

Association Between Direct Measures of Body Composition and Prognostic Factors in Chronic Heart Failure

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OBJECTIVE: To explore the covariate-adjusted associations between body composition (percent body fat and lean body mass) and prognostic factors for mortality in patients with chronic heart failure (CHF) (nutritional status, N-terminal pro-B-type natriuretic peptide [NT-proBNP], quality of life, exercise capacity, and C-reactive protein).

PATIENTS AND METHODS: Between June 2008 and July 2009, we directly measured body composition using dual energy x-ray absorptiometry in 140 patients with systolic and/or diastolic heart failure. We compared body composition and CHF prognostic factors across body fat reference ranges and body mass index (BMI) categories. Multiple linear regression models were created to examine the independent associations between body composition and CHF prognostic factors; we contrasted these with models that used BMI.

RESULTS: Use of BMI misclassified body fat status in 51 patients (41%). Body mass index was correlated with both lean body mass ($r=0.72$) and percent body fat ($r=0.67$). Lean body mass significantly increased with increasing BMI but not with percent body fat. Body mass index was significantly associated with lower NT-proBNP and lower exercise capacity. In contrast, higher percent body fat was associated with a higher serum prealbumin level, lower exercise capacity, and increased C-reactive protein level; lean body mass was inversely associated with NT-proBNP and positively associated with hand-grip strength.

CONCLUSION: When BMI is divided into fat and lean mass components, a higher lean body mass and/or lower fat mass is independently associated with factors that are prognostically advantageous in CHF. Body mass index may not be a good indicator of adiposity and may in fact be a better surrogate for lean body mass in this population.

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6MWD = 6-minute walk distance; BMI = body mass index; CHF = chronic heart failure; CRP = C-reactive protein; DEXA = dual energy x-ray absorptiometry; HRQoL = health-related quality of life; NT-proBNP = N-terminal pro-B-type natriuretic peptide; WHO = World Health Organization

Population-based cohort studies have identified obesity as a major risk factor for the development of chronic heart failure (CHF).¹ In contrast, in patients with acute or stable heart failure, a higher body mass index (BMI) is strongly associated with decreased mortality.^{2,3} These paradoxical observations have been referred to as *reverse epidemiology*^{4,5} or the *obesity paradox*⁶ and, assuming they are valid, call into question the practice of extrapolating BMI targets derived from the general population to the CHF population.

A number of potential explanations for the obesity paradox have been proposed.⁶ Because the paradox has been

almost exclusively reported in studies that use BMI to classify obesity in CHF (with the exception of one study that used skinfold measurements⁷) and because BMI is an indirect measure of body fat, the paradox may be an artifactual finding that results from the use of an inaccurate surrogate for obesity. Alternatively, the obesity paradox may represent a valid finding that reflects a greater amount of favorable metabolic reserve or lower levels of circulating N-terminal pro-B-type natriuretic peptide (NT-proBNP) in obese patients compared with their normal-weight counterparts.⁸

Our objectives were to (1) characterize the body composition of obese, overweight, and normal-weight patients with CHF using dual energy x-ray absorptiometry (DEXA); (2) explore the covariate-adjusted associations between body composition (both body fat and lean body mass) and prognostic factors for mortality in CHF (nutritional status, NT-proBNP, health-related quality of life [HRQoL], 6-minute walk distance [6MWD], and C-reactive protein [CRP]); and (3) com-

For editorial comment, see page 605

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pare the results of covariate-adjusted models incorporating body composition with those incorporating BMI to examine differences in their association with CHF prognostic factors.

PATIENTS AND METHODS

Between June 2008 and July 2009, 140 consecutive patients with CHF (systolic and/or diastolic) were recruited from the University of Alberta Heart Function Clinic, Edmonton, Alberta, Canada, a tertiary care clinic staffed by a multidisciplinary team of physicians, specialized nurses, pharmacists, dieticians, and social workers. Patients 18 years or older who were able to give informed consent, who had heart failure diagnosed on the basis of Framingham Heart Study criteria,⁹ and who were deemed to be clinically euvoletic by the clinic physician were included. Patients who were unable to lay flat or who exceeded the 136 kg (300 lb) weight limit for the DEXA scan were excluded. The University of Alberta Health Research Ethics Board approved the study.

DEXA Scans

Body composition was measured by DEXA performed with a Hologic Series 4500W Fan Beam X-ray Bone Densitometer with version 12.4 software (Hologic Inc, Bedford, MA). Three experienced technicians performed all scans in a standard fashion. Scans were analyzed using the whole-body fan beam method to determine lean mass and fat mass. Quality control tests were run every morning using a standard block of tissue-equivalent material. Patients were asked to refrain from drinking more than 500 mL of fluid an hour before their scan.

PROGNOSTIC FACTORS OF MORTALITY

The following 4 markers were chosen to measure nutritional status: serum albumin, serum prealbumin, hand-grip

strength, and the Simplified Nutrition Appetite Questionnaire. Grip strength was measured with a calibrated Jamar Hydraulic Hand Dynamometer (Sammons Preston Roylean, Bolingbrook, IL). The highest result of 2 attempts for the dominant hand was recorded and compared against age- and sex-specific reference ranges¹⁰ and then categorized as average, above average, or below average.

Inflammation was measured with high-sensitivity CRP by standard enzyme-linked immunosorbent assay. The NT-proBNP level was measured with the Elecsys Roche assay (Elecsys Roche, Indianapolis, IN) and used to quantify severity of CHF. The 6MWD test was used to measure exercise capacity and was administered according to the American Thoracic Society guidelines.¹¹

The HRQoL was measured using the Kansas City Cardiomyopathy Questionnaire, the EuroQol visual analog scale, and the Center for Epidemiological Studies Depression Short Form Scale. The Kansas City Cardiomyopathy Questionnaire is a 23-item instrument that quantifies physical function, symptoms, social function, self-efficacy and knowledge regarding the disease, and quality of life specific to patients with CHF.¹² The overall summary score is calculated as the mean of scores from the 5 domains. A higher score indicates better HRQoL. The EuroQol visual analog scale is a generic measure on which respondents are asked to rate their own health state relative to full health (score of 100) and worst imaginable health (score of 0).¹³ The Center for Epidemiological Studies Depression Short Form Scale 10 is a 10-item scale, with a higher total score indicating worse depressive symptoms.¹⁴

STATISTICAL ANALYSES

As shown in Table 1, patients were grouped according to DEXA-measured body fat categories (low-normal, over-

TABLE 1. Predicted Percentage Body Fat by Sex and Ethnicity Based on 4-Compartment Estimates of Percentage Body Fat

Age (y) and weight categories	White		African American		Asian	
	Men	Women	Men	Women	Men	Women
20-39						
Underweight	≤8.0	≤21.0	≤8.0	≤20.0	≤13.0	≤25.0
Normal weight	8.0-20.9	21.0-32.9	8.0-19.9	20.0-31.9	13.0-22.9	25.0-34.9
Overweight	21.0-25.9	33.0-38.9	20.0-25.9	32.0-37.9	23.0-27.9	35.0-39.9
Obese	≥26.0	≥39.0	≥26.0	≥38.0	≥28.0	≥40.0
40-59						
Underweight	≤11.0	≤23.0	≤9.0	≤21.0	≤13.0	≤25.0
Normal weight	11.0-22.9	23.0-34.9	9.0-21.9	25.0-33.9	13.0-23.9	25.0-35.9
Overweight	23.0-28.9	35.0-40.9	22.0-26.9	34.0-38.9	24.0-28.9	36.0-40.9
Obese	≥29.0	≥41.0	≥27.0	≥39.0	≥29.0	≥41.0
≥60						
Underweight	≤13.0	≤25.0	≤11.0	≤23.0	≤14.0	≤26.0
Normal weight	13.0-24.9	25.0-37.9	11.0-22.9	23.0-34.9	14.0-23.9	26.0-35.9
Overweight	25.0-30.9	38.0-42.9	23.0-28.9	35.0-40.9	24.0-28.9	36.0-40.9
Obese	≥31.0	≥43.0	≥29.0	≥41.0	≥29.0	≥41.0

Adapted from *Am J Clin Nutr*,¹⁵ with permission.

weight, and obese) proposed by Gallagher et al¹⁵ as the reference standard. These reference ranges are specific to age, sex, and race. Body fat was also assessed indirectly using the traditional World Health Organization (WHO) BMI categories calculated as weight in kilograms divided by height in meters squared: normal (18.5-24.9), overweight (25.0-29.9), and obese (≥ 30.0).¹⁶ Patients of races other than white, African American, and Asian (n=9) were classified according to the body fat reference table for white populations. Patient characteristics and prognostic factors were compared among the body fat categories using χ^2 tests for linear trend for categorical variables or Jonckheere-Terpstra tests for continuous variables to account for the ordered nature of the body fat and BMI categories. We determined the concordance of body fat status classification between the BMI and Gallagher percent body fat categories. We also assessed the relationship between body composition and BMI by calculating the partial Pearson correlation coefficients among BMI, percent body fat, and lean body mass, adjusted for age and sex. Next, separate linear regression models were constructed to determine the independent association between BMI (as a continuous variable) and each CHF prognostic factor. Finally, regression models were rebuilt by removing BMI and inserting percent body fat and absolute lean body mass (in kilograms), with all other predictor variables remaining the same. Because of the skewed nature of the NT-proBNP and CRP distributions, both were transformed using the natural logarithm. Models were built by choosing clinically relevant variables and variables identified from prior published studies. In addition, variables that changed the β -coefficient of the outcome variable by 10% or more (as a measure of confounding) were added. Age and sex were included in all models. Model results are presented as β -coefficients with 95% confidence intervals. $P < .05$ was considered statistically significant.

Normality of variables was inspected visually by histograms, and homoscedasticity of the variance of errors was checked by visual examination of scatterplots. Multicollinearity was assessed by examining the variance inflation factor of each variable. Analyses were performed using SPSS statistical software, version 16.0 (SPSS Inc, Chicago, IL), and graphs were created with STATA statistical software, version 10.1 (StataCorp, College Station, TX).

RESULTS

Of the 221 consecutive eligible patients approached, 140 consented to participate. Reasons for refusal included lack of time, poor noncardiac health, lack of transportation to attend appointments, and unwillingness to undergo x-ray exposure.

Mean age of the cohort was 63 years, 103 (74%) of the patients were male, and 126 (90%) were white. When cat-

TABLE 2. Patient Characteristics by Gallagher Body Fat Categories

Characteristics	Low-normal (n=39)	Overweight (n=39)	Obese (n=62)	P value for trend
Age (y)	66±16	62±12	62±13	.10
Female	9 (23.1)	9 (23.1)	19 (30.6)	.37
White	35 (89.7)	34 (87.2)	57 (91.9)	.66
Percent body fat	21.7±7.1	30.4±5.3	38.4±6.3	.001
Lean body mass (kg)	49.6±9.0	53.2±12.1	52.8±13.1	.25
BMI	23.8±3.0	28.3±4.2	32.4±5.3	.001
Correct BMI classification (%)	66.7	48.7	61.3	
Time followed up in clinic (y)	2.6±3.3	2.6±3.3	2.8±2.7	.30
Time since diagnosis (y)	4.5±4.6	5.6±5	4.9±4.6	.79
Weight change in previous 6 mo				.74
Gain >5%	2 (5.1)	6 (15.4)	7 (11.3)	
Loss >5%	5 (12.8)	3 (7.7)	5 (8.1)	
Smoking history				
Current	9 (23.1)	6 (15.4)	7 (11.3)	.10
Previous	16 (41.0)	20 (51.3)	40 (64.5)	.02
Internal cardiac defibrillator or pacemaker	14 (35.9)	14 (35.9)	29 (46.8)	.25
Ejection fraction (%)	38±14	35±13	36±15	.45
Type of failure				.93
Systolic	35 (89.7)	37 (94.9)	56 (90.3)	
Diastolic	4 (10.3)	2 (5.1)	6 (9.7)	
Hospitalized for HF in previous year	10 (25.6)	11 (28.2)	18 (29.0)	.72
History of alcohol abuse	6 (15.4)	7 (18.0)	13 (21.0)	.49
NYHA classification				.02
1	18 (46.2)	14 (35.9)	20 (32.3)	
2	21 (53.8)	23 (59.0)	32 (51.6)	
3	0	2 (5.1)	10 (16.1)	
Heart rate (beats/min)	68±14	67±10	69±11	.58
Blood pressure (mm Hg)				
Systolic	118±21	119±23	120±17	.29
Diastolic	70±11	73±10	74±10	.04
Diabetes mellitus	8 (20.5)	8 (20.5)	23 (37.1)	.05
Hypertension	17 (43.6)	23 (59.0)	39 (62.9)	.07
Valvular insufficiency	12 (30.8)	12 (30.8)	12 (19.4)	.17
Coronary artery disease	21 (53.8)	20 (51.3)	33 (53.2)	.98
Atrial fibrillation or flutter	17 (43.6)	17 (43.6)	24 (38.7)	.60
GI disease	14 (35.9)	12 (30.8)	19 (30.6)	.61
Cerebrovascular disease	7 (18.0)	4 (10.3)	10 (16.1)	.90
Kidney function				.15
EGFR ≥ 60	23 (59.0)	25 (64.1)	40 (64.5)	
EGFR 30-59	12 (30.8)	13 (33.3)	22 (35.5)	
EGFR <30	4 (10.3)	1 (2.6)	0	

Categorical values are No. (percentage) of patients, and continuous values are mean \pm SD unless otherwise indicated. BMI = body mass index; EGFR = estimated glomerular filtration rate; GI = gastrointestinal; HF = heart failure; NYHA = New York Heart Association.

egorized according to directly measured body fat, 39, 39, and 62 patients were in the low-normal, overweight, and obese body fat groups, respectively (Table 2). Only 2 patients in the low-normal group were below the normal body

fat reference range. Although BMI was moderately positively correlated with percent body fat ($r=0.67$; $P<.001$), the WHO BMI classification system concordantly classified only 26 (66.7%), 19 (48.7%), and 38 (61.3%) of the patients in the low-normal, overweight, and obese body fat categories, respectively. Both female patients with directly measured body fat levels below normal were classified as having normal weight by WHO BMI criteria. Body mass index had a slightly higher correlation with lean body mass ($r=0.72$; $P<.001$) than with percent body fat.

Patient characteristics by WHO BMI categories are listed in Table 3. Although comorbidities and renal function were relatively similar between the Gallagher body fat categories and the WHO BMI categories, patients with a higher percent body fat and a higher BMI reported poorer functional capacity (New York Heart Association classification) and a higher prevalence of previous smoking. Patients with a higher BMI were younger than patients with a lower BMI, but no significant differences in age were found between percent body fat categories. Diuretic use was more prevalent in patients with higher BMI and percent body fat levels; however, other cardiac medication use (cholesterol-lowering agents, angiotensin-converting enzyme inhibitors, β -blockers, acetylsalicylic acid, spironolactone, and digoxin) was similar among the groups (data not shown). Higher percent body fat and BMI were significantly associated with higher fasting glucose, higher triglycerides, and lower high-density lipoprotein levels (data not shown). As expected, percent body fat significantly increased with increasing body fat and BMI categories. However, lean body mass was not significantly different among Gallagher body fat categories and was weakly associated with percent body fat ($r=-0.2$; $P<.06$), whereas lean body mass significantly increased with increasing BMI category.

To further examine the misclassification of obesity by BMI, we graphed percent body fat against BMI for each of the 3 Gallagher body fat categories (Figure). The obese and overweight Gallagher categories displayed large variability in BMI, with 2 obese patients being misclassified as having normal weight and 2 patients with normal body fat levels classified as being obese according to BMI. Misclassification was in both directions; 11 patients (28.2%) with normal body fat levels were misclassified as overweight, and 22 patients (35.5%) with high body fat levels (considered obese by Gallagher reference) were misclassified as overweight by BMI.

The CHF prognostic factors by BMI and Gallagher body fat categories are presented in Table 4 and Table 5, respectively. Data were missing in 16 patients (11.4%) for CRP and in 20 patients (14.3%) for NT-proBNP measurements. The BMI category was significantly associated with

TABLE 3. Patient Characteristics by World Health Organization Body Mass Index Categories

Characteristics	Low-normal (n=36)	Overweight (n=52)	Obese (n=52)	P value for trend
Age (y)	66±16	66±13	58±12	.001
Female	10 (27.8)	15 (28.8)	12 (23.1)	.59
White	32 (88.9)	48 (92.3)	46 (88.5)	.89
Percent body fat	23.7±9.0	32.7±8.5	35.7±7.0	.001
Lean body mass (kg)	45.0±9.1	48.8±9.3	59.9±11.2	.001
Time followed up in clinic (y)	2.5±3.4	2.8±3.3	2.6±2.6	.38
Time since diagnosis (y)	5.7±5.7	4.7±4.4	4.7±4.4	.51
Weight change in previous 6 mo				
Gain >5%	4 (11.1)	4 (7.7)	7 (13.5)	
Loss >5%	4 (11.1)	4 (7.7)	5 (9.6)	>.99
Smoking history				
Current	9 (25.0)	5 (9.6)	8 (15.4)	.30
Previous	12 (33.3)	32 (61.5)	32 (61.5)	.02
Internal cardiac defibrillator or pacemaker	17 (47.2)	16 (30.8)	24 (46.2)	.92
Ejection fraction (%)	37±14	39±15	34±14	.21
Type of failure				
Systolic	32 (88.9)	46 (88.5)	50 (96.2)	
Diastolic	2 (5.6)	5 (9.6)	1 (1.9)	.19
Hospitalized for HF in previous year	6 (16.7)	19 (36.5)	14 (26.9)	.40
History of alcohol abuse	6 (16.7)	7 (13.5)	13 (25.0)	.29
NYHA classification				.03
1	13 (36.1)	25 (48.1)	29 (55.8)	
2	21 (58.3)	26 (50.0)	29 (55.8)	
3	2 (5.6)	1 (1.9)	9 (17.3)	
Heart rate (beats/min)	67±10	68±13	70±10	.15
Blood pressure (mm Hg)				
Systolic	121±23	117±19	119±18	.89
Diastolic	70±9	72±11	74±10	.12
Diabetes mellitus	7 (19.4)	9 (17.3)	23 (44.2)	.006
Hypertension	22 (61.1)	24 (46.2)	33 (63.5)	.67
Valvular insufficiency	10 (27.8)	16 (30.8)	10 (19.2)	.31
Coronary artery disease	20 (55.6)	27 (51.9)	27 (51.9)	.75
Atrial fibrillation or flutter	14 (38.9)	24 (46.2)	20 (38.5)	.89
GI disease	14 (38.9)	17 (32.7)	14 (26.9)	.24
Cerebrovascular disease	9 (25.0)	5 (9.6)	7 (13.5)	.19
Kidney function				.10
EGFR ≥60	20 (56.6)	33 (63.5)	35 (67.3)	
EGFR 30-59	13 (36.1)	18 (34.6)	16 (30.8)	
EGFR <30	3 (8.3)	1 (1.9)	1 (1.9)	

Categorical values are No. (percentage) of patients and continuous values are mean ± SD unless otherwise indicated. EGFR = estimated glomerular filtration rate; GI = gastrointestinal; HF = heart failure; NYHA = New York Heart Association.

serum prealbumin level and highest NT-proBNP quartile in males. Body fat category was also significantly associated with serum prealbumin level, in addition to a CRP level of 2.0 g/L or higher, 6MWD, depressive symptoms, and general HRQoL and borderline significantly associated

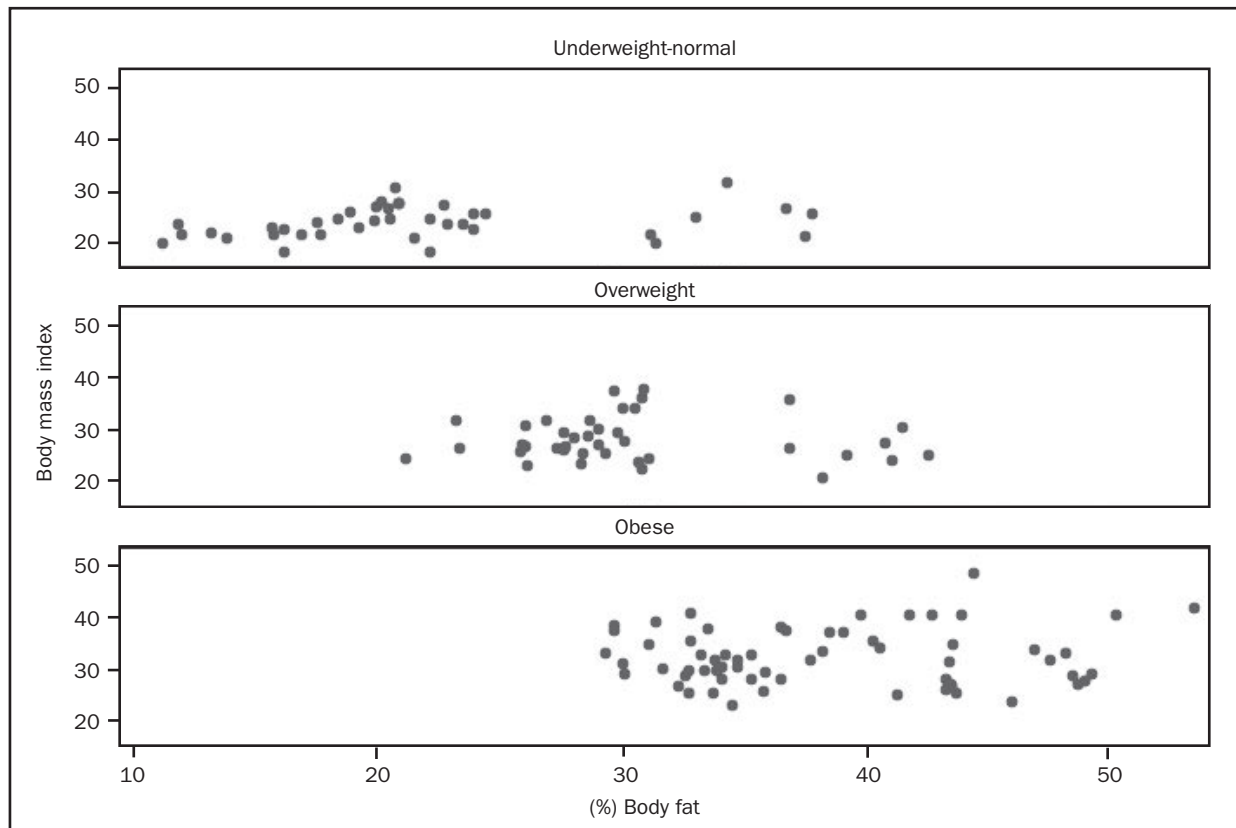


FIGURE. Relationship between percent body fat and body mass index stratified by Gallagher body fat category.

with disease-specific HRQoL. Because the WHO has also proposed a definition of obesity as greater than 25% body fat in men and greater than 35% body fat in women,¹⁶ we compared the prognostic factors between 2 obese and non-obese categories. According to this definition, 71% of the cohort was obese. Similar to the comparison by Gallagher body fat category, obese patients (>25% in men and >25% in women) had significantly higher prealbumin and CRP levels but lower 6MWD and general HRQoL compared with nonobese patients.

Results of the multiple regression models exploring the associations among BMI, percent body fat, lean body mass, and CHF prognostic factors are shown in Table 6. After covariate adjustment, BMI was significantly inversely associated with NT-proBNP and the 6MWD but not associated with any of the nutritional markers, CRP, or HRQoL. In contrast, body composition as assessed by DEXA correlated with more of the CHF prognostic factors: percent body fat was significantly and positively associated with CRP and serum prealbumin level and inversely associated with 6MWD, whereas lean body mass was significantly inversely associated with NT-proBNP and positively associated with hand-grip strength.

Although the obesity paradox has been demonstrated in patients with diastolic heart failure and systolic failure,⁵ we repeated all analyses excluding the 9% of patients with only diastolic dysfunction as a sensitivity analysis. Results were similar when only patients with systolic function were analyzed.

DISCUSSION

In this cross-sectional study, we found that increasing BMI was significantly associated with lower NT-proBNP levels and lower exercise capacity. However, when directly measuring body composition, we found significant associations between increasing body fat and unfavorable changes in prognostic factors, such as higher inflammation and lower exercise capacity, whereas increasing lean mass was associated with favorable changes, such as better hand-grip strength and lower NT-proBNP levels. To our knowledge, this is the first study that examines the associations between body composition and several prognostic factors of mortality in CHF.

We also demonstrate that the WHO BMI categories misclassified 41% of the patients into the wrong Gallagher

TABLE 4. Chronic Heart Failure Prognostic Factors by Body Mass Index Category

Factors	Low-normal (<24.9)	Overweight (25.0-29.9)	Obese (≥30.0)	P value for trend
Nutritional markers				
Albumin (g/L)	42	42	43	
median (IQR)	(39-44)	(39-44)	(40-44)	.42
Prealbumin (g/L)	0.25	0.28	0.29	
median (IQR)	(0.21-0.27)	(0.24-0.32)	(0.25-0.32)	.004
SNAQ score	16±2	15±2	16±2	.57
Grip strength (n=140)				
Above average	17 (47.2)	24 (47.1)	32 (62.7)	.19
Below average	6 (16.7)	15 (29.4)	10 (19.6)	
Severity of HF (n=120)				
Highest NT-proBNP quartile				
Male	9 (47.4)	9 (27.3)	4 (11.4)	.03
Female	2 (28.6)	3 (21.4)	3 (25.0)	.38
NT-proBNP (pg/mol) median (IQR)				
Male	189 (31-357)	689 (30-226)	49 (11-165)	.07
Female	142 (75-353)	86 (33-183)	67 (27-192)	.15
Inflammation (n=124)				
CRP ≥2 mg/L	12 (42.9)	24 (50.0)	27 (56.3)	.26
CRP (mg/L)	1.4	2.0	2.2	
median (IQR)	(0.8-2.3)	(0.8-3.7)	(1.2-4.7)	.10
Distance walked on the 6-min walk distance test (m)				
	438±91	437±105	423±94	.53
HRQoL and depressive symptoms				
KCCQ summary score				
	79±19	78±17	74±17	.08
EQ VAS				
	68±22	71±17	63±19	.09
CES-D 10 score				
	6.1±5.2	7.2±5.6	8.1±5.8	.10

Categorical values are No. (percentage) of patients, and continuous values are mean ± SD unless otherwise indicated. CES-D 10 = Center for Epidemiological Studies Depression Short Form Scale; CRP = C-reactive protein; EQ VAS = EuroQol visual analog scale; HF = heart failure; HRQoL = health-related quality of life; IQR = interquartile range; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SNAQ = Simplified Nutritional Appetite Questionnaire.

body fat categories. Body mass index is considered a surrogate for obesity; however, it does not discriminate between fat and lean mass.¹⁷ In fact, BMI had a slightly higher correlation to lean body mass compared to percent body fat in our study. In addition, although lean body mass is positively associated with BMI, there is no relationship between lean body mass and percent body fat, which explains the observation that lean body mass increases with increasing BMI category but not with increasing Gallagher body fat category, making BMI an imprecise estimate of risk in patients with CHF. If a high BMI is being used as a surrogate for adiposity, one must be aware that it is reflecting an increase in body mass, but not necessarily an increase in body fat, and that this may lead to incorrect assump-

TABLE 5. Chronic Heart Failure Prognostic Factors by Gallagher Body Fat Categories

Factors	Low-normal (<24.9)	Overweight (25.0-29.9)	Obese (≥30.0)	P value for trend
Nutritional markers				
Albumin (g/L)	42	43	41	
median (IQR)	(39-44)	(40-45)	(39-44)	.46
Prealbumin (g/L)	0.25	0.28	0.29	
median (IQR)	(0.21-0.28)	(0.23-0.31)	(0.26-0.32)	.002
SNAQ score	16±2	16±2	15±2	.15
Grip strength (n=140)				
Above average	7 (18.4)	11 (28.9)	14 (22.6)	.60
Below average	11 (28.9)	9 (23.7)	13 (21.0)	
Severity of HF (n=120)				
Highest NT-proBNP quartile				
Male	9 (37.5)	5 (20.8)	8 (20.5)	.22
Female	2 (28.6)	1 (14.3)	5 (26.3)	.98
NT-proBNP (pg/mol) median (IQR)				
Male	80 (14-325)	68 (36-175)	68 (12-202)	.67
Female	94 (29-204)	75 (142-176)	73 (49-210)	.69
Inflammation (n=124)				
CRP ≥2 mg/L	10 (30.3)	33 (51.5)	58 (62.1)	.004
CRP (mg/L)	0.9	2.0	2.8	
median (IQR)	(0.6-2.2)	(0.9-3.5)	(1.3-4.6)	.001
Distance walked on the 6-min walk distance test (m)				
	460±101	440±105	411±87	.04
HRQoL and depressive symptoms				
KCCQ summary score				
	82±15	75±19	75±17	.05
EQ VAS				
	74±16	66±23	64±18	.01
CES-D 10 score				
	5.7±4.6	7.5±3.6	8.2±5.8	.05

Categorical values are No. (percentage) of patients, and continuous values are mean ± SD unless otherwise indicated. CES-D = Center for Epidemiological Studies Depression Short Form Scale; CRP = C-reactive protein; EQ VAS = EuroQol visual analog scale; HF = Heart failure; HRQoL = health-related quality of life; IQR = interquartile range; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SNAQ = Simplified Nutritional Appetite Questionnaire.

tions about any purported relationship between obesity and a given outcome in CHF.

Obesity as indexed by BMI was associated with a reduced exercise capacity measured by 6MWD, which is consistent with previous findings in studies of the general population.¹⁸ We also confirmed previously reported findings that BMI is not associated with a heightened inflammatory state (higher CRP level) in patients with CHF and extended these observations by demonstrating that directly measured body fat is independently associated with higher CRP levels.¹⁹

A high BMI has been associated with lower BNP levels in patients with CHF²⁰; however, as has been demonstrated in the general population,⁸ the inverse association between BMI and NT-proBNP may actually reflect an inverse rela-

TABLE 6. Linear Regression β -Coefficients (95% Confidence Intervals) for Separate Models Containing Body Mass Index and Dual Energy X-ray Absorptiometry-Measured Body Composition^a

	Body mass index (per unit increase)	<i>P</i> value	Percent body fat (per % increase)	<i>P</i> value	Lean body mass (per kg increase)	<i>P</i> value
Nutritional markers ^b						
Serum albumin	0.03 (−0.08 to 0.13)	.56	−0.03 (−0.10 to 0.05)	.49	0.04 (−0.03 to 0.12)	.34
Serum prealbumin	0.001 (−0.001 to 0.003)	.22	0.002 (0.001 to 0.003)	.005	0.0015 (−0.001 to 0.003)	.71
SNAQ score	0.02 (−0.05 to 0.09)	.60	−0.03 (−0.08 to 0.02)	.18	0.02 (−0.02 to 0.07)	.25
Grip strength of dominant hand	0.26 (−0.03 to 0.54)	.08	−0.05 (−0.23 to 0.14)	.61	0.36 (0.18 to 0.55)	.001
Severity of heart failure ^c						
Log NT-proBNP	−0.05 (−0.09 to −0.01)	.01	−0.01 (−0.04 to 0.02)	.44	−0.03 (−0.05 to −0.003)	.03
Inflammation ^d						
Log CRP	0.009 (−0.03 to 0.05)	.73	0.03 (0.003 to 0.061)	.03	−0.02 (−0.05 to 0.008)	.24
Physical fitness ^e						
6-min walking distance	−3.5 (−6.4 to −0.7)	.02	−2.8 (−4.9 to −0.8)	.008	0.6 (−1.2 to 2.4)	.48
HRQoL and depressive symptoms ^f						
KCCQ summary score	−0.29 (−0.83 to 0.25)	.36	−0.25 (−0.62 to 0.12)	.21	−0.27 (−0.62 to 0.08)	.12
EQ VAS	−0.27 (−0.92 to 0.37)	.36	−0.35 (−0.79 to 0.09)	.11	−0.19 (−0.61 to 0.23)	.39
CES-D 10 score	0.14 (−0.01 to 0.29)	.08	0.07 (−0.03 to 0.18)	.24	0.06 (−0.04 to 0.16)	.19

^a CES-D = Center for Epidemiological Studies Depression Short Form Scale; CRP = C-reactive protein; EQ VAS = EuroQol visual analog scale; HRQoL = health-related quality of life; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SNAQ = Simplified Nutritional Appetite Questionnaire.

^b Nutritional markers adjusted for age, sex, ejection fraction, heart failure cause, blood urea nitrogen level, serum sodium level, hemoglobin level, total cholesterol level, serum creatinine level, New York Heart Association (NYHA) class, gastrointestinal disease, and diabetes mellitus.

^c NT-proBNP adjusted for age, sex, race, hypertension, diabetes mellitus, dyslipidemia, serum creatinine level, coronary artery disease, ejection fraction, NYHA class, and medications (eg, spironolactone, angiotensin-converting enzyme inhibitor, and angiotensin receptor blocker).

^d CRP adjusted for age, sex, dyslipidemia, diabetes mellitus, coronary artery disease, NYHA class, hypertension, smoking, pulmonary disease, and medications (eg, angiotensin-converting enzyme inhibitor and angiotensin receptor blocker).

^e Six-minute walking distance adjusted for age, sex, diabetes mellitus, coronary artery disease, NYHA class, smoking, pulmonary disease, peripheral arterial disease, and ejection fraction.

^f HRQoL adjusted for age, sex, race, household income, social support, coronary artery disease, pulmonary disease, diabetes mellitus, malignancy, smoking, digoxin, NYHA class, and ejection fraction.

relationship between lean tissue and NT-proBNP, not between body fat and NT-proBNP.

Similar to a previous study in CHF,²¹ we found that BMI was not associated with serum albumin levels. Percent body fat was positively and independently associated with serum prealbumin but not albumin levels. Prealbumin is more sensitive to recent changes in protein-energy status than albumin, and its concentration reflects recent dietary intake rather than overall nutritional status.²² Thus, a low prealbumin concentration can be regarded as a marker identifying a patient at risk of developing malnutrition rather than a patient who is already malnourished.²³ Although higher prealbumin levels in obese patients may indicate greater nutritional reserve, it is also possible that obese patients with CHF have a higher caloric intake,^{24,25} which leads to a relative increase in serum prealbumin levels but not albumin levels compared with normal-weight patients.

Lean body mass, BMI, and percent body fat were not independently associated with HRQoL or depressive symptoms after adjustment of clinical, psychosocial, and socioeconomic characteristics. Our results differ from a previous study²⁶ that found that CHF patients with a BMI of 30 or higher had worse HRQoL compared with nonobese patients.

Collectively, these observations indicate that, when BMI is divided into fat and lean mass components, a higher lean body mass and/or a lower fat mass is independently associated with factors that are prognostically advantageous in CHF. The single previous observational study⁷ in patients with CHF that examined body fat (measured by skinfold thickness) and adverse cardiovascular events found that a higher percent body fat was independently associated with a lower composite outcome of cardiovascular death and urgent cardiac transplant. However, the investigators could not accurately measure or adjust for lean body mass. A higher reserve of adipose tissue may have independent protective effects against mortality in the CHF population; however, further well-powered prospective studies examining the relationship of direct measures of adiposity and lean body mass to survival in CHF are needed to determine this. Our results suggest that differentiating between body fat and lean body mass may explain some of the apparently paradoxical associations between BMI and prognosis in heart failure and are supported by a recent cohort study of patients undergoing maintenance hemodialysis (another population exhibiting the obesity paradox), which demonstrated the highest survival rates in patients with greater muscle mass.²⁷

Several limitations of our study should be noted. First, the cross-sectional design provides associative, not causal, evidence. Second, there is no current consensus on established healthy body fat ranges. The Gallagher body fat categories were developed on the basis of age, sex, and race and also on the WHO BMI cutoffs. However, the reference ranges by Gallagher et al¹⁵ are widely cited and have been cross-validated by others.²⁸ In addition, we used percent body fat as a continuous variable in our adjusted analysis instead of as a categorical variable. Third, the number of patients in each body fat or BMI category was relatively small, and comparisons may have been underpowered. Fourth, hand-grip strength as a marker of nutritional status has not been validated in the CHF population. However, it has been validated in the hemodialysis^{29,30} and elderly populations,^{31,32} 2 other populations that exhibit the obesity paradox. Fifth, we used surrogates of mortality in CHF but did not directly assess survival in this study. Whether body fat and/or lean body mass is predictive of mortality and/or hospitalization remains to be examined. Finally, DEXA measurement of lean body mass cannot distinguish between body water and muscle mass. However, ingestion of small fluid volumes (<500 mL) 1 hour before DEXA scanning does not bias the estimates of body composition,³³ and patients were enrolled and tested only after they were found to be clinically euvolemic. In addition, if we were overestimating lean body mass in fluid overloaded patients, then any bias should have been operant in the opposite direction to our findings.

CONCLUSION

In this study of patients with CHF in whom body composition was directly measured, using BMI as the measure of body fat lead to misclassification of 41% of patients with CHF. Directly measured body composition was also found to be more closely linked to indicators of prognosis in patients with CHF than BMI. Significant associations were found between increasing body fat and unfavorable changes in certain important CHF prognostic factors, whereas increasing lean body mass was associated with favorable changes in other important factors. Given that BMI was similarly correlated to lean body mass and percent body fat in patients with CHF, as well as the lack of relationship between lean body mass and percent body fat, BMI may not be a good indicator of adiposity and may in fact be a better surrogate for lean body mass in this population. Using BMI as a proxy for adiposity may lead to incorrect assumptions about the relationship between obesity and outcomes in CHF, and division of this surrogate marker into lean and fat components may be a more precise estimate of risk in this population. Prospective studies with direct measures

of body composition should be performed in patients with CHF to better characterize the relationship between adiposity and subsequent morbidity and mortality.

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