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RESEARCH ARTICLE

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Impact of malnutrition on prognosis in patients with pulmonary arterial hypertension

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Abstract

Pulmonary arterial hypertension is a life-threatening disease that coexists with right heart failure. We evaluated the relationship between malnutrition and prognosis in patients with pulmonary arterial hypertension, as malnutrition is known as a prognosis determinant in chronic heart failure. We retrospectively reviewed data of patients with pulmonary arterial hypertension before treatment. The Geriatric Nutritional Risk Index, Prognostic Nutritional Index, and Controlling Nutritional Status scores on the day of diagnosis were calculated to assess the nutritional status. Clinical endpoints were defined as composite outcomes of all-cause death or lung transplantation. Eighty patients were enrolled (mean age, 50 years; 23 men). The mean pulmonary arterial pressure was 47 ± 19 mmHg, Geriatric Nutritional Risk Index was 99.9 ± 12.0, and Prognostic Nutritional Index was 46.3 ± 10.0. The median Controlling Nutritional Status score was 2 (1–4). During the median 5.5-year follow-up period, 28 composite events occurred. Kaplan-Meier analysis demonstrated significant differences in the incidence of clinical endpoints between groups divided by each median Geriatric Nutritional Risk Index, Prognostic Nutritional Index, and Controlling Nutritional Status score ($p = 0.007$, 0.039, and 0.010, respectively). In multivariate Cox regression analysis, clinical endpoints were significantly associated with Geriatric Nutritional Risk Index (hazard ratio: 0.953, 95% confidence interval: 0.918–0.990), Prognostic Nutritional Index (hazard ratio: 0.942, 95% confidence interval: 0.892–0.996), and Controlling Nutritional Status score (hazard ratio: 1.230, 95% confidence interval: 1.056–1.433) after adjustment for factors associated in univariate Cox regression analysis. Malnutrition at diagnosis is a useful prognostic predictor for patients with pulmonary arterial hypertension.

KEYWORDS
Controlling Nutritional Status score, Geriatric Nutritional Risk Index, nutritional status, Prognostic Nutritional Index

INTRODUCTION

Pulmonary arterial hypertension (PAH) is known to have a poor prognosis, but recent advances in PAH-specific therapies have significantly improved patient outcomes.[1] Predictive prognostic markers have been investigated, with cardiac index and brain natriuretic peptide (BNP) reported to be associated with prognosis[2,3] and included in prognosis risk assessment guidelines. These risk assessments include factors indicating clinical symptoms or the hemodynamic status, such as presence of syncope, echocardiography findings, and right heart catheterization. However, other factors indicating nonhemodynamic status, such as nutritional status, were not included in these assessments due to lack of data regarding the prognostic impact.

Heart failure causes malnutrition from reduced appetite and absorption; it is associated with poor prognosis in heart failure,[4] and assessment of nutritional status is recommended in these patients.[5] Objective assessments of nutritional status, such as the Geriatric Nutritional Risk Index (GNRI), Prognostic Nutritional Index (PNI), and Controlling Nutritional Status (CONUT) score, are widely used,[6–8] and research have confirmed the association with heart failure prognosis.[9–12] Although previous reports regarding the relationship between heart failure and nutrition status have mainly targeted left-sided heart failure, the assessment of nutritional status may also be important in patients with right-sided heart failure; right-sided heart failure may be related to malnutrition due to hemodynamic disorders, such as bowel edema and hypoperfusion, as well as left-sided heart failure.[4,5,13–15] However, it has not been fully elucidated whether nutritional status is associated with the prognosis of patients with PAH, which causes right-sided heart failure.

A recent study reported that GNRI, one of the widely used indices of nutritional status, was associated with prognosis in patients with PAH and chronic thromboembolic pulmonary hypertension.[16] However, this study simultaneously analyzed patients with not only PAH but also chronic thromboembolic pulmonary hypertension, which has a drastically different pathology. In addition, GNRI was calculated using serum albumin and body mass index (BMI).[6] A lower serum albumin level, which is an important marker for malnutrition, was significantly associated with worse prognosis in patients with PAH.[17] However, serum albumin level is influenced by not only nutritional status but also other factors such as liver dysfunction and inflammation.[18] Thus, it is uncertain whether the relationship between lower serum albumin levels and worse prognosis in patients with PAH was caused by malnutrition. Additionally, although BMI is an important factor of nutritional status, the impact of BMI on prognosis in patients with PAH is controversial and paradoxical.[19–24] Thus, whether the relationship between poor nutritional index score and prognosis in patients with PAH is reproducible remains uncertain.

To clarify whether nutritional status could predict prognosis for patients with PAH, we evaluated the association between nutritional indices (GNRI, PNI, and CONUT score) and all-cause death or pulmonary transplantation after PAH diagnosis.

METHODS

Study protocol

This was a single-center, retrospective study. From January 1997 to October 2018, patients diagnosed with PAH via right heart catheterization at Okayama University Hospital were enrolled. Pulmonary hypertension was defined as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest, as assessed via right heart catheterization.[25] Patients with pulmonary hypertension were clinically classified according to the guidelines,[1] and 104 patients were categorized as having PAH, defined as pulmonary wedge pressure ≤15 mmHg and pulmonary vascular resistance (PVR) > 3 wood units. Figure 1 shows the flow diagram of the study design. After excluding patients who received PAH-targeted drugs before visiting our institution, 84 patients with an initial diagnosis of pulmonary hypertension were identified. Among them, four patients without clinical data on nutritional status were additionally excluded. Finally, 80 patients with various causes of PAH were analyzed (idiopathic/heritable, $n = 18$; associated with drugs and toxins, $n = 2$; associated with connective tissue disease, $n = 28$; associated with portopulmonary hypertension, $n = 10$; associated with congenital heart disease, $n = 22$).

This investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the institutional review boards of Okayama University Graduate School of Medicine (2210-037). The requirement for obtaining informed consent was waived because of the low-risk nature of the study and because consent could not be directly obtained from all enrolled patients.

Nutritional status

Results of the physical examination and blood results from the time of PAH diagnosis were used to calculate

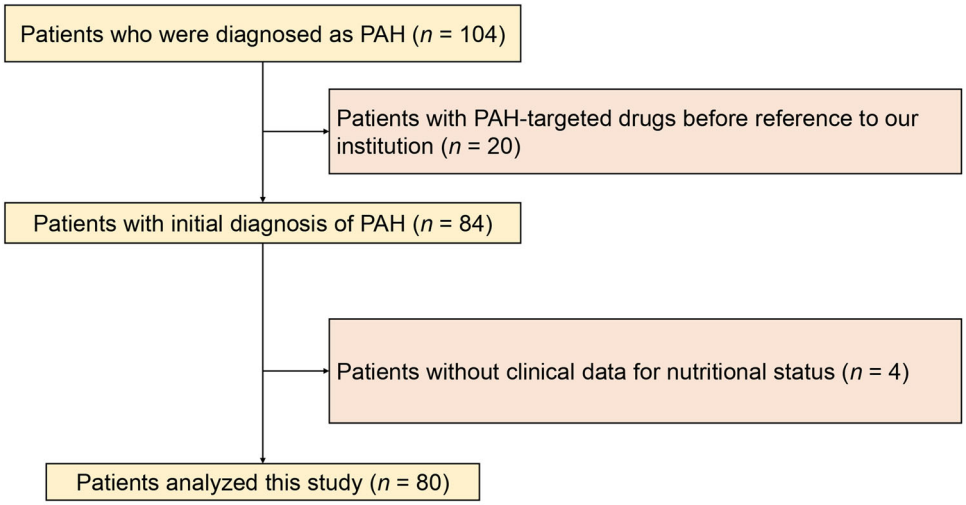

FIGURE 1 Flow diagram of patient selection. Among 104 patients who were diagnosed with pulmonary arterial hypertension (PAH), this study identified 84 patients with an initial diagnosis of PAH. From these, those without clinical data for nutritional status were excluded. A total of 80 patients were finally analyzed.

the scores. In this study, we evaluated three nutritional indices: GNRI, PNI, and COUNT score, because they are widely used for objective nutritional assessment and their utility for management in patients with heart failure has been reported.[6–12,26,27] GNRI and PNI were calculated as follows, with lower scores correlating with worse outcomes: GNRI = 14.89 × serum albumin (g/dL) + 41.7 × [BMI (kg/m^2)/22], PNI = 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per μL).[6,7] The CONUT score was calculated using sum of point values assigned to different ranges of laboratory results as follows, with higher scores correlating with worse outcomes: serum albumin ≥3.5 (g/dL), 0 points; 3.49–3 (g/dL), 2 points; 2.99–2.5 (g/dL), 4 points; and <2.5 (g/dL), 6 points; lymphocytes ≥1600 (/μL), 0 points; 1200–1599 (/μL), 1 point; 800–1199 (/μL), 2 points; and <800 (/μL), 3 points; and total cholesterol ≥180 (mg/dL), 0 points; 140–179 (mg/dL), 1 point; 100–139 (mg/dL), 2 points; and <100 (mg/dL), 3 points (Table 1).[8] Measurement of BNP as a part of hemodynamic assessment and routine laboratory tests was performed using an automated analyzer at Okayama University Hospital.

Hemodynamic assessment

Right-heart catheterization was performed for diagnosis of PAH and hemodynamic assessment before treatment was initiated. The mPAP, cardiac index, and PVR were measured. In addition, World Health Organization functional class and 6-min walking distance were investigated to assess symptoms and exercise tolerance capacity.

TABLE 1 Assessment of nutritional status by Controlling Nutritional Status score.

	Nutritional degree (higher = worse)			
Variables	**Normal**	**Light**	**Moderate**	**Severe**
Serum albumin (g/dL)	≥3.5	3.0–3.49	2.5–2.99	<2.5
Score	0	2	4	6
Total lymphocyte count (/μL)	≥1600	1200–1599	800–1199	<800
Score	0	1	2	3
Total cholesterol (mg/dL)	≥180	140–179	100–139	<100
Score	0	1	2	3

Clinical endpoints and follow-up

The incidence of clinical endpoints was investigated by retrospective review of the medical records or telephone interviews when laboratory data was blinded. Clinical endpoints were defined as the composite outcome of all-cause death or lung transplantation after diagnosis. Patients who underwent the above clinical endpoints during the follow-up period were defined as nonsurvivors, and patients without clinical endpoints were defined as survivors.

Statistical analysis

Categorical variables are presented as numbers (%) and were compared using the χ^2 test or Fisher's exact test, as

appropriate. Continuous variables that were normally distributed are presented as means ± standard deviation and were compared using Student's *t*-test. Continuous variables that were not normally distributed are presented as medians with interquartile ranges (IQRs) and were compared using the Mann–Whitney *U* test. Data normality was evaluated using the Shapiro–Wilk test. To assess clinical endpoints, a receiver-operating characteristic curve analysis was performed for the nutritional indices. The optimal cut-off value was defined as the point maximizing the Youden index (=max [sensitivity + specificity − 1]). Patients were classified into groups according to three different cut-off values; the median values in this study population, the cut-off values as stated in previous studies investigating the prognosis of patients with heart failure,[9,11] and the above optimal cut-off values of nutritional indices. Cumulative event-free rates of the clinical endpoints during follow-up were compared between groups using Kaplan–Meier curves, post-hoc comparisons, and log-rank tests. The effects of right heart catheterization findings, laboratory data, and nutritional indices on clinical endpoints were evaluated using Cox proportional hazards analysis. The results are reported as hazard ratios and 95% confidence intervals (CIs). The multivariate Cox proportional hazards analyses were performed after adjustment for variables considered as confounding factors by five models as follows. Model 1 was adjusted for variables that had statistically significant associations with clinical endpoints in the univariate analysis. Model 2 was adjusted for general patient characteristics: age and sex. Model 3 was adjusted for clinical symptoms per World Health Organization functional class. Model 4 was adjusted for hemodynamic parameters: right atrial pressure, mPAP, and cardiac index. Model 5 was adjusted for hematocyte findings: hemoglobin and platelet count. Model 6 was adjusted for total bilirubin and whether the etiology of PAH was associated with portopulmonary hypertension; this corrected for liver dysfunction. Total lymphocyte count, serum albumin, and total cholesterol were not included in multivariate analysis because they are components of the calculation for the nutritional indices. The association between nutritional indices and hemodynamic parameters, which includes World Health Organization functional class, 6-min walking distance, and right heart catheterization, was also investigated using Spearman's rank correlation analysis. Continuous variables that were not normally distributed were applied to the regression analysis after natural logarithmic transformation. Statistical significance was set at $p < 0.05$. These analyses were performed using SPSS statistical software (version 25; IBM Corp.).

RESULTS

Patient characteristics and clinical endpoints during the follow-up period

Table 2 shows the patients' clinical characteristics. Mean age was 50 ± 19 years, and 23 (28.8%) individuals were men. The median follow-up period was 5.5 years. Twenty-four patients died, and three patients underwent lung transplantation. There were significant differences between nonsurvivors and survivors in sex (44.4% women and 20.8% men, $p = 0.027$), 6-min walking distance (272 ± 114 m and 386 ± 128 m, $p = 0.002$), and right atrial pressure (7.8 ± 4.8 mmHg and 5.5 ± 3.8 mmHg, $p = 0.020$). BMI, mPAP, cardiac index, and PVR did not differ between groups.

Table 3 shows the laboratory data and nutritional indices. There were significant differences between nonsurvivor and survivor serum albumin (3.5 ± 0.7 g/dL and 4.0 ± 0.6 g/dL, $p = 0.002$), total cholesterol (154.3 ± 44.4 mg/dL and 174.9 ± 40.7 mg/dL, $p = 0.041$), serum creatinine (0.8 [0.7–1.0] mg/dL and 0.7 [0.6–0.8] mg/dL, $p = 0.044$) and BNP measurements (257.3 [63.7–472.0] pg/mL and 78.6 [23.7–214.8] pg/mL, $p = 0.008$). The total lymphocyte count did not differ among groups (1.4 [0.8–2.1] $10^3/\mu L$ and 1.6 [1.0–2.2] $10^3/\mu L$, $p = 0.395$). The mean GNRI and PNI of all patients were 99.9 ± 12.0 and 46.3 ± 10.0, respectively. The median CONUT score of all patients was 2.[1–4] Figure 2 shows the distribution of the three nutritional indices. Nonsurvivors had worse values than survivors in all three nutritional indices (GNRI, 94.9 ± 10.6 and 102,4 ± 12.0, $p = 0.007$; PNI, 42.9 ± 11.0 and 48.1 ± 9.0, $p = 0.027$; CONUT score, 3 [1.5–6] and 2 [1–3], $p = 0.023$).

Relationship between nutritional indices and clinical endpoints

The C-statistics in the receiver-operating characteristic curve analysis for clinical endpoint prediction were: GNRI, 0.687 (95% CI, 0.566–0.808; $p = 0.006$) with a sensitivity of 59.3% and a specificity of 73.6%; PNI, 0.656 (95% CI, 0.523–0.788; $p = 0.024$) with a sensitivity of 44.4% and a specificity of 86.3%; and CONUT score 0.655 (95% CI, 0.522–0.788; $p = 0.025$) with a sensitivity of 37.0% and a specificity of 88.2%. The optimal cut-off values maximizing the Youden index were GNRI, 96.1; PNI, 41.2; and CONUT score, 4.5. Figure 3A shows the Kaplan–Meier analysis for all patients. Figure 3B–D shows the Kaplan–Meier analyses of patients stratified

TABLE 2 Baseline clinical characteristics of this study.

Variables	All patients ($n = 80$)	Nonsurvivors ($n = 27$)	Survivors ($n = 53$)	p Value
Age, years	50 ± 19	53 ± 19	48 ± 19	0.251
Male	23 (28.8)	12 (44.4)	11 (20.8)	0.027
Body mass index (kg/m^2)	21.5 (19.3–25.6)	21.1 (18.7–25.6)	21.6 (19.5–25.4)	0.618
Etiology of PAH				0.560
Idiopathic/heritable	18 (22.5)	7 (25.9)	11 (20.8)	
Associated with drugs and toxins	2 (2.5)	0 (0.0)	2 (3.8)	
Associated with CTD	28 (35.0)	11 (40.7)	17 (32.1)	
Associated with PoPH	10 (12.5)	4 (14.8)	6 (11.3)	
Associated with CHD	22 (27.5)	5 (18.5)	17 (32.1)	
WHO-FC, *n*				0.402
I/II/III/IV	4/34/35/7	2/8/14/3	2/26/21/4	
6MWD, m	353.5 ± 127	272 ± 114	386 ± 118	0.002
Right heart catheterization				
Right atrial pressure (mmHg)	6 (3–8)	7 (4–11)	5 (3–8)	0.035
mPAP (mmHg)	47 ± 19	47 ± 20	48 ± 18	0.624
Cardiac index (L/min/m^2)	2.5 (1.9–3.2)	2.3 (1.8–3.1)	2.5 (2.0–3.2)	0.340
PVR (dyn s/cm^5)	672 (343–1223)	672 (320–1784)	675 (380–941)	0.539
Treatment				
ERA	48 (60.0)	17 (63.0)	31 (58.5)	0.699
PDE5i and sGC stimulator	46 (57.5)	14 (51.9)	32 (60.4)	0.466
Oral prostacyclin analogs and prostacyclin receptor agonists	21 (26.3)	9 (33.3)	12 (22.6)	0.304
i.v. prostacyclin analogs	11 (13.8)	5 (18.5)	6 (11.3)	0.377
Monotherapy	22 (27.5)	9 (33.3)	13 (24.5)	0.404
Dual-combination therapy	26 (20.0)	6 (22.2)	20 (37.7)	0.161
Triple-combination therapy	19 (23.8)	6 (22.2)	13 (24.5)	0.819

Note: Data are presented as the number (%), mean ± standard deviation, or median (25th–75th percentile).

Abbreviations: 6MWD, 6-min walking distance; CHD, congenital heart disease; CTD, connective tissue disease; ERA, endothelin receptor antagonist; i.v., intravenous; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; PoPH, porto-pulmonary hypertension; PVR, pulmonary vascular resistance; sGC, soluble guanylate cyclase; WHO-FC, World Health Organization functional class.

according to the median values, established cut-off values, and the above-optimal cut-off values for nutritional indices. Patients with worse nutritional indices had significantly poorer prognoses. As shown in Table 4, the univariate Cox regression analysis showed that the clinical endpoints were significantly associated with right atrial pressure, total lymphocyte count, serum albumin, total cholesterol, serum creatinine, serum ferritin, BNP, GNRI, PNI, and CONUT score. As shown in Table 5, GNRI, PNI, and CONUT score were also significantly associated with clinical endpoint incidence in the multivariate Cox regression analysis.

Association between the nutritional indices and hemodynamic parameters

Table 6 shows Spearman's rank correlation among the nutritional indices and hemodynamic parameters, including right heart catheterization findings. The

TABLE 3 Laboratory data findings and nutritional induces at baseline.

Variables	All patients ($n = 80$)	Nonsurvivors ($n = 27$)	Survivors ($n = 53$)	p Value
Laboratory data				
White blood cell count ($10^3/\mu L$)	6.7 ± 2.6	7.1 ± 2.9	6.4 ± 2.5	0.310
Total lymphocyte count ($10^3/\mu L$)	1.5 (1.0–2.2)	1.4 (0.8–2.1)	1.6 (1.0–2.2)	0.395
Hemoglobin (g/dL)	13.7 ± 2.9	13.6 ± 3.1	13.8 ± 2.8	0.769
Platelet count ($10^9/L$)	198.6 ± 102.4	202.5 ± 123.0	196.6 ± 91.3	0.808
Serum albumin (g/dL)	3.8 ± 0.7	3.5 ± 0.7	4.0 ± 0.6	0.002
Total bilirubin (g/dL)	0.9 (0.6–1.3)	1.0 (0.6–1.6)	0.8 (0.6–1.3)	0.631
Total cholesterol (mg/dL)	167.9 ± 42.8	154.3 ± 44.4	174.9 ± 40.7	0.041
Serum creatinine (mg/dL)	0.7 (0.6–0.9)	0.8 (0.7–1.0)	0.7 (0.6–0.8)	0.044
Serum iron (μg/dL)	70.0 ± 41.2	64.5 ± 48.4	72.7 ± 37.5	0.437
Transferrin saturation (%)	19 (11.5–27.5)	16 (11–27)	19 (12–28)	0.555
Serum ferritin (μL/L)	67.3 (23.6–139.1)	68.2 (20.3–127.7)	66.3 (32.8–182.5)	0.527
BNP (pg/mL)	119.0 (32.5–323.2)	257.3 (63.7–472.0)	78.6 (23.7–214.8)	0.008
Nutritional index				
GNRI	99.9 ± 12.0	94.9 ± 10.6	102.4 ± 12.0	0.007
PNI	46.3 ± 10.0	42.9 ± 11.0	48.1 ± 9.0	0.027
CONUT score	2 (1–4)	3 (1.5–6)	2 (1–3)	0.023

Note: Data are presented as the number (%), mean ± standard deviation, or median (25th–75th percentile).

Abbreviations: BNP, brain natriuretic peptide; CONUT, Controlling Nutritional Status; GNRI, Geriatric Nutritional Risk Index; PNI, Prognostic Nutritional Index.

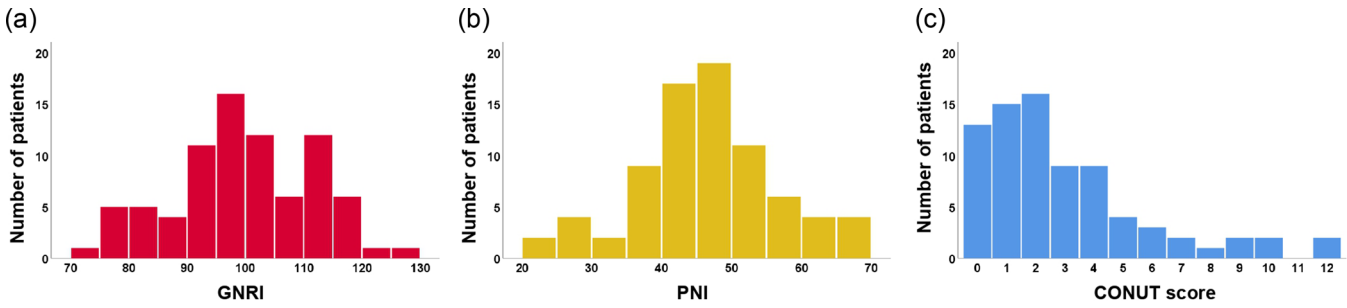

FIGURE 2 Distribution of geriatric nutritional risk indices. (a) Geriatric Nutritional Risk Index (GNRI); (b) Prognostic Nutritional Index (PNI); (c) Controlling Nutritional Status (CONUT) score.

6-min walking distance was significantly correlated with GNRI ($r = 0.350$, $p = 0.034$), but not PNI or CONUT score ($p = 0.208$ and $p = 0.098$, respectively). The mPAP and PVR were significantly and positively correlated with PNI ($p < 0.001$ and $p = 0.002$, respectively) and reversely CONUT score ($p = 0.004$ and $p = 0.029$, respectively). Right atrial pressure, cardiac index, and BNP were not significantly correlated with any of the three nutritional indices.

DISCUSSION

This study investigated the relationship between nutritional indices (GNRI, PNI, and CONUT score) and the composite outcomes of all-cause death or lung transplantation in patients with PAH. Poor index values were significantly associated with increased incidence of the clinical endpoints, independent of confounding factors, including the mPAP and cardiac indices. Lower PNI and higher CONUT

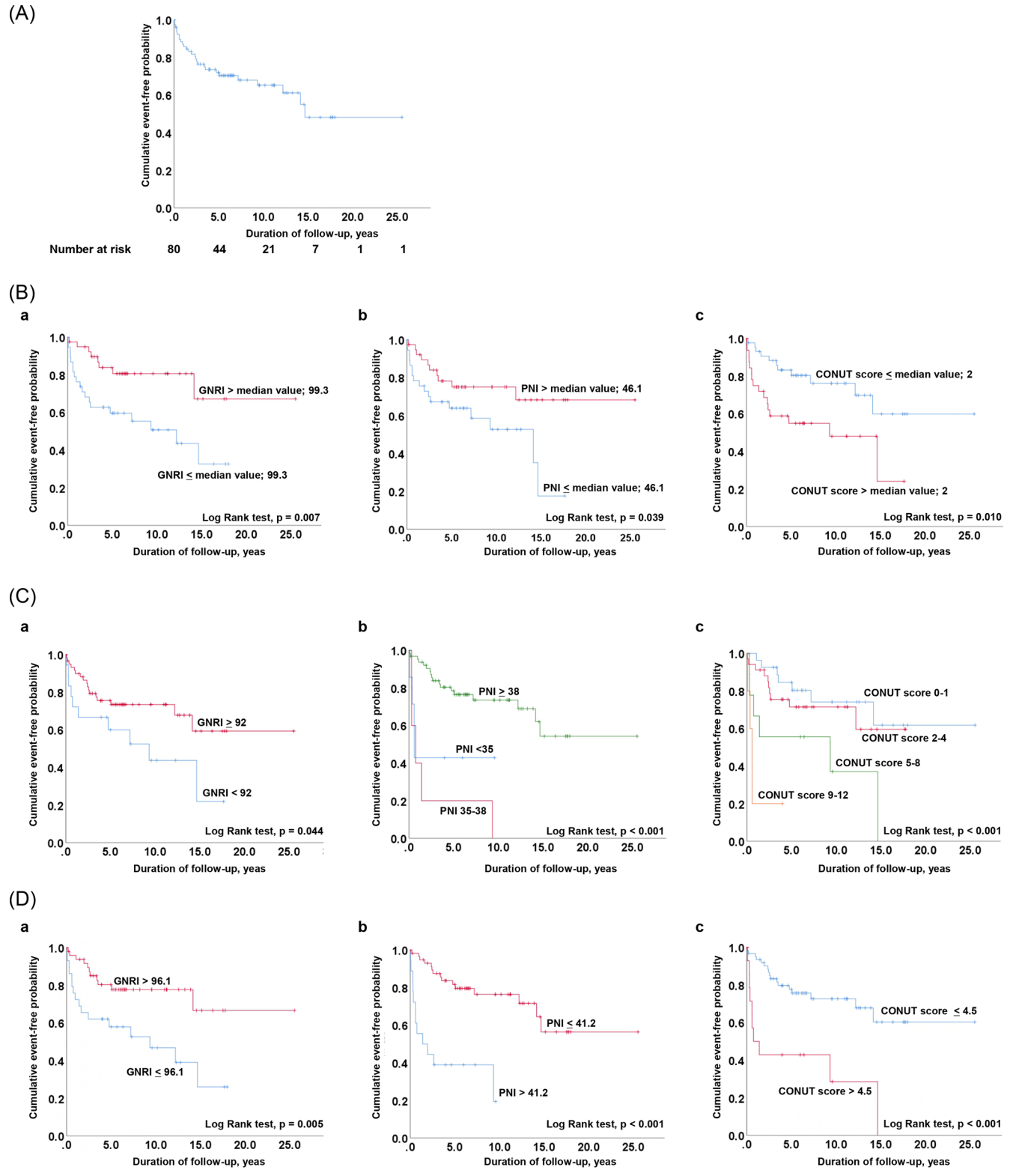

FIGURE 3 Kaplan–Meier analysis of the event-free rate of all-cause death or lung transplantation. (A) Survival rate of the entire cohort of patients. The median follow-up period from diagnosis was 5.5 years (2.4–10.6), with 1-, 5-, 10- and 15-year survival rates of 87.1%, 72.0%, 65.3%, and 48.2%, respectively. (B) Survival rates of patients stratified by the median value of each nutritional index: (a) Geriatric Nutritional Risk Index (GNRI), 99.3; (b) Prognostic Nutritional Index (PNI), 46.1; (c) Controlling Nutritional Status (CONUT) score, 2. (C) Survival rates of patients stratified by the established cut-off of each nutritional index: (a) GNRI; (b) PNI; (c) CONUT score. (D) Survival rates of patients stratified by the optimal cut-off of each nutritional index: (a) GNRI, 96.1; (b) PNI, 41.2; (c) CONUT score, 4.5.

TABLE 4 Univariate Cox regression analysis for all-cause death or lung transplantation.

Variable	Hazard ratio	95% confidence interval	*p* Value
Age, per year	1.019	0.996–1.042	0.100
Male	2.377	1.111–5.087	0.026
Associated with PoPH	2.338	0.799–6.842	0.121
WHO-FC	1.671	0.943–2.958	0.078
Right atrial pressure[a] (mmHg)	2.274	1.243–4.157	0.008
mPAP, per mmHg	0.990	0.968–1.013	0.399
Cardiac index[a] (per point)	0.561	0.166–1.902	0.354
PVR[a] (per point)	1.083	0.719–1.630	0.704
White blood cell count (per $10^3/\mu L$)	1.045	0.893–1.222	0.586
Total lymphocyte count[a] (per point)	0.465	0.225–0.961	0.039
Hemoglobin (per g/dL)	0.948	0.824–1.090	0.454
Platelet count (per $10^9/L$)	0.999	0.995–1.003	0.683
Serum albumin (per g/dL)	0.368	0.216–0.627	<0.001
Total bilirubin[a] (per point)	1.418	0.791–2.541	0.241
Total cholesterol (per mg/dL)	0.984	0.974–0.995	0.004
Serum creatinine[a] (per point)	1.952	1.166–3.268	0.011
Serum iron (per μg/dL)	0.996	0.984–1.007	0.462
Transferrin saturation[a] (per point)	0.781	0.428–1.425	0.420
Serum ferritin[a] (per point)	1.476	1.032–2.111	0.033
BNP[a] (per point)	1.543	1.119–2.128	0.008
GNRI (per point)	0.958	0.927–0.989	0.008
PNI (per point)	0.930	0.890–0.972	<0.001
CONUT score (per point)	1.285	1.138–1.451	<0.001

Abbreviations: 6MWD, 6-min walking distance; BNP, brain natriuretic peptide; CHD, congenital heart disease; CONUT, Controlling Nutritional Status; CTD, connective tissue disease; ERA, endothelin receptor antagonist; GNRI, Geriatric Nutritional Risk Index; i.v., intravenous; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; PNI, Prognostic Nutritional Index; PoPH, porto-pulmonary hypertension; PVR, pulmonary vascular resistance; sGC, soluble guanylate cyclase; WHO-FC, World Health Organization functional class.

[a]Values are logarithm-transformed.

score were significantly correlated with lower mPAP and PVR. To our knowledge, this is the first study to evaluate whether nutritional indices reflect prognosis in patients with PAH, independently of hemodynamic status.

Nutritional status and prognostic impact of heart failure

Nutritional status has recently been regarded as important in patients with heart failure, with malnutrition worsening their prognosis.[4] Malnutrition leads to loss of weight and muscle mass, which worsens the prognosis of patients with PAH.[4,28,29] Heart failure's association with malnutrition is due to bacterial translocation, malabsorption, and loss of appetite and correlates with neurohormonal and immune abnormalities.[13,30] GNRI, PNI, and CONUT score are used as practical assessments of nutritional status and are associated with prognosis in heart failure.[6–12] PAH is a major cause of right-sided heart failure, but there is limited research on the role malnutrition plays in this condition.[1,5] This study showed the significant association between malnutrition assessed by GNRI, PNI, and CONUT score and worse outcomes among patients with PAH, suggesting these nutritional indices are useful predictive tools.

TABLE 5 Multivariate Cox regression analysis of nutritional indues for all-cause death or lung transplantation.

Variable	Hazard ratio	95% confidence interval	*p* Value
Model 1[a]			
GNRI, per point	0.947	0.913–0.982	0.003
PNI, per point	0.942	0.894–0.993	0.026
CONUT score, per point	1.224	1.055–1.420	0.008
Model 2[b]			
GNRI, per point	0.956	0.924-0.990	0.011
PNI, per point	0.932	0.890–0.977	0.003
CONUT score, per point	1.275	1.127–1.443	<0.001
Model 3[c]			
GNRI, per point	0.957	0.926–0.989	0.009
PNI, per point	0.928	0.886–0.972	0.002
CONUT score, per point	1.326	1.161–1.516	<0.001
Model 4[d]			
GNRI, per point	0.946	0.914–0.979	0.001
PNI, per point	0.941	0.898–0.987	0.012
CONUT score, per point	1.280	1.115–1.469	0.001
Model 5[e]			
GNRI, per point	0.957	0.923–0.992	0.017
PNI, per point	0.905	0.855–0.959	0.001
CONUT score, per point	1.455	1.217–1.739	<0.001
Model 6[f]			
GNRI, per point	0.956	0.924–0.988	0.008
PNI, per point	0.933	0.892–0.975	0.002
CONUT score, per point	1.278	1.124–1.452	<0.001

Abbreviations: BNP, brain natriuretic peptide; CONUT, Controlling Nutritional Status; GNRI, Geriatric Nutritional Risk Index; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PoPH, porto-pulmonary hypertension; PNI, Prognostic Nutritional Index; WHO-FC, World Health Organization functional class.

*Values are logarithm-transformed.

[a]Adjusted for gender, right atrial pressure*, serum creatinine*, serum ferritin* and BNP*.

[b]Adjusted for age and gender.

[c]Adjusted for WHO-fc.

[d]Adjusted for right atrial pressure*, mPAP and cardiac index*.

[e]Adjusted for hemoglobin and platelet count.

[f]Adjusted for total bilirubin* and whether the etiology of PAH associated with PoPH or not.

Nutritional indices as prediction markers of prognosis in patients with PAH

According to current guidelines, natrium peptides are recommended as a prognostic marker for risk assessment of patients with PAH.[1] Despite not currently being included in the guidelines, some previous reports describe the relationship between nutritional status and prognosis of patients with PAH. Whereas the relationship between nutritional status and left-sided heart failure has been previously described,[4,5,13–15] the role of nutritional status in right-sided heart failure or PAH has not been fully elucidated. However, bowel edema and hypoperfusion may lead to malabsorption and a less diverse microbiome of the gut in patients with PAH.[31–33] Indeed, animal experiments have reported that rat

TABLE 6 Correlation analyses between nutritional indues and hemodynamic parameters.

	GNRI		PNI		CONUT score	
Variable	***r***	***p* value**	***r***	***p* value**	***r***	***p* value**
WHO-FC	−0.175	0.121	−0.174	0.127	0.134	0.242
6MWD	0.350	0.034	0.212	0.208	−0.276	0.098
Right atrial pressure	0.167	0.145	−0.035	0.761	−0.198	0.084
mPAP	0.078	0.492	0.446	<0.001	−0.327	0.004
Cardiac index	−0.172	0.132	−0.099	0.393	0.142	0.220
PVR	0.081	0.483	0.345	0.002	−0.253	0.029
BNP	−0.140	0.227	−0.223	0.056	0.205	0.079

Abbreviations: 6MWD, 6-min walking distance; BNP, brain natriuretic peptide; CONUT, Controlling Nutritional Status; GNRI, Geriatric Nutritional Risk Index; mPAP, mean pulmonary arterial pressure; PNI, Prognostic Nutritional Index; PVR, pulmonary vascular resistance; WHO-FC, World Health Organization functional class.

models with PAH showed gut microbiota dysbiosis.[34,35] Similarly, patients with PAH were also reported to have intestinal microbiota imbalances.[36–38] In addition, patients with PAH are known to suffer from iron and vitamin D deficiency. Previous reports indicate that supplementation might improve outcomes, suggesting the evaluation and treatment of malnutrition is similarly important in patients with PAH and those with heart failure.[39–41] This study evaluated three nutritional indices reportedly associated with heart failure prognosis.[9–12] Of these, GNRI was calculated using serum albumin and BMI.[6] In previous studies, serum albumin and GNRI were reported to be associated with prognosis in patients with PAH.[16,17] However, serum albumin may be influenced by various clinical conditions, such as inflammation or albuminuria, and the significance of BMI in patients with PAH is controversial.[19–24] Thus, it is unclear whether serum albumin and GNRI always accurately reflect nutritional status, especially for patients with PAH who have various pathological backgrounds. In contrast, the calculation formulas of PNI and CONUT score include total lymphocyte count, which reflects fat and the immune system.[7,8] Total lymphocyte count has been used as an indicator of immune defences; it is also recognized as an index of nutritional status, because malnutrition leads to impaired immune function.[42,43] Moreover, the CONUT score includes factors of the lipid metabolic system and total cholesterol in its calculation. Despite a high total cholesterol level being widely recognized as an important risk factor for the development of atherosclerosis, it has been reported that a low total cholesterol level is associated with worse prognosis in patients with heart failure, reflecting malnutritional status due to caloric depletion, dietary intake, or lower anabolic status.[44–49] In addition, the pathology of heart failure is considered to be associated with increased endotoxin and inflammatory cytokines caused by bowel-wall edema and altered gut permeability for bacteria and endotoxins.[50] The circulating cholesterol is also presumed to bind and detoxify bacterial endotoxins.[51] Therefore, serum total cholesterol may have a favorable effect in patients with heart failure, and lower total cholesterol levels may relate to worse prognoses in these patients, reflecting impaired nutritional and inflammatory conditions. Total cholesterol level was also reported to be lower in patients with pulmonary hypertension than in those without pulmonary hypertension, and lower total cholesterol was associated with worse prognosis in patients with PAH.[52–54] Although the pathological relationship between total cholesterol and PAH has not been fully clarified, lower total cholesterol levels may be associated with worse prognosis in patients with PAH, reflecting worse conditions of malnutrition and inflammation; this is similar to that observed in patients with heart failure. These findings may indicate that elevated total cholesterol levels, which contribute to lower and better CONUT score values, relate to a better prognosis in patients with PAH. In the present study, all three indices showed significant association with prognosis in patients with PAH. These findings strengthen the evidence of a relationship between nutritional status, including fat and immune conditions, and prognosis in patients with PAH.

In addition, some previous studies reported that delayed initiation of treatment for PAH was associated with worse prognosis.[55,56] If malnutrition was caused by bacterial translocation, malabsorption, and loss of appetite due to right-sided heart failure, the worse nutritional indices demonstrated in this study might reflect delayed diagnosis of PAH and prolonged right-sided heart failure before initial treatment. Patients with worse nutritional indices may have worse multiorgan dysfunction secondary

to this. Evaluation of nutritional status may be a useful marker for the presence of systematic conditions in patients with PAH.

If the nutritional status assessments truly reflect the prognosis in patients with PAH, they may be useful for determining appropriate management for PAH. The specifical medication therapies for PAH may cause gastrointestinal symptoms. Prostacyclin analogs, prostacyclin receptor agonists, and riociguat have side effects of diarrhea and nausea.[57–59] Phosphodiesterase type 5 inhibitors were also reportedly related to dyspepsia.[60] In addition, bosentan, one of the endothelin receptor antagonists, has a high prevalence of liver disorder as a side effect.[61] These side effects may worsen the nutritional status of patients with PAH, suggesting that careful management and follow-up after these PAH treatments are needed, especially in patients with PAH who have poor nutritional status before treatment. Not only PAH targeting therapy but also other drugs, such as diuretics, that may be prescribed to patients with PAH reportedly cause taste or smell disorders.[62,63] These disorders can lead to worsening of a patient's nutritional status.[62] Moreover, polypharmacy, which refers to multidrug treatment, itself may cause taste disorders and malnutrition.[64,65] Long-term intake of multiple drugs can also cause impairment of the digestive tract, increased drug interactions, and increased undesirable side effects.[64] These conditions can lead to worsening of the nutritional status. Most drugs must be used according to the treatment necessities. However, these undesirable effects after polypharmacy treatment may be more critical for patients with PAH who already have an impaired nutritional status before treatment. Thus, it may be necessary to carefully select medications and avoid polypharmacy as much as possible in these patients. Further studies are needed to investigate these aspects for the management of PAH in patients with malnutrition.

This study had several limitations. First, it was a single-center, retrospective study and had a relatively small sample size; a muticenter prospective study with a lager sample size is required. Second, data regarding dietary intake was absent due to the retrospective study design. Although dietary intake is an important factor related to malnutrition, other factors such as bacterial translocation or malabsorption also affect nutritional status.[13,30] Thus, among patients with PAH, malnutrition can progress, even if patients had preserved dietary intake. Therefore, it may be reasonable to assess nutritional status using nutritional indices instead of actual energy intake. Further studies are needed to clarify the clinical impacts of dietary intake for nutritional status and prognosis in patients with PAH. Third, the nutritional indices were evaluated at diagnosis, and changes in nutritional status during the follow-up period remain unclear; for example, cachexia in patients with heart failure is reported to improve after some heart failure treatments. Although it is unknown whether specific therapies for PAH similarly improve nutritional status, the nutritional indices might change after diagnosis and treatment, impacting clinical courses.[30,66,67] Finally, the definition of pulmonary hypertension was based on mean pulmonary artery pressure ≥25 mmHg[25] in this study, because the patients were diagnosed before the latest definition of pulmonary hypertension in the European Society of Cardiology heart failure guidelines was changed in 2022.[1] In the 2022 European Society of Cardiology pulmonary hypertension guidelines, the definition of pulmonary hypertension was defined as mean pulmonary artery pressure >20 mmHg.[1] Therefore, patients whose pulmonary artery pressure was 21–24 mmHg were not included in this study. The effect of nutritional status and prognosis in patients with PAH might thus not have been accurately estimated.

In conclusion, poor nutritional index scores (GNRI, PNI, and CONUT) were significantly associated with poorer prognoses in patients with PAH. In the clinical setting, the evaluation of malnutrition at PAH diagnosis may be important for assessing the risk of future adverse events.

AUTHOR CONTRIBUTIONS

Mitsutaka Nakashima contributed to the conception of the work, acquisition, analysis, and interpretation of the data, and drafting of the paper. Satoshi Akagi contributed to interpretation of data and revised the article critically for important intellectual content. Kentaro Ejiri contributed to the acquisition of data. Kazufumi Nakamura and Hiroshi Ito helped revise the article critically for important intellectual content. All authors read and approved the final version to be submitted.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The de-identified participant data will be shared upon reasonable request directly to the corresponding author. Data on patient and procedural characteristics and long-term outcomes will be shared, and the study protocol will be available. The data will be available for 2 years after publication of the manuscript. It will be shared through PDF files sent by e-mail.

ETHICS STATEMENT

This investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the institutional review boards of Okayama University Graduate School of Medicine (2210-037).

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