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Geriatric Nutritional Risk Index Is Associated With Prognosis in Patients With Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension

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Background: The Geriatric Nutritional Risk Index (GNRI) is a simple tool for assessing nutritional risk that predicts prognosis in patients with heart failure. This study evaluated associations between the GNRI at first hospitalization and prognosis in patients with pulmonary artery hypertension (PAH) and those with chronic thromboembolic pulmonary hypertension (CTEPH).

Methods and Results: This retrospective investigation included 104 patients with either PAH or CTEPH who were treated at Kagoshima University Hospital in Japan. Patients were divided into a high (≥92) and low (<92) GNRI groups. Body mass index and serum albumin levels were significantly lower in the low GNRI group (P<0.001). Over a median follow-up period of 24 months, the incidence of pulmonary hypertension rehospitalization was higher in the low GNRI group (P=0.04). Kaplan-Meier analysis revealed that the cumulative event-free rate was significantly lower in the low GNRI group (P=0.002). Low GNRI was significantly associated with a poorer outcome after adjusting for different sets of confounding factors, including: age and sex (P=0.004); age, sex, and PAH (P=0.043); and age, sex, and mean pulmonary artery pressure (P=0.003).

Conclusions: The GNRI at first hospitalization is useful for predicting prognosis in PAH and CTEPH patients.

Key Words: Chronic thromboembolic pulmonary hypertension (CTEPH); Geriatric Nutritional Risk Index (GNRI); Pulmonary artery hypertension (PAH); Undernutrition

Pulmonary hypertension (PH) refers to a specific type of high pressure that involves right ventricular dysfunction and heart failure (HF). In the currently prevailing clinical classifications of PH, precapillary PH includes patients in Group 1 (pulmonary artery hypertension [PAH]), Group 3, and Group 4 (chronic thromboembolic PH [CTEPH]), as well as some patients in Group 5.[1] In contrast, HF caused by left ventricular disease, such as HF with either reduced or preserved ejection fraction, causes postcapillary PH due to backward transmission of elevated left-sided filling pressures into the pulmonary circulation.[1,2]

PAH is characterized by remodeling of the precapillary pulmonary arteries, with endothelial cell dysfunction contributing to endothelial and pulmonary artery smooth muscle cell proliferation.[3] PAH is a rare progressive disease associated with significant morbidity. Notably, however, there have been advances in PAH-specific drug therapies in recent decades.[1]

CTEPH is a rare, progressive pulmonary vascular disease that has a poor outcome if left untreated. Recent insights have revealed that CTEPH involves not only persistent organized thrombi in the proximal pulmonary arteries, but also small-vessel disease.[4] Pulmonary endarterectomy is the standard treatment for CTEPH. In patients who are ineligible for pulmonary endarterectomy, targeted medical therapy is beneficial.[1] Percutaneous balloon pulmonary angioplasty is an emerging option for patients with technically inoperable disease or with an unfavorable risk-to-benefit ratio for surgery.[1,5,6] However, the predicted improvements in PAH and CTEPH in these patients are insufficient. In such patients, accurate determination of prognostic predictors would be highly beneficial in order to facilitate optimal treatment interventions.

Chronic HF may lead to loss of appetite, malabsorption, and a catabolic state, which can then lead to undernutrition. Malnutrition is common in patients with HF, and is one of the most significant determinants of poor clinical outcomes

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Table 1. Baseline Patient Characteristics According to GNRI Score

	Overall (n=104)	GNRI score		P-value
		<92 (n=22)	≥92 (n=82)	
Age (years)	60±14	54±17	61±13	0.047
Female sex	88 (84.6)	19 (86.4)	69 (84.1)	0.905
BMI (kg/m²)	23.2±5.0	19.2±2.5	24.3±4.9	<0.001
Height (cm)	154.2±7.3	154.4±6.3	154.2±7.6	0.891
WHO functional class II/III/IV	33/61/10	8/11/3	25/50/7	
Comorbidity				
Coronary artery disease	3 (2.9)	1 (4.6)	2 (2.4)	0.620
Hypertension	12 (11.5)	1 (4.6)	11 (13.4)	0.206
Diabetes	7 (6.7)	1 (4.6)	6 (7.3)	0.631
Group 1: PAH	56 (54)	20 (91)	36 (44)	<0.001
Laboratory data				
Hemoglobin (g/dL)	13.5±0.3	12.0±0.5	13.9±0.3	0.002
Albumin (g/dL)	3.8±0.6	3.1±0.5	3.9±0.5	<0.001
Total cholesterol (mg/dL)	188±42	173±52	192±39	0.067
BNP (pg/mL)	92.3 [37–272.7]	128.5 [46.4–691.5]	65.6 [36.4–264.2]	0.258
Hemodynamic data				
mPAP (mmHg)	40.1±13.4	42.3±19.1	39.5±11.6	0.397
PAWP (mmHg)	8 [5–10]	7 [5–10.5]	8 [5.3–10]	0.886
RA (mmHg)	5 [3–8]	5 [3.8–10.5]	4 [3–7]	0.218
CO (L/min)	3.80±1.34	3.67±1.17	3.84±1.39	0.590
PVR (dyn·s/cm⁵)	583.4 [408.5–904]	586 [369.8–1,173.3]	583.5 [412–904]	0.880

Unless indicated otherwise, data are given as n (%), the mean±SD or median [interquartile range]. BMI, body mass index; BNP, B-type natriuretic peptide; CO, cardiac output; GNRI, Geriatric Nutritional Risk Index; mPAP, mean pulmonary artery pressure; PAH, pulmonary artery hypertension; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial pressure; WHO, World Health Organization.

in patients with HF.[7–14] Precapillary PH leads to right ventricular overload associated with right-sided HF. Nutritional changes are more prevalent in precapillary PH patients than in the general population. Undernutrition may trigger or aggravate disease progression. However, it is unclear whether undernutrition at the point of diagnosis is significantly associated with prognoses in patients with precapillary PH. PAH and CTEPH are included in "precapillary PH". Treatments for PAH and CTEPH are progressing, but little attention has been paid to nutritional status. Previous studies have identified several nutritional indicators that predict cardiovascular events, including serum albumin, body mass index (BMI), and total cholesterol.[15–17] The Geriatric Nutritional Risk Index (GNRI) is a simple and well-established nutritional screening tool for use in elderly patients.[18–21] Recent studies suggest that the GNRI is helpful for predicting the prognosis of HF.[22–26] The aim of the present study was to investigate whether GNRI scores at the time of diagnosis predicted prognosis in patients with either PAH or CTEPH.

Methods

Patients and Study Design

In all, 188 patients with precapillary PH were followed-up at Kagoshima University Hospital between January 2010 and May 2019. All patients were untreated for PH at the time of their first hospitalization. Precapillary PH was diagnosed based on mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest and pulmonary artery wedge pressure ≤15 mmHg at rest, in accordance with current guidelines.[1] Forty of these 188 patients were excluded from the present study because of missing GNRI data. The remaining patients were then categorized as belonging to Group 1, 3, 4, or 5 according to the clinical classification of PH,[1] and 104 patients with Group 1 PAH or Group 4 CTEPH were ultimately included in the study. PAH was classified into connective tissue disease-related PAH (n=33), congenital heart disease-related PH (n=13), portopulmonary hypertension (n=6), and idiopathic PAH (n=4). The causative diseases in patients with connective tissue disease-related PH were systemic sclerosis in 16, systemic lupus erythematosus in 10, mixed connective tissue disease in 4, and other diseases in the remaining 3. All measurements were taken at the time of the first hospitalization. In the present study, the GNRI score on admission was calculated using the following validated formula:[14,22]

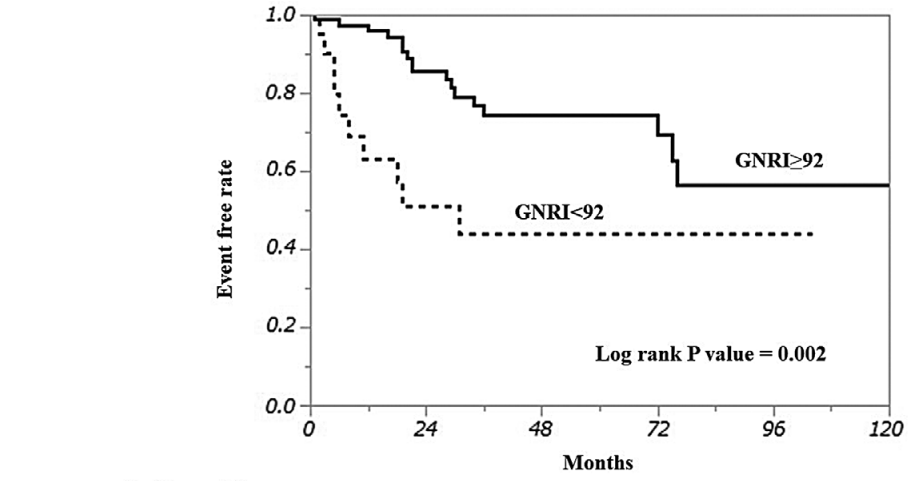
$$\text{GNRI score} = 14.89 \times \text{serum albumin (g/dL)} + 41.7 \times (\text{BMI}/22)$$

In the present study, a GNRI cut-off value of 92 was used, in accordance with Kinugasa et al.[22] Specifically, a "low" GNRI was defined as a score <92, and a "high" GNRI was defined as a score ≥92. Previous reports suggest that these groups correspond to moderate to severe nutritional risk and to low or no nutritional risk, respectively.[22–25] Medical records were reviewed retrospectively to extract information pertaining to patient age, sex, height, weight, clinical classification, date of diagnosis, World Health Organization (WHO) functional class, comorbidity, laboratory data, and hemodynamic data. In addition, BMI was calculated for each patient. After being diagnosed, all PAH patients underwent PAH-specific optimal drug therapy,[1] whereas most CTEPH patients underwent percutaneous balloon

Table 2. Cumulative Incidence of All-Cause Death or PH Rehospitalization

	GNRI score		P-value (log rank)
	<92 (n=22)	≥92 (n=82)	
Composite endpoint*	10 (45)	17 (21)	0.002
All-cause death	6 (27)	10 (12)	0.05
PH-related death	2 (9)	4 (5)	0.39
Non-PH-related death	4 (18)	6 (7)	0.07
PH rehospitalization	6 (27)	11 (13)	0.04

Unless indicated otherwise, data are given as n (%). *The composite endpoint was pulmonary hypertension (PH) rehospitalization or all-cause death. GNRI, Geriatric Nutritional Risk Index.



GNRI<92	Incidence (%)		48.9	56.2	56.2	56.2	56.2
	No. at risk	22	7	4	2	1	1
GNRI ≥ 92	Incidence (%)		14.6	25.6	30.8	43.4	43.4
	No. at risk	82	44	25	11	3	1

Figure. Kaplan-Meier curves of event-free rates in the low (score <92) and high (score ≥92) Geriatric Nutritional Risk Index (GNRI) groups.

pulmonary angioplasty in addition to receiving drug treatment. Both all-cause death and PH rehospitalization during the follow-up period were assessed. Causes of death were classified as PH or non-PH based on the available clinical information.

Statistical Analysis

Frequencies and percentages were calculated for categorical variables, which were compared using Fisher's exact test or the Chi-squared test. Normally distributed continuous variables are presented as the mean±SD, and were compared using Student's t-test. For non-normally distributed continuous variables, data are presented as the median and interquartile range (IQR), with values compared using the Wilcoxon test. Cumulative incidences were estimated using the Kaplan-Meier method, and the significance of differences was assessed using a log-rank test. Multivariate analysis incorporating a Cox proportional hazards model was used to assess associations between GNRI and the incidence of composite outcomes after adjustment for potentially confounding variables.

Three different models were constructed, each incorporating adjustment for a different set of variables. Model 1 was adjusted for age and sex. Models 2 and 3 were adjusted for the baseline demographic characteristics that differed significantly by GNRI: Model 2 was adjusted for age, sex, and clinical PH classification, whereas Model 3 was adjusted for age, sex, and hemoglobin. Model 4 was adjusted for factors with potential clinical effects, namely age, sex, and mPAP. All P-values are 2-tailed, and $P<0.05$ was deemed to indicate statistical significance. All statistical analyses were performed using SAS software (JMP version 14.0).

Results

Baseline patient characteristics are given in **Table 1**. The mean age of the 104 patients in the study was 60±14 years, 88 (84.6%) were female, and 71 (68.3%) were WHO functional class III or IV. The number of patients with PAH was significantly higher in the low than high GNRI group. Hypertension was the most common comorbidity (12/104; 11.5%). Patients with low GNRI were significantly younger

than those with high GNRI (P=0.047). BMI, serum albumin levels, and hemoglobin were significantly lower in the low than high GNRI group (P<0.001). There were no significant differences in total cholesterol, B-type natriuretic peptide concentrations, or hemodynamic parameters between the 2 groups.

During the median follow-up period of 24 months 16 of 104 patients (15.4%) died (**Table 2**). Death was PH related in 6 (37.5%) patients, whereas in the remaining 10 patients (62.5%) the primary causes of death were infectious disease (n=3), respiratory disease (n=4), cancer (n=2), and "other" (n=1). The composite outcome of either PH rehospitalization or all-cause death occurred in 10 of 22 patients (45.5%) in the low GNRI group and in 17 of 82 patients (20.7%) in the high GNRI group. The incidence of PH rehospitalization was higher in patients with low than high GNRI (log-rank P=0.04).

In Kaplan-Meier analysis, patients in the high GNRI group had a significantly higher cumulative event-free rate than those in the low GNRI group (log-rank P=0.002; **Figure**). Finally, Cox proportional hazards model analysis revealed that low GNRI was significantly associated with higher all-cause death or PH rehospitalization than high GNRI after adjustment for various different sets of potentially confounding factors (**Table 3**). Taken together, these results suggest that undernutrition at the time of diagnosis is a potent prognosticator in patients with PH.

Table 3. Cox Analysis of the Predictive Value of the GNRI for All-Cause Death or PH Rehospitalization

	HR (95% CI)	P-value
Unadjusted	3.22 (1.47–7.08)	0.004
Model 1	3.76 (1.63–8.66)	0.002
Model 2	2.40 (1.03–5.59)	0.043
Model 3	3.74 (1.53–9.12)	0.004
Model 4	3.63 (1.56–8.47)	0.003

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, and clinical PH classification. Model 3 was adjusted for age, sex, and hemoglobin. Model 4 was adjusted for age, sex, and mPAP. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Tables 1,2.

Discussion

To the best of our knowledge, the present study is the first to determine that nutritional status at first hospitalization is significantly associated with prognosis in patients with PAH or CTEPH. All-cause death or PH rehospitalization occurred more frequently in PAH and CTEPH patients with a low GNRI than in those with a high GNRI, and the difference remained significant after adjusting for numerous potentially confounding covariates. The GNRI score at first hospitalization was a significant predictor of prognosis.

The GNRI is calculated based on serum albumin and BMI, and was developed by Bouillanne et al[18] for use as a simple and accurate tool to predict the risk of morbidity and mortality in elderly hospitalized patients. Serum albumin levels and BMI are often used as indicators of nutritional status, and many studies have shown that these parameters predict clinical outcomes in patients with HF.[15,16,27,28] Notably, however, serum albumin concentrations are affected by several factors, including fluid status, hepatic congestion, renal dysfunction, and inflammation.[16,28] Actual body weight is also affected by fluid status, which can be a problem in patients with precapillary PH. To reduce the effects of those factors on nutritional assessment in the present study, only treatment-naïve patients with PAH or CTEPH at first hospitalization were included. The incorporation of both serum albumin and BMI into the GNRI may overcome the shortcomings of using either indicator alone, because increased extracellular fluid volume reduces serum albumin but increases actual body weight. In the present study, the GNRI was a more informative parameter for predicting PH rehospitalization or all-cause death than either BMI or serum albumin alone.

Cachexia is a serious complication that is associated with a high risk of death in HF patients.[29,30] Right ventricular dysfunction reportedly often coexists with cachexia and is associated with accelerated weight loss, abnormal body composition, and a worse prognosis in patients with advanced HF.[31] Many mechanisms are thought to be involved in the development of cardiac cachexia. The condition is related to hemodynamic parameters of HF, including PH,[32] as well as increased cytokine responses[33] and impaired gastrointestinal function.[34] Only a few studies have investigated PAH and nutritional status.[35–38] As reported previously, malabsorption as a consequence of gastrointestinal edema, due to reduced right ventricular function and changes in the gut microbiome, results in reduced nutrient uptake.[37]

The prevalence of malnutrition in patients with chronic HF ranges from 16% to 62%.[39–42] According to Lin et al,[42] a reduction in skeletal muscle strength and disruption of immune function due to undernutrition may contribute to an increase in the severity of HF, and thus result in increased morbidity and mortality in HF patients. In a previous study, inflammatory cytokines were predictors of survival in patients with PAH. Furthermore, serum cytokine concentrations were more closely related to survival than mPAP and cardiac index measured at the time of right-heart catheterization.[43]

In the present study, the severity of PH was not associated with the GNRI score at the time of first hospitalization. The impaired muscle strength that accompanies undernutrition at any level of pulmonary artery pressure may reduce exercise tolerance in patients with precapillary PH. Furthermore, undernutrition at the initial stage of diagnosis may also be a driver of disease progression as part of a vicious cycle associated with cytokine activation and cachexia.

There were significantly more PAH patients in the low than high GNRI group in the present study. Because of the relatively small sample size, it was difficult to analyze the clinical classification of PH. Serum albumin concentrations, total cholesterol, and hemoglobin were significantly lower in PAH than CTEPH patients (P<0.05). Furthermore, 59% of PAH patients had connective tissue disease-related PAH. Malnutrition is often seen in the context of connective tissue disease. The etiology of PAH may have affected the results of this study. Therefore, the multivariate model included the clinical classification of PH as a covariate. Further prospective investigations are needed to confirm the findings of the present study in another large cohort.

The present study has several limitations. First, it was a retrospective study with a relatively small sample size. Therefore, the number of indices that could be incorporated into the logistic analysis models was small. In addition, GNRI scores were only evaluated once; thus, changes in

GNRI were not assessed. Several studies reported that iron and vitamin D predict prognosis in patients with PH.[44–46] However, we were not able to evaluate other nutrients in the present retrospective study. Finally, the possibility of selection bias and unmeasured confounding factors may not have been completely excluded.

Although undernutrition and weight loss are frequently evident in PAH and CTEPH patients, little is known about the effectiveness of nutrition interventions in these patients. Further investigations are required to evaluate the effects of comprehensive nutritional intervention on morbidity and mortality in malnourished precapillary PH patients.

Conclusions

The present study suggests that the GNRI score at first hospitalization may be a simple predictor of prognosis in patients with PAH and CTEPH. Adjunct nutritional therapies may improve outcomes in such patients.

Conflicts of Interest

The authors report no relationships that could be construed as a conflict of interest.

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IRB Information

This study was approved by the Ethics Committee on Epidemiological Studies, Kagoshima University (Reference no. 190100 疫).

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