Malnutrition is Associated With Cognitive Impairment in Patients With Repeated Hospitalization for Acute Heart Failure

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The purpose was to assess the nutritional characteristics of patients repeatedly hospitalized with acute heart failure (AHF). We enrolled 60 patients with hospitalized at least three times within four years. The Geriatric Nutritional Risk Index (GNRI) was used as a nutritional index. The patients were divided into three groups based on changes in GNRI: (1) Good group, good or mild decrease in nutritional status (GNRI \geq 92); (2) Change group, nutritional status changed; and (3) Poor group, moderate to severe malnutrition status (GNRI <92). Of the 60 patients, there were 23 in the Good group (38.3%), 23 in the Change group (38.3%), and 14 in the Poor group (23.4%). The overall GNRI decreased at every hospitalization. The rate of cognitive impairment (CI) was highest and handgrip strength was lowest in the Poor group. In multivariate analysis, CI was independently associated with the Poor group. The patients with persistent malnutrition were characterized by CI.

Keywords: acute heart failure, cognitive impairment, Geriatric Nutritional Risk Index

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INTRODUCTION

The prevalence of heart failure (HF) is rapidly increasing worldwide, representing a significant global health concern [1]. This trend has also been observed in Japan, where the number of patients affected by HF is projected to reach 11.3 million by 2025–2030 [2].

Anorexia, malabsorption due to gastrointestinal edema, chronic inflammation, loss of skeletal muscle mass, and medication side effects are common in HF patients, contributing to malnutrition [3]. Approximately 20–42% of chronic HF (CHF) patients suffer from malnutrition, which has a series of negative consequences [4, 5].

Nutritional management should be implemented concurrently with HF treatment, as nutritional status tends to deteriorate with disease progression. Research into energy intake in CHF patients has revealed median values of around 1,600 kcal/day, with 10–30% of patients demonstrating inadequate caloric intake [6]. Those studies also demonstrated that insufficient caloric intake is associated with poorer prognosis. Compared to CHF, acute HF (AHF) exacerbates catabolism and lipolysis through the activation of inflammatory cytokines, stimulation of the catecholamine system, and activation of the natriuretic peptide system. Furthermore, the augmented respiratory muscle workload, diminished albumin synthesis due to hepatic congestion and compromised nutrient absorption caused by intestinal edema collectively contribute to a declining nutritional status among individuals with AHF [7-

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9]. Moreover, the presence of congestion and the administration of diuretic treatment pose difficulties in accurately assessing the nutritional status of individuals due to the fluctuating nature of body weight (BW) and serum albumin levels. Although several studies have focused on malnutrition in CHF, research into patients with AHF remains limited.

In addition, Stage D is defined as HF that does not improve beyond New York Heart Association (NYHA) III even with standard medical treatment after two or more repeated hospitalizations for HF per year [10]. Patients in the present study who have been hospitalized three or more times within four years are mainly in the transition stage from stage C to D or are already in stage D. Very few studies have focused on such end-stage cases of HF.

The purpose of this study was to evaluate the nutritional status of patients with end-stage HF and to identify associated factors.

METHODS

Study population

This retrospective, single-center observational study enrolled 60 patients who had been hospitalized at least three times for treatment of AHF between January 2018 and December 2021. AHF was defined as rapid onset or worsening of clinical symptoms or signs of congestion and/or peripheral hypoperfusion according to European Society of Cardiology guidelines [11]. We excluded patients with acute coronary syndrome on admission, liver cirrhosis, dialysis, and in-hospital deaths. This study was conducted in accordance with the Declaration of Helsinki. All study protocols were approved by the Ethics Committee of Matsue Red Cross Hospital (Approval No. 537).

Data collection

Data collected from the electronic medical records of patients included demographic characteristics, medical history, comorbidities, laboratory data, echocardiograms, medications, cognitive evaluations, physical function assessment, and clinical courses after the third discharge.

Evaluations

The Mini-Cog [12] or Mini-Mental State Examination (MMSE) [13] was administered to all patients as an evaluation of cognitive impairment (CI). A Mini-Cog score <3 or MMSE ≤ 23 was taken to indicate CI [13, 14]. Gait speed and handgrip strength were measured as a physical function assessment. Gait speed <1 m/sec was defined as slow walking speed based on the diagnostic criteria for sarcopenia [15]. Handgrip strength was measured using a Grip-D hand dynamometer (Takei Scientific Instrument, Niigata, Japan). Measurements were performed twice, adopting the highest value. Decreased muscle strength was defined as grip strength <28 kg for men or <18 kg for women [15]. Cognitive and physical assessments were assessed once during any of the three hospitalizations.

HF stage D is an advanced HF defined as patients with repeated hospitalizations for HF beyond grade III of the NYHA Functional Classification, averaging twice a year or more, despite treatment with pharmacological and non-drug therapies [10].

As outcomes, we examined rehospitalization with HF and all-cause death within 1 year after the third discharge.

Assessment of nutritional status

We calculated the geriatric nutritional risk index $(GNRI)$ [16] before discharge, as a reliable and straightforward method for nutritional assessment. GNRI is calculated using the following formula: 14.89 \times serum albumin (g/dL) + 41.7 \times body mass index (BMI)/22. A GNRI ≥98 indicates normal nutritional status, while scores between ≥ 92 and <98, between ≥ 82 and <92, and <82 represent low, moderate, and severe risk of malnutrition, respectively. Patients with GNRI <92 are classified as malnourished [17]. The GNRI evaluates serum albumin and BMI based on data collected prior to hospital discharge once the condition of the patient has stabilized.

Patients in the present study were divided into three groups based on changes in GNRI in three hospitalizations. The first was the Good group, as the group in which all GNRIs remained at no risk or at low risk for three hospitalizations. The second was the Change group, where the first GNRI showed no risk or low risk, but the patient subsequently declined to moderate or high risk. The third was the Poor group, in which GNRI showed moderate to high risk in all hospitalizations.

Estimation of energy needs

Energy needs for caloric intake were estimated using the following formula: basal metabolic rate (BMR) multiplied by the activity factor and stress factor [18]. This formula was referenced in the Scientific Statement on Nutritional Assessment and Management in Heart Failure Patients [19].

The Harris–Benedict Calculator [20-23] was employed to calculate the BMR, taking into account factors such as sex, age, height, and BW using the formula 66.5 + $(13.8 \times BW$ in kg) + $(5.0 \times$ height in cm) - $(6.75 \times age)$ for males and 655.1 $+$ (9.6 \times BW in kg) + (1.850 \times height in cm) - $(4.7 \times age)$ for females. The activity factor was set at 1.3, considering that most patients were active outside of bed, and the stress factor was set at 1.0, reflecting the stable state prior to discharge based on previous reports [23].

Assessment of dietary calorie intake

Dietary calorie intake was assessed by calculating the estimated energy intake based on the calorie content of hospital food and the average intake recorded during the stable period approximately one week prior to discharge. We defined adequate energy intake as dietary energy intake adequacy $\geq 60\%$ based on a previous study $[6]$. In addition, we also examined the rate of hospital diets with a regular meal form and the rate of salt restriction (6 g/day) .

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation for normally distributed variables, and as median and interquartile range for non-normally distributed variables. The normality of continuous variables was tested using the Shapiro–Wilk test. Categorical variables are expressed as numbers and percentages. One-way analysis of variance, the Welch test, and the Kruskal–Wallis test were used to compare the three groups. In this study, multivariate analysis was performed to understand the characteristics of the Poor group, but the Poor group

was small, containing only 14 patients. Sufficient correction for confounding factors was thus difficult. We used a covariate adjustment method in which a propensity score was created for each single variable to use in the regression model. Propensity scores were created for age, sex, prior history of HF, left ventricular ejection fraction (LVEF), NYHA class, serum creatine, hemoglobin, and log-transformed brain natriuretic peptide (BNP) on first admission as independent variables.

All analyses were performed using EZR version 4.1.2 (Saitama Medical Centre, Jichi Medical University, Tochigi, Japan) [24].

RESULTS

Table 1 shows the background characteristics of patients, including age, vital signs, medications, and laboratory data at first hospitalization. Among the 60 patients, 23 (38.3%) were classified as belonging to the Good group, 23 (38.3%) to the Change group, and 14 (23.4%) to the Poor group. No significant differences in age or sex distribution were apparent between groups.

The Poor group exhibited higher heart rate (HR), frequency of NYHA class IV and BNP level than the other groups, while the Good group showed a higher prevalence of prior HF hospitalization than the other groups. However, no significant differences between groups were apparent for LVEF, rate of LVEF >50%, HF etiology, comorbidities, or medications.

Fig. 1 shows the changes in mean GNRI. Overall GNRI decreased with each hospitalization (1st: 96.8 \pm 11.2; 2nd: 91.6 \pm 10.4; 3rd: 90.1 \pm 11.4; p < 0.05).

Comparing the three groups, GNRI was significantly decreased on the second and third hospitalizations compared to the first for both the Good and Change groups, but no change was observed in the Poor group. GNRI differed significantly among the three groups during all hospitalizations. Fig. 2 shows changes in BMI and serum albumin among the three groups. For BMI, only the Good group showed a decrease in the third hospitalization compared to the first and second hospitalizations ($p <$ 0.05), and the other two groups showed no change

NYHA: New York Heart Association, LVEF: left ventricular ejection fraction, BNP: B-type natriuretic peptide,

ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin II receptor blocker, MRA: mineralocorticoid receptor antagonist

		Good group Change group Poor group		
<0.001 vs. 1st hospitalization				

+p<0.05 vs. 1st hospitalization

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 ≈ 0.001 vs. 1st hospitalization; ϵ < 0.05 vs. 1st hospitalization

Figure 2. Changes to BMI and serum albumin in the three groups $+p < 0.05$ vs. 1st hospitalization; *p < 0.05 vs. 2nd hospitalization BMI: body mass index, Alb: serum albumin

during the three hospitalizations. Serum albumin was decreased in the third hospitalization compared to the first only in the Change group.

Table 2 shows nutritional changes in the three groups. Required energy for all three hospitalizations was approximately 1,500 kcal for the Good group, 1,300 –1,400 kcal for the Change group, and approximately 1,200–1,300 kcal for the Poor group. On the other hand, the energy intake was low at around 1,440 kcal for the Good group, about 1,300–1,440 kcal for the Change group, and 1,000– 1,100 kcal for the Poor group. In the Poor group, the rate of inadequate energy intake (dietary energy intake adequacy $\leq 60\%$ gradually increased from 21.4% to 35.7% from the first to third hospitalizations. At the third hospitalization, the Poor group showed a significantly lower rate of inadequate energy intake than the other two groups. In addition, salt restriction was consistently applied for approximately 60–90% of patients, showing no significant temporal or intergroup differences.

Table 3 shows HF stage and hospitalization details of the three groups for the three hospitalizations. The overall rate of HF stage D increased with each hospitalization, reaching an average of 46.7% at the third hospitalization, with the Poor group exhibiting a higher rate (71.4%) compared to the other groups. The rate of discharge to home was significantly lower in the Poor group. No significant differences in median hospital stays or interval between hospitalizations were apparent among the three groups.

Table 4 shows the results for the cognitive and physical assessments. The Poor group displayed the highest rate of CI (64.3%). The overall rate of an inability to walk or reduced walking speed $(\leq 1 \text{ m})$ sec) was notably high (91.7%), reaching 100% in the Poor group. Handgrip strength was weakest in the Poor group $(p < 0.05)$, with weak grip identified in 76.9% of patients in the Poor group.

Table 5 shows the results of multivariate logistic regression analysis adjusted for the prognostic factors of age, sex, prior history of HF, LVEF, NYHA, serum creatine, hemoglobin, and log-transformed BNP at first hospitalization as independent variables. CI (odds ratio [OR] 6.01, 95% confidence interval [95% CI] 1.110–32.70; $p < 0.05$) was considered a significant independent factor associated with the

Table 2. Change in nutritional status

Table 3. HF stage and hospitalization details

Table 4. Cognitive and physical assessments

Table 5. Factors independently associated with the Poor group

	$HR(95\% CI)$	P value
Cognitive impairment	$6.01(1.110-32.70)$	< 0.05
Weak grip	$2.21(0.281-17.40)$	0.451

Adjusted for age, sex, prior history of HF hospitalization, LVEF, NYHA, Cr, Hg, and log BNP on first hospitalization

Poor group, but weak grip was not (OR 2.21, 95% CI $0.281 - 17.40$; $p = 0.451$.

In terms of outcome, there were no significant differences in rates of rehospitalization with HF (all, 41.4%; Good group, 56.5%; Change group, 36.4%; Poor group, 23.1%; $p = 0.127$ or all-cause mortality within 1 year (all, 31.7%; Good group, 21.7%; Change group, 30.4%; Poor group, 57.1%; $p =$ 0.082).

DISCUSSION

This study assessed the nutritional status of patients with repeated hospitalizations for AHF. Since nutritional status also changes as the pathological condition of HF changes, it is important to look at changes in nutrition rather than just a single-point assessment.

Three main results were identified. First, three distinct groups can be categorized based on GNRI during each hospitalization for AHF: a "Good group" characterized by consistent maintenance of nutritional status across hospitalizations (38.3%); a "Change group" exhibiting progressive deterioration in nutritional status with each hospitalization (38.3%); and a "Poor group" consistently demonstrating suboptimal nutritional status throughout all hospitalizations (23.3%). Second, the Poor group was characterized by higher rates of inadequate energy intake, lower rates of home discharge, higher rates of stage D at third hospitalization, and higher levels of physical frailty and CI compared to the other groups. Third, CI was the strongly independent factor in the Poor group.

HF contributes to the development of malnutrition, which is associated with poor prognosis in patients with CHF $[4, 6]$ or AHF $[25-27]$. In the past, the main nutritional guidance for HF was to restrict salt and calories. However, sufficient energy intake and protein intake have recently been recognized as important [25]. There is evidence regarding nutritional management in CHF; however, particularly in cases of AHF, BW and albumin differ greatly depending on congestion and treatment using diuretics, making evaluation of nutritional status and appropriate energy calculation difficult. There is little evidence on optimal energy intake and recommended salt intake for patients with AHF, especially for stages C and D, and they remain unclear.

The commonly used nutritional assessment tools are Global Leadership Initiative on Malnutrition (GLIM) criteria [28], the short-form mini-nutritional assessment (MNA-SF) [29], controlling nutritional status (CONUT) score [30] and GNRI [16, 31]. GNRI is easy to evaluate and appears to have strong prognostic impact on survival among HF patients [32, 33]. Ono *et al*. compared GNRI on admission (a-GNRI) and at discharge (d-GNRI), and lower d-GNRI, but not a-GNRI, was independently associated with long-term all-cause mortality in patients with AHF [34].

We also evaluated d-GNRI, and overall GNRI decreased every hospitalization (1st: 96.8 ± 11.2 ; 2nd: 91.6 \pm 10.4; 3rd: 90.1 \pm 11.4; p < 0.05). However, in a comparison of the three groups, GNRI decreased over time only in the Good and Change groups but remained low only in the Poor group.

BMI changed only in the Good group because the average BMI remained around 25 kg/m^2 during the three hospitalizations, making weight loss easier to detect. In contrast, the other two groups had very low BMI. The second and third hospitalizations in the Change group and all hospitalizations in the Poor group met the low BMI criteria of the GLIM criteria (Asian people aged 70 years or older: BMI $\langle 20 \text{ kg/m}^2 \rangle$ [28], which is the reason why there was no change in the two groups.

Hypoalbuminemia is an independent predictor of mortality in AHF [35, 36] and CHF [37]. Recently, changes in serum albumin levels during hospitalization or follow-up have shown a prognostic impact for clinical outcomes, rather than single-point assessments [9, 38]. In this study, only the Change group decreased sharply during the first and second hospitalizations. Serum albumin is difficult to use as a simple nutritional indicator because it is associated with multiple factors, including congestion [36, 39] and inflammation [40]. However, in the Change group, the decrease in energy intake (from 1,440 kcal/day to 1,296 kcal/day) and the decrease in albumin (from 3.6 g/dL to 3.3 g/dL) were parallel from the first to the second hospitalization. This reflects some degree of deterioration in nutritional status.

Regarding energy intake, some reports have shown that insufficient caloric intake is associated with worse clinical outcomes [5], but there are few reports on detailed caloric intake calculated from food intake in HF. A previous study of outpatients with CHF reported a median intake energy of 1,628 kcal/day, 30% having inadequate energy intake and an increased risk of all-cause mortality and rehospitalization for worsening HF [6]. The median caloric intake for all patients in this study was approximately 1,300–1,400 kcal over the three hospitalizations. The percentage of patients with inadequate energy intake ranged from 15.0 to 21.7% overall, but there was a notable increase with each hospitalization particularly in the Poor group (21.4% to 35.7%). The difference in energy intake between the present study and a previous report $\begin{bmatrix} 6 \end{bmatrix}$ is likely due to patient background (inpatients with AHF vs. outpatients with CHF) and median age (78 years vs. 67 years).

Excessive intake of salt causes hypertension, cardiovascular disease, and HF [41, 42]. So, the Japanese guideline recommends ≤ 6 g/day [10], and in our hospital, patients admitted to the cardiovascular department are usually set on a 6 g/day salt-restricted diet as standard. However, Japanese people ingest an average of 10 g/day, and the elderly are reported to have even higher levels [43]. Sudden salt restriction after hospitalization may lead to changes in electrolytes and anorexia, which promote malnutrition. Studies on Japanese elderly people have shown that salt restriction to 1 g/day results in a decrease in energy intake of approximately 100–130 kcal/day

[44]. Some intervention studies have found no benefit from combining strict salt and fluid restriction in AHF [45]. Additionally, the 2022 ACC/HFSA Guidelines have removed previous guidelines regarding specific daily salt intake [46]. In this study, salt restriction was approximately 60-95% in all three groups over the three hospitalizations, making us reconsider whether patients need salt restriction.

In terms of differences in characteristics, cognition, and physical function between groups, patient characteristics showed HR, the rate of NYHA class IV, and BNP levels on admission were notably higher in the Poor group, suggesting a higher severity of HF on admission. The rates of previous hospitalization for HF were highest in the Good rather than the Poor group, and the exact reason for this is unknown. However, particularly in elderly patients with HF, hospitalization for HF may be influenced not only by the severity of HF but also by factors such as family support, access to a hospital, comorbidities, and so on [47]. In addition, the Poor group showed a low rate of home discharge, and a high rate of HF stage D at the third hospitalization, high rate of CI, and low grip strength. These findings indicate lower cognitive and physical function[48, 49]. Multivariate analysis showed that CI was a factor independently associated with the Poor group.

The prevalence of CI in the general population is approximately 20% but is significantly higher at approximately 40% in HF patients [50]. A correlation exists between HF and CI, and mechanisms such as decreased cerebral perfusion and atrial fibrillation (AF) have been reported. HF results from decreased cerebral perfusion due to decreased cardiac output. This leads to increased neurodegeneration of brain neurons due to oxidative stress and acidosis [51]. Furthermore, approximately 40% of Japanese HF patients have concurrent AF [52], which is consistent with the results of this study of 48.3%. AF is involved in CI through inflammation, microbleeds, cerebral atrophy, and cerebral infarction due to thrombosis [53]. In addition, CI with HF is particularly characterized by executive and memory dysfunction, and executive dysfunction has been reported to develop earlier than memory decline [54]. Impairments in executive function were directly associated with reduced self-care, including regular food intake and personal hygiene such as toileting and bathing [55]. CI also causes a decline in physical function, including gait disturbance, muscle weakness, and loss of strength [56], which are associated with decreasing BMI. CI and decreased activity are associated with poor nutritional status in HF patients.

In this study, no association was seen between GNRI group and outcome. While all-cause death tended to be highest in the Poor group, rates of hospitalization for HF did not differ significantly among the three groups. Many previous studies have reported that low GNRI, insufficient caloric intake, and low albumin levels are associated with prognosis in HF. One cause of this may be patient characteristics, including both HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). Previous studies have shown that GNRI is associated with prognosis with HFpEF in American regions [57] and Asian regions [27], but not HFrEF [1]. We could not separate HFpEF and HFrEF, because only 60 patients were included. In addition, approximately 30% of the Poor group was discharged to another facility or hospital rather than to their homes. Medication and meal control are stricter in facilities and hospitals, which may be related to the comparable rate of HF admissions in the three groups. However, for elderly HF patients, the goal may not be to suppress events such as allcause death or readmission for HF, but to focus on quality of life (QOL) and well-being. In that sense, consideration of nutrition and CI is very important. The nutritional intervention by dietitians is important for improving the QOL of elderly people [49, 56] by eliminating unnecessary nutritional and salt restrictions.

This study had several limitations. First, this was a single-center study with a small number of patients. The number of patients who had been admitted to the hospital three or more times within the 4-year study period was not that large. Second, cognitive function tests were conducted once during the three hospitalizations, precluding the observation of longitudinal changes between groups over time. Third, nutritional evaluation was only performed during hospitalization. Adding nutritional assessment

at home would provide a more continuous and better nutritional assessment, but accurate assessment is considered difficult due to the large number of elderly patients and social frailty. Fourth, required energy was calculated using the Harris–Benedict formula according to previous reports, but the error with this method is known to be large. Fifth, since this study was a retrospective data analysis of hospitalized patients from 2018 to 2021, the current rate of administration of common oral medications such as angiotensin receptor neprilysin inhibitor (ARNI) and sodium–glucose cotransporter-2 (SGLT-2) is low, so no analysis was performed.

In conclusion, among patients with repeated hospitalizations for AHF, the group with persistent malnutrition was characterized by CI.

Ethical approval

This study was approved by the Ethics Committee of Matsue Red Cross Hospital (Approval No. 537).

Conflict of interests

The authors declare that there are no conflicts of interest.

Data availability

The datasets used and analyzed during this study are available from corresponding authors on reasonable request.

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