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Prevalence and Prognostic Significance of Malnutrition Using 3 Scoring Systems Among Outpatients With Heart Failure

A Comparison With Body Mass Index

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ABSTRACT

OBJECTIVES The authors sought to report the prevalence, clinical associations, and prognostic consequences of malnutrition in outpatients with heart failure (HF).

BACKGROUND Malnutrition may be common in HF and associated with adverse outcomes, but few data exist.

METHODS We applied the geriatric nutritional risk index (GNRI), controlling nutritional status (CONUT) score, and prognostic nutritional index (PNI) to consecutive patients referred with suspected HF to a clinic serving a local population (n = 550,000).

RESULTS Of 4,021 patients enrolled, HF was confirmed in 3,386 (61% men; median age: 75 years; interquartile range [IQR]: 67 to 81 years, median N-terminal pro-B-type natriuretic peptide [NT-proBNP]: 1,103 ng/l [IQR: 415 to 2,631 ng/l]). Left ventricular ejection fraction was <40% in 35% of patients. Using scores for GNRI ≤91, CONUT >4, and PNI ≤38, 6.7%, 10.0%, and 7.5% patients were moderately or severely malnourished, respectively; 57% were at least mildly malnourished by at least 1 score. Worse scores were most strongly related to older age, lower body mass index, worse symptoms and renal function, atrial fibrillation, anemia, and reduced mobility. During a median follow-up of 1,573 days (IQR: 702 to 2,799 days), 1,723 (51%) patients died. For patients who were moderately or severely malnourished, 1-year mortality was 28% for CONUT, 41% for GNRI, and 36% for PNI, compared with 9% for those with mild malnutrition or normal nutritional status. A model including only age, urea, and logNT-proBNP, predicted 1-year survival (C-statistic: 0.719) and was slightly improved by adding nutritional indices (up to 0.724; $p < 0.001$) but not body mass index.

CONCLUSIONS Malnutrition is common among outpatients with HF and is strongly related to increased mortality. (J Am Coll Cardiol HF 2018;6:476–86) © 2018 by the American College of Cardiology Foundation.

Although often ignored, malnutrition is common in patients with chronic heart failure (HF) (1) and associated with a high mortality (2,3). Severe HF may lead to loss of appetite, malabsorption, and a catabolic state, leading to malnutrition (1). Malnutrition may also be a driver of disease progression as part of a vicious cycle associated with cytokine activation, autonomic dysfunction, and cachexia (4).

Screening patients with HF for malnutrition might identify patients at high risk of adverse outcomes who might benefit from tailored treatments or interventions to prevent deterioration in HF and improve prognosis (5). There are many screening tools for malnutrition, but no consensus on which to use for patients with HF (6–8). Among malnutrition scores, the controlling nutritional status (CONUT) index, the prognostic nutritional index

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(PNI), and the geriatric nutritional risk index (GNRI) have been studied in HF (9). The prevalence of malnutrition varies depending on the screening tool used and has been reported to be as high as 69% in some HF populations (9). Malnutrition determined by any of these scoring methods is an independent predictor of worsening HF and/or mortality (9); however, the studies conducted so far have been small and may not have been epidemiologically representative of the general population with HF.

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Accordingly, we investigated the prevalence and prognostic importance of malnutrition using 3 different scoring systems in a large, well-characterized cohort of ambulatory patients with HF.

METHODS

STUDY POPULATION. Consecutive consenting patients referred to a community HF clinic between 2000 and 2016 with suspected HF were enrolled. HF was defined as the presence of symptoms or signs of HF and evidence of cardiac dysfunction; either left ventricular ejection fraction (LVEF) <40% or raised plasma concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (>125 ng/l) (10). We excluded patients from this analysis if they had no measurement of height, weight, or NT-proBNP recorded; we also excluded 6 patients with a diagnosis of chronic lymphocytic leukemia (Online Figure 1).

Patients with HF were phenotyped as reduced ejection fraction (HFrEF: LVEF <40%, or at least moderate left ventricular systolic dysfunction by visual inspection on echocardiography if LVEF was not available) or normal ejection fraction (HFnEF: LVEF ≥40%, or better than, or equal to, mild-moderate left ventricular systolic dysfunction by visual inspection on echocardiography if LVEF was not available, and NT-proBNP >125 ng/l) (10). Patients with LVEF ≥40% and NT-proBNP ≤125 ng/l were considered not to have HF. Patients with HF were stratified by plasma NT-proBNP concentration: ≤400, 401 to 1,000, 1,001 to 2,000, 2,001 to 4,000, and >4,000 ng/l.

A medical history and findings on physical examination were recorded. Ischemic heart disease was defined as any medical history of acute coronary syndrome, percutaneous coronary intervention or coronary artery bypass surgery, or diagnosis of myocardial ischemia based on invasive or noninvasive diagnostic tests. Cerebrovascular disease (CVD) was defined as any previous history of stroke or transient ischemic attack. Peripheral vascular disease (PVD) was defined as evidence of extracardiac arterial disease at ultrasound, such as those of the lower limbs and abdominal aorta. Chronic obstructive pulmonary disease, hypertension, and active cancer were defined as a clinical history of the diagnoses recorded in patients' notes. Significantly deranged liver function test was defined as serum alanine aminotransferase >50% upper limit of normal.

Blood was taken for standard hematology and biochemistry profiles and NT-proBNP. Patients had an electrocardiogram and echocardiogram done by an experienced sonographer using a Vivid 5, 7, or 9 Scanner (GE, Fairfield, Connecticut). All patients had left ventricular systolic function evaluated by visual assessment recorded (ranging from normal to severely impaired), whereas LVEF was calculated using the Simpson method. Patients were weighed in their casual wear without shoes. Body mass index (BMI) was calculated using the formula: BMI = weight in kilograms/(height in meters)^2. Patients were classified into 5 BMI (kg/m^2) categories: underweight (BMI <18.5), normal (BMI 18.5 to 24.9), overweight (BMI 25.0 to 29.9), obese (BMI 30.0 to 39.9), and morbidly obese (BMI ≥40) (11).

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All subjects gave their written informed consent for their data to be used for research.

MALNUTRITION SCREENING TOOLS. Patients were screened for malnutrition using 3 indices (Online Table 1). The GNRI is calculated using the formula: 1.489 × serum albumin (g/l) + 41.7 × (body weight in kilograms/ideal body weight) (7). We calculated the ideal body weight using the formula: 22 × square of height in meters (12). A score >98 was considered normal; scores of 92 to 98, 82 to 91, and <82 reflect mild, moderate, and severe malnutrition, respectively.

The CONUT score was developed by Ulibarri and colleagues in 2005 as a screening tool for the nutritional status of hospitalized patients (6). It takes into account serum albumin, cholesterol, and total lymphocyte count. A score of 0 to 1 is considered normal; scores of 2 to 4, 5 to 8, and 9 to 12 reflect mild, moderate, and severe malnutrition, respectively.

The PNI is calculated using the formula: 10 × serum albumin (g/dl) + 0.005 × total lymphocyte count

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CI = concordance index

CVD = cerebrovascular disease

CONUT = controlling nutritional status index

GNRI = geriatric nutritional risk index

HFnEF = heart failure with normal ejection fraction

HFrEF = heart failure with reduced ejection fraction

HF = heart failure

IQR = interquartile range

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PNI = prognostic nutritional index

PVD = peripheral vascular disease

TABLE 1 Baseline Characteristics of all Patients Referred With Suspected HF

	No HF	HF			p Value*	
	(LVEF ≥40% and NT-proBNP ≤125 ng/l) (n = 635)	HFrEF (LVEF <40%) (n = 1,198)	HFnEF (LVEF ≥40% and NT-proBNP >125 ng/l) (n = 2,188)	Missing	HF vs. no HF	HFrEF vs. HFnEF
Demographics						
Age, yrs	67 (59-73)	73 (64-79)	76 (70-82)	0	<0.001	<0.001
Male	342 (54)	895 (75)	1,168 (53)	0	0.001	<0.001
Height, m	1.67 (1.60-1.74)	1.69 (1.62-1.76)	1.65 (1.58-1.73)	0	0.06	<0.001
Weight, kg	85 (73-97)	78 (66-90)	79 (67-92)	0	<0.001	0.01
BMI, kg/m^2	30 (27-34)	27 (24-31)	29 (25-33)	0	<0.001	<0.001
BP systolic, mm Hg	144 (129-159)	128 (113-143)	145 (127-162)	5	<0.001	<0.001
BP diastolic, mm Hg	82 (74-91)	76 (67-87)	78 (70-89)	5	<0.001	<0.001
HR, beats/min	72 (64-82)	75 (64-88)	72 (62-83)	13	0.08	<0.001
NYHA functional class				0	<0.001	<0.001
I	302 (48)	165 (14)	547 (25)			
II	244 (38)	598 (50)	1,062 (49)			
III	83 (13)	401 (33)	551 (25)			
IV	5 (1)	34 (3)	29 (1)			
Comorbidities						
CVD	20 (3)	104 (9)	133 (6)	0	<0.001	0.004
IHD	153 (24)	768 (64)	838 (38)	0	<0.001	<0.001
PVD	13 (2)	72 (6)	74 (3)	0	0.007	<0.001
Diabetes	169 (27)	274 (23)	546 (25)	0	0.19	0.18
HTN	252 (40)	367 (31)	878 (40)	0	0.16	<0.001
COPD	63 (10)	113 (9)	212 (10)	0	0.80	0.81
Cancer	33 (5)	94 (8)	208 (10)	0	0.002	0.11
Significantly deranged liver function test	2 (0)	9 (1)	7 (0)	0	0.59	0.08
Reduced mobility	210 (33)	620 (52)	1203 (55)	0	<0.001	0.07
Blood tests						
Hb, g/dl	14.0 (13.2-15.0)	13.5 (12.3-14.7)	13.2 (12.0-14.3)	10	<0.001	<0.001
Urea, mmol/l	5.2 (4.2-6.3)	7.1 (5.4-9.9)	6.6 (5.1-9.1)	1	<0.001	<0.001
Creatinine, μmol/l	82 (71-96)	105 (88-133)	95 (79-121)	7	<0.001	<0.001
K+, mmol/l	4.3 (4.0-4.5)	4.4 (4.1-4.7)	4.3 (4.0-4.6)	24	<0.001	0.003
Na+, mmol/l	139 (137-141)	139 (136-140)	139 (137-140)	6	<0.001	0.009
Lymphocyte, ×10^9/l	1.9 (1.6-2.3)	1.6 (1.2-2.1)	1.7 (1.3-2.1)	0	<0.001	0.46
Albumin, g/l	40 (37-41)	38 (35-40)	38 (35-40)	0	<0.001	0.09
Cholesterol, mmol/l	4.9 (4.1-5.8)	4.4 (3.7-5.3)	4.5 (3.7-5.4)	0	<0.001	0.08
NT-proBNP, ng/l	64 (38-92)	1,974 (831-4,534)	812 (309-1,845)	0	NA	<0.001
Treatment at referral						
Loop diuretic	184 (29)	904 (76)	1,243 (57)	42	<0.001	<0.001
MRA	23 (4)	369 (31)	262 (12)	42	<0.001	<0.001
ACEi	226 (36)	858 (72)	1,094 (51)	42	<0.001	<0.001
ARB	69 (11)	112 (9)	280 (13)	42	0.63	0.003
ACEi or ARB	292 (47)	966 (81)	1,349 (62)	42	<0.001	<0.001
BB	169 (27)	758 (64)	1,119 (52)	42	<0.001	<0.001
Statin	299 (48)	634 (53)	1,093 (51)	42	0.09	0.10
Digoxin	10 (2)	203 (17)	384 (18)	42	<0.001	0.65

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(mm^3) (8). A score >38 is considered normal; scores of 35 to 38 and <35 reflect moderate and severe malnutrition, respectively. Note there is no "mild" category for PNI.

ENDPOINTS AND FOLLOW-UP. Patients were followed until July 19, 2016. The primary endpoint was all-cause mortality. Our hospital is the only 1 in the region offering acute medical services. We have access to all primary and secondary care records. Outcome is censored at the point of last medical contact in primary or secondary care. Data regarding deaths were collected from the hospital's electronic systems and were entered into a dedicated database, stored on a secure National Health Services server.

STATISTICAL ANALYSIS. Continuous data are expressed as a median with interquartile range (IQR)

TABLE 1 Continued

	No HF	HF			p Value*	
	(LVEF ≥40% and NT-proBNP ≤125 ng/l) (n = 635)	HFrEF (LVEF <40%) (n = 1,198)	HFnEF (LVEF ≥40% and NT-proBNP >125 ng/l) (n = 2,188)	Missing	HF vs. no HF	HFrEF vs. HFnEF
ECG and echocardiography						
Cardiac rhythm				0	<0.001	<0.001
AF	0	278 (23)	695 (32)			
Sinus	628 (99)	833 (70)	1,382 (63)			
Unknown	6 (1)	87 (7)	112 (5)			
EF, %	59 (54–64)	30 (25–35)	54 (46–60)	1,779	<0.001	NA
LV impairment				0	<0.001	<0.001
None/trivial	581 (91)	0	1,499 (69)			
Mild/mild-moderate	54 (9)	108 (9)	634 (29)			
Moderate to severe	0	1,090 (91)	55 (2)			
LVEDD, cm	4.8 (4.4–5.2)	6.2 (5.7–6.8)	5.0 (4.5–5.5)	619	<0.001	<0.001
Prevalence of malnutrition						
CONUT						
Normal (0–1)	450 (71)	552 (46)	1,010 (46)	0	<0.001	0.09
Mild (2–4)	181 (29)	507 (42)	979 (45)			
Moderate (5–8)	3 (<1)	129 (11)	190 (9)			
Severe (9–12)	0	10 (1)	10 (<1)			
GNRI						
Normal (>98)	614 (96)	969 (81)	1,874 (86)	0	<0.001	0.003
Mild (92–98)	16 (3)	133 (11)	183 (8)			
Moderate (82–91)	4 (1)	71 (6)	106 (5)			
Severe (<82)	0	25 (2)	26 (1)			
PNI						
Normal (>38)	633 (100)	1,101 (92)	2,023 (93)	0	<0.001	0.65
Moderate (35–38)	1 (0)	53 (4)	86 (4)			
Severe (<38)	0	44 (4)	72 (3)			

Values are median (interquartile range), n (%), or n, unless otherwise indicated. *p value for trend except when there are ≥2 categories (e.g., NYHA functional class, cardiac rhythm).

ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BB = beta blocker; BMI = body mass index; BP = blood pressure; CONUT = controlling nutritional status; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; ECG = electrocardiogram; EF = ejection fraction; GNRI = geriatric nutritional risk index; Hb = hemoglobin; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFnEF = heart failure with normal ejection fraction; HR = heart rate; HTN = hypertension; IHD = ischemic heart disease; K+ = potassium; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NA = not available; Na+ = sodium; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; NYHA = New York Heart Association class; PNI = prognostic nutritional index; PVD = peripheral vascular disease.

(25th to 75th centiles) and categorical data are expressed as n (%). Independent *t*- and nonparametric tests were used to compare medians across ordered groups for normally and non-normally distributed variables, respectively. The chi-square test was used to compare proportions between groups. Pearson's correlation coefficients were used to assess the correlations between pairs of variables. Venn diagrams were used to illustrate the relationship between indices.

Time-to-event data are presented graphically using Kaplan-Meier curves. Log-rank tests were used to compare survival between groups. Univariable and multivariable analyses with Cox proportional hazard regression were used to determine significant predictors of events. Log transformation was applied when the data were very right-skewed.

Cross-validation, using an intuitive approach, brings both consistency and variability to prognostic model development (13). The "1-stop prognostic model" approach, although still favored by many, fell into disrepute more than 30 years ago (14). We therefore used k-fold cross-validation (k = 25 here) to generate 25 prognostic models. Cross-fold validation splits the data randomly into 25 partitions. For each partition, the specified Cox regression model was fitted using the other *k*-1 (i.e., 24) groups, and the results were used to predict the dependent variable in the unused group.

The variables listed in Online Tables 2 and 3 were included in the Cox models except for albumin, cholesterol, and lymphocyte counts, which are included in the CONUT score and PNI; weight, height, and BMI are included in the GNRI.

An arbitrary level of 5% statistical significance (2-tailed) was assumed for a covariate to be included in the model. The frequency of inclusion in all 25 prognostic models was calculated. Variables with an arbitrary inclusion frequency of ≥18 (in at least 70% of the 25 prognostic models) were used to form a malnutrition base model. Variables adjusted for in the base model included: age, sex, diastolic blood pressure, heart rate, New York Heart Association (NYHA) functional class III + IV versus I + II, urea, logNT-proBNP, CVD, and PVD. We added each of the malnutrition indices and BMI alone (linear and decile) in turn to the base model and used Harrell's concordance index (CI) (15) and log-likelihood ratio (LLR) to evaluate model discrimination in survival analysis, noting that the CI is overoptimistic for censored survival data (16). The CI is defined as the probability that predictions and outcomes are concordant (the same). A CI of 0.5 means that the relationship is no better than chance. The more negative the LLR, the bigger the improvement in model performance from addition of malnutrition indices to base model.

All statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, Illinois) and The Stata (14th version, StataCorp, College Station, Texas) statistical computer package.

RESULTS

PATIENT CHARACTERISTICS. Of the 4,021 patients enrolled, 3,386 had HF: 1,198 (35%) had HFrEF; 2,188 (65%) patients had HFnEF; and 635 did not have HF. Most patients with HF were men (61%) and the median age was 75 years (IQR: 67 to 81 years). Median LVEF was 44% (IQR: 33% to 56%) and median NT-proBNP was 1,103 ng/l (IQR: 415 to 2,631 ng/l). One-third of patients (30%) had severe symptoms (NYHA functional class III or IV), the most common comorbid condition was ischemic heart disease (48% of cases), and 36% were obese (BMI ≥30 kg/m^2). Baseline characteristics of patients with HFrEF, HFnEF, and without HF are shown in **Table 1**.

PREVALENCE AND CLINICAL ASSOCIATIONS OF MALNUTRITION. By GNRI and CONUT scores, 316 (9%) and 1,486 (44%) patients with HF had mild malnutrition, respectively. By GNRI, CONUT, and PNI calculations, 228 (7%), 339 (10%), and 255 (8%) patients had moderate to severe malnutrition, respectively (**Table 1,** Online Tables 4a to 4c). Although malnutrition scores correlated with each other (CONUT vs. GNRI: r = 0.36; CONUT vs. PNI: r = 0.72; GNRI vs. PNI: r = 0.42; all $p < 0.001$), only 5% were classified as malnourished (any degree of malnutrition) by all 3 scores, and only 42% were *not* malnourished by any (Online Figure 2). Because PNI has no mild category for malnutrition, the overlap among patients identified as moderately or severely malnourished by the different scores is more striking.

Compared with those with normal nutritional status, patients with malnutrition measured by any of the 3 malnutrition scores were older, more likely to be men, had lower BMI, had worse symptoms and renal function, and were also more likely to have atrial fibrillation, anemia, and reduced mobility (Online Tables 4a to 4c). By CONUT score, 54% of patients with HFrEF and HFnEF were malnourished, whereas <30% of those without HF were malnourished. By GNRI, malnutrition was more common in patients with HFrEF (19%) than HFnEF (14%) or patients without HF (4%). By PNI, malnutrition was equally common in patients with HFrEF (8%) and HFnEF (7%), whereas it was rare in patients without HF (**Table 1**). The prevalence of moderate to severe malnutrition measured by any of the 3 indices was much higher in patients with plasma NT-proBNP >4,000 ng/l (**Table 2**).

Not surprisingly, the highest prevalence of malnutrition was found in patients who were underweight (BMI <18.5 kg/m^2; 1.4% of patients with HF). A substantial proportion of patients with BMI ≥30 kg/m^2 (36% of patients with HF) were malnourished defined by CONUT (50%) or PNI (5%) scores, but none by GNRI (**Table 2**).

MALNUTRITION SCORES AND MORTALITY. During a median follow-up of 1,573 days (IQR: 702 to 2,799 days), 1,723 (50.9%) patients died; 351 (10%), 600 (18%), and 818 (24%) after 1, 2, and 3 years, respectively. Worsening malnutrition status was associated with worse outcome regardless of the malnutrition screening tool used (**Figure 1**).

Univariable and multivariable predictors of mortality for the overall population and for the different HF phenotypes are shown in **Table 3** and Online Tables 2a and 2b. Worsening malnutrition was associated with worse outcome regardless of LVEF.

The following variables were independently associated with adverse outcome in 100% of the 25 prognostic Cox regression models developed using cross-validation: increasing age, urea, NT-proBNP, NYHA functional class (III/IV vs. I/II), worse CONUT or GNRI score, male, CVD, PVD, and diastolic blood pressure; PNI was an independent predictor in 20 models (80%) (Online Table 3).

A base model (including age, sex, diastolic blood pressure, heart rate, NYHA class III/IV vs. I and II, urea, logNT-proBNP, CVD, and PVD) for predicting

TABLE 2 Prevalence of Malnutrition and 1-Year Mortality of Patients With HF Stratified by BMI and NT-proBNP

	BMI Categories (kg/m²)				
	Underweight <18.5 (n = 48)	**Normal 18.5-24.9 (n = 854)**	**Overweight 25-29.9 (n = 1,256)**	**Obese 30-39.9 (n = 1,061)**	**Morbidly Obese ≥40 (n = 167)**
CONUT					
Malnourished (any degree)	77	59	54	49	56
Malnourished (moderate-severe)	21	15	9	7	11
1-yr mortality malnutrition (moderate-severe vs. mild vs. none)	56 vs. 42 vs. 9	38 vs. 17 vs. 8	23 vs. 11 vs. 6	17 vs. 9 vs. 5	33 vs. 5 vs. 9
GNRI					
Malnourished (any degree)	96	49	6	0	0
Malnourished (moderate-severe)	88	20	1	0	0
1-yr mortality malnutrition (moderate-severe vs. mild vs. none)	40 vs. 0 vs. 50	41 vs. 15 vs. 8	43 vs. 20 vs. 9	NA	NA
PNI					
Malnourished (moderate-severe)	26	11	7	4	7
1-yr mortality malnutrition (moderate-severe vs. none)	50 vs. 32	50 vs. 12	26 vs. 9	24 vs. 7	36 vs. 8
	NT-proBNP Categories (ng/l)				
	≤400 (n = 822)	**401-1,000 (n = 776)**	**1,001-2,000 (n = 697)**	**2,001-4,000 (n = 553)**	**>4,000 (n = 538)**
CONUT					
Malnourished (any degree)	39	47	54	62	78
Malnourished (moderate-severe)	3	4	8	12	31
1-yr mortality malnutrition (moderate-severe vs. mild vs. none)	10 vs. 4 vs. 3	19 vs. 8 vs. 5	20 vs. 11 vs. 5	25 vs. 12 vs. 11	37 vs. 31 vs. 20
GNRI					
Malnourished (any degree)	5	10	15	22	38
Malnourished (moderate-severe)	2	4	5	7	20
1-yr mortality malnutrition (moderate-severe vs. mild vs. none)	29 vs. 7 vs. 3	25 vs. 5 vs. 6	25 vs. 13 vs. 8	28 vs. 14 vs. 12	57 vs. 30 vs. 22
PNI					
Malnourished (moderate-severe)	2	3	6	9	23
1-yr mortality malnutrition (moderate-severe vs. none)	20 vs. 3	27 vs. 6	26 vs. 8	30 vs. 12	47 vs. 25

Values are %. There is no underweight patient classified as mildly malnourished by GNRI.
Abbreviations as in Table 1.

mortality achieved a Harrell's CI = 0.719 (Table 4). Each malnutrition score, when added individually, improved the performance of the base model, with GNRI improving base model performance most. Addition of BMI (linear or decile) alone did not improve performance of the base model. Online Table 5 summarizes the findings from other studies, which reported the role of malnutrition scores in predicting outcomes using different risk models.

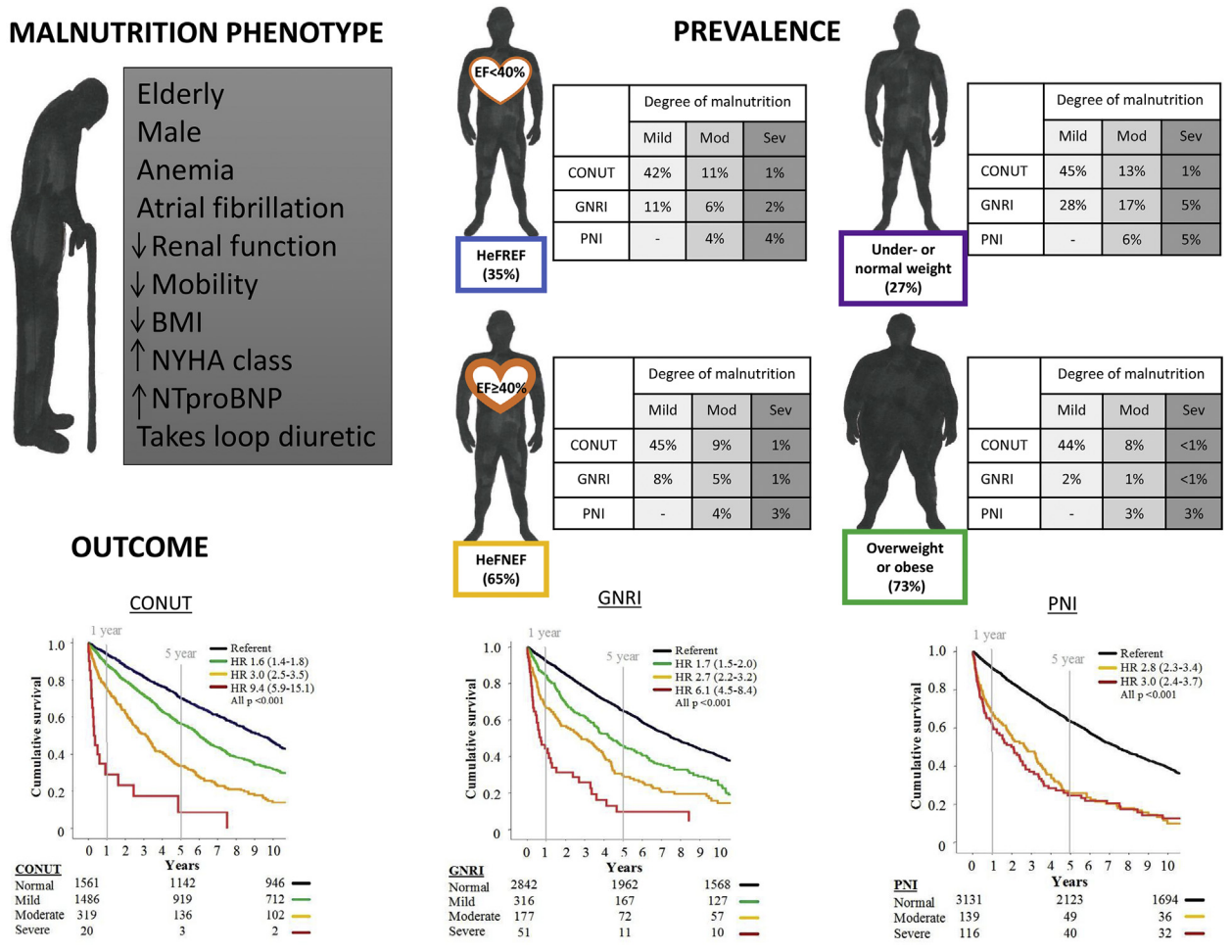
Patients with any indication of malnourishment who were also underweight had the worst outcome. For those with higher BMI, 1-year mortality was substantially higher in the presence of moderate-severe malnutrition by any of the indices used. Patients with an NT-proBNP >4,000 ng/l and moderate or severe malnutrition had a particularly high 1-year mortality, ranging from 37% to 57% by different indices (Table 2).

DISCUSSION

Malnutrition, as defined by existing scores, is common in outpatients with chronic HF and is associated with a poor prognosis regardless of the screening tools used and regardless of left ventricular systolic function, circulating levels of natriuretic peptides, or BMI. Although, malnutrition scores provided only a modest increase in the statistical accuracy of multivariable prognostic models, they may be important for at least 2 reasons: the wide availability of the variables required for their calculation and malnutrition as a potentially modifiable risk and therapeutic target.

The prevalence of malnutrition is, however, highly dependent upon the tool used, ranging from 8% (by PNI) to 54% (by CONUT) in the same cohort of patients. According to Lin et al. (9), who conducted a

FIGURE 1 Screening Tool for Malnutrition



(Upper left) Characteristics of malnourished patients. **(Upper right)** Prevalence of malnutrition in different subgroups of patients with HF: overweight/obese vs. underweight/normal weight; HFrEF vs. HFnEF. **(Lower)** Kaplan-Meier curves for all-cause mortality by CONUT, GNRI, and PNI categories. BMI = body mass index; CONUT = Controlling Nutritional Status; GNRI = geriatric nutritional risk index; HFnEF = heart failure with normal ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; NT-proBP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PNI = prognostic nutritional index.

systematic review on nutritional screening and assessment tools in HF, the prevalence of malnutrition in patients with chronic HF ranged from 16% to 62%. The differences among studies in the prevalence of reported malnutrition might be due either to differences in the severity of HF or the use of different scoring systems. In our cohort, concordance among scores for milder degrees of malnutrition was rather poor, suggesting that they are not interchangeable; however, there was a greater degree of concordance for moderate to severe malnutrition amongst the 3 scores, perhaps reflecting the similarity of the variables on which they are based.

The CONUT score is calculated from variables reflecting protein and lipid metabolism as well as immune function measured from blood tests. PNI is similar to CONUT but does not include cholesterol. The CONUT score suggested that many more patients were malnourished compared with GNRI or PNI, but this may reflect low plasma cholesterol resulting from statin therapy. Although the benefits of statins are dubious in HF (17), they are still commonly

TABLE 3 Univariable and Multivariable Analyses of Factors Predicting Mortality in Patients With Chronic HF (Overall Population)

	Overall HF Population					
	Univariate			Multivariate		
Worse Outcome per Unitary Increase	HR (95% CI)	Wald Chi-Square	p Value	HR (95% CI)	Wald Chi-Square	p Value
Age, yrs	1.055 (1.05–1.06)	362.8	<0.001	1.05 (1.04–1.06)	209.0	<0.001
Male vs. female	1.17 (1.06–1.29)	10.0	0.002	1.29 (1.15–1.45)	18.1	<0.001
Height, m	0.26 (0.17–0.42)	32.4	<0.001			
Weight, kg	0.99 (0.986–0.991)	70.5	<0.001			
BMI, kg/m^2	0.97 (0.96–0.98)	41.6	<0.001			
BP systolic, mm Hg	0.99 (0.99–1.00)	34.1	<0.001			
BP diastolic, mm Hg	0.98 (0.98–0.98)	129.6	<0.001	0.99 (0.99–1.00)	14.7	<0.001
HR, beats/min	1.01 (1.00–1.01)	22.9	<0.001	1.01 (1.00–1.01)	9.7	0.002
NYHA functional class III/IV vs. I/II	2.03 (1.84–2.24)	200.7	<0.001	1.56 (1.40–1.74)	64.4	<0.001
Hb, g/dl	0.82 (0.80–0.85)	195.4	<0.001			
Urea, mmol/l	1.06 (1.05–1.06)	343.2	<0.001	1.03 (1.02–1.04)	21.8	<0.001
Creatinine, μmol/l	1.00 (1.00–1.00)	183.1	<0.001			
K+, mmol/l	1.01 (0.91–1.11)	0.02	0.90			
Na+, mmol/l	0.94 (0.93–0.95)	76.8	<0.001			
Lymphocyte, $\times 10^9$/l	0.67 (0.62–0.72)	100.7	<0.001			
Albumin, g/l	0.90 (0.88–0.91)	328.1	<0.001			
Cholesterol, mmol/l	0.94 (0.90–0.97)	12.0	0.001			
Log NT-proBNP, ng/l	2.80 (2.57–3.06)	524.7	<0.001	1.75 (1.56–1.97)	93.0	<0.001
Loop diuretic, yes vs. no	2.10 (1.90–2.40)	180.6	<0.001			
MRA, yes vs. no	1.21 (1.08–1.37)	9.9	0.002			
ACEi, yes vs. no	1.04 (0.94–1.14)	0.5	0.46			
ARB, yes vs. no	0.89 (0.75–1.04)	2.2	0.14			
ACEi or ARB, yes vs. no	1.00 (0.90–1.11)	0.003	0.96			
BB, yes vs. no	0.70 (0.64–0.77)	53.3	<0.001			
Statin, yes vs. no	0.77 (0.70–0.84)	30.0	<0.001			
Digoxin, yes vs. no	1.43 (1.27–1.60)	35.2	<0.001			
Cardiac rhythm, AF vs. sinus	1.32 (1.19–1.47)	26.3	<0.001			
EF, %	0.99 (0.98–0.99)	36.7	<0.001			
LVEDD, cm	1.05 (1.00–1.11)	4.0	0.046			
CVD, yes vs. no	1.55 (1.31–1.83)	26.8	<0.001			
IHD, yes vs. no	1.11 (1.01–1.22)	4.8	0.029			
PVD, yes vs. no	1.80 (1.48–2.20)	34.0	<0.001	1.66 (1.35–2.05)	22.7	<0.001
Diabetes, yes vs. no	1.13 (1.01–1.27)	4.2	0.04			
Reduced mobility, yes vs. no	2.11 (1.89–2.36)	175.1	<0.001			
Prevalence of malnutrition						
CONUT						
Normal	1.00					
Mild malnutrition	1.58 (1.43–1.75)	76.0	<0.001			
Moderate malnutrition	2.96 (2.54–3.45)	195.3	<0.001			
Severe malnutrition	9.41 (5.89–15.06)	87.5	<0.001			
GNRI						
Normal	1.00			1.26 (1.15–1.37)	27.2	<0.001
Mild malnutrition	1.72 (1.48–2.00)	50.8	<0.001			
Moderate malnutrition	2.68 (2.23–3.22)	111.4	<0.001			
Severe malnutrition	6.14 (4.49–8.40)	129.2	<0.001			
PNI						
Normal	1.00					
Moderate malnutrition	2.75 (2.26–3.36)	101.2	<0.001			
Severe malnutrition	2.99 (2.41–3.72)	97.4	<0.001			

CI = confidence interval; other abbreviations as in Table 1.

TABLE 4 Addition of Malnutrition Indices to Base Model Improves Model Performance in Predicting All-Cause Mortality

Model	Concordance Index	LLR Improvement From Base	p Value for LLR Improvement From Base
Base model*	0.719		
Base* + CONUT score	0.721	−16.2	0.001
Base* + GNRI	0.724	−31.4	<0.001
Base* + PNI	0.721	−12.1	0.002
Base* + BMI (linear)	0.719	0	NA
Base* + BMI (decile)	0.720	−3.0	0.16

Improvement in model performance was measured using Harrell's concordance index (CI) and LLR: the more negative the LLR, the bigger the improvement in model performance. Among the malnutrition scores, GNRI improves model performance most compared with the base model. *Variables adjusted for in the base model: age, sex, diastolic BP, HR, NYHA functional class III + IV vs. I + II, urea, logNT-proBNP, CVD, PVD. The model + CONUT score from base means that CONUT has been "adjusted" for our 9 covariates.

LLR = log-likelihood ratio; other abbreviations as in Table 1.

prescribed, and thus CONUT score is perhaps not the ideal tool. PNI identifies far fewer patients as malnourished compared with CONUT because it does not include cholesterol. Because PNI only identifies patients as moderately or severely malnourished, it may therefore underestimate the overall prevalence of malnutrition.

Among the 3 screening tools used, GNRI had the greatest incremental value in predicting risk. GNRI is the only tool of the 3 malnutrition indices we studied that takes into account both anthropometric factors (the ratio of body weight to ideal body weight) and serum markers (albumin level). The CONUT score and PNI both consider serum markers only. GNRI might be a better malnutrition screening tool than CONUT or PNI because it is multidimensional; however, because GNRI considers low body weight to be a marker of malnutrition, it might underestimate malnutrition in overweight patients.

Although we found that indices of malnutrition increased the prognostic value of the models we constructed, the modest increase in CI is of little value for the individual patient. Given the effect in a substantial population of patients, however, the increase in C-statistic does emphasize that there is some component of "malnutrition" that is related to prognosis above and beyond the usual clinical variables taken into account when constructing prognostic models. In turn, that statistical result suggests that there may be some value in exploring malnutrition, and, perhaps, its treatment, further.

In patients with HF, BMI is not an ideal measure of body size and composition and should not be used as a surrogate of nutritional status. Patients with HF and higher BMI have, on average, lower plasma concentrations of natriuretic peptides and better outcomes than those with lower BMI, a phenomenon sometimes termed the "obesity paradox" (18). Using CONUT and PNI criteria, malnutrition is not only common in underweight patients, but is also highly prevalent in those who are overweight, obese, or even morbidly obese. We have found that the malnutrition scores we used were more highly related to outcome than BMI, and that their inclusion in predictive models of outcome increased the predictive power of the models, whereas including BMI did not. Despite the apparent protective effects of greater BMI, overweight patients who are malnourished by these 2 indexes have a higher mortality than those who do not, highlighting that malnutrition does not simply manifest as being underweight.

Once present, malnutrition may progress to overt cardiac cachexia, a global wasting process affecting all body compartments including skeletal muscle, fat, and bone (1). The causes of cachexia in HF are multifactorial and might arise as a result of malnutrition, impaired protein and calorie balance, proinflammatory immune activation, neurohormonal derangement, physical deconditioning, and prolonged immobilization leading to catabolic anabolic imbalance (19). Screening for malnutrition using the most appropriate tool for patients with HF might enable early identification and characterization of patients at risk of developing cachexia. Future studies should focus on studying whether better use of available treatments or novel treatments might improve nutritional status and eventually outcomes in these at-risk patients with HF.

STUDY LIMITATIONS. This is a single-center study with advantages and disadvantages. It is much easier to develop a system to enroll a large number of consecutive patients and apply consistent criteria and evaluations in a single center. On the other hand, our patients and processes may differ from other centers; however, variations in patient selection among centers, often coupled with poor enrollment, may make multicenter studies less epidemiologically representative than a well-conducted single-center study. Nonetheless, confirmation of our findings by other investigators and other countries with different health care and social systems would be welcome. We used only 3 of the large number scores developed to screen for malnutrition. We did not compare the prognostic value of nutritional screening tools with more complex comprehensive nutritional assessments (20).

Whether it is appropriate to attribute low serum albumin solely to malnutrition is unclear. Hepatic disease and congestion or protein-losing gastrointestinal or renal disease could cause serum albumin to fall. Indeed, in CONUT, scores for mild malnutrition appeared to be driven largely by statin therapy. Some of our patients were naïve to, or required optimization of treatment for HF, which might improve nutritional status and outcome, particularly those with HFrEF. Not everyone will agree with our definition of HFnEF, for which there is no universal diagnostic agreement; however, malnutrition was much more common and prognosis much worse for patients who fulfilled our definition of HFnEF compared with patients considered not to have HF.

We did not investigate the changes in nutritional status over time and the relationship between malnutrition scores and body composition. Because reduced mobility occurred significantly in patients with HF who were classified as malnourished, it might also be worthwhile investigating whether an association between malnutrition and physical deconditioning exists.

CONCLUSIONS

Recognition of the high prevalence (and poor prognosis associated with) malnutrition in patients with HF should stimulate further research into its definition and management. We found that simple malnutrition scores were more closely related to outcome than BMI, which is thus not an ideal measure of body size and composition. BMI should not be used as surrogate of nutritional status in patients with HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Malnutrition is common in ambulatory patients with HF, with a prevalence of up to 54% depending on severity and screening tool used. Malnutrition was more common when BMI was low or plasma NT-proBNP was high and in older patients.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Malnutrition is associated with a poor prognosis regardless of the screening tools used, LVEF, NT-proBNP, or BMI.

TRANSLATIONAL OUTLOOK: Recognition of the high prevalence and poor prognosis of malnutrition in patients with HF should stimulate further research into its definition and management.

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KEY WORDS BMI, CONUT, GNRI, heart failure, malnutrition, mortality, PNI

APPENDIX For supplemental figures and tables, please see the online version of this paper.