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ORIGINAL ARTICLE
Heart Failure

Geriatric Nutritional Risk Index Predicts Functional Dependency and Mortality in Patients With Heart Failure With Preserved Ejection Fraction

Yoshiharu Kinugasa, MD, PhD; Masahiko Kato, MD, PhD; Shinobu Sugihara, MD, PhD; Masayuki Hirai, MD; Kensaku Yamada, MD; Kiyotaka Yanagihara, MD, PhD; Kazuhiro Yamamoto, MD, PhD

Background: The clinical significance of nutritional risk assessment in patients with heart failure with preserved ejection fraction (HFpEF) remains undefined. Geriatric nutritional risk index (GNRI) is a simple nutritional assessment tool for elderly subjects. Its predictive value was evaluated in patients with HFpEF, a common HF phenotype in the elderly population.

Methods and Results: The present study enrolled 152 consecutive patients (mean age, 77±11 years; male, 53.9%) who were hospitalized with HFpEF at the authors' institution. GNRI on admission was calculated as follows: 14.89×serum albumin (g/dl)+41.7×body mass index/22. Characteristics and mortality (median follow-up of 2.1 years) were compared between 2 groups: low GNRI (<92) with moderate or severe nutritional risk; and high GNRI (≥92) with no or low nutritional risk. Patients in the low-GNRI group were more often female, and had lower serum hemoglobin and sodium, but higher serum blood urea nitrogen (BUN), C-reactive protein, and B-type natriuretic peptide (BNP) compared to those in the high-GNRI group ($P<0.05$, respectively). Physical activity at discharge measured by Barthel index was significantly lower in the low-GNRI group than the high-GNRI group ($P<0.05$). On Cox hazard analysis, lower GNRI predicted increased mortality independent of age, gender, prior HF hospitalization, and higher BUN and BNP ($P<0.01$).

Conclusions: GNRI may be useful for predicting functional dependency and mortality in patients with HFpEF. (*Circ J* 2013; **77**: 705–711)

Key Words: Body mass index; Geriatric nutritional risk index; Heart failure with preserved ejection fraction; Hypoalbuminemia

Malnutrition is common, and is associated with increased mortality risk in patients with heart failure (HF).[1,2] Previous studies have shown that several nutritional indicators, including body mass index (BMI), serum albumin, total cholesterol, and total lymphocyte count, predict survival in patients with HF with reduced ejection fraction (HFrEF).[3–6] The clinical significance of nutritional risk assessment in patients with HF with preserved ejection fraction (HFpEF), however, has not been well established.

Editorial p604

Nutritional assessment should be practical, easy to perform, non-invasive, requiring no use of devices, and applicable at the bedside.[7] The geriatric nutritional risk index (GNRI) is a simple and well-established nutritional assessment tool for elderly subjects.[8–12] Recent studies have shown that a similar index (nutritional risk index; NRI) predicts survival in patients with HFrEF.[13,14] The predictive value of GNRI in patients with HFpEF, however, remains undefined.

The aim of the present study was to evaluate the clinical significance of GNRI in patients with HFpEF, a common HF phenotype in the elderly population.[15]

Methods

Subjects

The present study enrolled a total of 194 consecutive patients who were hospitalized in Tottori University Hospital with a primary diagnosis of HFpEF from January 2004 to April 2011.

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Division of Cardiovascular Medicine, Department of Molecular Medicine and Therapeutics, Faculty of Medicine, Tottori University, Yonago, Japan

Mailing address: Yoshiharu Kinugasa, MD, PhD, Division of Cardiovascular Medicine, Department of Molecular Medicine and Therapeutics, Faculty of Medicine, Tottori University, 86 Nishi-cho, Yonago 683-8503, Japan. E-mail: ykinugasa-circ@umin.ac.jp

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Table 1. Baseline Patient Characteristics vs. GNRI

	Overall (n=152)	High GNRI (≥92) (n=79)	Low GNRI (<92) (n=73)	P-value
Age (years)	77±11	76±10	78±11	0.309
Male (%)	53.9	62.0	45.2	0.038
BMI (kg/m²)	21.7±4.0	23.3±3.7	19.9±3.4	<0.001
NYHA class III/IV	83.3	80.0	87.1	0.620
SBP (mmHg)	151±37	152±38	150±37	0.858
Heart rate (beats/min)	90±25	92±28	88±23	0.440
Prior HF hospitalization (%)	14.4	15.2	13.7	0.794
Comorbidity (%)				
Coronary artery disease	32.9	30.4	35.6	0.492
Hypertension	61.8	64.6	58.9	0.474
Atrial fibrillation	53.3	57.0	49.3	0.345
Diabetes	39.5	40.5	38.4	0.786
Dyslipidemia	27.6	32.9	21.9	0.130
COPD	9.2	7.6	11.0	0.474
Cerebrovascular disease	19.7	20.3	19.2	0.868
Laboratory data				
Hemoglobin (g/dl)	11.1±2.4	11.8±2.3	10.3±2.3	<0.001
Sodium (mEq/L)	139±5	140±4	138±5	<0.001
BUN (mg/dl)	25.0 (19.0–39.0)	23.0 (16.5–34.5)	27.0 (20.0–42.0)	0.026
Creatinine (mg/dl)	1.1 (0.8–1.8)	1.1 (0.8–1.5)	1.1 (0.9–1.9)	0.991
eGFR (ml·min⁻¹·1.73m⁻²)	48.0 (27.0–65.9)	49.8 (30.2–64.5)	45.7 (21.1–67.3)	0.189
Total protein (g/dl)	6.7±0.7	6.8±0.5	6.3±0.7	<0.001
Albumin (g/dl)	3.5±0.5	3.8±0.3	3.1±0.4	<0.001
Total cholesterol (mg/dl)†	158±39	169±39	146±35	<0.001
LDL-C (mg/dl)†	91±31	99±31	82±28	0.002
HDL-C (mg/dl)†	49±16	52±15	46±16	0.019
CRP (mg/dl)	0.58 (0.18–2.55)	0.39 (0.16–1.38)	1.12 (0.20–3.66)	0.010
BNP (pg/ml)	434 (243–699)	358 (155–575)	578 (306–1,250)	<0.001
Echocardiography				
LVDdI (mm/m²)	33.2±6.1	32.6±5.1	33.9±7.0	0.193
LVMI (g/m²)	133.8±55.5	136.5±59.8	131.0±50.8	0.539
Relative wall thickness	0.45±0.12	0.44±0.10	0.46±0.14	0.228
LVEF (%)	56.8±11.1	56.4±10.6	57.1±11.6	0.713
Medication prior to admission (%)				
ACEI/ARB	55.9	59.5	52.1	0.356
β-blocker	27.0	27.8	26.0	0.801
Mineralocorticoid blocker	13.2	17.7	8.2	0.083

Data given as mean±SD or median (interquartile range). †Data available for 130 subjects.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; GNRI, geriatric nutritional risk index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVDdI, left ventricular diastolic diameter index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NYHA, New York Heart Association; SBP, systolic blood pressure.

HFpEF was defined as follows: (1) HF symptoms defined by Framingham criteria; (2) preserved left ventricular ejection fraction (LVEF) ≥40% as previously described;[16] and (3) absence of the following HF etiology: severe valve disease, congenital disease, complete atrial ventricular block, pericardial disease, primary pulmonary hypertension, pulmonary artery embolism, or acute myocardial infarction. Patients with cancer (n=18) or liver cirrhosis (n=2), or on dialysis (n=1) were excluded. Twenty-one patients were also excluded because of lack of body weight or laboratory data. Finally a total of 152 patients were enrolled in the present study. The study was approved by the Institutional Review Board for Human Investigation in Tottori University.

Data Collection

Medical records were retrospectively reviewed with regard to demography, medical history, comorbidity, laboratory data, echocardiograms, medication, and clinical course. All measurements except for Barthel index were taken at the time of hospital admission. BMI was calculated as weight in kilograms divided by height² (m²). Estimated glomerular filtration rate (eGFR) was determined by using a previously described formula.[17] Left ventricular (LV) end-diastolic diameter was indexed to body surface area (LV end-diastolic diameter index:

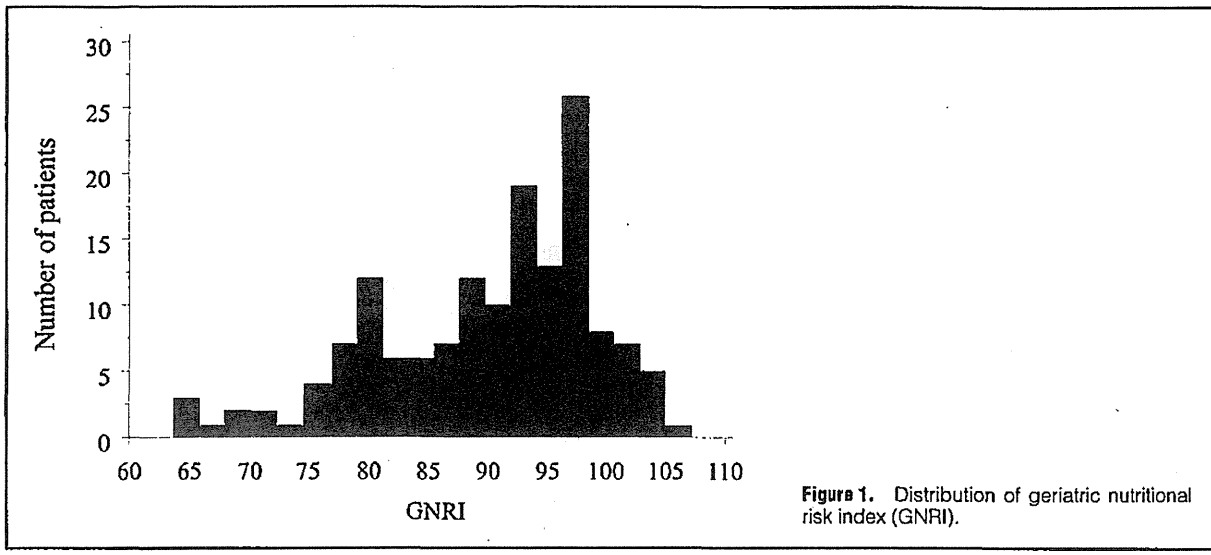

Figure 1. Distribution of geriatric nutritional risk index (GNRI).

LVDdI). LVEF, relative wall thickness, and LV mass index were calculated as previously described.[18,19] Follow-up data were obtained from medical records or telephone interview (median follow-up of 2.1 years after hospital admission; interquartile range [IQR], 1.2–3.6).

GNRI

Baseline GNRI was calculated from serum albumin and BMI obtained on hospital admission as previously described:[10]

$$\text{GNRI}=14.89\times\text{serum albumin (g/dl)}+41.7\times\text{present body weight}/[(\text{height})^2(\text{m}^2)\times 22]$$
$$=14.89\times\text{serum albumin (g/dl)}+41.7\times\text{BMI}/22$$

Clinical characteristics and mortality were compared between 2 groups: low GNRI (<92) with moderate or severe nutritional risk; and high GNRI (≥92) with low or no nutritional risk according to the previous report.[8]

Activities of Daily Living

The Barthel index was measured by well-trained nurses at hospital discharge, except for 5 patients who died in hospital. The Barthel index measures a patient's functional status for basic daily activities, with scores ranging from 0 (total dependence) to 100 points (independence) as previously described.[20,21]

Clinical Outcomes

We evaluated both all-cause mortality and HF re-hospitalization during the follow-up period. The cause of death was classified as cardiovascular and non-cardiovascular based on the clinical information. Death from a cardiovascular cause was defined as death due to HF, sudden death, and vascular events (myocardial infarction, stroke, or other vascular diseases). Other causes of death were defined as non-cardiovascular cause death.

Statistical Analysis

Continuous variables are expressed as mean±SD for normally distributed variables, and median and IQR for non-normally distributed variables. Categorical variables are expressed as percentages. Differences in continuous variables are compared using t-test for normally distributed variables, and Mann-Whitney U-test for non-normally distributed variables. Categorical variables are compared using chi-square test. Event-free survival curve after hospital admission was estimated using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards model, which was performed as stepwise regression with forward selection, was used to assess independent predictors of all-cause mortality in the subjects. Age, sex, and all baseline variables associated with mortality on univariate analysis ($P<0.10$) were entered into the model; BMI and serum albumin level used in the calculation of GNRI were excluded. Age and sex were forced into the model to adjust for age and gender effects. The area under the receiver operating characteristic curves (AUC) was used to compare the predictive value of BMI, serum albumin level, and GNRI for predicting all-cause mortality. To adjust for age and gender effect, we developed each risk score model including age and gender based on the regression coefficient as previously described.[18] $P<0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 20 and EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0).

Results

Baseline Patient Characteristics

Baseline patient characteristics are listed in Table 1. The mean age of the overall cohort was 77±11 years, and 53.9% were male; elderly patients aged over 65 years comprised 86.2%. The mean LVEF was 56.8±11.1%. New York Heart Association (NYHA) functional class III or IV was found in 83.4% of patients on hospital admission. Coronary artery disease was prevalent in 32.9% of patients. Hypertension (61.8%) was the most common comorbidity, followed by atrial fibrillation (53.3%) and diabetes (39.5%). Moderate or severe impaired renal function (eGFR $<30\,\text{ml}\cdot\text{min}^{-1}\cdot 1.73\,\text{m}^{-2}$) was found in 30.9% of patients. Angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blockers (ARBs), β-blocker, and mineralocorticoid blocker were prescribed to 55.9%, 27.0%, and 13.2% of patients prior to hospital admission, respectively.

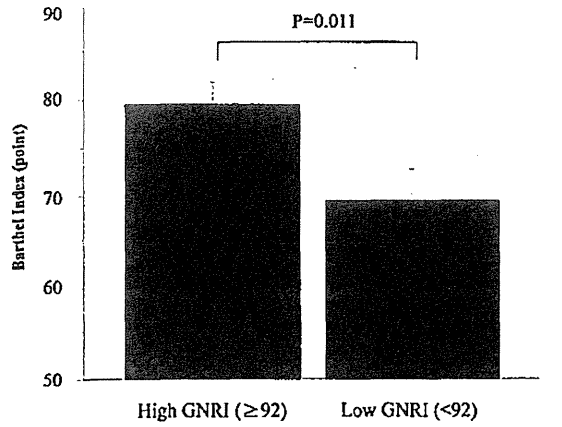

Figure 2. Barthel index at discharge vs. geriatric nutritional risk index (GNRI).

Patient Characteristics According to GNRI

Figure 1 shows the distribution of GNRI. The mean GNRI was 90.0±9.3. Patients in the low-GNRI group were more often female. BMI and serum hemoglobin, sodium, total protein, albumin, total cholesterol, and low-density and high-density lipoprotein cholesterol were significantly lower, whereas serum blood urea nitrogen (BUN), C-reactive protein, and B-type natriuretic peptide (BNP) were significantly higher in the low-GNRI group than the high-GNRI group. There were no significant differences of age, NYHA class, the prevalence of comorbidities, LVEF, LV geometry, and pre-hospital medications between the 2 groups. The 2 groups (except for 5 patients who died in hospital) had no significant difference in medication at discharge (low GNRI, n=68 vs. high GNRI, n=79: ACEI/ARB, 77.9% vs. 83.5%, P=0.388; β-blocker, 44.1% vs. 46.8%, P=0.742; mineralocorticoid blocker, 29.4% vs. 20.3%, P=0.198, respectively).

GNRI and Activities of Daily Living

Figure 2 shows Barthel index at discharge between the 2 groups. Patients in the low-GNRI group had significantly lower Barthel index than those in the high-GNRI group.

GNRI and Mortality

During the median follow-up of 2.1 years (IQR, 1.2–3.6 years), 55 patients died. Of these, 39 patients (70.9%) had cardiovascular cause death: HF death (n=22, 40.0%), vascular death (n=11, 20.0%), and sudden death (n=6, 10.9%). Sixteen patients (29.1%) had non-cardiovascular cause death: infectious disease (n=7, 12.7%), respiratory disease (n=3, 5.5%), gastrointestinal disease (n=2, 3.6%), and others (n=4, 7.3%).

Kaplan-Meier survival analysis for all-cause mortality is given in **Figure 3**. Patients in the low-GNRI group had significantly higher mortality compared to those in the high-GNRI group (hazard ratio [HR], 2.667; 95% confidence interval [CI]: 1.527–4.651, P<0.001). The increased mortality risk was found in both cardiovascular (HR, 2.469; 95% CI: 248–4.902, P<0.001) and non-cardiovascular disease (HR, 3.086; 95% CI: 1.172–8.130, P=0.023). On stepwise Cox hazard analysis, lower GNRI as a continuous variable was an independent predictor of all-cause mortality as well as advanced age, previous history of HF hospitalization, and higher BUN and BNP (**Table 2**). In contrast, there was no significant difference in HF re-hospitalization between the 2 groups (HR, 0.962; 95% CI: 0.517–1.795, P=0.905).

Predictive Value of GNRI

Figure 4 shows the receiver operating characteristics curve of 3 risk score models based on BMI, serum albumin, and GNRI for predicting all-cause mortality. The AUC of GNRI, but not albumin, was significantly higher compared to that of BMI,

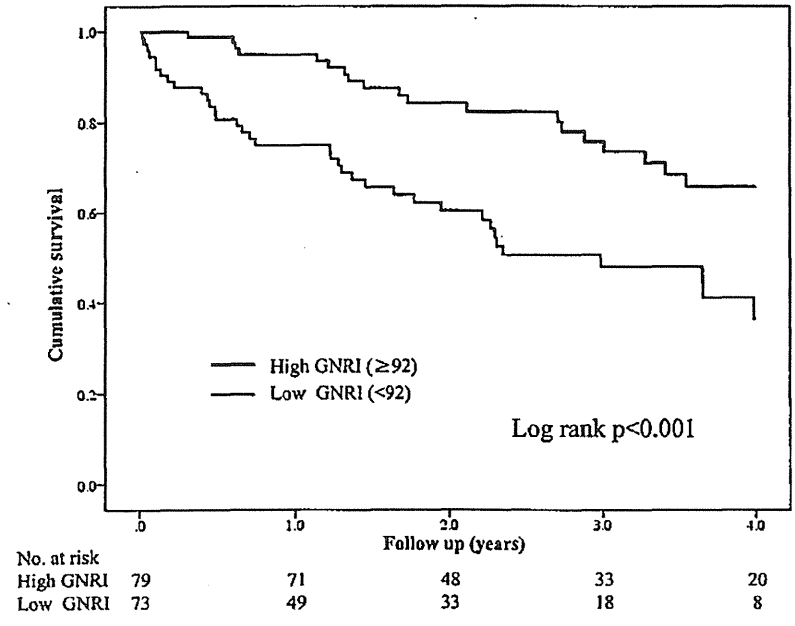

Figure 3. Kaplan-Meier analysis for all-cause mortality vs. geriatric nutritional risk index (GNRI).

Table 2. Independent Predictors of All-Cause Mortality in HFpEF

	Univariate analysis		Stepwise multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	1.066 (1.031–1.101)	<0.001	1.062 (1.026–1.100)	<0.001
Male	0.872 (0.513–1.481)	0.612	0.877 (0.510–1.543)	0.672
Prior HF hospitalization	2.857 (1.590–5.128)	<0.001	2.364 (1.230–4.545)	0.010
Coronary artery disease	1.695 (0.976–2.941)	0.0610		
GNRI	0.950 (0.926–0.974)	<0.001	0.947 (0.920–0.975)	<0.001
Hemoglobin (g/dl)	0.906 (0.816–1.006)	0.0650		
Sodium (mEq/L)	0.939 (0.888–0.994)	0.0293		
BUN (mg/dl)	1.024 (1.013–1.035)	<0.001	1.018 (1.006–1.030)	0.003
eGFR (ml·min^{-1}·1.73 m^{-2})	0.979 (0.968–0.991)	<0.001		
BNP (per 100 pg/ml)	1.031 (1.010–1.051)	0.003	1.028 (1.005–1.052)	0.016

CI, confidence interval; HFpEF, HF with preserved ejection fraction; HR, hazard ratio. Other abbreviations as in Table 1.

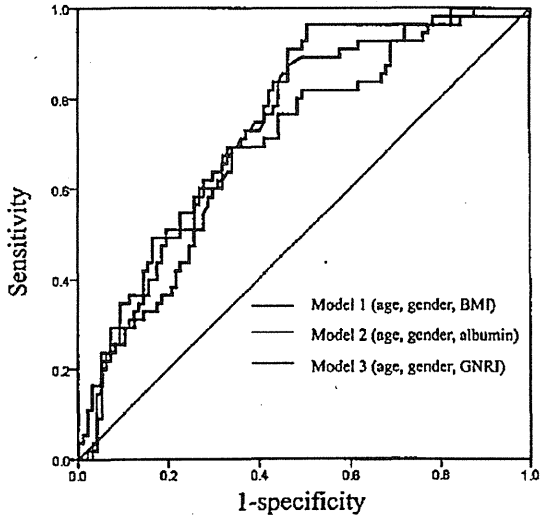

Figure 4. Area under the receiver operating characteristics curve of risk score model for predicting all-cause mortality. BMI, body mass index; GNRI, geriatric nutritional risk index.

Table 3. AUC of Risk Score Model for Predicting All-Cause Mortality

	AUC (95% CI)	P-value
Model 1 (age, gender, BMI)	0.696 (0.611–0.781)	(Reference)
Model 2 (age, gender, albumin)	0.731 (0.650–0.811)	0.302
Model 3 (age, gender, GNRI)	0.752 (0.676–0.829)	0.049

Model 1, 0.057×age+0.157×male (1)/female (0)−0.117×BMI; model 2, 0.064×age+0.064×male (1)/female (0)−0.750×albumin; model 3, 0.061×age+0.153×male (1)/female (0)−0.052×GNRI. AUC, area under the receiver operating characteristics curve. Other abbreviations as in Tables 1,2.

indicating that GNRI had the highest predictive value for predicting mortality (Table 3).

Discussion

The present study has demonstrated the clinical significance of nutritional risk assessment using GNRI in patients with HFpEF. We found that low GNRI was significantly associated with decreased activities of daily living (ADL), and increased mortality independent of age, gender, and well-known prognostic factors (previous history of HF hospitalization, BUN, and BNP). These results suggest that GNRI is a useful index to stratify the risk of morbidity and mortality in patients hospitalized with HFpEF.

GNRI was first described by Bouillanne et al to predict malnutrition-related complications (bedsores and infections) and mortality in hospitalized elderly patients.[8] It was developed by modifying the NRI for elderly subjects, and has been reported to be significantly correlated with biochemical and anthropometric markers of nutritional status.[8–12]

There are a few previous reports about the relationship between NRI and mortality risk in patients with HFrEF. Aziz et al reported that NRI was associated with the composite endpoints all-cause mortality and HF readmission in patients with acute decompensated HF.[13] Al-Najjar and Clark have also shown that NRI predicts mortality in outpatients with HFrEF.[14] We have further extended previous findings by demonstrating the clinical significance of the GNRI, a modified NRI, in HFpEF patients for the first time.

Serum albumin level and BMI are often used as indicators of nutritional status in routine clinical practice, and recent studies have shown that these indicators predict survival in both HFrEF and HFpEF patients.[3,4,22,23] In patients with HF, however, serum albumin level is influenced by several non-nutritional factors including fluid status, hepatic congestion, renal dysfunction (albuminemia), and inflammation.[4,18,23] Similarly, BMI is influenced by fluid status,[3,22] indicating that the measurement of albumin or BMI alone is insufficient as a nutritional risk assessment. In contrast, GNRI measured using both serum albumin and BMI may overcome the shortcomings of each indicator. We found that the predictive value of GNRI tended to be higher than that of BMI or serum albumin alone. For one thing, increased extracellular fluid volume decreases serum albumin, whereas it increases BMI. Considering such a counteracting effect, GNRI as a combined index of albumin and BMI may lead to minimization of the effect of fluid status, and identify nutritional risk better than each of them.[13]

Several other nutritional screening tools such as Subjective Global Assessment (SGA), Mini Nutritional Assessment-Screening Form (MNA-SF), Malnutrition Universal Screening Tool (MUST), and Nutritional Risk Screening 2002 (NRS 2002) are available for nutritional risk assessment in elderly subjects.[11] These indexes require subjective assessment, which may be affected by the examiner's experience. In addition, they require body weight change, which is affected by fluid status in patients hospitalized with HF. In contrast, GNRI consists of simple objective measurements, BMI and serum albumin, which can be easily obtained on admission in patients with HF. Therefore, GNRI may be more easily used in HF patients than other indexes, although further investigations are necessary to evaluate which nutritional index is more specific to patients with HF.

HF is characterized by limited exercise tolerance, which is mainly determined by decreased cardiac output, abnormal respiratory response, and skeletal muscle dysfunction.[24] Exercise intolerance and symptoms may lead to activity restriction, and recent studies have shown that low physical activity level predicts poor outcome in patients with HF.[21,24] The relationship between low GNRI and decline in ADL may be involved with reduced exercise capacity, reflecting HF severity. In addition, patients in the low-GNRI group required intensive care such as inotropic support and prolonged hospital stay (data not shown), which may lead to bed-rest deconditioning, and result in decreased ADL. Impaired muscle strength with malnutrition and cachexia may affect the decreased physical activity of patients with low GNRI.[12,25] Cognitive impairment and motor dysfunction caused by cerebrovascular or orthopedic disease are also important factors associated with decreased ADL in elderly subjects.[26] Because these factors were not taken into account in this study, further investigations are required to clarify the relationship between GNRI and precise functional assessment in patients with HFpEF.

There are several potential explanations for the relationship between low GNRI and cardiovascular/non-cardiovascular mortality in patients with HFpEF. Low GNRI is accompanied by low BMI and hypoalbuminemia, reflecting malnutrition and inflammation, which are associated with worse HF outcome.[3,4,18,22,23] Hypoalbuminemia is associated with increased mortality in several non-cardiac comorbidities such as end-stage renal disease, infection, and pulmonary disease.[18] This may explain the increased non-cardiovascular mortality of patients in the low-GNRI group. In contrast, there was no significant difference in HF re-hospitalization between the 2 groups. One potential reason is that the cause of HF re-hospitalization is multifactorial, and is related not only to the severity of HF, but also patient self-care and socioenvironmental factors.[27]

In patients with HFpEF, morbidity and mortality still remain high.[15,28] Unfortunately, there is currently no particular pharmacological treatment for these patients.[15] Thus, additional management strategies with involvement of non-pharmacological approaches urgently need to be developed to improve outcome. Nutritional intervention may be a potential management strategy for these patients. Several small studies have shown that nutritional supplementation has a beneficial effect on cardiac metabolism, resulting in improved cardiac function and exercise capacity.[29–31] Malnutrition, however, is often present in cachexia, which is a complex metabolic syndrome characterized by anorexia, weight loss, inflammation, insulin resistance, and increased muscle protein breakdown.[25] An ongoing loss of muscle mass cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[25,32] Thus, it may be necessary to apply comprehensive intervention, including nutritional supplementation, muscle anabolic therapy, and anti-inflammatory or anti-cytokine agents along with appropriate physical training.[2,25,32] Further investigations are required to evaluate the effect of comprehensive nutritional intervention on morbidity and mortality in malnourished HFpEF patients as assessed using GNRI.

This study had several limitations. The present study evaluated GNRI at a single time point and did not asses the changes in GNRI. This study was retrospective, and the sample size was relatively small. Further prospective investigations are necessary to confirm the present findings in another large cohort.

In conclusion, GNRI may be a simple and useful index for predicting functional dependency and mortality in patients with HFpEF.

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