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ORIGINAL RESEARCH ARTICLE

Geriatric nutritional risk index predicts all-cause deaths in heart failure with preserved ejection fraction

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Abstract

Aims The objective of the study was to evaluate whether the geriatric nutritional risk index (GNRI) at discharge may be helpful in predicting the long-term prognosis of patients hospitalized with heart failure (HF) with preserved ejection fraction (HFpEF, left ventricular ejection fraction ≥50%), a common HF phenotype in the elderly.

Methods and results Overall, 110 elderly HFpEF patients (≥65 years) from the Ibaraki Cardiovascular Assessment Study-HF (*n* = 838) were enrolled. The mean age was 78.5 ± 7.2 years, and male patients accounted for 53.6% (*n* = 59). All-cause mortality was compared between the low GNRI (<92) with moderate or severe nutritional risk group and the high GNRI (≥92) with no or low nutritional risk group. Cox proportional hazard regression models were constructed to evaluate the influence of the GNRI on all-cause death with the following covariates using forward stepwise selection: age, sex, nutritional status based on the GNRI as a categorical variable, history of HF hospitalization, haemoglobin level, estimated glomerular filtration rate, log brain natriuretic peptide levels (logBNP), history of hypertension, log C-reactive protein levels, left ventricular ejection fraction, left ventricular mass index, and the New York Heart Association functional classification (I/II or III class). The prognostic value of the GNRI was compared with that of serum albumin using C-statistics. The GNRI was added to the logBNP, serum albumin or the body mass index was added to the logBNP, and the C-statistic was compared using DeLong's test. Cox regression analysis revealed that age and a low GNRI were independent predictors of all-cause death ($P < 0.05$, $n = 103$; hazard ratio = 1.095, 95% confidence interval = 1.031–1.163, for age, and hazard ratio = 3.075, 95% confidence interval = 1.244–7.600, for the GNRI). DeLong's test for the two correlated receiver operating characteristic curves [area under the receiver operating characteristic curve (AUROC) of serum albumin, 0.71; AUROC of the GNRI, 0.75] demonstrated significant differences between the groups ($P = 0.038$). Adding the GNRI to the logBNP increased the AUROC for all-cause death significantly (0.71 and 0.80, respectively; $P = 0.040$, $n = 105$). The addition of serum albumin or the body mass index to the logBNP did not significantly increase the AUROC for all-cause death ($P = 0.082$ and $P = 0.29$, respectively).

Conclusions Nutritional screening using the GNRI at discharge is helpful to predict the long-term prognosis of elderly HFpEF patients.

Keywords Brain natriuretic peptide; Heart failure with preserved ejection fraction; Inflammation; Nutritional screening; Undernutrition

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Introduction

The prevalence of cardiovascular disorders has increased markedly because of a rapidly ageing society and the westernization of lifestyle, both of which increase the risk of developing coronary artery disease and other cardiovascular disease. The growing prevalence of heart failure (HF) is also an important problem among the elderly because HF is observed predominantly in that population. According to the Acute Decompensated Heart Failure Syndromes registry in Japan, the mean age of patients with HF was 73.0 years, and 42.0% were women. Moreover, almost half of the patients presented a preserved ejection fraction (pEF), defined as a left ventricular ejection fraction (LVEF) >40%, and the endpoint of 1 year all-cause mortality was achieved in 17.0% of patients.[1] In clinical trial populations, the LVEF value used to define a 'pEF' ranged from 40 to 45%, and outcomes were better in patients with HF with preserved ejection fraction (HFpEF) than in those with a reduced ejection fraction (HFrEF).[2] In previous studies, the LVEF value used to define the 'pEF' ranged from 40 to 55%, but current guidelines recommend a partition value of 50%.[3–5] According to a recent analysis of a large national registry-based cohort,[6] cardiovascular and HF rehospitalizations rates are higher for patients with HFrEF (LVEF ≤ 40%) and those with HF with borderline ejection fraction (HFbEF) (LVEF 41–49%) than for those with HFpEF (LVEF ≥ 50%). However, patients with HFrEF, HFbEF, and HFpEF had very high rates of 5 year mortality (75–76%) and rehospitalization (82–86%) rates, which were similar. There are many effective treatment strategies for patients with HFrEF; unfortunately, effective treatment strategies for patients with HFpEF are lacking.

In HF patients, undernutrition is not uncommon[7–15] and represents one of the most significant determinants of poor clinical outcomes.[7–17] The geriatric nutritional risk index (GNRI) is a simple and well-established nutritional screening tool for elderly HF patients.[18–20] However, the predictive value of the assessment of nutritional status using GNRI in patients with HFpEF remains unclear.

In a multicentre registry setting, the present study evaluated whether determining the GNRI at discharge may be helpful to predict the long-term prognosis of patients hospitalized with HFpEF (LVEF ≥ 50%), a common HF phenotype in the elderly population (≥65 years).

Methods

Study population

A total of 838 patients with HF symptoms were hospitalized between June 2012 and March 2015 and were enrolled in the Ibaraki Cardiovascular Assessment Study-HF registry.[7,17,21] Follow-ups were conducted until 31 March 2016. The Ibaraki Cardiovascular Assessment Study is a multicentre registry study involving 11 hospitals in the Ibaraki Prefecture of Japan. The Ibaraki Cardiovascular Assessment Study registry inclusion criteria were patient age ≥20 years and the fulfilment of the Framingham criteria for HF.[22] The registry exclusion criteria were age <20 years, not providing informed consent to the attending physician, limited life expectancy due to malignant neoplasms, patients in whom the 2 year observation was predicted to be impossible, and patients who were judged as medically inappropriate by the attending physician. Written informed consent was obtained from all patients, and data collection for this study was approved by the institutional review boards of the 11 participating hospitals. Additionally, the Ibaraki Cardiovascular Assessment Study registry study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Data from the Ibaraki Cardiovascular Assessment Study registry were retrospectively analysed. Two parameters are used to calculate the GNRI: serum albumin level and body mass index (BMI). We stratified the study patients into three groups: HF patients with in-hospital death, HF patients who were discharged after alleviation of symptoms, and HF patients who were transferred elsewhere for continued medical care.[7] Among the 838 patients enrolled in the registry, 590 patients were aged ≥65 years and were discharged after alleviation of symptoms. Seven patients on dialysis were excluded. Registry patients for whom GNRI could not be estimated were also excluded (n = 187). Ultimately, a total of 110 HFpEF patients with complete GNRI data were enrolled in this study (*Figure 1*).

Data collection

Baseline clinical data were collected for each patient. Patient-related information collected at discharge included medical history, laboratory test results, echocardiographic findings, and prescriptions, and data were recorded in a computer database. Blood tests were performed to determine haemoglobin, sodium, serum creatinine, plasma brain natriuretic peptide (BNP), albumin, total cholesterol, and C-reactive protein levels. The estimated glomerular filtration rate (eGFR) was calculated using the following formula: eGFR = 194 × serum creatinine$^{-1.094}$ × age in years$^{-0.287}$ for male patients. The adjusted eGFR value for female patients was calculated using the following formula: eGFR female = eGFR × 0.739.[23] The BMI was calculated as body weight in kilogrammes divided by the square of the height in metres.

Assessment of nutritional status using geriatric nutritional risk index

The GNRI was developed by Bouillanne *et al*.[24] as a screening tool for undernutrition in a hospital population. In the

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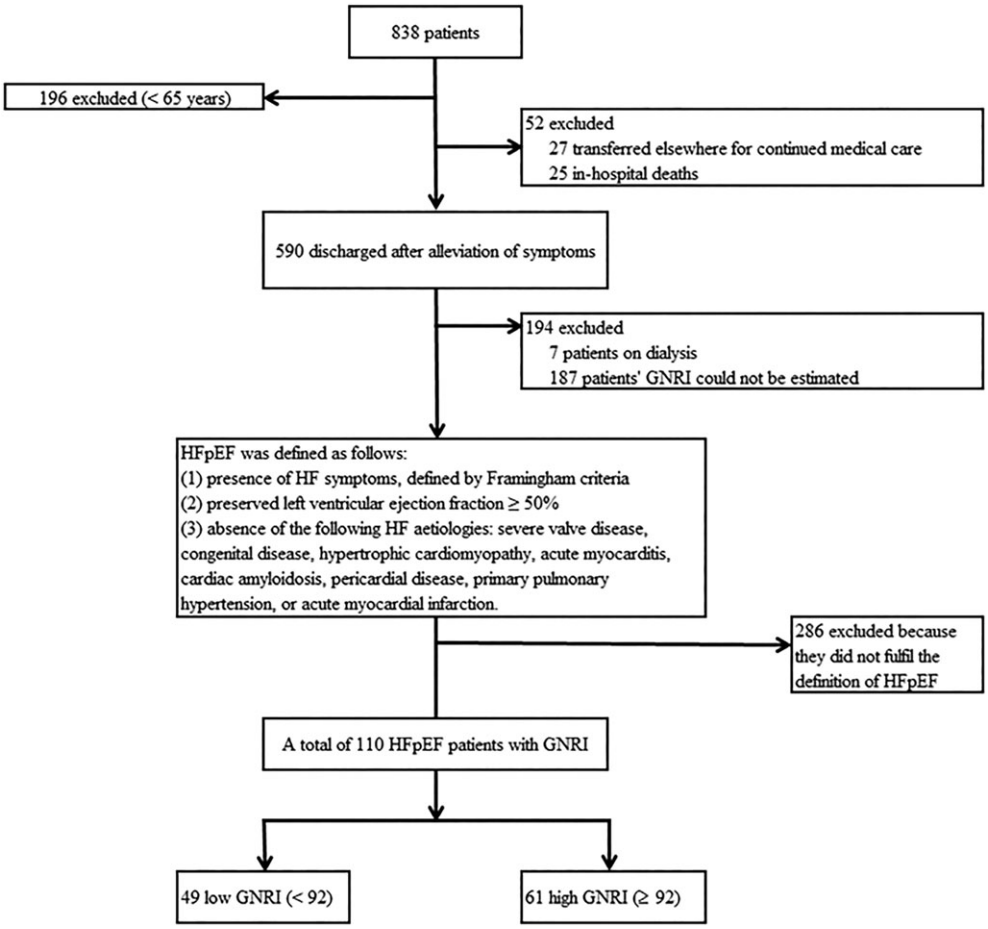
Figure 1 Study flow diagram. We included a total of 110 elderly heart failure (HF) with preserved ejection fraction (HFpEF) patients with geriatric nutritional risk index (GNRI) data. Low GNRI, group of HFpEF patients with moderate or severe nutritional risk; high GNRI, group of HFpEF patients with low or no nutritional risk.



present study, the GNRI was calculated from serum albumin and BMI obtained at discharge. We adopted Kinugasa's measurement method[18] as follows:

$$\begin{aligned}\text{GNRI} &= 14.89\times\text{serum albumin (g/dL)} \\ &\quad + 41.7\times\text{present body weight}/\left[(\text{height})^2\ (\text{m}^2)\times 22\right] \\ &= 14.89\times\text{serum albumin (g/dL)} + 41.7\times\text{BMI}/22.\end{aligned}$$

BMI/22 was set to 1 when the patient's BMI/22 was greater than 1.

The GNRI cut-off values were also adopted from the study by Bouillanne *et al.*[24] From these GNRI values, four grades of nutrition-related risk were defined: major risk (GNRI $<$ 82), moderate risk (GNRI 82 to $<$92), low risk (GNRI 92 to $<$98), and no risk (GNRI $\geq$ 98). In the present study, we defined the GNRI cut-off value as 92. Clinical characteristics and mortality were compared between the low GNRI ($<$92) with moderate or severe nutritional risk group and the high GNRI ($\geq$92) with low or no nutritional risk, according to previous reports.[18,19,25]

Correlation between brain natriuretic peptide levels and nutritional status

The correlation between the GNRI as a continuous variable and the logarithmically transformed plasma BNP (logBNP) level was evaluated. Blood was collected into tubes containing ethylenediaminetetraacetic acid, and plasma BNP concentrations were measured using a validated and commercially available immunoassay kit (Tosoh Co. Ltd., Tokyo, Japan). The upper limit of normal plasma BNP level was 18.4 pg/mL. The minimal and maximal detectable levels of BNP were 4 and 2000 pg/mL, respectively.

Assessment of prognosis using the geriatric nutritional risk index

We divided the study patients into two groups: (i) HFpEF patients with low or no nutritional risk (patients with a GNRI of

≥92) and (ii) HFpEF patients with moderate or severe nutritional risk (patients with GNRI of <92).

We investigated whether nutritional status assessed using the GNRI was associated with all-cause death and cardiovascular death. Cardiovascular death was defined as death attributable to cardiovascular origin.

Assessment of heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction was defined as follows: (i) presence of HF symptoms defined by the Framingham criteria[22]; (ii) preserved LVEF ≥ 50%, as previously described[3–5]; and (iii) absence of HF aetiologies, including severe valve disease, congenital disease, hypertrophic cardiomyopathy, acute myocarditis, cardiac amyloidosis, pericardial disease, primary pulmonary hypertension, or acute myocardial infarction.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation if normally distributed and as median [inter-quartile range (IQR)] if non-normally distributed. Differences between the two groups were compared using an unpaired Student's *t*-test or a Mann–Whitney *U* test, as appropriate. The chi-squared test was used to compare categorical variables. Pearson's correlation analysis was used to evaluate the correlation between the GNRI and the logBNP or log C-reactive protein concentration. A partial correlation analysis was performed between the GNRI and the logBNP while controlling for the eGFR. Kaplan–Meier analysis with the log-rank test was performed to determine whether nutritional screening using GNRI at discharge could be helpful in predicting long-term prognosis in patients hospitalized with HFpEF. In addition, a Cox proportional hazards model analysis was performed to determine the significant predictors of prognosis. To evaluate the influence of the GNRI on all-cause death, the following four Cox proportional hazard regression models were constructed: Model 1, unadjusted; Model 2, age and sex adjusted; and Model 3, age and logBNP adjusted. In Model 4, the following covariates were included using forward stepwise selection: age, sex, nutritional status based on the GNRI as a categorical variable, previous history of HF hospitalization, haemoglobin level, eGFR, logBNP, history of hypertension, log C-reactive protein, LVEF, left ventricular mass index, and New York Heart Association (NYHA) functional classification (I/II or III class). The prognostic value of the GNRI was compared with that of serum albumin using the C-statistic. We added the GNRI to the logBNP or the model of age and logBNP and compared the C-statistics using DeLong's test. We also added the serum albumin or BMI to the logBNP and compared the C-statistics using DeLong's test. As a severity assessment of HF, the BNP value is very useful; it is generally known that the BNP value at the post-stability phase has a stronger prognostic ability than the value at the time of admission. A *P*-value of <0.05 was considered statistically significant. All statistical analyses except the C-statistics were performed using StatView 5.0 (SAS Institute Inc., Cary, NC, USA), SPSS version 24 (IBM Corp., Armonk, NY, USA), or EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) for Windows. Statistical analysis using C-statistics of the results was performed by R software package (version 3.3.3, R Development Core Team, https://www.r-project.org/).

Results

Clinical characteristics of study patients

Tables 1 and *2* show the clinical characteristics of the HFpEF patients with GNRI data according to the risk of undernutrition. At the time of admission, based on the NYHA functional classification, 10 patients were classified as Class II, 38 patients as Class III, and 62 patients as Class IV. Conversely, at the time of discharge, based on the NYHA functional classification, 52 patients were classified as Class I, 52 patients as Class II, and 6 patients as Class III. None of the patients were classified as Class IV. The median plasma BNP level of the overall study population was 206.9 (IQR 105.7–355.1) pg/mL, and as the distribution of BNP levels was highly skewed, we normalized the data through a logarithmic transformation. The median GNRI of the overall study population was 93.8 (IQR 84.9–98.3). Of the 110 enrolled HFpEF patients for whom GNRI could be calculated, 73 (66.4%) had low-to-major nutrition-related risks (low, 21.8%; moderate, 23.6%; and major, 20.9%) at discharge.

The 110 HFpEF patients in the study population were categorized as follows: HFpEF patients with low GNRI (<92, *n* = 49) with moderate or major nutrition-related risk and patients with high GNRI (≥92, *n* = 61) with low or no nutrition-related risk. The clinical characteristics of the patients enrolled in the two groups are also shown in *Tables 1* and *2*. Patients' age, weight, BMI, hypertension history, haemoglobin level, plasma BNP level, serum albumin level, total cholesterol level, C-reactive protein level, left ventricular mass index, and LVEF differed significantly between the two groups. However, factors such as sex, NYHA class, systolic blood pressure, heart rate, smoking status, HF-related admission history, population of HF patients with ischaemic aetiology, dyslipidaemia, diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, sodium level, eGFR, left ventricular end-diastolic diameter, left atrial volume index, E/mean E′, and the use of diuretics, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, beta-blockers, and

Table 1 Clinical characteristics of the patients by GNRI

	Overall (n = 110)	High GNRI (≥92) (n = 61)	Low GNRI (<92) (n = 49)	P-value
Age (years)	78.5 ± 7.2	77.0 ± 6.5	80.4 ± 7.7	0.016
Male, n (%)	59 (53.6)	30 (49.2)	29 (59.2)	0.34
NYHA (2/3/4) on admission	10/38/62	5/23/33	5/15/29	0.73
NYHA (3 or 4) on admission, n (%)	100 (90.9)	56 (91.8)	44 (89.8)	0.75
Clinical scenarios (1/2/3/4/5) on admission	67/39/3/0/1	40/17/3/0/1	27/22/0/0/0	—
NYHA (1/2/3) at discharge	52/52/6	26/32/3	26/20/3	—
NYHA (1 or 2) at discharge, n (%)	104 (94.5)	58 (95.1)	46 (93.9)	1
Weight (kg) at discharge	55.6 ± 11.1	59.8 ± 9.5	50.3 ± 10.7	<0.001
BMI (kg/m^2) at discharge	23.1 ± 4.1	25.0 ± 3.5	20.6 ± 3.5	<0.001
BMI (kg/m^2) <18.5 at discharge, n (%)	10 (9.1)	0 (0)	10 (20.4)	<0.001
BMI (kg/m^2) <22.0 at discharge, n (%)	47 (42.7)	12 (19.7)	35 (71.4)	<0.001
SBP (mmHg) at discharge	120.0 [108.0–130.3]	120.0 [108.0–126.8]	121.5 [108.0–136.0]	0.81
Heart rate (b.p.m.) at discharge	64.5 [58.0–71.0]	64.0 [56.0–69.0]	65.0 [58.8–75.3]	0.182
Medical history				
Current or past smoker, n (%)	55 (50.0)	30 (49.2)	25 (51.0)	1
Readmission count for HF (0/1/2/≥3)	81/12/7/10	45/6/5/5	36/6/2/5	—
Previous history of HF hospitalization, n (%)	29 (26.4)	16 (26.2)	13 (26.5)	1
HF aetiology, ischaemic, n (%)	28 (25.5)	13 (21.3)	15 (30.6)	0.28
Atrial fibrillation, n (%)	36 (32.7)	22 (36.1)	14 (28.6)	—
Hypertension, n (%)	83 (75.5)	51 (83.6)	32 (65.3)	0.044
Dyslipidaemia, n (%)	43 (39.1)	28 (45.9)	15 (30.6)	0.119
Diabetes mellitus, n (%)	54 (49.1)	31 (50.8)	23 (46.9)	0.71
COPD, n (%)	8 (7.3)	4 (6.6)	4 (8.2)	1
Cerebrovascular disease, n (%)	12 (10.9)	10 (16.4)	2 (4.1)	0.062

BMI, body mass index; COPD, chronic obstructive pulmonary disease; GNRI, geriatric nutritional risk index; HF, heart failure; n, number of patients; NYHA, New York Heart Association; SBP, systolic blood pressure.
Results are expressed as mean ± standard deviation or the median [inter-quartile range]. Data were missing for the following characteristics: SBP, for six HF patients with high GNRI and three HF patients with low GNRI. 'Atrial fibrillation' demonstrates the rhythm at discharge.

statins did not differ significantly between the two groups. When the log C-reactive protein level was plotted against the GNRI as a continuous variable for the overall patient population, there was a weak significant inverse correlation (r = −0.287, P = 0.002, n = 110), indicating that a greater increase in GNRI was associated with a greater decrease in C-reactive protein levels.

Correlation between brain natriuretic peptide levels and nutritional status

When the logBNP was plotted against the GNRI as a continuous variable for the overall patient population, there was a weak significant inverse correlation (r = −0.30, P = 0.002, n = 105), indicating that a greater increase in GNRI was associated with a greater decrease in plasma BNP levels. After controlling for eGFR, the association between the GNRI and the logBNP persisted (r [partial] = −0.285, P = 0.003, n = 105).

Impact of nutritional screening using geriatric nutritional risk index for all-cause death

During the follow-up period (503.5 [IQR 328.0–790.0] days), 24 deaths occurred. Of these, 14 patients (58.3%) had a cardiovascular death: HF death (n = 7, 29.2%), sudden death (n = 4, 16.7%), and death due to other reasons (n = 3, 12.5%). Ten patients (41.7%) experienced non-cardiovascular-related (n = 8) or unknown (n = 2) deaths.

The Kaplan–Meier analysis revealed that all-cause deaths occurred more frequently in HFpEF patients with a low GNRI (n = 17) compared with HFpEF patients with a high GNRI (n = 7) (log-rank P < 0.001). *Table 3* shows the impact of nutritional screening using GNRI on all-cause death. The analysis revealed that HFpEF patients with a low GNRI had an increased risk of all-cause death compared with patients in the high GNRI group (P < 0.05) but not in Model 3 (*Table 3*). In Model 4, the multivariate Cox regression analysis using forward stepwise selection revealed that age and a low GNRI as a categorical variable were independent predictors of all-cause death [P < 0.05, n = 103; hazard ratio (HR) = 1.095, 95% confidence interval (CI) = 1.031–1.163, for age, and HR = 3.075, 95% CI = 1.244–7.600, for the GNRI]. After adjusting for age, all-cause deaths occurred more frequently in HFpEF patients with a low GNRI compared with HFpEF patients with a high GNRI (P = 0.009, n = 110; HR = 3.334; 95% CI = 1.354–8.207) (*Figure 2*). The Cox proportional hazard analyses also revealed that each per point increase in the GNRI was associated with a decreased risk of all-cause death (*Table 3*). In Model 3, using the GNRI as a continuous variable, Cox proportional hazard analyses also revealed that advanced

Table 2 Laboratory data, echocardiographic data, and medications at discharge by GNRI

	Overall (n = 110)	High GNRI (≥92) (n = 61)	Low GNRI (<92) (n = 49)	P-value
Laboratory measurement at discharge				
Haemoglobin (g/dL)	11.5 ± 2.2	12.0 ± 2.3	10.8 ± 1.9	0.006
Sodium (mEq/L)	139.1 ± 3.7	139.2 ± 3.3	138.9 ± 4.1	0.64
Estimated GFR (mL/min/1.73 m^2)	41.5 [31.8–56.0]	43.4 [32.8–54.9]	36.4 [25.6–56.6]	0.36
Estimated GFR <60 (mL/min/1.73 m^2), n (%)	91 (82.7)	52 (85.2)	39 (79.6)	0.46
BNP (pg/mL)	206.9 [105.7–355.1]	126.3 [76.0–264.9]	297.0 [147.6–478.3]	<0.001
logBNP	2.26 ± 0.40	2.12 ± 0.42	2.42 ± 0.32	0.001
Albumin (g/dL)	3.60 [3.20–3.90]	3.80 [3.60–4.20]	3.10 [2.75–3.33]	<0.001
Total cholesterol (mg/dL)	167.1 ± 34.7	175.2 ± 34.3	155.9 ± 32.5	0.007
C-reactive protein (mg/dL)	0.36 [0.16–0.92]	0.29 [0.15–0.56]	0.47 [0.19–1.77]	0.015
GNRI	93.8 [84.9–98.3]	98.3 [95.3–104.2]	84.5 [77.3–88.4]	<0.001
Echocardiography at discharge				
LVDd (mm)	49.2 ± 5.9	48.6 ± 5.8	50.0 ± 6.0	0.22
Left atrial volume index (mL/m^2)	48.5 [36.4–61.5]	51.7 [38.1–61.8]	44.3 [33.1–56.5]	0.162
Left atrial volume index >34 (mL/m^2), n (%)	86 (78.2)	51 (83.6)	35 (71.4)	0.164
LVMI (g/m^2)	119.4 ± 35.0	113.0 ± 34.4	127.3 ± 34.4	0.033
E/mean E′	13.4 [11.0–17.7]	13.5 [11.1–17.5]	13.0 [10.3–18.4]	0.79
LVEF (%)	60.0 [54.1–66.5]	61.6 [55.9–68.7]	58.3 [53.2–64.7]	0.034
Medication at discharge				
Diuretics, n (%)	96 (87.3)	54 (88.5)	42 (85.7)	0.78
Loop diuretics, n (%)	87 (79.1)	49 (80.3)	38 (77.6)	0.81
Thiazide diuretics, n (%)	10 (9.1)	6 (9.8)	4 (8.2)	1
Tolvaptan, n (%)	8 (7.3)	5 (8.2)	3 (6.1)	0.73
Aldosterone antagonist, n (%)	59 (53.6)	36 (59.0)	23 (46.9)	0.25
ACEIs/ARBs, n (%)	71 (64.5)	42 (68.9)	29 (59.2)	0.32
Beta-blocker, n (%)	78 (70.9)	40 (65.6)	38 (77.6)	0.21
Statin, n (%)	44 (40)	29 (47.5)	15 (30.6)	0.081

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BNP, brain natriuretic peptide; GFR, glomerular filtration rate; GNRI; geriatric nutritional risk index; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; n, number of patients.
Results are expressed as mean ± standard deviation or the median [inter-quartile range]. Data were missing for the following characteristics: BNP, for four heart failure patients with high GNRI and for one heart failure patient with low GNRI; total cholesterol, for six heart failure patients with high GNRI and nine heart failure patients with low GNRI; LVMI, for one heart failure patient with high GNRI and for one heart failure patient with low GNRI; and E/mean E′, for six heart failure patients with high GNRI.

Table 3 Impact of nutritional screening using GNRI on all-cause death

	No. of events (all-cause deaths)/ at risk (%)	Model 1: unadjusted		Model 2: adjusted for age and sex		No. of events (all-cause deaths)/ at risk (%)	Model 3: adjusted for age and logBNP	
		HR (95% CI)	P-value	HR (95% CI)	P-value		HR (95% CI)	P-value
GNRI Low vs. high (high as per reference)[a]	24/110 (21.8)	4.311 (1.784–10.415)	0.001	3.202 (1.295–7.918)	0.012	24/105 (22.9)	2.444 (0.953–6.267)	0.063
GNRI as a continuous variable		0.912 (0.877–0.949)	<0.001	0.927 (0.889–0.967)	<0.001		0.921 (0.880–0.964)	<0.001

BNP, brain natriuretic peptide; CI, confidence interval; GNRI, geriatric nutritional risk index; HR, hazard ratio.
Data were missing for the following characteristics: logBNP for five patients.
[a]Primary outcomes are presented as HR for the low GNRI (<92) using the high GNRI (≥92) as a reference.

age and higher logBNP were associated with an increased risk of all-cause death (HR = 1.081, 95% CI = 1.018–1.147, for age; HR = 4.872, 95% CI = 1.358–17.477, for logBNP). In addition, the Kaplan–Meier analysis also revealed that cardiovascular deaths occurred more frequently in HFpEF patients with a low GNRI (n = 9) compared with HFpEF patients with a high GNRI (n = 5) (P = 0.025 by the log-rank test).

Comparison with other nutritional indices

The C-statistic of the GNRI was compared with that of serum albumin to assess its validity as a nutritional risk screening tool in elderly patients hospitalized with HFpEF (*Figure 3*). DeLong's test for two correlated receiver operating characteristic curves [area under the receiver operating characteristic curve (AUROC) of serum albumin, 0.71;

Figure 2 Survival curve adjusted for age. After adjusting for age, the analysis revealed that heart failure with preserved ejection fraction (HFpEF) patients with a low geriatric nutritional risk index (GNRI) had an increased risk of all-cause death compared with patients in the high GNRI group (P = 0.009, n = 110; hazard ratio = 3.334; 95% confidence interval = 1.354–8.207). Low GNRI, group of HFpEF patients with moderate or severe nutritional risk; high GNRI, group of HFpEF patients with low or no nutritional risk.

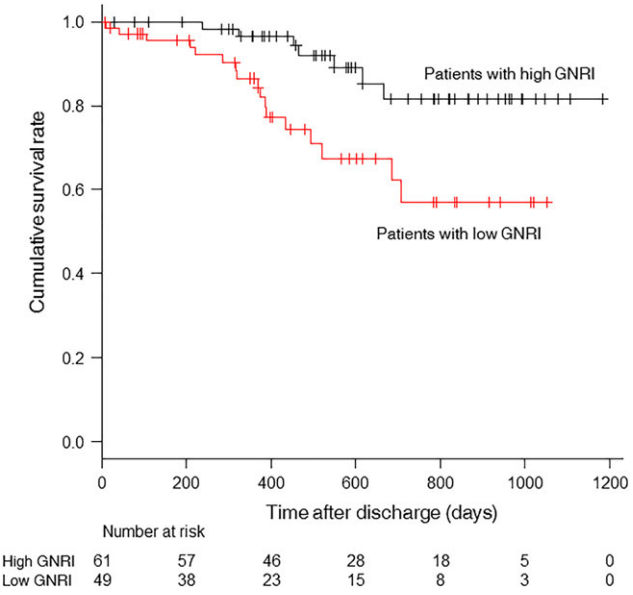
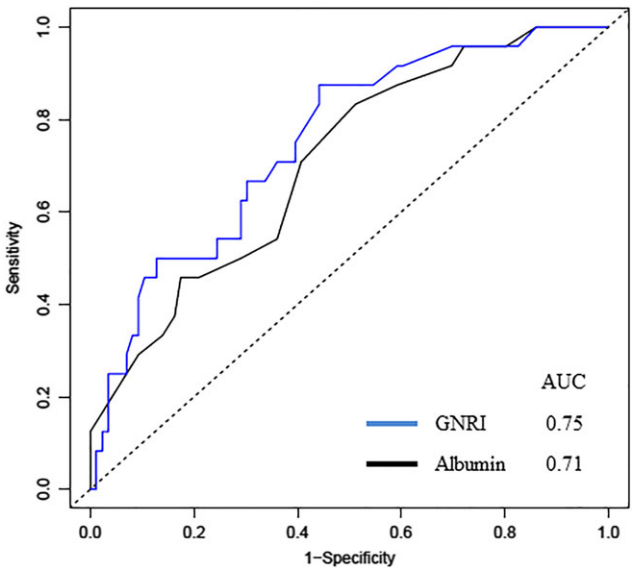


Figure 3 Predictive performance of serum albumin and the geriatric nutritional risk index (GNRI) for all-cause death. AUC, area under the curve.



AUROC of the GNRI, 0.75] demonstrated significant differences between the two groups (P = 0.038). We assessed whether the evaluation of the GNRI levels in addition to the other predictor improved the stratification of the risk of mortality in elderly patients hospitalized with HFpEF. Adding the GNRI to the logBNP increased the AUROC for all-cause death significantly (0.71 and 0.80, respectively; P = 0.040, n = 105). However, adding the GNRI to the model of age and logBNP did not significantly increase the AUROC for all-cause death (0.78 and 0.81, respectively; P = 0.197, n = 105). Conversely, adding serum albumin levels or BMI to the logBNP did not significantly increase the AUROC for all-cause death (P = 0.082 and P = 0.29, respectively).

Discussion

In the present study, patient nutritional status, assessed using the GNRI at discharge, was examined to determine its usefulness in predicting the long-term prognosis of patients hospitalized with HF in a multicentre registry setting. Our results showed that all-cause death occurred more frequently in HFpEF patients with moderate or major nutrition-related risk than in those with low or no nutrition-related risk (*Table 3* and Model 4). Evidence in support of a lower GNRI at discharge as a significant predictor of the occurrence of all-cause death in patients hospitalized with HFpEF includes the following: a per point increase in the GNRI was associated with a lower risk of all-cause death (*Table 3*). The results of the present study indicate that screening nutritional status using a GNRI at discharge further refines risk assessment in patients hospitalized with HFpEF.

Undernutrition is known as one of the most critical determinants of poor clinical outcomes in HF patients.[7–20] However, to our knowledge, all but one[18] of the previous studies reported on so-called HF patients, and therefore, our specific findings for 'HFpEF patients' are novel. Kinugasa *et al.*[18] reported that malnutrition assessed by the GNRI on admission was an independent determinant of long-term death in acute HF with pEF. This finding[18] supports those of the present study, which demonstrated that a lower GNRI is a significant predictor of the occurrence of all-cause death in patients hospitalized with HFpEF.

Fluid status, in particular, has been shown to influence serum albumin levels and the BMI. Increased extracellular fluid volume decreases serum albumin, whereas it increases BMI. Considering such a counteracting effect, the GNRI, which is a combined index of albumin and BMI, may lead to a minimization of the effect of fluid status. However, the influence of serum albumin and BMI may influence the calculation of GNRI, as GNRI might prefer the stable state. In addition, HFpEF has been variably classified as LVEF $>$ 40, $>$45, $>$50, and $\geq$55%.[4] Currently, HF patients with an ejection fraction in the range of 41–49% are allocated to HFbEF.[4] HFbEF patients present a mild systolic dysfunction, but in the clinical setting, there are many cases with a similar pathophysiology as HFpEF.[5] Therefore, HFbEF patients are often treated with guideline-directed

medical therapy that is similar to that used in patients with HFpEF,[4] whereas efficient therapeutic agents for HFpEF are poorly established. However, unlike for HFpEF, sufficient evidence-based therapy for HFrEF patients may also be effective for HFbEF patients.[5] For example, in patients with HFbEF, data suggest that HFrEF therapeutic agents such as beta-blockers are also effective.[26] According to Tsuji *et al*., the prognostic impacts of these agents in HFbEF differ from those in HFpEF but are almost comparable with those in HFrEF. Thus, the use of beta-blockers has been positively associated, and the use of diuretics has been negatively associated with improved mortality in HFbEF and HFrEF but not in HFpEF patients.[26] The HFpEF criterion used in the study by Kinugasa *et al*.[18] was LVEF $\geq$ 40% and included HFbEF. Conversely, in our study, the HFpEF criterion was LVEF $\geq$ 50% and did not include HFbEF. Unfortunately, there are a lack of effective treatment strategies for patients with HFpEF, and the investigation of the potential predictive value of nutritional status assessment using the GNRI in patients with HFpEF is important.

Inflammation may play an important role in the pathogenesis of HFpEF owing to its significant contribution to myocardial fibrosis.[27] Koller *et al*.[27] reported that C-reactive protein was a strong prognostic marker for risk stratification in patients with HFpEF. Recently, in emerging pathophysiological models of HFpEF, systemic microvascular endothelial inflammation related to coexisting conditions has been proposed as an additional mechanism leading to myocardial inflammation and fibrosis, increased oxidative stress, and alterations in cardiomyocyte signalling pathways.[28] These alterations promote cardiomyocyte remodelling and dysfunction, in addition to microvascular dysfunction and rarefaction in cardiac and skeletal muscle.[28] Conversely, the GNRI was developed as a screening tool to assess not only the nutritional but also the inflammatory status of older inpatients.[29] The GNRI has been shown to correlate well with indicators of inflammation and length of hospital stay.[29] Indeed, in the present study, the C-reactive protein level was significantly higher in the moderate or major nutrition-related risk group (low GNRI, 0.47 [IQR 0.19–1.77]) than in the low or no nutrition-related risk group (high GNRI, 0.29 [IQR 0.15–0.56], $P < 0.05$). In addition, when the log C-reactive protein was plotted against the GNRI as a continuous variable in the overall patient population, there was a weak but significant inverse correlation ($r = -0.287$, $P = 0.002$, $n = 110$), indicating that a greater increase in GNRI would be associated with a greater decrease in C-reactive protein levels. Intestinal oedema or anorexia-induced low nutritional intake, liver dysfunction, cytokine-induced hypercatabolism, insulin resistance, and other mechanisms may all lead to HF-related undernutrition.[12] HF patients with undernutrition enter a vicious cycle of inflammation, catabolic drive, and undernutrition, which further exacerbates HF.[30] Unfortunately, because effective treatment options are currently unavailable for HFpEF, this might be considered a valuable target for intervention in the future.

Several limitations of the present study should be mentioned. The total number of HFpEF patients enrolled in the Ibaraki Cardiovascular Assessment Study registry and the number of all-cause deaths and cardiovascular death events were not large. Therefore, the number of indices that could be incorporated into the Cox proportional hazard regression models was small. In addition, we did not exclude co-morbid diseases such as nephrotic syndrome, liver cirrhosis, cancer, collagen disease, the presence of infectious diseases, and blood disorders, all of which may affect albumin levels. In general, female HFpEF patients have occupied two thirds of the entire HFpEF study population.[31] Conversely, in some cohort studies, female HFpEF patients represented only 48–50% of the entire HFpEF patient population.[32,33] Similarly, in our sample, there was a lower number of women (46%) enrolled, which is in contrast with the epidemiology of HFpEF in the real-world setting. Because our study differs from a complete case registration study, the proportion of female patients with HFpEF was likely lower.

Conclusions

This multicentre registry study suggests that nutritional screening using GNRI at discharge from hospital is helpful in predicting the long-term prognosis of elderly patients hospitalized with HFpEF.

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Conflict of interest

None declared.

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