 indicating complete dependence or requirement for total assistance. The maximum score of the FIM-Cognitive is 35 and that for the FIM-Physical is 91; achievement of these scores implies total independence. The minimum FIM-Cognitive and FIM-Physical scores are 5 and 13, respectively, indicating the need for full assistance in all items assessed. The Mini-Mental Status Examination (MMSE) [12] is the most widely used screening method to detect cognitive impairments; however, changes in the MMSE score do not reflect true clinical improvement or decline of cognitive function [13]. By contrast, the FIM is a reliable method of assessing changes in ADL capacity in response to rehabilitation or medical interventions.

Sequential CR through inter-hospital cooperation between acute care and rehabilitation hospitals has been reported to result in significant improvement in ADL [11]. The regional comprehensive care ward system, started in 2014 in Japan, requires full-time coordination with a rehabilitation therapist. This system has been essential in bridging the gap in the transition from the acute care hospital to home medical care.

The aim of this study was to elucidate the predictors of cognitive function and the influences of multidisciplinary CR on cognitive function in post-CIC patients. To achieve this goal, we examined factors associated with the FIM-Cognitive function, the influence of multidisciplinary CR on the FIM-Cognitive function, and potential predictors of changes in FIM-Cognitive function in patients who were transferred from acute care hospitals to our regional comprehensive care ward.

Materials and methods

Study population

We enrolled consecutive inpatients who were transferred from acute care hospitals and who had participated in the multidisciplinary CR program for at least 7 days at the Heisei Tohya Hospital between April 2017 and March 2019. The study excluded individuals indicated for palliative terminal management.

Evaluation of covariates

The FIM scores were measured by trained physical therapists and nurses upon admission and discharge. FIM scores at discharge were reviewed by analysts who were blinded to all admission FIM score identifiers. Data, including blood test results, electrocardiograms, body mass index (BMI) values, and the Mini-Nutrition Assessment-Short Form (MNA-SF) [14] were recorded within the first 24 h after admission to represent baseline information. The diagnosis of atrial fibrillation (AF) was confirmed on admission electrocardiograms.

The study patients were stratified into two groups based on the median value of the FIM-Cognitive score at the time of admission: impaired cognition and preserved cognition groups. The clinical characteristics of the two groups were compared.

Ethical considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki and followed the guidelines of the ethics committee of our institution. The protocol was approved by the Heisei-Tohya Hospital Institutional Review Board. Written informed consent was obtained from each patient prior to participation.

Multidisciplinary CR program

The multidisciplinary CR program was started on the day of admission to our hospital according to the Japanese Circulation Society guidelines [7]. Briefly, the program included supervised exercise training sessions and patient education. The exercise training consisted mainly of aerobic exercises (walking, bicycle training, and calisthenics). The aerobic exercise intensity was determined on an individual bases based on either the 50–60% heart rate reserve (Karvonen's equation, $k=0.5$–0.6) [15] or the heart rate at the anaerobic threshold (AT), which was defined as the heart rate at levels 11–13 ("light to somewhat hard") on the Borg Rating of Perceived Exertion Scale (total range, 6–20). Among patients who did not perform symptom-limited stress testing or who had AF, exercise was initiated to achieve a heart rate of 20 beats faster than the resting value, with the intensity being increased according to levels 11–13 of the Borg Rating of Perceived Exertion Scale. Some resistance training using light weights and exercise machines was also performed [16]. Each exercise involved 7–10 repetitions per set with three sets per day, 2–3 times per week.

After screening and assessment of nutritional status using the MNA-SF, registered dietitians determined the appropriate nutritional interventions, including energy requirements, protein intake, sodium restriction, and necessity of oral nutrition supplementation [17]. The process was monitored closely via follow-up evaluations to maintain and improve nutritional status.

All patients and their families received individualized counseling on exercise prescriptions, drug management, and ADL from physicians, physical therapists, registered dietitians, pharmacists, and nurses during the course of the CR.

Statistical analysis

Continuous variables were expressed as medians [interquartile ranges (IQRs)]. Differences between groups were examined using Student's unpaired *t* test or the Mann–Whitney *U* test, as appropriate. Categorical values were presented as percentages and compared using the Chi-square test or Fisher's exact test, as appropriate. The Spearman rank coefficient was used to evaluate possible associations between two skewed distributive parameters.

Variables with highly right-skewed distributions were transformed logarithmically before application, to fulfill the conditions required for the type of analysis. To determine the independent factors for the presence of an impaired cognition score, we first selected all parameters that had a p value < 0.05 in the simple logistic regression analysis followed by multiple logistic regression analysis in the forced entry model. The Hosmer–Lemeshow goodness-of-fit Chi-square value was used to assess model calibration.

Many patients achieved the maximum score (35 points), indicating that cognitive function was preserved in those who did not demonstrate increased FIM-Cognitive scores, that is, the ceiling effect. To investigate this further, we performed subgroup analysis of the impaired cognition group. To determine the independent factors for increased FIM-Cognitive score, we first selected all baseline characteristics that had a p value < 0.05 in the simple linear regression analysis followed by multiple linear regression analysis in the forced entry model. The multiple correlation coefficient (R^2) was applied to assess model calibration. Two-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 22.0 (SPSS Japan Inc., Tokyo, Japan).

Results

A total of 120 patients were admitted from acute hospitals to our comprehensive care ward during the study period. Three patients whose care plan was palliative care were excluded. Five patients were transferred back to acute hospitals within 7 days (worsening heart failure, 2 patients; cerebral infarction, 1 patient; acute limb obstruction, 1 patient; and aspiration pneumonia, 1 patient). One patient was discharged home. Finally, we analyzed 111 patients (Fig. 1).

The FIM-Cognitive score was significantly and positively correlated with the FIM-Physical score (Fig. 2; $\rho = 0.688$; $p < 0.001$). The median FIM-Cognitive score upon admission was 32 points. We divided the study population into two groups according to the median score: an impaired cognition group (FIM-Cognitive score ≤ 32 points; $n = 56$ and a preserved cognition group (FIM-Cognitive score > 32 points; $n = 55$).

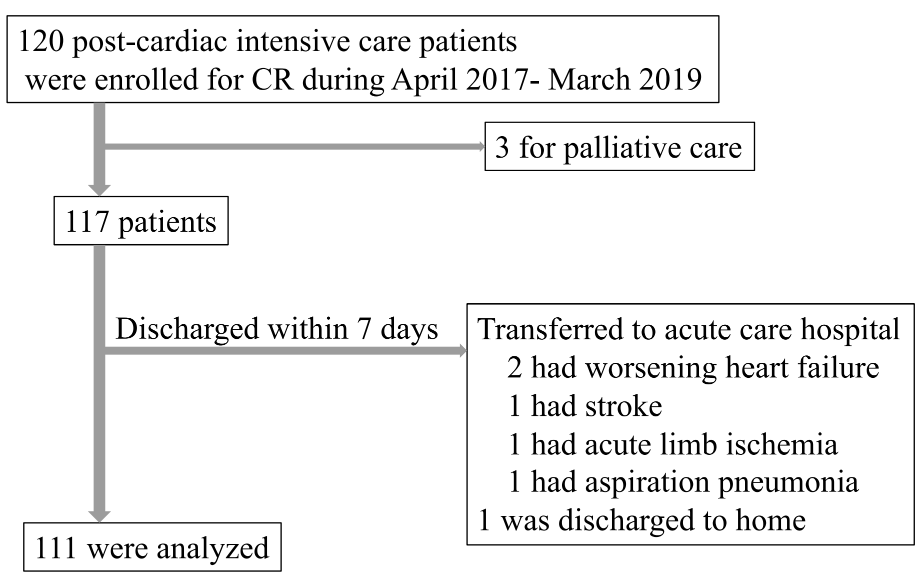


Fig. 1 Flowchart of patients included in the present study. *CR* cardiac rehabilitation

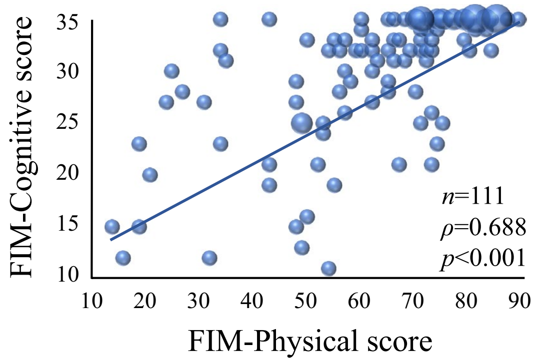


Fig. 2 Correlation between the FIM-Physical and FIM-Cognitive scores. The Spearman rank coefficient was used to evaluate associations between these two parameters because the variables were not normally distributed. *FIM* functional independence measure

FIM-cognitive scores and clinical determinants

Table 1 summarizes the overall clinical characteristics of the two groups upon admission. The impaired cognition group showed significantly higher age (83 [79, 87] vs. 76 [68, 82] years; $p=0.001$) and lower diastolic blood pressure (DBP; 62 [54, 70] vs. 68 [58, 76] mmHg; $p=0.017$), serum albumin level (3.2 [2.9, 3.5] vs. 3.6 [3.2, 3.9] g/dL; $p=0.001$), MNA-SF score (6 [5, 8] vs. 9 [8, 11] points; $p=0.001$), left ventricular ejection fraction (LVEF; 53 [36, 64] vs. 63 [50, 65] %; $p=0.038$), and FIM-Physical score (56 [43, 68] vs. 75 [68, 81] points; $p=0.001$) than the preserved cognition group.

The simple logistic regression analysis showed that age [odds ratio (OR) 1.09; 95% confidence interval (95% CI) 1.04–1.15; $p=0.001$], DBP (OR 0.96; 95% CI 0.93–0.99; $p=0.019$), serum albumin level (OR 0.19; 95%

Table 1 Clinical characteristics of the study patients

	Total ($n=111$)	Impaired group ($n=56$)	Preserved group ($n=55$)	p value
Age, years	77 [71, 85]	83 [79, 87]	76 [68, 82]	0.001
Male, %	50	52	47	0.634
Smoking, %	34	33	35	0.839
AF, %	32	39	26	0.157
AMI, %	7	14	0	0.004
HF, %	65	63	67	0.702
NYHA functional class (1/2/3/4), %	0/14/57/29	0/9/54/37	0/19/59/22	0.068
Cardiac surgery, %	18	12	24	0.111
Acute aortic syndrome, %	10	11	9	0.825
BMI, kg/m^2	22 [20, 26]	21 [19, 23]	23 [22, 25]	0.058
HR, beats/min	71 [66, 80]	72 [66, 81]	71 [66, 80]	0.689
SBP, mmHg	110 [100, 121]	108 [99, 117]	110 [102, 123]	0.470
DBP, mmHg	65 [55, 73]	62 [54, 70]	68 [58, 76]	0.017
Hemoglobin, g/dL	11.3 [10.4, 12.5]	11.0 [9.7, 12.3]	11.9 [10.9, 12.5]	0.998
BNP, pg/mL	255 [116, 534]	251 [124, 671]	262 [115, 435]	0.115
HbA1c, %	6.0 [5.6, 6.3]	5.9 [5.6, 6.6]	6.0 [5.6, 6.2]	0.381
hsCRP, mg/dL	0.9 [0.3, 2.3]	0.9 [0.3, 3.3]	0.8 [0.3, 2.1]	0.770
Creatinine, mg/dL	1.1 [0.8, 1.5]	1.2 [0.9, 1.6]	1.0 [0.8, 1.4]	0.045
eGFR, mL/min/1.73m^2	43 [32, 56]	41 [28, 52]	45 [38, 60]	0.020
Uric acid, mg/dL	6.2 [4.9, 8.0]	6.5 [5.2, 8.2]	6.1 [4.4, 7.6]	0.386
Sodium, mEq/L	139 [137, 142]	140 [136, 143]	139 [137, 142]	0.667
Potassium, mEq/L	4.1 [3.8, 4.5]	4.1 [3.8, 4.5]	4.1 [3.9, 4.4]	0.897
Albumin, g/dL	3.4 [3.0, 3.7]	3.2 [2.9, 3.5]	3.6 [3.2, 3.9]	0.001
MNA-SF score	8 [6, 10]	6 [5, 8]	9 [8, 11]	0.001
LVEF, %	58 [43, 65]	53 [36, 64]	63 [50, 65]	0.038
FIM-Physical score	67 [53, 75]	56 [43, 68]	75 [68, 81]	0.001
FIM-Cognitive score	32 [27, 35]	27 [21, 31]	35 [32, 35]	NA
Anti-dementia drug, %	11	14	7	0.265

Data are presented as median [interquartile range] or percentages

AF atrial fibrillation, *AMI* acute myocardial infarction, *BNP* brain natriuretic peptide, *DBP* diastolic blood pressure, *FIM* functional independence measure, *HbA1c* glycated hemoglobin, *HF* heart failure, *hsCRP* high-sensitivity C-reactive protein, *LVEF* left ventricular ejection fraction, *MNA-SF* mini-nutrition assessment-short form, *NA* not assessed, *NYHA* New York Heart Association, *SBP* systolic blood pressure

CI 0.08–0.47; $p=0.001$), MNA-SF (OR 0.60; 95% CI 0.49–0.74; $p=0.001$), LVEF (OR 0.97; 95% CI 0.95–1.00; $p=0.042$), and FIM-Physical score (OR 0.90; 95% CI 0.87–0.94; $p=0.001$) were significantly associated with impaired cognition (Table 2). Multiple logistic regression analysis, which included factors associated with impaired cognition in the simple logistic regression analysis, showed that age (OR 1.06; 95% CI 1.00–1.13; $p=0.042$), MNA-SF (OR 0.73; 95% CI 0.56–0.95; $p=0.017$), and FIM-Physical score (OR 0.94; 95% CI 0.90–0.99; $p=0.012$) were significantly and independently associated with impaired cognition. The Hosmer–Lemeshow goodness-of-fit Chi-square value was 5.041, with a p value of 0.753.

Effects of the multidisciplinary CR program

The median length of hospital stay was 28 [18, 43] days. There were no significant differences in the heart rate, systolic blood pressure (SBP), and DBP values between admission and discharge (71 [66, 80] vs. 70 [65, 78] beats per minute, $p=0.126$; 110 [100, 121] vs. 110 [100, 124] mmHg, $p=0.249$; 65 [55, 73] vs. 67 [59, 73] mmHg, $p=0.138$, respectively) (Fig. 3a–c). The FIM-Cognitive and FIM-Physical scores significantly increased from admission to discharge (32.0 [27.0, 35.0] vs. 34.0 [29.0, 35.0] points, $p<0.001$; 67.0 [53.0, 75.0] vs. 85.0 [73.5, 89.0] points, $p<0.001$, respectively) (Fig. 3d, e).

We identified 4 patients with worsened FIM-Cognitive scores (an 85-year-old woman with heart failure whose FIM-Cognitive score decreased from 21 points at admission to 17 at discharge; a 71-year-old man with acute aortic dissection whose score decreased from 31 to 28; a 67-year-old man and a 71-year-old man both with heart failure whose scores decreased from 32 to 28 points and from 35 to 33 points, respectively). The FIM-Physical score of the 85-year-old woman declined because of worsening heart failure, and she returned to the acute care hospital.

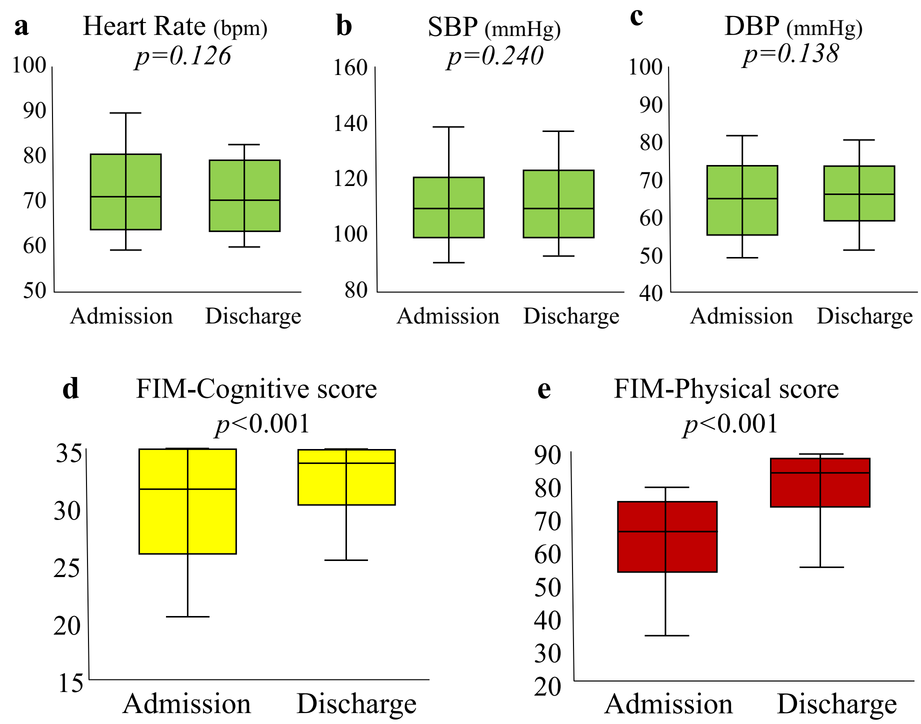
In the impaired cognition group, an increased FIM-Cognitive score positively and significantly correlated with an increased FIM-Physical score (Fig. 4; $\rho=0.450$; $p=0.001$).

Table 2 Logistic regression analysis examining the impaired cognition group

	Simple analysis			Multiple analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	1.09	1.04–1.15	0.001	1.06	1.00–1.13	0.042
Male gender	1.15	0.55–2.41	0.715		–	
Smoking	0.97	0.45–0.97	0.938		–	
AF	1.62	0.72–3.65	0.242		–	
BMI	1.01	0.98–1.03	0.583		–	
HR	1.01	0.98–1.04	0.487		–	
SBP	0.99	0.97–1.02	0.525		–	
DBP	0.96	0.93–0.99	0.019	0.97	0.93–1.01	0.152
Hemoglobin	1.00	0.93–1.08	0.443		–	
ln(BNP)	1.09	0.77–1.55	0.310		–	
ln(HbA1c)	4.18	0.12–143.59	0.428		–	
ln(hs-CRP)	1.01	0.81–1.26	0.902		–	
ln(Creatinine)	2.36	0.93–6.00	0.071		–	
eGFR	0.98	0.96–1.00	0.025		Not selected	
Uric acid	1.07	0.90–1.28	0.442		–	
Sodium	1.03	0.93–1.14	0.616		–	
Potassium	1.02	0.52–2.01	0.961		–	
Albumin	0.19	0.08–0.47	0.001		Not selected	
MNA-SF	0.60	0.49–0.74	0.001	0.73	0.56–0.95	0.017
LVEF	0.97	0.95–1.00	0.042	0.98	0.95–1.01	0.248
FIM-Physical score	0.90	0.87–0.94	0.001	0.94	0.90–0.99	0.012
Anti-dementia medication	2.00	0.57–7.07	0.282		–	

AF atrial fibrillation, *BNP* brain natriuretic peptide, *CI* confidence interval, *DBP* diastolic blood pressure, *FIM* functional independence measure, *HbA1c* glycated hemoglobin, *hs-CRP* high-sensitivity C-reactive protein, *LVEF* left ventricular ejection fraction, *MNA-SF* mini-nutrition assessment-short form, *OR* odds ratio, *SBP* systolic blood pressure

Fig. 3 Heart rate, systolic and diastolic blood pressure, and FIM-Cognitive and FIM-Physical scores upon admission and discharge. *bpm* beats per minute, *DBP* diastolic blood pressure, *FIM* functional independence measure, *SBP* systolic blood pressure



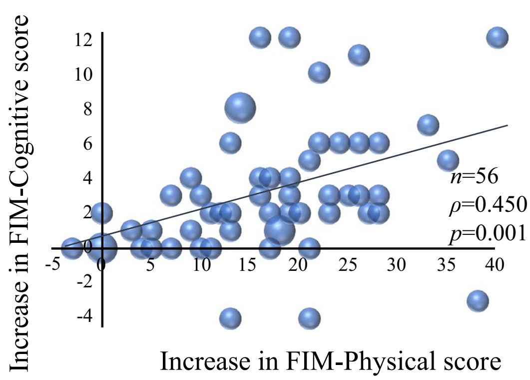


Fig. 4 Correlation between the increase in FIM-Physical and FIM-Cognitive scores The Spearman rank coefficient was used to evaluate associations between these two parameters because the variables were not normally distributed. *FIM* functional independence measure

Predictors of increased FIM-cognitive scores in the impaired cognition group

The simple linear regression analysis showed that an increased FIM-Cognitive score was significantly correlated with AF ($\gamma = -0.29$, $p = 0.033$), DBP ($\gamma = -0.29$, $p = 0.026$), ln(glycated hemoglobin; HbA1c) ($\gamma = 0.39$, $p = 0.003$), and ln(high-sensitivity C-reactive protein; hs-CRP) ($\gamma = -0.32$, $p = 0.018$) (Table 3).

The multiple linear regression analysis, which included factors that correlated with increased FIM-Cognition score in the univariate model, revealed that ln(HbA1c) ($\beta = 0.29$, $p = 0.018$) was positively correlated and that AF ($\beta = -0.29$, $p = 0.016$) and ln(hs-CRP) ($\beta = -0.26$, $p = 0.034$) were negatively correlated with increasing FIM-Cognitive score, significantly and independently ($R^2 = 0.377$; $p = 0.001$).

Discussion

To the best of our knowledge, this study is the first to evaluate improvements in cognitive and physical functions among patients who underwent subsequent multidisciplinary CR in the regional comprehensive care ward system after CIC. This study demonstrated that among post-CIC patients who needed inpatient multidisciplinary CR, the FIM-Cognitive scores were significantly and independently correlated with the FIM-Physical scores, i.e., patients in this program had improved physical and cognitive function. Among the patients with impaired cognition function, increases in the FIM-Cognitive score were positively and significantly correlated with increases in the FIM-Physical score, and an increased FIM-Cognitive score was significantly and independently associated with AF, HbA1c, and hs-CRP levels upon admission.

The median FIM-Physical score upon admission was 67; that is, the average of the scored items associated with physical impairment and activity limitation was 5.2 points. This indicates that the patients exhibited at least moderate dependence with respect to their physical ADL (e.g.,

Table 3 Linear regression analysis examining the increases in FIM-Cognitive scores in the impaired cognition group

	Simple analysis		Multiple analysis	
	γ	*p* value		*p* value
Age	0.04	0.747		–
Male gender	0.07	0.557		–
Smoking	– 0.04	0.769		–
AF	– 0.29	0.033	– 0.29	0.016
BMI	0.26	0.054		–
HR	– 0.10	0.445		–
SBP	– 0.24	0.077		–
DBP	– 0.29	0.026	–0.16	0.220
Hemoglobin	0.12	0.366		–
ln(BNP)	– 0.03	0.981		–
ln(HbA1c)	0.39	0.003	0.29	0.018
ln(hs-CRP)	– 0.32	0.018	– 0.26	0.034
ln(Creatinine)	– 0.10	0.477		–
eGFR	0.14	0.306		–
Uric acid	– 0.11	0.432		–
Sodium	– 0.04	0.746		–
Potassium	0.03	0.857		–
Albumin	0.08	0.553		–
MNA-SF	– 0.14	0.312		–
LVEF	– 0.11	0.938		–
FIM-Physical score	0.02	0.886		–
Anti-dementia medication	0.02	0.876		–

AF atrial fibrillation, *BNP* brain natriuretic peptide, *DBP* diastolic blood pressure, *FIM* functional independence measure, *HbA1c* glycated hemoglobin, *hs-CRP* high-sensitivity C-reactive protein, *LVEF* left ventricular ejection fraction, *MNA-SF* mini-nutrition assessment-short form; *S-* serum, *SBP* systolic blood pressure

feeding, grooming, bathing, dressing, toileting, transferring, continence, and locomotion).

Determinants of cognitive impairment in post-CIC patients

Upon admission, the FIM-Cognitive scores were independently and positively correlated with the FIM-Physical scores. Disuse contributes to skeletal muscle weakness in heart failure and critically ill patients, but it is not the sole mechanism. Other factors such as systemic nervous system activation, inadequate perfusion, and/or pathophysiological metabolic mechanisms might be important and could contribute to both brain and skeletal muscle malfunction [18–20]. Our results suggest that cognitive and physical dysfunctions are not isolated events but are an integral part of the process leading to multi-organ dysfunction.

The MNA-SF scores upon admission were independently associated with the FIM-Cognitive scores. As energy and several nutrients play important roles in proper brain functioning, nutritional stability is essential. Acute critical illness is characterized by a state wherein catabolism exceeds anabolism [21]. Post-acute setting-associated factors alter certain aspects of nutritional status, such as the senses of smell and taste, the ability to chew and swallow, and gastrointestinal function [22]. Malnutrition can trigger a vicious cycle of cognitive dysfunction leading to decreased nutritional intake and deteriorating nutritional status, which itself contributes to the acceleration of underlying heart disease and cognitive dysfunction [23, 24]. While clinical guidelines support a low-sodium, fluid, and energy restriction diet, we recommend evaluating the nutritional status and instituting a protocol that includes multidisciplinary and patient-specific nutritional support therapies.

We found that a lower DBP was associated with impaired cognition. Low DBP was reported to be associated with the risk of further cognitive decline [25, 26]. Cerebral blood perfusion depends on the mean blood pressure, which is calculated as 2/3 × DBP + 1/3 × SPB. Thus, DBP may be important for maintaining cerebral function. In this study, advanced age was an independent factor associated with impaired cognition. Elderly patients have wide pulse pressures owing to poor arterial compliance [27]. Targeting SBP management in patients with the cardiovascular disease might lead to lower DBP and impaired cognitive function, especially in elderly patients.

Effects of CR on the FIM-cognitive scores

The median FIM-Cognitive score at baseline was 32 points, and many patients achieved the maximum score (35 points), indicating that cognitive function was preserved in the majority of patients who did not demonstrate increased FIM-Cognitive scores. To investigate the ceiling effect further, we analyzed the effect of CR on the FIM-Cognitive score in the impaired cognition group.

Following multidisciplinary CR, the FIM-Cognitive scores were significantly increased and were significantly correlated with FIM-Physical score. The exact mechanisms by which the improvement in cognitive function was associated with that of physical activity are unclear. Exercise training is reported to have a protective effect against cognitive decline in elderly patients without dementia [28] and is associated with improved cognitive function in elderly patients with dementia [29]. Exercise improves vascular health and systemic inflammation and enhances endothelial function [30], all of which are associated with the maintenance of cerebral perfusion and function. Myokines are produced, expressed, and released by muscle fibers in response to muscle contractions [31]. These myokines then exert autocrine, paracrine, and endocrine effects. Brain-derived neurotrophic factor (BDNF) is released during muscle contractions and acts locally to affect fat oxidative metabolism in muscles.

BDNF is associated with beneficial epigenetic changes, improved cognitive function, mood, and memory. Plasma BDNF levels are decreased in patients with acute decompensated heart failure [32]. Exercise may also preserve neuronal structures and promote neurogenesis, synaptogenesis, and capillarization, which may be associated with exercise-induced increases in BDNF. Exercise reinstates hippocampal function by enhancing the expression of BDNF and other growth factors that promote neurogenesis, angiogenesis, and synaptic plasticity [33].

Potential factors predicting increased FIM-Cognitive scores

Patients with AF had minimal ability to rebound from cognitive dysfunction compared to patients without AF. AF is reported to be associated with cognitive impairment [34]. The pathophysiological link between AF and cognitive dysfunction is likely multifactorial. Certainly, cerebral infarcts, including silent strokes, play a central role; however, several non-stroke-related mechanisms including cerebral hypoperfusion, vascular inflammation, brain atrophy, genetic factors, and shared risk factors have also been proposed to explain the link [35]. Our findings support this relationship.

The patients in this study with higher levels of hs-CRP also had lower cognitive functional recovery. Systemic inflammation has been associated with neurocognitive malfunction [36], and several prospective studies have found greater rates of cognitive decline among individuals with higher levels of circulating inflammatory markers [37, 38]. Our study findings are consistent with previous reports suggesting that cognitive reserve may be vulnerable to the effects of systemic inflammation.

Our study demonstrated that patients with higher HbA1c levels have better cognitive resilience. It has been reported that high blood glucose concentrations could be a mechanism by which diabetes impairs cognition and that glycemic control might improve it [39]. In this study, the median HbA1c level was 6.0%, suggesting that many patients had normal glucose metabolism. Increased red blood cell turnover is known to result in lower HbA1c levels [40]. We postulate that conditions that reduce the lifespan of red blood cells in CIC setting might result in lower HbA1c levels and low cognitive recovery.

Late-onset cognitive impairments

Although found in only a small percentage of the total number of patients, worsening cognitive impairment was observed in some patients who underwent post CIC. Cognitive impairments have been reported to persist after critical illnesses, even among previously healthy patients [41]. It remains unclear which mechanisms of critical illness underlie late-onset cognitive deficits. As cited above, systemic inflammation in organs such as the brain could stimulate mechanisms that increase the risk of worsening long-term cognitive outcomes after intensive cardiac illness. We must recognize that CIC may be an important risk factor for future cognitive impairment.

The three independent predictors of impaired cognitive function at baseline (age, nutritional state, and physical function) did not predict improvement in cognitive function and these results may be confused. We found that increased physical function was associated with increased cognitive function, suggesting that efforts to improve physical and nutritional status might improve cognitive function.

Limitations

Several limitations to this study need to be acknowledged. First, the study was limited by its small sample size and single hospital setting. In this study population, we found that age, hs-CRP, HbA1c, and low blood pressure were associated with impairment or recovery of cognitive function. These have previously been reported to be significant predictors of cognitive function, suggesting that our study population was representative. Second, the study did not include a control group that did not participate in multidisciplinary CR. Therefore, it could be argued that the observed improvements in cognitive function were related to the natural course of healing after CIC. We believe that the significant correlation between increased cognitive and physical functions negate this possibility. Furthermore, it would be unethical to have a control group because clinical guidelines recommend multidisciplinary CR for all patients needing CIC. Third, given that the nature of CIC is mostly unplanned, we were unable to assess each participant's cognitive and physical functions prior to their illness. Furthermore, we could not evaluate the use and duration of mechanical ventilation, the presence of delirium, or administration of sedative or analgesic medications.

Conclusions

In this observational study, cognitive function was significantly and independently associated with physical function in post-CIC patients. Exercise and physical activity assessments and interventions, together with nutritional interventions, improved both cognitive and physical function. Cognitive recovery declined in patients with AF, low HbA1c, and high hs-CRP, reflecting underlying systemic risks. Further large-scale studies are needed to confirm these results and define the utility of multidisciplinary CR programs for restoring cognitive function.

Multidisciplinary CR using the regional comprehensive care ward system is an effective strategy that can be used to restore physical and cognitive function post-CIC. This can help bridge the gap in transition from the acute care hospital setting to home medical care.

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Compliance with ethical standards

Conflict of interest Dr. Tsujita has received honoraria from Bayer Yakuhin, Ltd., Daiichi Sankyo Co., Ltd., Kowa Pharmaceutical Co. Ltd., MSD K.K., Sanofi K.K., and Takeda Pharmaceutical Co., Ltd.; has received trust research/joint research funds from AstraZeneca K.K., Sugi Bee Garden, and Japan Medical Device Technology Co., Ltd.; and has received grants from ITI Co., Ltd., Astellas Pharma Inc, Abbott Vascular Japan Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Kaneka Medix Co., Ltd., Goodman Co., Ltd., GM Medical Co., Ltd., Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma, Chugai Pharmaceutical Co., Ltd., TERUMO Co., Ltd., Boehringer Ingelheim Japan, Medtronic Japan Co., Ltd., Japan Lifeline Co., Ltd., Novartis Pharma K.K., Fides-One, Inc., Bristol-Myers K.K., Boston Scientific Japan K.K., Cardinal Health Japan, and MSD K.K. Dr. Sugiyama is on the Speaker's Bureau of MSD, Inc., and AstraZeneca Pharmaceuticals LP, Ono Pharmaceutical CO., LTD, and Bayer Yakuhin Ltd.

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Affiliations

Hitoshi Sumida[1] · Yuichi Yasunaga[1] · Kensei Takasawa[1] · Aya Tanaka[1] · Seiko Ida[1] · Tadaoki Saito[1] · Seigo Sugiyama[2] · Kunihiko Matsui[3] · Koichi Nakao[4] · Kenichi Tsujita[5] · Yuji Tohya[1]

Yuichi Yasunaga
ysng.bob.pt@gmail.com

Kensei Takasawa
kensei.takasawa@gmail.com

Aya Tanaka
h-eiyou@tohya.or.jo

Seiko Ida
s-ida@tohya.or.jp

Tadaoki Saito
hidaki@tohya.or.jp

Seigo Sugiyama
SeigoSugiyama@jinnouchi.or.jp

Kunihiko Matsui
kmatsui@kumamoto-u.ac.jp

Koichi Nakao
koichi-nakao@saiseikaikumamoto.jp

Kenichi Tsujita
tsujita@kumamoto-u.ac.jp

Yuji Tohya
y.108hp@i.softbank.jp

[1] Division of Cardiology, Heisei Tohya Hospital, 8-2-15, Idenakama Minami-ku, Kumamoto 862-0963, Japan

[2] Division of Cardiology, Jinnouchi Hospital, 6-2-3, Kuhonji Chuo-ku, Kumamoto 862-0976, Japan

[3] Department of Community, Family, and General Medicine, Graduate School of Medical Sciences, Kumamoto University, 1-1-1, Honjo Chuo-ku, Kumamoto 862-8556, Japan

[4] Department of Cardiovascular Medicine, Saiseikai Kumamoto Hospital, 5-3-1, Chikami Minami-ku, Kumamoto 862-4116, Japan

[5] Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, 1-1-1, Honjo Chuo-ku, Kumamoto 862-8556, Japan