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# Effects of malnutrition on disease severity and adverse outcomes in idiopathic pulmonary arterial hypertension: a retrospective cohort study

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## Abstract

**Background** Malnutrition is common in patients with chronic cardiovascular disease and is associated with significantly higher all-cause mortality. Approximately one-third of patients with heart failure are malnourished. However, the relationship between malnutrition and idiopathic pulmonary arterial hypertension (IPAH) remains unclear. This study aimed to clarify the prognostic value of malnutrition in patients with IPAH.

**Methods** A total of 432 consecutive participants with IPAH were included in this study between March 2013 and August 2021. Three common malnutrition assessment tools, including the geriatric nutritional risk index (GNRI), prognostic nutritional index (PNI), and controlling nutritional status (CONUT) score, were used to evaluate the nutritional status of patients with IPAH. The relationships between the malnutrition tools and long-term adverse outcomes were determined using restricted cubic splines and multivariate Cox regression models.

**Results** During a mean follow-up of 3.1 years, 158 participants experienced clinical worsening or all-cause death. Patients were stratified into the low-, intermediate- and high-risk groups based on the European Society of Cardiology (ESC) risk stratification, and the PNI (55.9 ± 5.7 vs. 54.4 ± 7.2 vs. 51.1 ± 7.1, P = 0.005) and CONUT score (2.1 ± 0.9 vs. 2.5 ± 1.2 vs. 3.3 ± 1.1, P < 0.001) identified these patient groups better than the GNRI. All three malnutrition tools were associated with well-validated variables that reflected IPAH severity, such as the World Health Organization functional class, 6-min walk distance, and N-terminal pro-brain natriuretic peptide level. The CONUT score exhibited better predictive ability than both the GNRI (ΔAUC = 0.059, P < 0.001) and PNI (ΔAUC = 0.095, P < 0.001) for adverse outcomes and significantly improved reclassification and discrimination beyond the ESC risk score. Multivariable Cox regression analysis indicated that only the CONUT score (hazard ratio = 1.363, 95% confidence interval 1.147, 1.619 per 1.0-standard deviation increment, P < 0.001) independently predicted adverse outcomes.

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**Conclusions** The malnutrition status was associated with disease severity in patients with IPAH. The CONUT score provided additional information regarding the risk of clinically worsening events, making it a meaningful risk stratification tool for these patients.

**Keywords** Malnutrition, Idiopathic pulmonary arterial hypertension, Controlling nutritional status, Severity, Outcome

## Introduction

Pulmonary arterial hypertension (PAH) is a chronic disease characterized by a progressive elevation in pulmonary artery pressure and pulmonary vascular resistance, which eventually leads to right heart failure (HF) and death [1]. Among patients with PAH, those with idiopathic pulmonary arterial hypertension (IPAH) account for the highest proportion and have the worst prognosis, imposing a heavy economic burden [2]. Malnutrition is common in patients with chronic cardiovascular disease. A previous study indicated that approximately one-third of patients with HF are malnourished and that malnutrition increases the risk of all-cause mortality in such patients [3]. The latest guidelines also recommend that those developing treatment strategies for pulmonary hypertension should include cardiologists, respiratory physicians, and nutritionists [1]. However, there is no consensus regarding the optimal assessment tool for malnutrition in patients with IPAH.

Malnutrition is defined as a lack of nutrient intake or impaired nutrient absorption with altered body composition, ultimately leading to function decline and worse clinical outcomes. Malnutrition tools are practical, noninvasive, and applicable for effectively assessing the nutritional status of hospitalized patients. The prognostic nutritional index (PNI) was initially used to assess the nutritional and immunological status of patients undergoing gastrointestinal surgery [4]. The geriatric nutritional risk index (GNRI) is used to study and predict nutrition-related complications in older adults [5]. The controlling nutritional status (CONUT) score assesses nutritional status, immune status, and energy expenditure; thus, is a screening tool for the early detection of malnutrition in hospitalized patients [6]. Recent evidence suggest that the GNRI and CONUT scores are associated with the prognosis of patients with various cardiovascular diseases, especially those with chronic HF [7, 8]. Considering that IPAH closely correlates with chronic HF, we hypothesized that the malnutrition status is similarly related to clinically worse outcomes in patients with IPAH. However, the application and prognostic value of malnutrition assessments for patients with IPAH have not been systematically reported.

To bridge this gap, this retrospective study evaluated the nutritional status of patients with IPAH and compared the relationships of three commonly used malnutritional tools with functional status, echocardiographic parameters, hemodynamic indices, and long-term adverse outcomes.

## Methods

### Study design and population

This retrospective cohort study was performed at Fuwai Hospital, Chinese Academy of Medical Sciences (Beijing, China). Consecutive patients with IPAH were recruited between March 2013 and August 2021. The baseline assessment included data acquired at the time of IPAH diagnosis in incident cases (those diagnosed after March 1, 2013) and data obtained at the most recent visit in prevalent patients (those diagnosed before March 1, 2013). The IPAH diagnosis was established by confirming precapillary pulmonary hypertension (elevated mean pulmonary artery pressure [mPAP] > 20 mmHg and pulmonary artery wedge pressure [PAWP] ≤ 15 mmHg) with elevated pulmonary vascular resistance (PVR > 2 wood units) [1]. Patients with findings typical of left heart disease, significant lung disease, chronic thromboembolic pulmonary hypertension, or other known causes of PAH were classified as having other types of pulmonary hypertension according to the European Society of Cardiology (ESC) guidelines and were excluded from the study, as were those with confusing or missing data (Fig. 1). The date of diagnosis was defined as the date of the first right heart catheterization (RHC) in patients who met the hemodynamic criteria for pre-capillary pulmonary hypertension. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was revised and approved by the local ethics committee. All patients provided written informed consent.

### Protocol

Demographic data, medical histories, and clinical parameters were recorded upon admission. Fasting peripheral venous blood samples were collected before RHC. Echocardiography was completed within 48 h of admission, and RHC was performed when the patients were in a stable condition, as previously described [9]. Hemodynamic parameters were measured, including right atrial pressure (RAP), mixed venous oxygen saturation ($S_VO_2$), mPAP, and PAWP. The cardiac index was calculated by dividing the cardiac output by the body surface area.

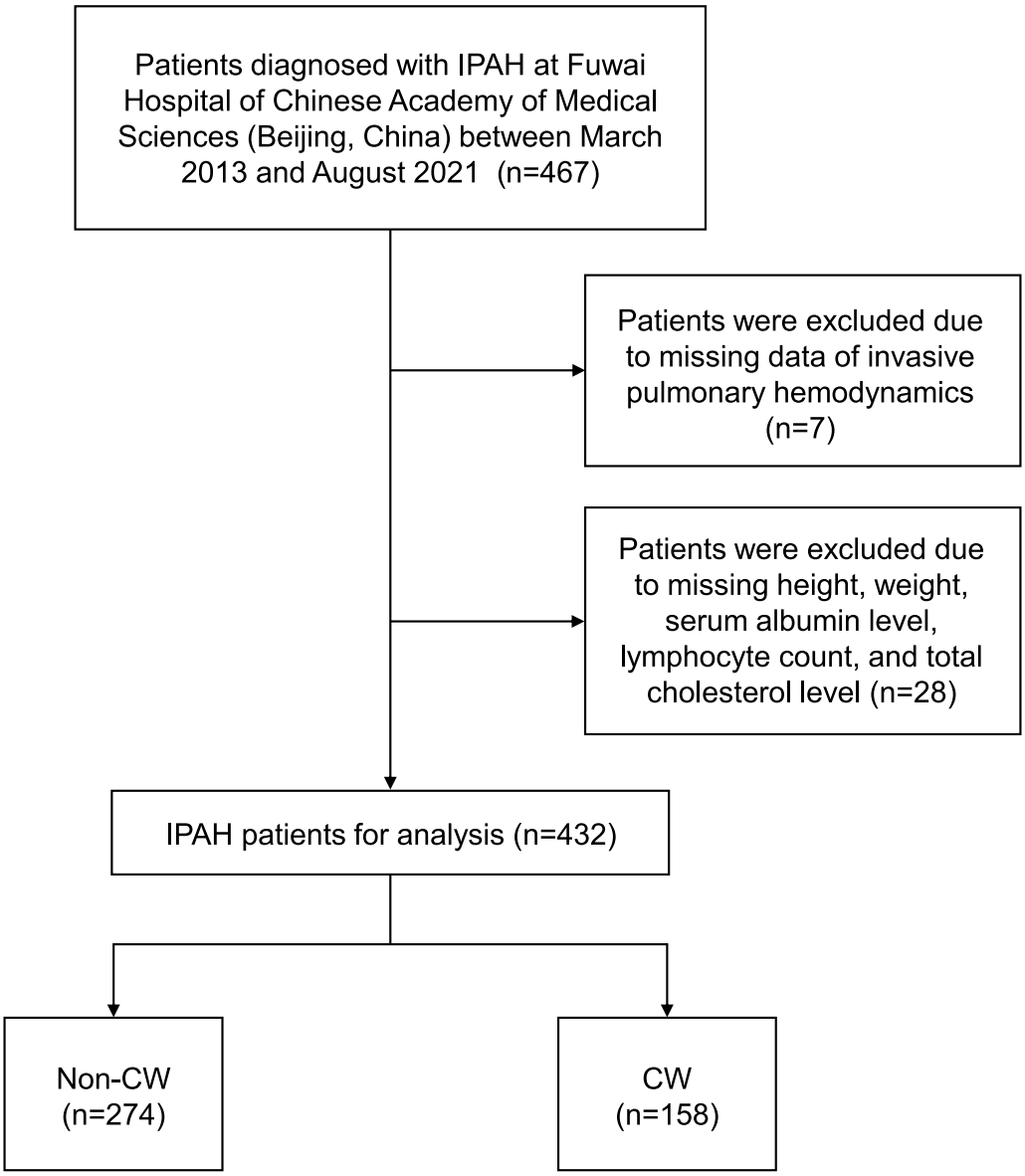


**Fig. 1** The flowchart of study participants. *CW* clinical worsening; *IPAH* Idiopathic pulmonary arterial hypertension

PVR was calculated using standard formulas [10]. During RHC, the transducer was placed at the zero level of the mid-thoracic line (the intersection of the frontal plane at the mid-thoracic level, transverse plane at the level of the fourth anterior intercostal space, and the midsagittal plane) and left atrium (the patient in a supine position, halfway between the anterior sternum and the bed surface) [11, 12].

An abbreviated ESC risk stratification strategy was used to categorize patients as low-, intermediate-, or high-risk [13]. One to three points were assigned to each parameter in the prediction model: World Health Organization functional class (WHO-FC), 6-min walk distance (6MWD), the N-terminal pro-brain natriuretic peptide (NT-proBNP) level, RAP, cardiac index, and $S_VO_2$ (Supplementary Table S1). The risk score for each patient was calculated as the sum of all points divided by the number of available variables (rounded to the nearest integer).

#### Malnutrition evaluation

In this study, three malnutrition tools (GNRI, PNI, and CONUT) were used to assess the baseline nutritional status of patients with IPAH.

The GNRI was calculated using a formula that incorporated the serum albumin level, body height, and weight: GNRI = 1.489 × serum albumin (g/L) + 41.7 × (actual body weight [kg]/ideal body weight [kg]) [5]. The ideal body weight was calculated using the following formula: 22 × height squared (meters) [14, 15]. A GNRI score above 98 was considered normal, and scores from 92 to 98 and < 92 indicated a low malnutrition risk and moderate-to-severe malnutrition, respectively [5].

The PNI was calculated using the following formula: 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count ($mm^3$) [16]. A PNI score of < 45 indicated malnutrition [4].

The CONUT score is an efficient screening tool that considers the serum albumin, total cholesterol, and total lymphocyte count levels and assigns scores ranging from 0 to 12 (Supplementary Table S2) [6]. CONUT scores of 0–1, 2–4, and ≥ 5 indicated a normal nutritional status, mild malnutrition, and moderate-severe malnutrition, respectively [6].

#### Endpoints and follow-up

Clinical worsening, the primary endpoint, was defined as the first occurrence of all-cause death, lung transplantation, hospitalization for HF, or escalation of PAH-specific treatment. Hospitalization for HF was defined as hospital admission owing to worsening HF symptoms requiring intravenous diuretic therapy. The data were collected by trained nurses using either outpatient clinical visits or telephone connections with patients or their relatives after discharge. The endpoints were carefully checked after reviewing the corresponding medical records. The endpoints were adjudicated by an independent committee.

#### Statistical analysis

Continuous variables were presented as means ± standard deviations (SD) or medians [25th–75th percentiles] and analyzed using Student's *t*-test (for normally distributed data) or the Mann–Whitney U test (for non-normally distributed data). Chi-square or Fisher's exact tests were used to compare categorical variables as counts (percentages).

Correlations between the malnutrition tools and established PAH severity markers were examined using Spearman's correlation coefficients. One-way analysis of variance was used to compare differences among different risk strata with least significant difference (LSD) post hoc tests. The area under the curve (AUC), continuous net reclassification improvement (cNRI), and integrated discrimination improvement (IDI) were calculated to evaluate and compare the reclassification and discrimination capacities of the malnutrition tools for predicting primary endpoint events. The goodness-of-fit of the model after adding them to the ESC risk stratification were assessed using the Akaike information criterion (AIC), Bayesian information criterion (BIC), and $\chi^2$ likelihood ratio tests.

Survival curves were derived using the Kaplan–Meier method and compared using the log-rank test. Restricted cubic spline curves were used to evaluate the relationship between malnutrition tools and clinical deterioration. Univariable Cox regression analysis was performed to identify risk factors for clinical worsening, and factors with P-values of < 0.05 or with clinical significance were retained in the multivariable Cox regression model. To exclude confounding factors, Model 1 was adjusted for age, sex, ethnicity and body mass index (BMI). Model 2 was adjusted for the factors in Model 1 plus the WHO-FC, 6MWD, ln (NT-proBNP), PAH-specific medication, $S_VO_2$, cardiac index, and PVR. According to BMI, the study participants was divided into three groups: underweight (< 18.5 kg/$m^2$), normal weight (18.5–23.9 kg/$m^2$), overweight and obesity (≥ 24 kg/$m^2$). The variance inflation factor method was used to test for collinearity. Subgroup analyses stratified by sex, age, BMI, incident/prevalent case, PAWP, inferior vena cava diameter and estimated plasma volume status (ePVS) were performed to determine the interaction effects, and the P value for the interaction was assessed by conducting likelihood ratio tests.

Statistical significance was set at P < 0.05 (two-sided). Data were analyzed using R-studio (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

## Results

#### Baseline characteristics

Overall, 432 consecutive patients with IPAH were included in this study (Fig. 1), with a median age of 32 years, of whom 77.1% were female and 96.8% were of Han ethnicity. Among them, 149 were prevalent patients (diagnosed before March 1, 2013) with a median time from diagnosis to enrollment of 2.0 [0.7–3.0] years. Prevalent cases showed lower NT-proBNP levels, and a higher proportion received PAH combination therapy compared with that of incident cases (Supplementary Table S3). During the follow-up period, 158 (36.6%) patients experienced clinical worsening. Table 1 presents the baseline characteristics of the participants with and without clinical worsening. Those with clinical worsening had worse WHO-FC, more restricted 6MWD, and a higher proportion of pericardial effusion than those without. Furthermore, 91.0% of the participants received targeted therapy for PAH during the index hospitalization. The remaining patients refused the therapy mainly because of the financial burden, intolerability, and caution regarding adverse effects. Patients with clinical worsening also had

**Table 1** Baseline characteristics of study population

| Variables | Non-CW (n = 274) | CW (n = 158) |
|---|---|---|
| Demographics and clinical evaluation | | |
| Age, years | 32 [27–38] | 32 [26–38] |
| Female, n (%) | 212 (77.4) | 121 (76.6) |
| Han ethnicity, n (%) | 269 (98.2) | 149 (94.3) |
| Incident case, n (%) | 179 (65.3) | 104 (65.8) |
| BMI, kg/m$^2$ | 22.8 [20.7–25.3] | 22.6 [20.2–25.4] |
| BMI (categorical), n (%) | | |
| < 18.5 kg/m$^2$ | 21 (7.7) | 20 (12.7) |
| 18.5–23.9 kg/m$^2$ | 153 (55.8) | 79 (50.0) |
| ≥ 24 kg/m$^2$ | 100 (36.5) | 59 (37.3) |
| Systolic BP, mmHg | 113 [105–123] | 111 [102–120] |
| Diastolic BP, mmHg | 70 [63–80] | 70 [64–80] |
| Heart rate, beats/min | 81 [73–91] | 84 [75–96] |
| WHO-FC, n (%) | | |
| I or II | 166 (60.6) | 58 (36.7) |
| III or IV | 108 (39.4) | 100 (63.3) |
| 6MWD, m | 430 [381–498] | 400 [322–464] |
| Current smoking, n (%) | 29 (10.6) | 18 (11.4) |
| Alcohol intake, n (%) | 16 (5.8) | 12 (7.6) |
| Hypertension, n (%) | 22 (8.0) | 23 (14.6) |
| Diabetes mellitus, n (%) | 11 (4.0) | 7 (4.4) |
| CHD, n (%) | 2 (0.7) | 4 (2.5) |
| COPD, n (%) | 4 (1.5) | 4 (2.5) |
| OSA, n (%) | 17 (6.2) | 8 (5.0) |
| Laboratory data | | |
| NT-proBNP, pg/mL | 789 [245–1604] | 1599 [977–2422] |
| Albumin, g/L | 44.7 ± 5.3 | 41.9 ± 5.2 |
| ALT, IU/L | 24.0 [16.0–35.8] | 24.0 [16.0–36.0] |
| AST, IU/L | 25.0 [21.0–34.0] | 25.0 [20.0–34.8] |
| Triglyceride, mmol/L | 1.3 [0.9–1.8] | 1.1 [0.9–1.5] |
| Cholesterol, mmol/L | 4.3 ± 0.9 | 3.7 ± 0.9 |
| Serum creatinine, umol/L | 72.0 [64.2–81.1] | 72.0 [61.5–82.8] |
| BUN, mmol/L | 5.2 [4.3–6.4] | 5.5 [4.5–6.8] |
| Lymphocyte, $10^9$/L | 2.1 [1.8–2.6] | 2.2 [1.6–2.7] |
| Hemoglobin, g/L | 152 [137–168] | 153 [135–168] |
| C-reactive protein, mg/dL | 2.3 [1.6–4.1] | 2.4 [1.7–4.1] |
| Echocardiography | | |
| Pericardial effusion, n (%) | 38 (13.9) | 42 (26.6) |
| LAD, mm | 30 [27–32] | 29 [26–32] |
| LVED, mm | 37.3 ± 5.8 | 34.9 ± 4.90 |
| LVEF, mm | 65 [60–69] | 63 [60–67] |
| RVED, mm | 32 [27–37] | 35 [27, 30–40] |
| sPAP, mmHg | 87 [74–102] | 92 [79–107] |
| Hemodynamics | | |
| $S_VO_2$, % | 71.2 [66.1–75.4] | 70.0 [65.2–73.8] |
| mRAP, mmHg | 4 [2–7] | 6 [2–9] |
| mPAP, mmHg | 54 [45–64] | 55 [49–69] |
| PAWP, mmHg | 7 [5–10] | 8 [5–11] |
| Cardiac index, L/min/m$^2$ | 2.8 [2.3–3.5] | 2.8 [2.3–3.3] |
| SVI, mL/m$^2$ | 34.5 [27.9–45.9] | 32.2 [25.8–40.9] |
| PVR, wood units | 11.4 [8.1–15.4] | 12.9 [9.8–16.2] |
| Treatment | | |
| PAH-specific treatment, n (%) | 246 (89.8) | 147 (93.0) |
| PAH combination therapy, n (%) | 108 (39.4) | 49 (31.0) |
| Parenteral prostacyclin, n (%) | 21 (7.7) | 21 (13.3) |
| Nutritional indices | | |
| GNRI | 106.6 ± 8.58 | 102.10 ± 8.13 |
| GNRI (categorical), n (%) | | |
| GNRI > 98 | 235 (85.77) | 112 (70.89) |
| GNRI 92 to 98 | 26 (9.49) | 29 (18.35) |
| GNRI < 92 | 13 (4.74) | 17 (10.76) |
| PNI | 55.92 ± 6.69 | 53.03 ± 6.39 |
| PNI < 45, n (%) | 13 (4.74) | 14 (8.86) |
| CONUT | 2.11 ± 1.02 | 2.87 ± 1.10 |
| CONUT (categorical), n (%) | | |
| CONUT 0–1 | 80 (29.20) | 8 (5.06) |
| CONUT 2–4 | 184 (67.15) | 136 (86.08) |
| CONUT ≥ 5 | 10 (3.65) | 14 (8.86) |

Data are presented as mean ± standard deviation, median [25th–75th percentile] or number (percentage)

*ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, BUN blood urea nitrogen, *BP* blood pressure, *CHD* coronary heart disease, *CONUT* controlling nutritional status, *COPD* chronic obstructive pulmonary disease, *CW* clinical worsening, *GNRI* geriatric nutritional risk index, *LAD* left atrium dimension, *LVED* left ventricular end-diastolic diameter, *LVEF* left ventricular ejection fraction, *mPAP* mean pulmonary arterial pressure, *6MWD* 6-min walk distance, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *OSA* obstructive sleep apnea, *PAWP* pulmonary arterial wedge pressure, *PAH* pulmonary arterial hypertension, *PNI* prognostic nutritional index, *PVR* pulmonary vascular resistance, *RAP* mean right atrial pressure, *RVED* right ventricular end-diastolic diameter, *sPAP* systolic pulmonary arterial pressure, $S_VO_2$ mixed venous oxygen saturation, *SVI* stroke volume index, *WHO-FC* World Health Organization functional class

a significantly higher heart rate, NT-proBNP level, right ventricular end-diastolic diameter, RAP, and PVR, but a lower albumin level, lipid level, left ventricular end-diastolic diameter, cardiac index, and stroke volume index (SVI) than those without clinical worsening. Moreover, patients with clinical worsening had substantially higher CONUT scores and lower GNRI and PNI scores than those without. Additional baseline characteristic details of the patients with different nutritional statuses based on the GNRI, PNI, and CONUT scores were presented in Supplementary Table S4, Supplementary Table S5, and Supplementary Table S6, respectively.

### Association between malnutrition and established disease severity markers of IPAH

Different malnutrition tools were associated with different guideline-recommended IPAH severity indicators (Table 2). For instance, the CONUT score weakly

correlated with the WHO-FC, 6MWD, NT-proBNP level, RAP, and $S_VO_2$. However, correlations were not observed between the CONUT score and pericardial effusion (r = 0.100, P = 0.106), mPAP (r = 0.056, P = 0.245), cardiac index (r = − 0.025, P = 0.683), SVI (r = − 0.080, P = 0.196), or PVR (r = 0.082, P = 0.088).

Figure 2 shows the levels and distributions of the 3 malnutrition tools in the low-, intermediate-, and high-risk groups using the abbreviated ESC 4-strata risk stratification. The GNRI [low- vs. intermediate- vs. high-risk: mean ± SD; 106.8 ± 7.5 vs. 103.9 ± 9.1 vs. 101.0 ± 10.3, P < 0.001], and PNI [55.9 ± 5.7 vs. 54.4 ± 7.2 vs. 51.1 ± 7.1, P = 0.005] values decreased as the ESC risk score increased, but the CONUT score increased as risk score increased [2.1 ± 0.9 vs. 2.5 ± 1.2 vs. 3.3 ± 1.1, P < 0.001]. The LSD test showed that the PNI and CONUT scores identified low-, intermediate-, and high-risk patients well, while the GNRI had a limited ability to distinguish between intermediate- and high-risk patients. As a sensitivity analysis, the relationship between the three malnutrition tools and the ESC 4-strata risk stratification was explored (details of the scoring methods are presented in Supplementary Table S7). The results showed that only the CONUT score was able to distinguish among low-,

**Table 2** Correlation analysis between malnutrition indices indices with established markers of PAH severity

| | GNRI | | PNI | | CONUT | |
|---|---|---|---|---|---|---|
| | **Coefficient (*r*)** | ***P* value** | **Coefficient (*r*)** | ***P* value** | **Coefficient (*r*)** | ***P* value** |
| WHO-FC | − 0.135 | 0.029 | − 0.152 | 0.014 | 0.156 | 0.012 |
| 6MWD | 0.132 | 0.033 | 0.184 | 0.003 | − 0.235 | < 0.001 |
| ln (NT-proBNP) | − 0.260 | < 0.001 | − 0.197 | 0.001 | 0.215 | < 0.001 |
| Pericardial effusion | − 0.131 | 0.034 | − 0.154 | 0.013 | 0.100 | 0.106 |
| RAP | − 0.120 | 0.053 | − 0.214 | < 0.001 | 0.248 | < 0.001 |
| mPAP | − 0.068 | 0.158 | 0.038 | 0.427 | 0.056 | 0.245 |
| Cardiac index | 0.071 | 0.253 | 0.083 | 0.180 | − 0.025 | 0.683 |
| SVI | 0.065 | 0.297 | 0.055 | 0.378 | − 0.080 | 0.196 |
| $S_VO_2$ | 0.149 | 0.016 | 0.164 | 0.008 | − 0.167 | 0.007 |
| PVR | − 0.145 | 0.003 | − 0.025 | 0.602 | 0.082 | 0.088 |

*CONUT* controlling nutritional status, *GNRI* geriatric nutritional risk index, *ln* logarithmically transformed, *mPAP* mean pulmonary arterial pressure, *6MWD* 6-min walking distance, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *PAH* pulmonary arterial hypertension, *PNI* prognostic nutritional index, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, $S_VO_2$ mixed venous oxygen saturation, *SVI* stroke volume index, *WHO-FC* World Health Organization functional class

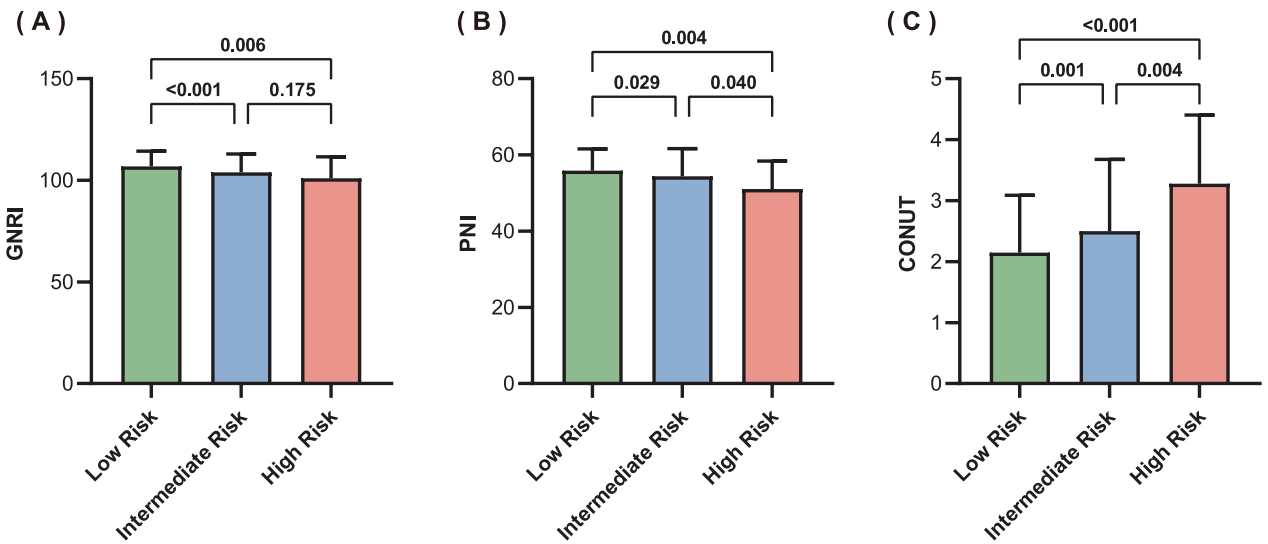


**Fig. 2** Associations between the malnutrition tools and ESC 3-strata risk score. Bar chart of the relationships between risk stratification and GNRI (**A**), PNI (**B**), and CONUT (**C**). Data are presented as means ± standard deviations. *CONUT* controlling nutritional status, *ESC* European Society of Cardiology, *GNRI* geriatric nutritional risk index, *PNI* prognostic nutritional index

intermediate-low-, intermediate-high-, and high-risk patients in both incident and prevalent cases (Supplementary Figure S1 and Supplementary Figure S2).

### Comparison of the different malnutrition tools in predicting clinical deterioration

Receiver operating characteristic (ROC) curves were constructed to explore the predictive ability of the three malnutrition tools (Fig. 3A) and the ESC risk model plus each malnutrition tool for clinical worsening (Fig. 3B). The CONUT score performed better than both the GNRI (ΔAUC = 0.059, P < 0.001) and PNI (ΔAUC = 0.095, P < 0.001) in predicting clinical worsening (Table 3). The sensitivity analysis indicated that the AUC of the CONUT score was better than all components, including the albumin level, lymphocyte count, and total cholesterol level (Supplementary Figure S3). The sensitivity, specificity, Youden index, accuracy, positive predictive values, and negative predictive values of the CONUT score, albumin level, lymphocyte count, and total cholesterol level were detailed in Supplementary Table S8.

In addition, the GNRI, PNI, and CONUT scores had significant incremental effects and significantly improved the reclassification and discrimination ability beyond ESC risk stratification (Supplementary Table S9). Adding each of the three malnutrition tools to the ESC risk score significantly improved the model's goodness-of-fit. The model that included both the ESC risk score and CONUT score was the best-fit model with the lowest AIC and BIC values, and the likelihood ratio test results were significant (Supplementary Table S10).

### Relationship between malnutrition and long-term outcome of IPAH

During the median follow-up period of 3.1 years, 158 (36.6%) patients experienced clinical worsening. We defined the three malnutrition tools as continuous variables with the median as the reference point and used restricted cubic spline regression to fit the unadjusted

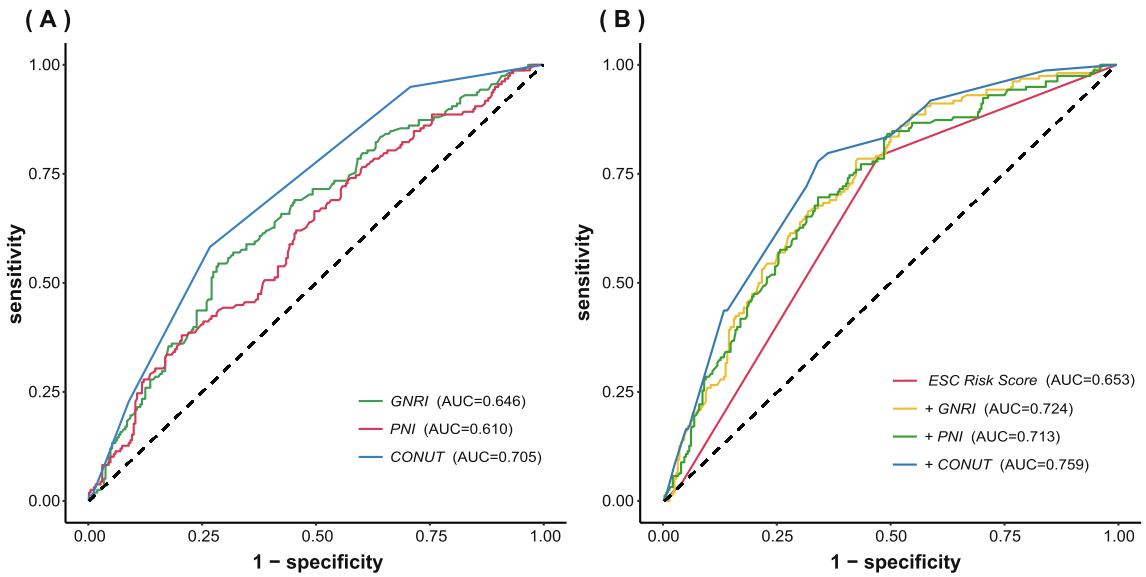


**Fig. 3** ROC curves of the malnutrition tools as markers for predicting clinical worsening: (**A**) using the malnutrition tools separately, and (**B**) based on the ESC risk score. *CONUT* controlling nutritional status, *ESC* European Society of Cardiology, *GNRI* geriatric nutritional risk index, *PNI* prognostic nutritional index, *ROC* receiver operator characteristic

**Table 3** Comparative analysis of the discrimination of each malnutritional indices for clinical worsening

| Comparison | △AUC | *P* value | cNRI | *P* value | IDI | *P* value |
|---|---|---|---|---|---|---|
| CONUT vs. GNRI | 0.059 | < 0.001 | 0.342 (0.149, 0.535) | < 0.001 | 0.054 (0.025, 0.084) | < 0.001 |
| CONUT vs. PNI | 0.095 | < 0.001 | 0.422 (0.230, 0.613) | < 0.001 | 0.071 (0.045, 0.097) | < 0.001 |
| GNRI vs. PNI | 0.036 | 0.077 | 0.201 (0.007, 0.395) | 0.042 | 0.017 (0.002, 0.031) | 0.025 |

△*AUC* the difference of area under curve, *CI* confidence interval, *cNRI* continuous net reclassification improvement, *CONUT* controlling nutritional status, *GNRI* geriatric nutritional risk index, *IDI* integrated discrimination improvement, *PNI* prognostic nutritional index

Cox proportional hazards model. The unadjusted spline plots suggested a monotonically increasing association between the degree of malnutrition and the hazard ratio (HR) for clinical worsening (Fig. 4). The Kaplan–Meier curve showed that individuals with mild or moderate-severe malnutrition based on the CONUT score exhibited notably inferior survival rates and experienced a shorter duration until clinical deterioration than those with a normal nutritional status (P for log-rank < 0.001, Fig. 5). To further evaluate the predictive value of the malnutrition tools for clinical worsening, we established Cox regression models to assess the impact per 1.0-SD increment and different nutritional statuses in the three tools on endpoint events (Table 4). After fully adjusting for covariates in Model 2, we found that for a 1.0-SD increment in the CONUT score, the risk of all-cause death, lung transplantation, hospitalization for HF, and escalation of PAH-specific treatment in patients with IPAH increased by 36% (HR = 1.363, 95% CI 1.147, 1.619 per 1.0-SD increment, P < 0.001). Compared with a normal nutritional status, mild or moderate-to-severe malnutrition based on the CONUT score was associated with a nearly threefold increased risk of long-term adverse outcomes. No collinearity problems were detected in the multivariable Cox analysis. Sex, age, BMI, incident case, and congestion status were used as modifiers for subgroup effect analysis, and no interaction effect between malnutrition and clinical deterioration was found with the above factors (Supplementary Table S11). In the sensitivity analyses, we further examined the association between nutritional status and mortality. The results of the survival analysis suggested that malnutritional status assessment using the CONUT score (HR = 1.593, 95% CI 1.224, 2.072 per 1.0-SD increment, P < 0.001) provides independent predictive value for all-cause death, compared to assessment with the GNRI and PNI (Supplementary Figure S4 and Supplementary Table S12).

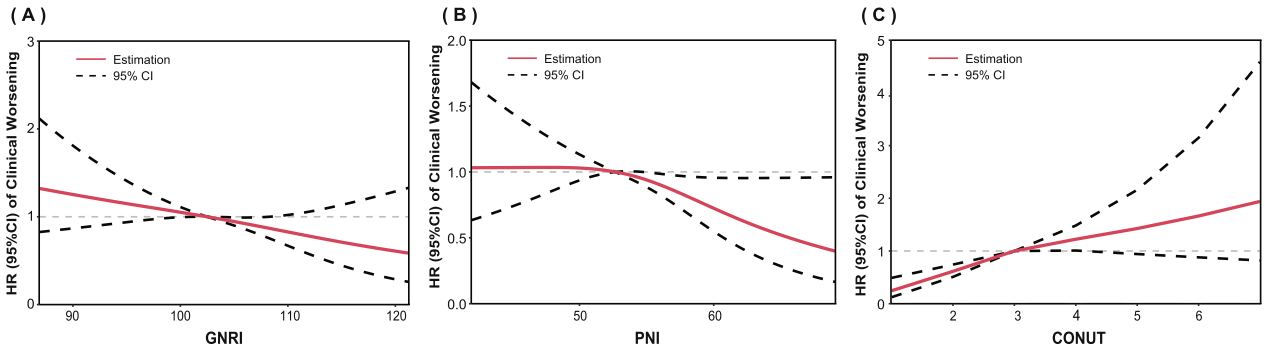


**Fig. 4** Hazard ratios of clinical worsening as a function of baseline malnutrition tools. GNRI (**A**), PNI (**B**), and CONUT (**C**) as continuous variables fitted an unadjusted Cox regression model using restricted cubic spline regression. *CONUT* controlling nutritional status, *GNRI* geriatric nutritional risk index, *PNI* prognostic nutritional index

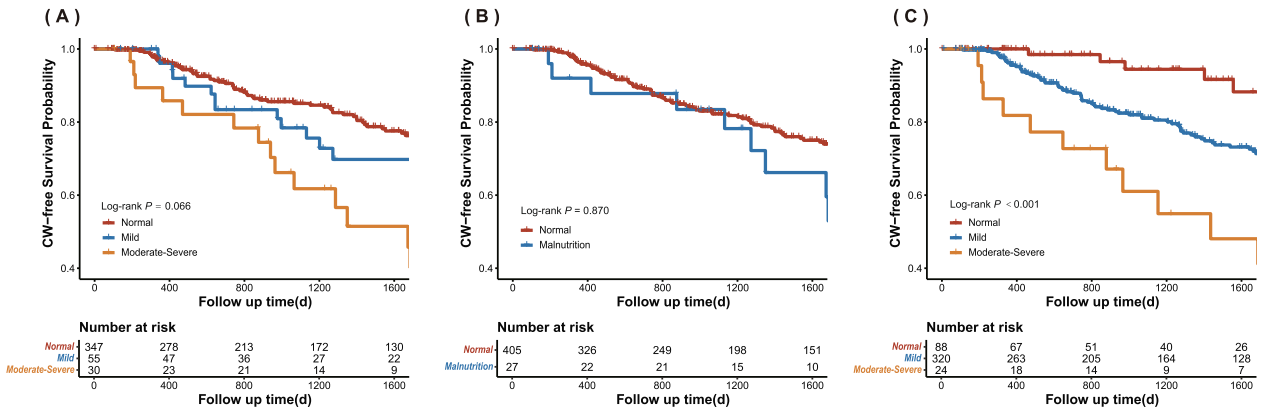


**Fig. 5** Kaplan–Meier curves illustrating the relationships between the GNRI (**A**), PNI (**B**), and CONUT (**C**) and clinical worsening. The log-rank test was used to compare clinical worsening among the groups. *CONUT* controlling nutritional status, *GNRI* geriatric nutritional risk index, *PNI* prognostic nutritional index

**Table 4** Predictive value of malnutrition indices for long-term clinical worsening

| | Unadjusted | | Model 1[a] | | Model 2[b] | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| GNRI | | | | | | |
| Per 1-SD increasement | 0.827 (0.702, 0.975) | 0.024 | 0.861 (0.723, 1.025) | 0.0917 | 0.964 (0.807, 1.150) | 0.681 |
| Normal | 1 [Reference] | | 1 [Reference] | | 1 [Reference] | |
| Mild | 1.068 (0.704, 1.620) | 0.758 | 1.006 (0.655, 1.548) | 0.977 | 0.762 (0.479, 1.210) | 0.249 |
| Moderate-Severe | 1.822 (1.092, 3.041) | 0.022 | 1.622 (0.939, 2.800) | 0.083 | 1.162 (0.654, 2.062) | 0.609 |
| PNI | | | | | | |
| Per 1-SD increasement | 0.835 (0.710, 0.982) | 0.029 | 0.858 (0.726, 1.015) | 0.073 | 0.934 (0.785, 1.110) | 0.436 |
| Normal | 1 [Reference] | | 1 [Reference] | | 1 [Reference] | |
| Malnutrition | 0.955 (0.547, 1.668) | 0.873 | 0.788 (0.445, 1.395) | 0.414 | 0.586 (0.32, 1.073) | 0.083 |
| CONUT | | | | | | |
| Per 1-SD increasement | 1.480 (1.285, 1.705) | < 0.001 | 1.489 (1.286, 1.723) | < 0.001 | 1.363 (1.147, 1.619) | < 0.001 |
| Normal | 1 [Reference] | | 1 [Reference] | | 1 [Reference] | |
| Mild | 3.550 (1.738, 7.252) | < 0.001 | 3.699 (1.800, 7.602) | < 0.001 | 2.817 (1.356, 5.851) | 0.006 |
| Moderate-Severe | 5.142 (2.147, 12.317) | < 0.001 | 4.973 (2.062, 11.992) | < 0.001 | 3.000 (1.158, 7.770) | 0.024 |

[a] Model 1: Adjusted for age, sex, ethnicity, and BMI (Categorical)

[b] Model 2: Adjusted for age, sex, ethnicity, BMI (Categorical), WHO-FC, 6MWD, ln (NT-proBNP), PAH specific medication, $S_VO_2$, cardiac index and PVR

*CI* confidence interval, *CONUT* controlling nutritional status, *GNRI* geriatric nutritional risk index, *HR* hazard ratio, *ln* logarithmically transformed, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *6MWD* 6-min walk distance, *PAH* pulmonary arterial hypertension, *PNI* prognostic nutritional index, *PVR* pulmonary vascular resistance, *SvO2* mixed venous oxygen saturation, *WHO-FC* World Health Organization functional class

## Discussion

To our knowledge, this is the first study to compare the performances of three commonly used malnutrition tools in predicting disease severity and long-term outcomes in patients with IPAH. First, three malnutrition tools were associated with established markers of disease severity in patients with IPAH. The malnutrition tools positively correlated with WHO-FC, the NT-proBNP level, RAP, $S_VO_2$, PVR, and pericardial effusion, and were negatively associated with 6MWD. Second, the CONUT score and PNI better identified patients with low-, intermediate-, and high-risk IPAH as defined by the ESC risk stratification compared to GNRI, which poorly distinguished between intermediate- and high-risk patients. Although all three improved the prognostic value of the ESC risk stratification, the model that included both the ESC risk score and CONUT score was the best-fit model. Third, after accounting for confounding factors, only the CONUT score was an independent predictor of all-cause death or clinical worsening in patients with IPAH, making it a clinically important risk stratification tool for these patients.

Hypoalbuminemia is considered as an independent prognostic factor in many cardiovascular diseases, such as coronary artery disease, HF, congenital heart disease, infective endocarditis and stroke, and also a prognostic predictor of PAH [17, 18]. In the pathophysiological processes of PAH, hepatic dysfunction, malnutrition, and systemic inflammation are consequences of progressive right ventricular failure due to PAH and can be reflected in serum albumin levels [18]. BMI is a traditional indicator of nutritional status, and has been linked to improved HF survival in multiple studies [19]. However, an increased extracellular fluid volume decreases serum albumin levels and increases BMI. Considering this counteracting effect, the GNRI, which is a combined index of the albumin level and BMI, may minimize the effect of the fluid status [20]. Nutritional status can also profoundly affect the immune function and resistance to infection [21]. The PNI assesses malnutrition using albumin levels and total lymphocyte counts, the latter of which can reflect the immune and nutritional status of hospitalized patients. Previous studies have indicated that the GNRI and PNI predict the long-term prognosis in patients with chronic HF [3, 22, 23], suggesting a relationship between malnutrition and poor outcomes in patients with chronic disease.

Considering that IPAH is also a chronic disease that can ultimately progress to right HF, several studies have explored the association between malnutrition indices and prognosis in patients with pulmonary hypertension (PH). Kubota et al. [24] concluded that the GNRI at first hospitalization helped predict the prognosis in patients with PAH and chronic thromboembolic pulmonary hypertension. However, this retrospective study had a small sample size and included patients with various

subtypes of PH, with large clinical heterogeneity in the sample and many confounding factors. Luo et al. [25] showed that a low PNI was associated with an increased risk of death in patients with PH. However, this study used data from the PH registry conducted in the 1980s, which may result in a poor representation of current patients with PH. Consequently, the limited size and poor representation of studies to date have not demonstrated the causalities between malnutrition status and disease severity and prognosis in patients with PAH. Our study fills this gap.

Our study found that the PNI and GNRI had a limited ability to recognize the long-term prognosis of patients with IPAH. This may be because the PNI only categorizes patients as non-malnourished or at least moderately malnourished. In our study, the PNI only identified 27 patients with a malnourished status, which may have overestimated the proportion of non-malnourished patients. Therefore, the results of the Cox regression analysis of PNI should be considered with caution. In addition, because the GNRI takes body weight into account, and patients with advanced IPAH often have severe HF and fluid retention, the GNRI may confound body weight with fluid status and underestimate malnutrition in obese patients. Given that right HF leads to congestion in the liver and gastrointestinal organs and is associated with malnutrition [26, 27], which may affect the predictive efficacy of malnutrition indices for the prognosis of IPAH, we performed subgroup analysis of the data using three metrics capable of characterizing the degree of congestion, PAWP, inferior vena cava internal diameter, and ePVS. The results showed no interaction was found, which suggested that the relationship between malnutrition and prognosis of IPAH was consistent across different degrees of congestion status.

CONUT, first proposed by Ignacio et al. [6] in 2005, contains three parameters: serum albumin, cholesterol, and lymphocytes, which are associated with protein reserves, caloric depletion, and immune defense. Recent studies have indicated that the CONUT score is a prognostic predictor of rehospitalization or all-cause mortality in patients with chronic HF [28, 29]. In our study, we verified that the CONUT score independently predicted death and clinical worsening events in patients with IPAH. CONUT includes the serum total cholesterol level as an indicator, compared with GNRI and PNI. Cholesterol levels are indicators of nutritional status and respond well to dietary intake [30]. A phenomenon called the "obesity paradox" has been observed in several chronic diseases including PAH, where a certain level of cholesterol has been associated with a lower, rather than a higher risk of death [31, 32]. It can be hypothesized that patients with chronic progressive disease are more likely to have a poorer prognosis due to malnutrition than a cardiovascular risk due to high lipid levels. IPAH is a group of diseases with insidious symptoms, and by the time patients receive medical care, the disease has often progressed to an end-stage with right HF. Therefore, we presume that a certain serum cholesterol level may protect patients with IPAH. In short, the CONUT score, which incorporates total cholesterol levels, albumin levels, and total lymphocyte counts, may provide a more comprehensive assessment of the malnutrition status, chronic inflammation, and immune status, leading to a more accurate prediction of clinical deterioration events in patients with IPAH.

The mechanism by which IPAH leads to malnutrition may be related to various factors, including loss of appetite, intestinal malabsorption, and an imbalance between anabolic and catabolic metabolism. Hypoxia is an important pathophysiological condition in patients with IPAH. Studies have shown that hypoxic exposure is associated with reduced appetite, possibly because hypoxia affects various hormonal markers involved in appetite regulation, such as leptin, glucagon-like peptide-1 and ghrelin [33, 34]. As patients with IPAH develop right HF, right heart insufficiency and systemic venous stasis can lead to gastrointestinal malabsorption, increased intestinal permeability, and bacterial translocation, the latter of which further contributes to a prolonged proinflammatory state in the body through the release of endotoxins [35, 36]. The persistent chronic inflammatory state and activation of the neuroendocrine system due to right HF induce increased catabolism and, ultimately, an imbalance between anabolic and catabolic metabolism [37]. Furthermore, patients with chronic HF develop cardiogenic cachexia in the advanced stages, and patients with advanced IPAH are no exception. According to Valentova et al. [27], right heart dysfunction is more pronounced in patients with cardiac cachexia than in non-cachectic patients with a similar left ventricular ejection fraction and New York Heart Association classifications. Odeh et al. [38] also reported that in patients with HF, the right ventricular ejection fraction negatively correlated with the tumor necrosis factor-α level, which is elevated in patients with cardiac cachexia and has a strong negative inotropic effect [39]. Thus, cardiac cachexia and right ventricular dysfunction may promote each other [40], emphasizing the importance of early nutritional intervention in patients with IPAH to prevent patients from falling into the vicious cycle of "malnutrition-inflammation-cardiac cachexia".

The CONUT score has several advantages as a tool for monitoring the nutritional status of patients with IPAH. First, CONUT involves common indicators that are easily accessible, economical and can be easily

applied at the bedside. Second, the CONUT score correlates with IPAH severity and long-term outcomes, which can improve the predictive ability of risk stratification recommended by the ESC guidelines. Therefore, CONUT is expected to be an effective risk assessment tool for patients with IPAH in the future.

This study has several limitations. First, this is a single-center retrospective study. Future studies with larger sample sizes are needed to externally validate our findings. Second, the nutritional status was evaluated at patient admission. Dynamic assessments of nutritional status were lacking. Therefore, whether improvements in malnutritional status are associated with better conditions and outcomes in patients with IPAH is unknown. Third, further explorations need to be conducted to clarify whether nutritional interventions could improve the prognosis of patients with IPAH.

## Conclusions

Nutritional status evaluated by GNRI, PNI, and CONUT score were associated with disease severity in patients with IPAH. The CONUT score provided additional information on clinically worsening events in patients with IPAH, making it a meaningful risk stratification tool for these patients.

## Supplementary Information

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Supplementary Material 1.

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**Author contributions**
ZL, QL and ZZ contributed to the conception of the study. SZ, SL, and LG performed the data analyses and wrote the manuscript. QZ, TY and QZ contributed significantly to analysis and manuscript preparation. ZH, XL, AD and YW contributed to data collection. All authors critically reviewed the manuscript for intellectual content and had final responsibility for the decision to submit for publication.

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**Availability of data and materials**
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
This study followed the institutional guidelines of the "Declaration of Helsinki Ethical Principles" for all procedures involving human participants and was approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences. Written informed consent was obtained from all patients.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declared that they have no conflicts of interest.

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## Publisher's Note