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Diagnostic Accuracy of the Malnutrition Universal Screening Tool and Mini Nutritional Assessment Short-Form in Outpatients With Pulmonary Hypertension

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ABSTRACT

Several disease related factors of pulmonary hypertension (PH) can negatively impact the nutritional status, leading to an increased risk of malnutrition. However, there are no studies on the best method for nutritional screening in PH patients. Therefore, the aim of this study was to determine the diagnostic accuracy of two screening tools: the Malnutrition Universal Screening Tool (MUST) and the Mini Nutritional Assessment Short-Form (MNA-SF). This cross-sectional single center study included PH outpatients. Cut-off values MUST ≥ 1 and MNA-SF ≤ 11 were used for state of (risk of) malnutrition. The diagnostic criteria of the Global Leadership Initiative on Malnutrition (GLIM) were used as reference for diagnosing malnutrition. Diagnostic accuracy was determined by sensitivity, specificity, predictive positive value, negative predictive value, Cohen's Kappa- value (K) and area under the curve. Out of the 103 PH patients (age 67 years (SD 11.5), 66% female), 27% were malnourished according to the GLIM criteria. Both MUST and MNA-SF had an insufficient sensitivity (60.7% [CI: 41%–97%] vs. 64.3% [CI: 44%–81%]). The MUST had a specificity of 100% [CI: 95%–100%], PPV 100% [CI:94%–100%] and NPV 87.2% [CI:79%–93%]. The specificity of the MNA-SF was 81.3% [CI:70%–89%], PPV 56.3% [CI: 39%–73%] and NPV 85.9% [CI: 77%–93%]. The MUST had a higher K-value 0.692 and AUC (0.804) compared to the K-value 0.437 and AUC (0.728) of the MNA-SF. This study indicated that both MUST and MNA-SF are inaccurate to detect (risk of) malnutrition in PH outpatients. Future studies are needed to strive for a more sensitive screening tool.

Pulmonary hypertension (PH) is a progressive vascular disease characterized by elevated blood pressure in the pulmonary circulation. This elevated pulmonary arterial pressure can lead to right-sided heart failure, which contributes to high mortality rates. PH is defined by a mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest and there are five clinical classifications of PH that focus on the underlying cause. Treatment of PH aims to inhibit progression of the disease, reduce symptoms and improve quality of life (QoL) [1].

Multiple disease related factors can have a negative impact on the nutritional status of PH patients. First of all, patients often

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suffer from exercise intolerance, fatigue and shortness of breath [2] contributing to muscle wasting and poor functional capacity [3, 4]. Additionally, PH patients may exhibit increased resting metabolism due to alterations in the immune system, chronic inflammations or increased insulin resistance [2, 5]. Finally, PH-specific drugs are associated with side effects such as nausea, loss of appetite, vomiting, jaw pain, diarrhea, bone/muscle pain, peripheral oedema and fatigue [1, 6]. Therefore, PH patients are at risk of being malnourished. Malnutrition is a condition caused by inadequate nutrient intake or absorption, resulting in reduced fat-free mass and body cell mass. Malnutrition is associated with a negative impact on QoL, reduced physical and mental function and an impaired clinical outcomes [7, 8]. This highlights the importance of identifying the nutritional status of PH patients. Because the knowledge of the prevalence is limited, it is uncertain what the extend of malnutrition in PH is [2].

The Global Leadership Initiative on Malnutrition (GLIM) established a two-step approach to diagnose malnutrition in adults. The first step is to perform a validated nutritional screening tool to identify patients at risk for malnutrition. If patients are at risk, the second step is to assess whether patients meet the diagnostic criteria of malnutrition [9]. A widely used tool to screen for (risk of) malnutrition is the Malnutrition Universal Screening Tool (MUST), which is performed in adult patients in diverse healthcare settings [10]. The MUST relies on current body weight by assessing body mass index (BMI), percentage of unintentional weight loss and acute disease for determining (risk of) malnutrition. However, in advanced stages of PH, right ventricular failure may lead to peripheral oedema or ascites [11]. This potentially results into unreliable changes in bodyweight and masking signs of muscle wasting. Therefore, weight-based nutritional screening tools in PH patients may be biased due to fluid retention.

Fluid retention is also a symptom in left-sided heart failure (HF) patients. In contrast to PH, multiple studies have been performed to investigate nutritional status and various nutritional screening tools within HF patients. Malnutrition is highly prevalent in patients with HF. Among nutritional screening tools, the Mini Nutritional Assessment-Short Form (MNA-SF) demonstrated the highest sensitivity (71%) in HF outpatients [12] and was identified as an independent predictor of mortality in HF patients (relative risk: 4.85; 95% CI: 2.0–11.75) [13]. A systematic review assessing five nutritional screening tools for predicting all-cause mortality in HF inpatients and outpatients also identified the MNA-SF as the most effective tool (hazard ratio: 1.94; 95% CI: 1.40–2.70) [14]. Next to BMI and weight loss, the MNA-SF assesses diverse dimensions of nutritional status. This broader scope suggests the potential accuracy of the MNA-SF in screening for (risk of) malnutrition in PH patients.

To our best knowledge, literature regarding malnutrition in PH patients is scarce, despite the increased chance of malnutrition and consequent negative impact on QoL and mortality [7, 8]. It is important to be able to identify PH patients that are at risk for malnutrition. However, there is no nutritional screening tool available which is validated for PH patients. Therefore, the aim of this study was to assess the diagnostic accuracy of two widely used screening tools, the MUST and the MNA-SF.

1 | Methods

1.1 | Study Design and Subjects

This prospective cross-sectional study was conducted between January 2022 and August 2023 in the St. Antonius Hospital, a PH expertise center in the Netherlands. This study includes PH outpatients, diagnosed according to the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines [1]. Exclusion criteria were pregnancy, possessing electrical implants such as a pacemaker or defibrillator, status after pulmonary endarterectomy and/or patients treated in palliative setting. Measurements took place on site, integrated with routine appointments with the physician and physiotherapist. The Medical Ethics Committee of the St. Antonius Hospital declared that this study was not subject to the Medical Research Involving Human Subject Act (Z21.068). Written informed consent was obtained from each patient.

1.2 | Nutritional Screening

Four trained dietitians conducted the MUST and MNA-SF and assessed the GLIM criteria. Self-reported weight and length were used since all patients routinely measure their body weight at home.

The MUST contains three questions: current BMI, percentage unintentional weight loss and the presence of acute disease which compromises nutritional intake for > 5 days. The total score of the MUST score ranges from 0 to 6 points and is used to calculate an overall risk of malnutrition: '0 points: no risk of malnutrition', '1 point: medium risk of malnutrition' or '≥ 2 points: high risk of malnutrition'. In this study cut-off value of MUST ≥ 1 was used and two categories were created for cross-tabulation: medium or high risk of malnutrition ($\geq$ MUST 1) versus low risk of malnutrition (MUST 0) [10].

The MNA-SF contains six questions about appetite, unintentional weight loss, mobility, psychological stress, neuropsychological problems and BMI. The total score of the MNA-SF ranges from 0 to 14 and is used to categorized patients: '12–14 points: normal nutritional status', '8–11 points: at risk of malnutrition', '0–7 points: malnourished'. In this study cut-off value of MNA-SF ≤ 11 was used and two categories were created for cross-tabulation: at risk of malnutrition or malnourished (MNA-SF ≤ 11) versus normal nutritional status (MNA-SF ≥ 12) [15].

1.3 | Reference Standard

In line with the consensus reached by GLIM, an international workgroup of clinical nutrition scientist, we used the diagnostic set of the GLIM criteria to diagnose malnutrition. This diagnostic set contains three phenotypic criteria (unintentional weight loss of $> 5\%$ in last 3 months or $> 10\%$ indefinite of time, low body mass index $< 20\,kg/m^2$ if < 70 years or BMI $< 22\,kg/m^2$ if ≥ 70 years, or reduced muscle mass) and three etiologic criteria (reduced food intake, assimilation loss or inflammation and disease burden). At least one phenotypic

criterion and one etiologic criterion are required to diagnose malnutrition. Patients classified as malnourished according to the GLIM criteria are distinguished as moderately malnourished (BMI $< 20\ kg/m^2 < 70$ years or $< 22\ kg/m^2 \geq 70$ years, or unintentional weight loss of $> 5\%$ within 6 months or $> 10\%$ after more than 6 months) or severely malnourished (BMI $< 18{,}5\ kg/m^2 < 70$ years or $< 20\ kg/m^2 \geq 70$ years, or unintentional weight loss of $> 10\%$ within 6 months of $> 20\%$ after more than 6 months) [9].

The phenotypic criteria reduced muscle mass is defined as fat free mass index (FFMI) $< 15\ kg/m^2$ for females and $< 17\ kg/m^2$ for males [16]. Bioelectrical vector analysis (BIVA) using the BIA 101 BIVA (Akern S.R.L., Florence, Italy) was conducted to assess hydration status, based on the vector plot which provides insight into total body water. Presences of fluid overload was defined as yes or no [17]. Furthermore, bioelectrical impedance analysis (BIA) was used to measure the impedance of the body with resistance, reactance and phase angle, which were used to calculate FFMI to assess muscle mass. Measurements were performed in accordance to the Standard Operational Procedure [18]. Kyle formula was used to calculate FFMI per kg/m^2 [17–19]. Given the increasing evidence implicating that PH is associated with an (chronic) inflammatory response, the decision was made to classify all patients positive on the etiologic criteria 'inflammation/disease burden' [20]. For the cross-tabulation two categories were made: 'well-nourished according to the GLIM criteria' or 'moderately or severe malnourished according to the GLIM criteria'.

1.4 | Additional Data

Clinical data including aerobic capacity assessed by the 6-min walking distance (6MWD) supervised by a physiotherapist and blood parameters (NT-pro BNP, eGFR and ferritin) were gathered on the day of inclusion. These data were extracted from the electronic patient record in combination with most recent available information on the severity of PH, such as the New York Heart Association classification functional class (NYHA). Pulmonary hemodynamic measurements by right heart catheterization at time of diagnosis (mean pulmonary arterial pressure (mPAP), pulmonary artery wedge pressure (PAWP), cardiac output (CO), pulmonary vascular resistance (PVR) expressed in Wood Unit (WU)) and current use of PH specific medication or oxygen therapy. Additionally, information on the current use of diuretics or statins and comorbidities were included.

All data were collected and managed using an electronic data capture tool: REDCap 14.0.19 (2024 Vanderbilt University) [21].

1.5 | Statistical Analyses

Descriptive statistics were used to express means with standard deviations (SD) in case of normal distribution, medians with interquartile range (IQR) in case of non-normal distribution and percentages and frequencies in case of categorical variables. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) from ROC-curves were calculated to express diagnostic accuracy. Cohen's Kappa (K) was used to determine concordance between screening tools and reference standard. Se, Sp, PPV and NPV are expressed as %, with the Clopper Pearson exact 95% confidence interval (CI). The following cut-off points were used to interpret diagnostic values of Se, Sp, PPV and NPV: $< 60\%$ poor, 60–70% insufficient, 70–80% fair, 80–90% good, 90–100% excellent [22]. For AUC and K-values the following values were used for the interpretation: AUC < 0.6 and K-value < 0.4 poor, AUC 0.6–0.8 and K-value 0.4–0.6 fair, AUC > 0.8 and K-value > 0.6 good [23]. Subgroup analyses were performed comparing patients aged < 65 years and ≥ 65 years of age, since the MNA-SF is originally designed for patients ≥ 65 years [15]. IBM SPSS statistics version 29 was used to perform statistical analyses.

2 | Results

In total 103 PH patients (66% women, mean age 67 years (SD 11.5) and 63% ≥ 65 years) were included in the study. The majority was diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH) (48.5%) followed by pulmonary arterial hypertension (PAH) (41.7%). The mean mPAP was 40.2 (SD 13.2) mmHg, mean PVR 6.5 (SD 3.9) WU, 48.5% of the included patients were in NYHA functional class III or IV and 94% was treated with at least one PH specific drug. The mean 6MWD was 385.2 (SD 125) meters. Baseline characteristics of the study population are presented in Table 1.

The mean BMI of the total population was 27.8 (SD 5.4) kg/m^2, 63.1% had a BMI $> 25\ kg/m^2$ and the mean FFMI was 18.2 (SD 2.6) kg/m^2. According to the GLIM criteria, 28 patients (27.2%) were malnourished. Malnutrition was mainly caused by a low muscle mass (50%) and/or unintentional weight loss (46.4%) in combination with inflammation and disease burden. Malnutrition caused by a low BMI was less prevalent (35.7%). The MUST identified seventeen patients (16.5%) as medium or high risk of malnutrition and 86 patients (83.5%) as low risk of malnutrition. The MNA-SF identified 32 (31.1%) patients at risk of malnutrition or malnourished and 71 patients (68.9%) with a normal nutrition status. Out of the 28 malnourished patients according to the GLIM criteria, only two patients scored a MUST ≥ 2 and only one patient was classified as MNA-SF ≤ 7.

Fluid overload based on the BIVA was present in 14.6% of the patients. In the 'well-nourished' group fluid overload was present in 13 patients (17%). None of these 13 patients were near the established cut-off values for a low BMI or low FFMI according to the diagnostic GLIM criteria. Nutritional variables of the study population are presented in Table 2.

The diagnostic accuracy of both screening tools is presented in Table 3. The MUST had an insufficient Se (60.7% (CI 41–79)), an excellent Sp (100% (CI 95–100)) and PPV (100% (CI 94–100)) and a good NPV (87.2% (CI 79–93)), K-value (0.692) and AUC (0.804). The MNA-SF had an insufficient Se (64.3% (CI 44–81)), a good Sp and NPV (81.3% (CI 70–89); 85.9% (CI 77–93)), a poor PPV (56.3% (CI 39–73)) and a fair K-value (0.437) and AUC (0.728).

TABLE 1 | Baseline characteristics of the total study population and stratified by nutritional status.

	Total population ($n = 103$)	Well-nourished according to the GLIM ($n = 75$)	Moderately or severe malnourished according to the GLIM ($n = 28$)
Female, *n* (%)	68 (66)	48 (64)	20 (71.4)
Age, mean (SD)	67 (11.5)	67 (11.4)	68 (12.0)
≥ 65 year, *n* (%)	65 (63.1)	45 (60)	20 (71.4)
6MWD in meters, mean (SD)	385.2 (125)	391 (122)	369.3 (133)
NT-prBNP pg/ml, median (IQR)	271 (73–739)	227 (597)	448 (1204)
eGFR, ml/min per 1,73 m^2, median (IQR)	65 (50–81)	65 (27)	70 (44)
Ferritin, µg/l, median (IQR)	69 (32–126)	75 (96)	54 (97)
Use of diuretics, *n* (%)	68 (66)	50 (66.7)	18 (64.3)
Use of statins, *n* (%)	29 (28.2)	19 (25.3)	10 (5.7)
O2 therapy, *n* (%)	30 (29.1)	22 (29.3)	8 (28)
Current smoker, *n* (%)	6 (5.8)	3 (4)	6 (5.8)
Comorbidity, *n* (%)			
Hypertension	23 (25)	15 (20)	8 (28.6)
Chronic obstructive pulmonary disease	10 (10.9)	7 (9.3)	3 (10.7)
Diabetes mellitus	12 (13.0)	7 (9.3)	5 (17.9)
Coronary artery disease	23 (25)	20 (26.7)	3 (10.7)
Trombo embolic event	46 (50)	34 (45.3)	12 (42.9)
WHO groups, *n* (%)			
I: Pulmonary arterial hypertension	43 (41.7)	30 (40)	13 (46.4)
II: PH as a result of left heart disease	7 (6.8)	6 (8)	1 (3.6)
III: PH as a result of lung diseases	3 (2.9)	2 (2.7)	1 (3.6)
IV: Chronic thromboembolic PH	50 (48.5)	37 (49.3)	13 (46.4)
Diagnosis in years, median (IQR)	2 (4)	3 (6)	2 (4)
Right heart catheterization			
mPAP, mmHg, mean (SD)	40.2 (13.2)	40.2 (13.8)	40 (12.1)
PAWP, mmHg, mean (SD)	11.6 (6.6)	12.2 (6.6)	10.1 (6.4)
CO, l/min, mean (SD)	5.2 (1.5)	5.4 (1.5)	4.8 (1.4)
PVR, WU, mean (SD)	6.5 (3.9)	6.2 (3.7)	7.2 (4.4)
NYHA classification, *n* (%)[a]			
– I	9 (8.7)	7 (9.3)	2 (7.1)
– II	43 (41.7)	34 (45.3)	9 (32.1)
– III	47 (45.6)	31 (41.3)	16 (57.1)
– IV	3 (2.9)	2 (2.7)	1 (3.6)
PH specific medication, *n* (%)			
– None	6 (5.8)	6 (8)	---

(Continues)

TABLE 1 | (Continued)

	Total population ($n = 103$)	Well-nourished according to the GLIM ($n = 75$)	Moderately or severe malnourished according to the GLIM ($n = 28$)
– Mono	18 (7.5)	13 (17.3)	5 (17.9)
– Dual	65 (63.1)	47 (62.7)	18 (64.3)
– Triple	14 (13.6)	9 (12)	5 (17.9)

[a]1 missing value.
Abbreviations: SD: standard deviation; IQR: Interquartile Range; GLIM: Global Leadership Initiative on Malnutrition; MUST: Malnutrition Universal Screening Tool; MNA-SF: Mini Nutritional Assessment—Short Form; PH: Pulmonary Hypertension; WHO: World Health Organisation; mPAP: mean Pulmonary Artery Pressure; PAWP: Pulmonary Arterial Wedge Pressure; CO: Cardiac Output; PVR: Pulmonic Valve Replacement; NYHA: New York Heart Association; 6MDW: 6 min Walking Distance; NT-prBNP: N-terminal pro B-type natriuretic peptide; eGFR: estimated Glomerular Filtration Rate.

TABLE 2 | Nutritional variables of the total study population and stratified by nutritional status.

	Total population ($n = 103$)	Well-nourished according to the GLIM criteria ($n = 75$)	Moderately or severe malnourished according to the GLIM criteria ($n = 28$)
Nutritional variables			
Weight, kg, mean (SD)	80.4 (16.8)	83.9 (16.7)	71.1 (13.2)
Fat free mass index, kg/m^2, mean (SD)	18.2 (2.6)	18.9 (2.4)	16.1 (1.8)
Fluid overload present, yes (%)	15 (14.6)	13 (17.3)	2 (7.1)
BMI, kg/m^2, mean (SD)	27.8 (5.4)	29.1 (4.9)	24.3 (5.1)
BMI > 25 kg/m^2, yes (%)	65 (63.1)	56 (74.7)	9 (32.1)
Phase angle, mean (SD)	5.6 (0.93)	5.7 (0.97)	5.1 (0.61)
GLIM phenotypic criteria, *n* (%)			
Unintentional weight loss	13 (12.6)	—	13 (46.4)
Low BMI	10 (9.7)	—	10 (35.7)
Low muscle mass	14 (13.6)	—	14 (50)
GLIM etiologic criteria	103 (100)	75 (100)	28 (100)
GLIM total score			
Well-nourished	75 (72.8)	75 (100)	—
Moderately malnourished	26 (25.3)	—	26 (92.9)
Severe malnourished	2 (1.9)	—	2 (7.1)
MUST, *n* (%)			
0, low risk of malnutrition	86 (83.5)	75 (100)	11 (39.3)
1, medium risk of malnutrition	15 (14.6)	—	15 (53.6)
≥ 2, high risk at malnutrition	2 (1.9)	—	2 (7.1)
MNA-SF, *n* (%)			
12–14 normal nutritional status	71 (68.9)	61 (81.3)	10 (35.7)
8–11 at risk of malnutrition	31 (30.1)	14 (18.7)	17 (60.7)
0–7 malnourished	1 (1.0)	—	1 (3.6)

Abbreviations: BMI: Body Mass Index; GLIM: Global Leadership Initiative on Malnutrition; MNA-SF: Mini Nutritional Assessment-Short Form; MUST: Malnutrition Universal Screening Tool; SD: standard deviation.

Subgroup analyses (< 65 years vs. ≥ 65 years) showed that the MNA-SF was more sensitive in patients ≥ 65 years (Se 37.5% (CI 9–76) vs. Se 75% (CI 51–91)) and Sp was higher for patients ≥ 65 years (76.7% (CI 58–90) vs. 84.4% (70–94)). The MUST showed a smaller difference in sensitivity after performing subgroup analyses for age groups (Se 50% (CI 16–84) vs. Se 65% (CI 41–85)). Sp of the MUST in both age groups was 100% (92–100; 88–100). See Table 4.

3 | Discussion

To our knowledge, this is the first prospective cross-sectional study that assessed diagnostic accuracy of nutritional screening tools in PH outpatients using the GLIM criteria as reference standard. This study found that over a quarter of the PH outpatients are malnourished according to the GLIM criteria. The MUST and MNA-SF are accurate to identify well-nourished patients, however both screening tools are insufficient to detect (risk of) malnutrition since 36–39% of the patients (at risk of) malnutrition were not identified.

TABLE 3 | Classification and diagnostic accuracy of the MUST (≥ 1) and MNA-SF (≤ 11) using GLIM criteria as reference standard.

	MUST ($n = 103$)	MNA-SF ($n = 103$)
True positive, *n* (%)	17 (61)	18 (64)
True negative, *n* (%)	75 (100)	61 (81)
False positive, *n* (%)	—	14 (19)
False negative, *n* (%)	11 (39)	10 (36)
Sensitivity, % (95% CI)	60.7 (41–79)	64.3 (44–81)
Specificity, % (95% CI)	100 (95–100)	81.3 (70–89)
Positive predictive value, % (95% CI)	100 (94–100)	56.3 (39–73)
Negative predictive value, % (95% CI)	87.2 (79–93)	85.9 (77–93)
K-value	0.692	0.437
AUC	0.804	0.728

Abbreviations: AUC, area under the curve from ROC; CI, confidence interval; GLIM, Global Leadership Initiative on Malnutrition; K-value derived from Cohen's Kappa statistics; MNA-SF, Mini Nutritional Assessment-Short Form; MUST, Malnutrition Universal Screening Tool.

While it is ideal for screening tools to provide both high sensitivity and specificity for accurately classifying patients' nutritional status, we argue that it is of greater importance to identify patients (at risk of) malnutrition, instead of identifying well-nourished patients, as they need dietetic interventions. Unfortunately, both MUST and MNA-SF demonstrated an insufficient sensitivity.

Several factors can contribute to this lack of sensitivity. One possible explanation is that alongside unintentional weight loss and low BMI, low muscle mass is part of the phenotypic criteria of the GLIM but there is an absence of muscle mass assessment in both screening tools. Our study found that 50% of the patients (at risk of) malnutrition had a low FFMI. This could have contribute to the discrepancy between the number of patients classified as malnourished according to the GLIM but not according to the screening tools. The presence of a low muscle mass without unintentional weight loss or low BMI is in accordance with an increased risk of sarcopenic obesity within PH patients. Sarcopenic obesity can be caused by reduced exercise function due to right heart failure [2]. Furthermore, due to the risk of fluid retention, body weight could be unreliable and possibly cover up muscle wasting and sarcopenic obesity. This is also observed in HF patients where BMI is unreliable to assess nutritional status [24]. To our best knowledge, there are no studies on the reliability of BMI in PH patients. In our study we did included BMI at baseline to describe our study population, also because it is a widely used variable in practice. However, we do not recommend using BMI as an single parameter to diagnose malnutrition, but to incorporate it alongside weight loss, muscle mass and hydration status. This is in line with the GLIM criteria, which emphasize assessing multiple phenotypic criteria, rather than relying on a single criteria [9].

In our study BIA was used to measure FFMI and account for hydration status. Contrary to our expectations, fluid overload

TABLE 4 | Diagnostic accuracy of the MUST (≥ 1) and MNA-SF (≤ 11) using GLIM criteria as reference standard, stratified by age group.

	MUST ($n = 38$) < 65 years	MUST ($n = 65$) ≥ 65 years	MNA-SF ($n = 38$) < 65 years	MNA-SF ($n = 65$) ≥ 65 years
True positive, *n* (%)	4 (50)	13 (65)	3 (37.5)	15 (75)
True negative, *n* (%)	30 (100)	45 (100)	23 (76.7)	38 (84.4)
False positive, *n* (%)	—	—	7 (23.3)	7 (15.6)
False negative, *n* (%)	4 (50)	7 (35)	5 (62.5)	5 (25)
Sensitivity, % (95% CI)	50 (16–84)	65 (41–85)	37.5 (9–76)	75 (51–91)
Specificity, % (95% CI)	100 (88–100)	100 (92–100)	76.7 (58–90)	84.4 (70–94)
Positive predictive value, % (95% CI)	100 (87–100)	100 (91–100)	30 (9–61)	68.2 (48–85)
Negative predictive value, % (95% CI)	88 (75–96)	87 (76–94)	82 (66–93)	88.4 (77–96)

Abbreviations: AUC, area under the curve from ROC; CI, confidence interval; GLIM, Global Leadership Initiative on Malnutrition; K-value derived from Cohen's Kappa statistics; MNA-SF, Mini Nutritional Assessment-Short Form; MUST, Malnutrition Universal Screening Tool.

was observed in only 15% of the patients based on this vector plot analysis. This might suggests that the possibility of masking low BMI and low FFMI was limited in our study. One of the explanations might be the fact that only outpatients under active treatment were included as the measurements were performed on the same day as the routine outpatient visits. As a result, patients were probably receiving effective treatment to prevent fluid retention, supported by the fact that almost 70% were using diuretics.

Another possible explanation for the poor sensitivity might be that all patients were classified positive on the etiology criteria inflammation/disease burden of the GLIM [25–27], which the MUST and MNA-SF may not adequately assess. Within the MUST, patients will only score positive for disease burden if acute disease is combined with the chance of more than 5 days no nutritional intake, which is unlikely in the outpatient setting. The MNA-SF asks patients if they suffered from psychological stress or acute disease in the past 3 months. In practice, this subjective question may cause a situation where patients with chronic disease burden score 'no' since they did not experience suffering. Therefore, the MUST and MNA-SF may not adequately assess the aspects of inflammation or disease burden.

The last explanation of the observed poor sensitivity can be found in the differences in population used for the derivation of the screening tools versus the study population. Our study included adults of all ages, whereas the MNA-SF is designed for those over 65 years. However, studies recommending the MNA-SF within HF patients also based their findings on adults of all ages [12, 28]. Taking the small numbers into account, subgroup analysis showed improved sensitivity for patients over 65 but good or excellent sensitivity was still not achieved. This indicates that the MNA-SF remains insufficient to screen for (risk of) malnutrition in PH outpatients.

The low sensitivity of both MUST and MNA-SF is remarkable since both screening tools are validated within various healthcare settings [7, 29]. A large recent study in the Netherlands examined the validity of five nutritional screening tools in a heterogeneous older population of hospitalized patients against the GLIM criteria, using different cut-off values. They found that these tools might not be sensitive enough to identify malnourished patients, which is in line with our results [30]. Given that the GLIM criteria were created after the screening tools were developed, the question is raised whether the screening tools are still valid today. Accordingly, future studies should be focusing on identifying or developing more sensitive nutritional screening tools for PH outpatients. Until more sensitive screening tools are available, we suggest considering the direct application of step two of the GLIM, the diagnostic criteria. Especially in high-risk patient groups such as systemic sclerosis-associated PAH. Screening for malnutrition, or possibly direct use of the diagnostic criteria, is recommended at the time of diagnosis and at follow-up visits with the nurse practitioner to identify malnourished patients at an early stage.

A limitation of the study is the exclusive use of liberal cut-off values (MUST ≥ 1 and MNA-SF ≤ 11) for calculating diagnostic accuracy, whereas more conservative cut-off values (MUST ≥ 2 and MNA-SF ≤ 7) are more common in practice. The liberal cut-off values were consciously chosen to also include patients at risk of malnutrition. Besides, the study lacks power to analyze conservative cut-off values, since only two malnourished patients based on the GLIM criteria were categorized as MUST ≥ 2 and only one patient scored MNA-SF ≤ 7. Nevertheless, the results of this study suggest an important insight: if these more conservative cut-off values are applied, malnourished PH outpatients will rarely be identified and the sensitivity of the screening tool will be close to zero. In this study all patients were scored on the etiologic criteria 'inflammation/disease burden', this might overestimate malnutrition based on the GLIM criteria. However, all patients diagnosed with PH are considered to have a significant disease burden, as PH is a severe, progressive and chronic disease. An underlying pathophysiological feature of all forms of PH, particularly PAH and CTEPH, is vasculopathy. This vasculopathy is both driven and maintained by inflammatory processes, which are central to the pathophysiology of the disease [25–27]. In addition, a study showed that levels of C-reactive protein (CRP), a marker of inflammation, were increased in PAH and CTEPH patients and that increased CRP levels may predicted mortality and adverse clinical outcomes in PAH patients [31]. There is also evidence that inflammation affects nutritional status in PAH patients, emphasizing the need for comprehensive screening tools [2].

Furthermore, all five groups of PH were included in this study, with CTEPH being the largest group (49%) followed by PAH (42%). CTEPH patients are generally older than PAH patients, which may explain the relatively high mean age in our study [1]. However, as the GLIM criteria use age-specific BMI cut-offs and age is included in the Kyle formula for FFMI calculation to identify low muscle mass, we expect that the effect of age on the results will be limited. Larger prospective multicenter studies are warranted to further clarify the influence of age, and to explore differences in nutritional status between different forms of PH since the pathophysiology differs related to the underlying cause of pulmonary hypertension. In addition, these future studies can give more insight into the prevalence and impact of malnutrition in PH.

In conclusion, this study presents important findings for clinical practice. Although the MUST and MNA-SF are accurate to identify well-nourished PH outpatients, they are less suitable for detecting (risk of) malnutrition. Given the importance of early identification and dietetic interventions for patients (at risk of) malnutrition, future research with a larger study population is necessary. These studies should focus on identifying or developing a more sensitive screening tool for PH outpatients, emphasizing the importance of objectively assessing the risk of low muscle mass, taking into account hydration status and the presence of (chronic) inflammation.

Author Contributions

E. Grimbergen conceived and designed the study, participated in data collection and statistical analyses, drafted and wrote the manuscript and coordinated the study. S.P.M. van Aarssen contributed to data collection, statistical analyses, data interpretation, drafting and writing the

manuscript. D.P. Staal contributed to data curation, drafting the original draft and writing/editing the manuscript. J. Peper helped with statistical analyses, data interpretation and writing/editing the manuscript. J.J. Mager, S. Boerman, B.J.M. Mulder reviewed and commented on the manuscript and supervised during the study. M.C. Post supervised in the conception and design of the study, data interpretation and writing/editing the manuscript. All authors read and approved the final manuscript.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The Medical Ethics Committee of the St. Antonius Hospital declared that this study was not subject to the Medical Research Involving Human Subject Act (Z21.068). Written informed consent was obtained from each patient.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. M. Humbert, G. Kovacs, M. M. Hoeper, et al., "2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension," *European Heart Journal* 43, no. 38 (2022): 3618–3731.

2. P. Vinke, S. M. Jansen, R. F. Witkamp, and K. van Norren, "Increasing Quality of Life in Pulmonary Arterial Hypertension: Is There a Role for Nutrition?," *Heart Failure Reviews* 23, no. 23 (2018): 711–722.

3. C. W. Le Roux, "The Putative Satiety Hormone PYY Is Raised in Cardiac Cachexia Associated With Primary Pulmonary Hypertension," *Heart* 91, no. 2 (2005): 241–242, http://heart.bmj.com/content/91/2/241.abstract.

4. M. Riou, M. Pizzimenti, I. Enache, et al., "Skeletal and Respiratory Muscle Dysfunctions in Pulmonary Arterial Hypertension," *Journal of Clinical Medicine* 9, no. 9 (2020): E1–E12.

5. C. T. Kwant, F. A. L. Horst, van der, H. J. Bogaard, F. S. Man, de, and A. Vonk Noordegraaf, "Nutritional Status in Pulmonary Arterial Hypertension," *Pulmonary Circulation* 12, no. 4 (2022): e12173.

6. L. H. Clapp, C. Picken, and K. C. Fragkos, et al, "Adverse Events of Prostacyclin Mimetics in Pulmonary Arterial Hypertension: A Systematic Review and Meta-Analysis," *Journal of Clinical Medicine* 8, no. 4 (2019): 481.

7. T. Cederholm, R. Barazzoni, P. Austin, et al., "ESPEN Guidelines on Definitions and Terminology of Clinical Nutrition," *Clinical Nutrition* 36, no. 1 (2017): 49–64.

8. H. Kruizenga, S. Beijer, G. Huisman-de-Waal, et al., *Richtlijn Ondervoeding* (Stuurgroep Ondervoeding, 2019). 1.

9. T. Cederholm, G. L. Jensen, M. I. T. D. Correia, et al., "GLIM Criteria for the Diagnosis of Malnutrition—A Consensus Report From the Global Clinical Nutrition," *Clinical Nutrition* 38, no. 1 (2019): 1–9.

10. P. Marinos Elia, The "MUST" Report THE "MUST" REPORT Nutritional Screening of Adults: A multidisciplinary responsibility Development and use of the "Malnutrition Universal Screening Tool" ('MUST') for Adults Chairman of MAG and Editor Advancing Clinical Nutrition.

11. R. W. Schrier and S. Bansal, "Pulmonary Hypertension, Right Ventricular Failure, and Kidney: Different From Left Ventricular Failure?," *Clinical Journal of the American Society of Nephrology* 3, no. 5 (2008): 1232–1237.

12. C. Joaquín, R. Puig, P. Gastelurrutia, et al., "Mini Nutritional Assessment Is a Better Predictor of Mortality Than Subjective Global Assessment in Heart Failure Out-Patients," *Clinical Nutrition* 38, no. 6 (2019): 2740–2746.

13. A. F. Osório, É. C. T. Ribeiro, S. M. Parahiba, G. C. Forte, N. O. Clausell, and G. C. Souza, "Prognostic Value of Nutritional Screening Tools in Hospitalized Patients With Decompensated Heart Failure: A Systematic Review and Meta-Analysis," *Nutrition Research (New York, N.Y.)* 120, no. 2023 (2023): 1–19, https://doi.org/10.1016/j.nutres.2023.09.009.

14. Y. Hu, H. Yang, Y. Zhou, et al., "Prediction of All-Cause Mortality With Malnutrition Assessed by Nutritional Screening and Assessment Tools in Patients With Heart Failure: A Systematic Review," *Nutrition, Metabolism, and Cardiovascular Diseases* 32, no. 6 (June 2022): 1361–1374.

15. L. Z. Rubenstein, J. O. Harker, A. Salvà, et al., "Screening for Undernutrition in Geriatric Practice: Developing the Short-Form Mini-Nutritional Assessment (MNA-SF) [Internet]," *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 56, no. 6 (2001): 366–372, https://academic.oup.com/biomedgerontology/article/56/6/M366/526432.

16. R. Barazzoni, G. L. Jensen, M. I. T. D. Correia, et al., "Guidance for Assessment of the Muscle Mass Phenotypic Criterion for the Global Leadership Initiative on Malnutrition (GLIM) Diagnosis of Malnutrition," *Clinical Nutrition* 41, no. 6 (2022): 1425–1433.

17. K. Norman, N. Stobäus, M. Pirlich, and A. Bosy-Westphal, "Bioelectrical Phase Angle and Impedance Vector Analysis—Clinical Relevance and Applicability of Impedance Parameters," *Clinical Nutrition* 31, no. 6 (2012): 854–861.

18. H. E. E. Zweers, Standard Operating Procedure - Single Frequency Bio-Impedantie Analyse (June 2021).

19. U. Kyle, "Bioelectrical Impedance Analysis—Part I: Review of Principles and Methods," *Clinical Nutrition* 23, no. 5 (2004): 1226–1243.

20. C. Guignabert, J. Aman, S. Bonnet, et al., "Pathology and Pathobiology of Pulmonary Hypertension: Current Insights and Future Directions," *European Respiratory Journal* 64, no. 4 (2024): 2401095.

21. P. A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, and J. G. Conde, "Research Electronic Data Capture (Redcap)-A Metadata-Driven Methodology and Workflow Process for Providing Translational Research Informatics Support," *Journal of Biomedical Informatics* 42, no. 2 (2009): 377–381, https://doi.org/10.1016/j.jbi.2008.08.010.

22. E. Leistra, J. A. E. Langius, A. M. Evers, et al., "Validity of Nutritional Screening With MUST and SNAQ in Hospital Outpatients," *European Journal of Clinical Nutrition* 67, no. 7 (2013): 738–742.

23. L. Power, D. Mullally, E. R. Gibney, et al., "A Review of the Validity of Malnutrition Screening Tools Used in Older Adults in Community and Healthcare Settings—A Manuel Study," *Clinical Nutrition ESPEN* 24 (2018): 1–13.

24. C. Joaquín, N. Alonso, J. Lupón, et al., "Nutritional Status According to the GLIM Criteria in Patients With Chronic Heart Failure: Association With Prognosis," *Nutrients* 14, no. 11 (2022): 2244.

25. M. Rabinovitch, C. Guignabert, M. Humbert, and M. R. Nicolls, "Inflammation and Immunity in the Pathogenesis of Pulmonary Arterial Hypertension," *Circulation Research* 115, no. 1 (2014): 165–175.

26. H. Zhao, J. Song, X. Li, et al., "The Role of Immune Cells and Inflammation in Pulmonary Hypertension: Mechanisms and Implications," *Frontiers in Immunology* 15, no. March (2024): 1–9.

27. R. Wang, T. Yuan, J. Wang, et al., "Immunity and Inflammation in Pulmonary Arterial Hypertension: From Pathophysiology Mechanisms to Treatment Perspective," *Pharmacological Research* 180 (2022): 106238.

28. N. Abdoul Carime, J. Cottenet, G. Clerfond, et al., "Impact of Nutritional Status on Heart Failure Mortality: A Retrospective Cohort Study," *Nutrition Journal* 21, no. 1 (2022): 2.

29. J. Kondrup, “ESPEN Guidelines for Nutrition Screening 2002,” *Clinical Nutrition* 22, no. 4 (2003): 415–421.

30. C. Dronkelaar, van, M. Tieland, T. Cederholm, E. M. Reijnierse, P. J. M. Weijs, and H. Kruizenga, “Malnutrition Screening Tools Are not Sensitive Enough to Identify Older Hospital Patients With Malnutrition,” *Nutrients* 15, no. 24 (2023): 5126.

31. R. Quarck, T. Nawrot, B. Meyns, and M. Delcroix, “C-Reactive Protein,” *Journal of the American College of Cardiology* 53, no. 14 (2009): 1211–1218.