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Association of nutritional status and mortality risk in patients with primary pulmonary hypertension

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Abstract

Malnutrition plays a crucial role in pulmonary hypertension (PH). The prognostic nutritional index (PNI) is a reliable indicator for nutritional status assessment. However, its relationship with mortality risk in PH patients has not yet been investigated. This study analyzed data from the Patient Registry for Primary PH. PNI was calculated through albumin and lymphocyte counts. Subjects with missing data for PNI calculation were excluded. The primary endpoint was all-cause mortality. Cox proportional hazard model was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). Of the 317 patients records available in the registry, we finally included 136 patients. The average age of the included subjects was 40.56 (14.91) years and 63.24% (86/136) were female. In our analysis of Cox regression, per 1-point increment of PNI was associated with 4% decreased risk of mortality in PH patients (age- and sex-adjusted HR: 0.96, 95% CI: 0.93–0.98, $p = 0.002$). We further categorized these subjects by quartiles of PNI. Compared to quartile 4, the age- and sex-adjusted HRs of death for quartiles 1, 2, and 3 were 2.39 (95% CI: 1.21–4.72, $p = 0.01$), 2.25 (95% CI: 1.15–4.39, $p = 0.02$), and 1.72 (95% CI: 0.84–3.52, $p = 0.14$). In addition, logistic regression analyses suggested a positive correlation of PNI with total lung capacity ($\beta = 0.98$, $p = 0.002$) and forced expiratory volume in 1 min ($\beta = 1.53$, $p = 0.03$). This study demonstrates that low PNI was associated with an increased risk of death in PH patients. These findings help to enlighten our understanding of the nutritional status and adverse outcomes in PH patients.

KEYWORDS
malnutrition, mortality, prognostic nutritional index, pulmonary function, pulmonary hypertension

INTRODUCTION

Malnutrition has been demonstrated as a predictor for inferior clinical outcomes in a variety of chronic diseases[1–3] and commonly affects patients with pulmonary hypertension (PH).[4–6] However, few studies have examined the effect of nutritional status on mortality risk in PH patients.[7–9]

As suggested by the global leadership initiative on malnutrition (GLIM), the diagnosis of malnutrition is suggested to include at least one phenotypic (e.g., non-volitional weight loss or reduced protein reserve) and one etiologic criterion (e.g., decreased consumption or chronic inflammation).[10] Serum albumin is a commonly used marker for poor nutrition.[11,12] A decreased concentration mainly results from insufficient food supply, hypercatabolic degradation, or increased loss from kidneys or intestines.[11,12] It has been reported as a significant predictor for reduced survival in patients with heart failure (HF) or PH.[8,13] Total lymphocyte count (TLC), a simple measure of immunologic status, is often reduced with malnutrition.[14,15] Low TLC not only represents the impaired immune response but also portends an increased risk of death in hip fracture patients.[16–18]

Thus, investigators tried to incorporate TLC and serum albumin as one indicator for nutritional assessment. Prognostic nutritional index (PNI), calculated from serum albumin and TLC, was first proposed in the 1980s and reflects both the inflammatory and catabolic status of patients.[19,20] It was initially developed to predict the risk of postoperative morbidity and mortality[19–21] and has been currently validated as a mortality predictor in various human diseases.[22–27]

However, its relationship with mortality risk in PH patients has not yet been reported. To explore the association between nutritional status, as indexed by PNI, and mortality risk in PH patients, we here used data from the Patient Registry for Primary Pulmonary Hypertension (PPH Registry), although PPH is outdated and currently known as idiopathic pulmonary arterial hypertension (IPAH).

SUBJECTS AND METHODS

We used a deidentified public PPH data set that was released at https://biolincc.nhlbi.nih.gov/studies/pphreg. The PPH Registry is one of the first large registries of PPH, which was established by the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) in 1981. The initial aim was to characterize the clinical determinants of PH and advance our understanding of the natural history of this deadly disease. The methodology and study design have been previously published.[28] Briefly, patients were enrolled from 32 medical centers throughout the United States. The diagnosis of PH was documented as a pulmonary artery pressure >25 mmHg at rest or 30 mmHg with exercise, and a resting pulmonary arterial wedge pressure or left atrial pressure not >12 mmHg in hemodynamic

measurements. Any congenital or secondary causes for PH were excluded, including congenital abnormalities of the heart and lungs, thorax and diaphragm, pulmonary thromboembolic disease, pulmonary airways disease, interstitial lung disease, hypoxic pulmonary hypertension associated with impaired ventilation, collagen vascular disease, parasitic disease, pulmonary venous hypertension, and multiple pulmonary artery thrombosis (secondary to sickle cell disease).[28] However, hepatic cirrhosis, collagen vascular disease, Raynaud's disease, and PH related to diet or drug were not excluded but reported as an "associated" condition. The study was approved by the institutional review boards (IRBs) from all centers. Written informed consent was obtained from all participants. In our study, nutritional status was assessed through PNI, which was computed from the formula of $10 \times$ albumin (g/dl) $+ 0.005 \times$ TLC (per mm^3).[20] Patients with insufficient data for PNI calculation were excluded.

Data assessment and outcome ascertainment

Patients' demographics (age, sex, race, smoking status), basic biochemistry (including routine blood tests, albumin), axillary examinations like pulmonary function test, and cardiac catheterization data were collected or measured at baseline. Height and body weight were measured in light clothing; body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). Routine blood tests and albumin were measured by a standardized protocol. Information on systolic blood pressure (SBP), diastolic blood pressure (DBP), pulmonary artery systolic pressure (sPAP), pulmonary artery diastolic pressure (dPAP), mean pulmonary artery pressure (mPAP), pulmonary artery wedge pressure (PAWP), mean right atrial pressure (RA), and cardiac output (CO) were obtained from the cardiac catheterization. Spirometry was performed with standardized equipment. Forced expiratory volume in 1 min (FEV1) was assessed as the volume of gas exchange in the first second of expiration. Forced vital capacity (FVC) was assessed as the volume of gas forcefully exhaled after maximal inspiratory effort.

The main outcome of this study was all-cause mortality. Patients were followed for 5 years and time to death was reported within 5 years of enrollment. For each death that occurred among registry patients, a cause-of-death form was completed by the investigator at the participating center. The reporting form presents a detailed description of death, including the date of death, cause of death, and whether an autopsy was performed.

Statistical analysis

Continuous variables were described with means (standard deviation) and categorical data were presented as numbers (percentages). χ^2 test or Student t test was used to assess differences between two groups while analysis of variance (ANOVA) was applied for comparing multiple groups. Cox proportional hazards regression was conducted to examine the associations between PNI and mortality risk. The proportional hazards assumption was examined by graphically plotting the image of (log-probability vs. log-survival time). PNI was modeled as both a continuous and categorical variable. We categorized the patients by quartiles of PNI, taking the highest quartile as the reference. In addition, we performed a sensitivity analysis by grouping subjects based on criteria used in HF studies. More specifically, a PNI score >38 represented as normal, while scores of 35–38 and <35 were considered as moderate or severe malnutrition.[24–26] Or, subjects were divided into normal versus malnutrition status by the cutoff value of 44.8.[23] To eliminate potential confounders, two adjusted models were applied and the results were reported as hazard ratios (HRs) and 95% confidence interval (95% CI). To reduce the impact of coexisting conditions (hepatic cirrhosis, collagen vascular disease, Raynaud's disease, and PH related to diet or drug) on the association, we repeated the Cox regression analysis after excluding these subjects ($n = 24$).

Additionally, other predictors for increased mortality were also analyzed. To better delineate the prognostic value of PNI, we conducted the receiver operating characteristic curves (ROC) analysis and compared the area under the curve (AUC) with a model involving PNI, albumin, TLC, or BMI. Furthermore, logistic regression analysis was performed to explore the correlated factors for PNI. All statistical analysis was performed using Stata 15.1 (StataCorp/SE). All p values were two-sided, and the significance level was set at 0.05.

IRB statement

This study was reviewed and approved by the Research Ethics Committee of Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences (approval number: No. GDREC2020228H).

RESULTS

Patient characteristics

Of the 317 patients records available in the NIH-PPH database, we finally included 136 patients in this study. One hundred eighty-one patients with missing data for albumin or TLC were excluded. The majority of the baseline characteristics were identical between the included and excluded patients (Table S1), except for older age in the included subjects (40.56 ± 14.91 vs. 36.57 ± 16.54 years, $p = 0.03$). Following up to the end of the study, 73 of the 136 (53.68%) subjects died in the included group while 84 of the 181 (46.41%) died in the excluded one.

Within the included patients, 63.24% (86/136) of them were female. The average BMI was 24.27 (5.27) kg/m^2, while the mean value of albumin was 3.71 (0.72) g/dl. As presented in Table 1, most of the demographic characteristics and hemodynamic data were similar across the PNI quartiles. The levels of hemoglobin, TLC, albumin, total lung capacity, FVC, and FEV1 were significantly higher in patients within higher PNI quartiles. Notably, 8% (11/136) of the included subjects were reported as associating with "hepatic cirrhosis," 6% (8/136) with "collagen diseases," and 4% (6/136) with "PH possibly related to the drug."

As shown, the distribution of New York Heart Association (NYHA) functional Class III/IV did not significantly differ across the PNI quartiles. When comparing PNI levels within each functional class (Figure 1), no significant trends were observed. The average levels of PNI for NYHA functional Class 1, 2, 3, and 4 were 63.28 (0), 46.30 (8.89), 47.68 (9.75), and 46.42 (7.86), respectively ($p = 0.29$).

PNI and mortality risk

In our analysis of Cox regression, per 1-point increment of PNI was associated with a 4% decreased risk of mortality in PH patients (age- and sex-adjusted HR: 0.96, 95% CI: 0.93–0.98, $p = 0.002$). Further adjustment of NYHA functional class, heart rate, mean right atrial pressure, mean pulmonary arterial pressure, and cardiac output strengthened this association (HR: 0.95, 95% CI: 0.92–0.99, $p = 0.005$). When categorizing patients by quartiles of PNI, a graded negative association was observed, with the higher cumulative hazard risk occurring in patients within the lowest quartile (Figure 2). Compared to quartile 4, the age- and sex-adjusted HRs of death for quartiles 1, 2, and 3 were 2.39 (95% CI: 1.21–4.72, $p = 0.01$), 2.25 (95% CI: 1.15–4.39, $p = 0.02$), and 1.72 (95% CI: 0.84–3.52, $p = 0.14$), respectively (Table 2). The results remained significant and the association was even stronger when excluding subjects with coexisting conditions (Table S2).

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TABLE 1 Baseline characteristics of the included patients by PNI quartiles

	Observation	Total	Quartile 1 ($n = 34$)	Quartile 2 ($n = 34$)	Quartile 3 ($n = 34$)	Quartile 4 ($n = 34$)	p value
Age (years)	136	40.56 (14.91)	42.03 (15.99)	40.24 (15.74)	42.24 (15.00)	37.74 (12.96)	0.58
Sex, female(%)	136	86 (63.24%)	25 (73.53%)	21 (61.76%)	20 (58.82%)	20 (58.82%)	0.54
Smoking	136	21 (15.44%)	6 (17.65%)	3 (8.82%)	6 (17.65%)	6 (17.65%)	0.68
Race	136						0.09
White		96 (70.59%)	23 (67.65%)	19 (55.88%)	26 (76.47%)	28 (82.35%)	
Nonwhite		40 (29.41%)	11 (32.35%)	15 (44.12%)	8 (23.53%)	6 (17.65%)	
Body mass index (kg/m^2)	69	24.27 (5.27)	23.40 (3.62)	26.50 (7.38)	22.27 (3.67)	25.96 (5.41)	0.05
Systolic blood pressure (mmHg)	128	121.7 (19.35)	124.24 (23.03)	123.03 (17.86)	117.41 (17.53)	121.67 (18.49)	0.55
Diastolic blood pressure (mmHg)	125	76.09 (12.73)	74.45 (13.37)	78.34 (12.81)	73.79 (11.60)	77.45 (13.03)	0.42
Heart rate (beats/min)	114	84.29 (17.44)	88.97 (17.56)	83.47 (16.86)	77.52 (19.63)	85.93 (14.38)	0.09
NYHA Class, III/IV	136	102 (75.00%)	27 (79.41%)	23 (67.65%)	25 (73.53%)	27 (79.41%)	0.63
Vasodilators	136	96 (70.59%)	27 (79.41%)	26 (76.47%)	25 (73.53%)	18 (52.94%)	0.07
Lab test							
Hemoglobin (g/dl)	136	15.08 (2.19)	13.95 (2.07)	15.06 (2.12)	15.26 (2.00)	16.05 (2.11)	<0.001
Total lymphocyte count (×10^3 mm^3)	136	2.02 (1.10)	1.09 (0.88)	1.75 (0.81)	2.31 (0.78)	2.93 (1.01)	<0.001
Platelet (×10^3 mm^3)	117	207.4 (79.98)	184.81 (95.22)	228.03 (83.38)	205.88 (64.96)	207.18 (71.17)	0.23
Albumin (g/dl)	136	3.71 (0.72)	2.99 (0.76)	3.61 (0.42)	3.92 (0.39)	4.32 (0.49)	<0.001
Prognostic nutritional index	136	47.20 (9.21)	35.29 (7.04)	44.89 (1.75)	50.75 (1.99)	57.87 (2.93)	<0.001
Lung function							
Total lung capacity (L)	113	5.07 (1.48)	4.54 (1.26)	4.76 (1.35)	5.45 (1.57)	5.40 (1.53)	0.05
Forced vital capacity (L)	124	3.36 (1.18)	2.96 (1.00)	3.16 (1.23)	3.77 (1.23)	3.50 (1.12)	0.04
Forced expiratory volume in 1 min (L)	125	2.59 (0.86)	2.20 (0.72)	2.48 (0.82)	2.87 (0.89)	2.75 (0.88)	0.01
Diffusion capacity for carbon monoxide	112	16.77 (7.41)	14.88 (8.16)	16.61 (6.85)	15.63 (6.81)	19.52 (7.30)	0.08
Hemodynamic parameters							
Mean right atrial pressure (mmHg)	127	9.28 (5.47)	9.41 (5.20)	9.50 (5.59)	8.77 (6.48)	9.39 (4.78)	0.95
Pulmonary artery wedge pressure (mmHg)	113	9.14 (5.44)	8.35 (5.15)	9.80 (5.58)	10.26 (6.80)	8.41 (4.31)	0.47
	135	89.59 (23.07)	85.94 (21.98)	90.79 (21.37)	92.48 (19.48)	89.21 (28.82)	0.69

TABLE 1 (Continued)

	Observation	Total	Quartile 1 (n = 34)	Quartile 2 (n = 34)	Quartile 3 (n = 34)	Quartile 4 (n = 34)	p value
Pulmonary artery systolic pressure (mmHg)							
Pulmonary artery diastolic pressure (mmHg)	135	41.13 (15.02)	37.62 (11.99)	40.85 (13.18)	41.36 (14.65)	44.71 (19.09)	0.29
Mean pulmonary artery pressure (mmHg)	130	58.2 (17.22)	52.88 (14.75)	58.82 (14.36)	60.23 (15.93)	60.82 (22.23)	0.23
Cardiac output (L/min)	118	3.83 (1.49)	3.95 (1.62)	4.02 (1.61)	3.59 (1.13)	3.74 (1.53)	0.71

Note: Data are presented as no. (%) or mean (SD).

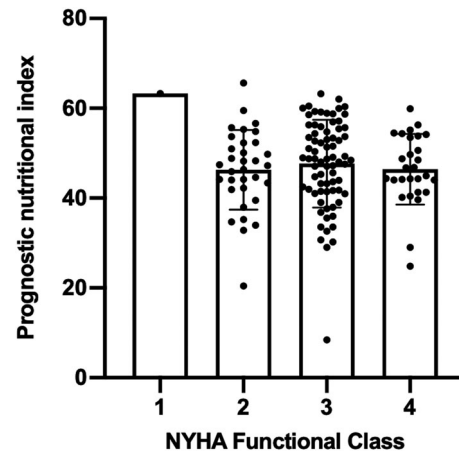Abbreviation: NYHA, New York Heart Association.

FIGURE 1 The distribution of prognostic nutritional index (PNI) across the New York Heart Association (NYHA) functional class
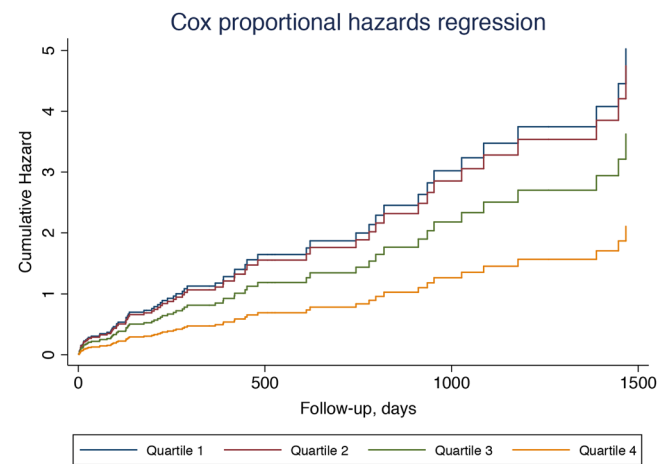

FIGURE 2 The cumulative hazard plots of quartiles of the prognostic nutritional index (PNI) and mortality risk in patients with primary pulmonary hypertension. Patients in lower PNI quartiles had a higher cumulative hazard risk for death

When grouped as normal versus malnutrition, malnutrition patients had 80% (age- and sex-adjusted HR: 1.80, 95% CI: 1.09–2.98, $p = 0.02$) to 104% (age- and sex-adjusted HR: 2.04, 95% CI: 0.95–4.36, $p = 0.07$) higher risk of death than those in normal status. The magnitude of the increased risks depended on which grouping criteria were selected (Table S3).

We further analyzed other predictors for increased mortality. As presented in Table 2, high NYHA functional class and heart rate, low TLC and cardiac output, the elevation of mean right atrial pressure, and mean pulmonary arterial pressure, were found to be related to increased risk of death in age- and sex-adjusted model. However, when further examined in the multivariable

TABLE 2 Cox regression analyses of mortality with potential predictors

Variables	Model 1		Model 2	
	HR (95% CI)	*p* value	HR (95%)	*p* value
Prognostic nutritional index, per 1-point	0.96 (0.93, 0.98)	0.002	0.95 (0.92, 0.99)	0.005
Prognostic nutritional index, categorical				
Quartile 1	2.39 (1.21, 4.72)	0.01	2.77 (1.18, 6.47)	0.02
Quartile 2	2.25 (1.15, 4.39)	0.02	3.97 (1.72, 9.17)	0.001
Quartile 3	1.72 (0.84, 3.52)	0.14	2.66 (0.96, 7.33)	0.06
Quartile 4	Reference	-	Reference	-
Race (White vs. non-White)	0.63 (0.36, 1.09)	0.10	-	-
Height (m)	1.38 (0.05, 40.35)	0.85	-	-
Weight (kg)	1.00 (0.98, 1.02)	0.94	-	-
Body mass index (kg/m^2)	1.06 (0.97, 1.17)	0.19	-	-
Systolic blood pressure (mmHg)	1.00 (0.98, 1.02)	0.96	-	-
Diastolic blood pressure (mmHg)	1.01 (0.98, 1.03)	0.59	-	-
NYHA functional class	1.60 (1.10, 2.34)	0.02	1.09 (0.61, 1.95)	0.76
Smoking status	0.63 (0.26, 1.53)	0.31	-	-
Heart rate (beat/min)	1.03 (1.01, 1.05)	0.006	1.01 (0.99, 1.04)	0.39
Hemoglobin (g/dl)	0.93 (0.82, 1.06)	0.27	-	-
Total lymphocyte count (×10^3/mm^3)	0.77 (0.62, 0.96)	0.02	-	-
Albumin (g/dl)	0.71 (0.50, 1.01)	0.06	-	-
Total lung capacity (L)	0.84 (0.67, 1.05)	0.12	-	-
Forced vital capacity (L)	0.75 (0.56, 1.01)	0.05	-	-
Forced expiratory volume in 1 min (L)	0.76 (0.54, 1.05)	0.10	-	-
Diffusion capacity for carbon monoxide	0.97 (0.93, 1.01)	0.13	-	-
Mean right atrial pressure (mmHg)	1.07 (1.02, 1.12)	0.008	1.12 (1.04, 1.21)	0.002
Pulmonary artery wedge pressure (mmHg)	1.06 (0.98, 1.14)	0.13	-	-
Mean pulmonary artery pressure (mmHg)	1.02 (1.01, 1.03)	0.004	1.02 (1.00, 1.04)	0.04
Cardiac output (L/min^2)	0.76 (0.58, 1.00)	0.05	1.06 (0.74, 1.52)	0.76

Note: Data were presented as hazard ratios (HR) and 95% confidence intervals (95% CI). Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, NYHA functional class, heart rate, mean right atrial pressure, mean pulmonary arterial pressure, and cardiac output.

Abbreviation: NYHA, New York Heart Association.

model, only mean right atrial pressure and mean pulmonary artery pressure remained significant.

ROC and correlation analysis of PNI

Based on the above factors and prior publications,[29,30] a baseline predictive model for morality was established, which included age, sex, NYHA functional class, mean pulmonary arterial pressure, mean right atrial pressure, and cardiac output. To delineate the predictive value of PNI, we compared the AUC for the baseline predictive model with models involving different nutritional indicators. As shown in Table S4, the AUC for the model involving PNI was increased in comparison to the baseline model (AUC = 0.8420 vs. 0.8333, *p* = 0.38), being the highest among all analyzed models.

The logistic regression analyses suggested a positive correlation of PNI with hemoglobin (β = .86, *p* = 0.002), total lung capacity (β = .98, *p* = 0.002), and FEV1 (β = 1.53, *p* = 0.03), while age, sex, BMI, blood pressure, NYHA functional class, and other hemodynamic parameters were not significantly correlated with PNI (Table 3).

TABLE 3 Correlation analysis of prognostic nutritional index

	Coefficient β (Std. Err.)	p value
Age (years)	0.02 (0.04)	0.58
Sex (female vs. male)	−2.22 (1.28)	0.09
Race (White vs. non-White)	0.28 (1.37)	0.84
Height (m)	1.04 (8.36)	0.90
Weight (kg)	0.03 (0.06)	0.66
BMI (kg/m^2)	0.06 (0.18)	0.73
Systolic blood pressure (mmHg)	−0.006 (0.03)	0.85
Diastolic blood pressure (mmHg)	0.03 (0.05)	0.61
NYHA class	−0.81 (1.44)	0.57
Smoking status	−0.35 (1.72)	0.84
Heart rate (beat/min)	−0.06 (0.04)	0.16
Hemoglobin (g/dl)	0.86 (0.28)	0.002
Total lung capacity (L)	0.98 (0.37)	0.009
Forced vital capacity (L)	0.86 (0.52)	0.10
Forced expiratory volume in 1 min (L)	1.53 (0.71)	0.03
Diffusion capacity for carbon monoxide	0.07 (0.09)	0.45
Mean right atrial pressure (mmHg)	−0.10 (0.12)	0.41
Pulmonary artery wedge pressure (mmHg)	0.07 (0.13)	0.57
Pulmonary artery systolic pressure (mmHg)	0.02 (0.03)	0.54
Pulmonary artery diastolic pressure (mmHg)	0.05 (0.04)	0.24
Mean pulmonary artery pressure (mmHg)	0.06 (0.04)	0.10
Cardiac output (L/min)	0.04 (0.47)	0.93

Abbreviations: BMI, body mass index; NYHA, New York Heart Association.

DISCUSSION

Main findings

This is the first study evaluating the association between PNI and mortality risk in PH patients. Our results demonstrate that low PNI was associated with an increased risk of death in PH patients. Specifically, patients in the lowest PNI quartile doubled the risk of death in comparison to those in the highest quartile. Intriguingly, PNI was not correlated with NYHA functional class and hemodynamic parameters but positively linked to the pulmonary function test.

Malnutrition and mortality risk in PH patients

Malnutrition is a complex issue with diverse etiologies and may finally progress to cachexia if left untreated.[3] The causes of malnutrition in PH patients are multiple, including appetite loss, malabsorption due to right HF, side effects of particular drugs, increased metabolic rate, or work of breathing.[5] Although malnutrition has been considered as a prognostic indicator in various human diseases, including HF and malignant cancers,[22–27] its association with mortality risk in PH patients has not been fully investigated. From the current study, we found that patients with poorer nutritional status, as indexed by lower PNI, was associated with an increased risk of death. This is consistent with the finding from Snipelisky et al., showing an association of low albumin levels and high mortality risk in PH patients.[8] However, a normal albumin level does not guarantee a healthy nutritional status. A reduced TLC, could also lead to low PNI and portend an increased risk of death.[17,18] From the pathophysiological view, the imbalance of inflammation and altered immunity could exacerbate the vascular remodeling in PH models.[3,31] In addition, specific micronutrient deficiencies, such as iron, vitamin D, and vitamin C, would possibly coexist with malnutrition and promote the progression of PH.[32–36] Given that detailed information on specific nutrient intakes were unavailable in the current study, its association with PNI remains uncertain and further studies are needed.

Nutritional assessment in PH patients

Although there are multiple screening tools for nutritional assessment,[25,37] none of them have been validated in PH patients. Hypoalbuminemia, low BMI, and decreased TLC are common signs of malnutrition.[14,15,17,18,38] However, discrepancies exist when separately used for nutritional assessment.[9,39–42] As stated previously, malnutrition is a multidimensional concept that should better incorporate phenotypic and etiologic criteria.[10] PNI, the parameter used in our study, is such an index considering both the catabolic state and inflammatory status.[11,12,14,15,43,44]

It was first proposed in the 1980s and has currently been reported as a survival predictor in various diseases.[19,20,22–27] Using the criteria defined in HF,[23–26] 14.7% (20/136, using the cutoff value of 38) to 39.7% (54/136, with the cutoff value of 44.8) of the patients

were diagnosed as malnutrition. Although diverse thresholds of PNI were used in defining malnutrition, it generally depicted a picture that lower PNI was associated with a higher risk of adverse outcomes. However, owing to the lack of comparison with a more comprehensive nutritional assessment, the validity of nutritional status evaluated by PNI warrants further investigation.

Correlations of PNI and clinical parameters

NYHA functional class is one of the most important components in risk assessment, highly representing the disease severity in PH patients.[45–47] From the current finding, we did not observe a significant correlation between PNI and NYHA function class. This is consistent with the finding from Anker et al., in which cachexia was found to be a strong predictor of mortality in HF patients independent of age, NYHA class, and LVEF.[48,49]

Notably, we found a positive link between PNI and the pulmonary function test. High degrees of malnutrition correlate with poorer lung function. As reported in previous studies, restrictive lung diseases or peripheral airway obstruction were commonly seen in PH patients.[50–53] Pathologic analysis of the explanted lungs from PH patients showed a prominent inflammation around the vessels and within the interstitial area.[53–55] Thus, the impaired lung function test may be a sign of progressive evolution of vascular remodeling caused by malnutrition; however, future study is required to confirm this hypothesis.

Limitations

Several limitations should be acknowledged. This is an observational study with unavoidable missing data. Only 36.66% of the patients had available data for PNI calculation. Although the baseline characteristics and outcome data were very much the same between the included and excluded patients, the possibility of selection bias may not be completely eliminated. In addition, lacking the data on 6-min walking distance and NT-proBNP, more objective risk assessment was unavailable. Second, this was a PH registry conducted in the 1980s and the enrolled patients might not be completely representative of the current PH population. Furthermore, although the diagnosis of PPH was mainly consistent with the current definition of IPAH, portopulmonary hypertension was not out of the exclusion criteria and its potential impact on serum albumin

could exist. However, we repeated the Cox regression analysis after excluding patients with coexisting conditions, the results of which remained significant. Third, given the observational nature of this study, we could not determine the causalities between low nutritional status and high mortality risk in PH patients. Finally, although PNI was well-validated as a nutritional marker in HF and cancer patients, its value in PH patients warrants further investigation. Confirmation of our findings in more contemporary PH patients or testing other screening tools for nutritional assessment would be essential.

In summary, this study first describes the association of PNI with mortality risk in primary PH patients and suggests that low PNI was associated with an increased risk of death. Although PNI has not been validated as a nutritional marker in PH patients, it helps to enlighten our understanding of adequate nutritional assessment and adverse outcomes in PH patients.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

ETHICS STATEMENT
This study was reviewed and approved by the Research Ethics Committee of Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences (approval number: No. GDREC2020228H). The original study was approved by the institutional review boards from all centers in the PPH registry. Written informed consent was obtained from all participants.

AUTHOR CONTRIBUTIONS
Dongling Luo and Caojin Zhang have full access to all the data in this study and take full responsibility as guarantors for the integrity of the data and the accuracy of the data analysis. Caojin Zhang and Dongling Luo contributed to the study design. Dongling Luo, Nanshan Xie, and Ziyang Yang contributed to analysis and data interpretation. Dongling Luo and Caojin Zhang drafted the manuscript and contributed to the final approval of

the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available upon reasonable request from https://biolincc.nhlbi.nih.gov/studies/pphreg.

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