Clinical Nutrition 34 (2015) 1233–1238

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

# Body mass index, body fat, and nutritional status of patients with heart failure: The PLICA study

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ARTICLE INFO

*Article history:*
Received 28 July 2014
Accepted 16 December 2014

*Keywords:*
Heart failure
Obesity paradox
Nutritional assessment
Prognosis
Undernourishment

SUMMARY

*Background & aims:* Nutritional assessment may help to explain the incompletely understood obesity paradox in patients with heart failure (HF). Currently, obesity is usually identified by body mass index (BMI). Our objective was to assess the prognostic influence of undernourishment in HF outpatients.
*Methods:* Two published definitions of undernourishment were used to assess 214 ambulatory HF patients. Definition 1 included albumin, total lymphocyte count, tricipital skinfold (TS), subscapular skinfold, and arm muscle circumference (AMC) measurements (≥2 below normal considered undernourishment). Definition 2 included TS, AMC, and albumin (≥1 below normal considered undernourishment). Patients were also stratified by BMI and body fat percentage and followed for 2 years. All-cause death or HF hospitalization was the primary endpoint.
*Results:* Based on BMI strata, among underweight patients, 60% and 100% were undernourished by Definitions 1 and 2, respectively (31% and 44% among normal-weight, 4% and 11% among overweight, and 0% and 3% among obese patients, respectively, according to the two definitions). The most prevalent undernourishment type was marasmus-like (18% of the total cohort). Undernourishment by both definitions was significantly associated with lower event-free survival. Following multivariable analysis, age, NYHA functional class, NTproBNP, and undernourishment (hazard ratio [HR] 2.25 [1.11–4.56] and 2.24 [1.19–4.21] for Definitions 1 and 2, respectively) remained in the model. In this cohort, BMI and percentage of body fat did not independently predict 2-year event-free survival.
*Conclusions:* Nutritional status is a key prognostic factor in HF above and beyond BMI and percentage of body fat. Patients in normal BMI range and even in overweight and obese groups showed undernourishment. The high mortality observed in undernourishment, infrequent in high BMI patients, may help to partly explain the obesity paradox. Proper undernourishment assessment should become routine in patients with HF.


## 1. Introduction

Soon after the first description of the relationship between body mass index (BMI) and survival after heart failure (HF) [1–5], several studies searched for explanations for the so-called "obesity paradox". Two main hypotheses were suggested. The first one proposed that fat, blocking tumor necrosis factor and lipopolysaccharides, or producing adipokines, may be protective. The second one proposed that a high BMI may relate to protective factors, like younger age, more muscle and serum protein, more muscle strength, and better functional capacity [5,6].

It is important to keep in mind that the obesity paradox is based on BMI. However, obesity is defined as an abnormal accumulation of body fat [7] and BMI does not measure fat; rather, it measures weight related to height.

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http://dx.doi.org/10.1016/j.clnu.2014.12.013
0261-5614/

HF is a congestive condition, and even non-decompensated patients have an excess of liquid compared to the normal population [8]; thus, some patients who are considered to be of normal weight may actually be underweight. However, few studies have included nutritional parameters other than BMI in their assessments of the obesity paradox [6,9,10]. There is no universal standard for nutritional assessment, and HF, a chronic disease associated with body wasting and water retention, may require specific considerations. Our group previously reported a pilot study that revealed that a more-accurate measurement of nutritional status actually identified undernourished patients among those in the normal and high BMI categories; being undernourished was found to be prognostically meaningful [11]. Accordingly, the aim of the current study was to assess a larger prospective cohort of ambulatory HF patients in terms of BMI, body fat, and nutritional status and to determine the relative prognostic value of these variables in long-term follow-up.

## 2. Methods

### 2.1. Study population

The PLICA (Nutritional Status and Prognosis in Heart Failure) study included 214 HF outpatients seen at a specialized clinic of a university hospital between March and July 2011. Criteria for referral to the HF clinic have been reported elsewhere [12,13]. HF diagnoses were made according to European Society of Cardiology guidelines [14] and at least one hospital admission for symptoms of HF or depressed (<40%) left ventricular ejection fraction (LVEF). The study complies with the Declaration of Helsinki, was approved by the Germans Trias i Pujol Ethics Committee, and all patients signed an informed consent. Patients attended the HF clinic at a regular visitation schedule [12,13] with extra visits if required by their clinical status. Event data was collected from medical history and patients' physicians and relatives, and verified against Catalan and Spanish Health System's databases. Clinical and demographic data were recorded at enrollment. The primary endpoint was all-cause death or HF hospitalization at 2 years. Emergency department visits shorter than 24 h were not considered hospital admissions.

### 2.2. BMI and body fat categories

Patients were stratified into four categories by BMI and by body fat percentage: underweight, normal weight, overweight, and obese. BMI was calculated as weight in kilograms divided by height in meters squared, and patients were grouped using the World Health Organization (WHO) classification: underweight, BMI < 18.5 kg/m$^2$; normal weight, BMI 18.5–24.99 kg/m$^2$; overweight, BMI 25–29.99 kg/m$^2$; and obese, BMI $\geq$ 30 kg/m$^2$ [15].

Percentage of body fat was assessed by calculating body density with the Durnin and Womersley formula [16], which requires four anthropometric measurements: bicipital skinfold (BS), tricipital skinfold (TS), subscapular skinfold (SS), and suprailiac skinfold (SIS), where density = c − [m × log (BS + TS + SS + SIS)], where c and m are the constants for age and sex, respectively, and the Siri formula [17]: percentage of body fat = [(4.95/density) − 4.50] × 100. Patients were stratified using the Gallagher percentage of body fat categories [18].

### 2.3. Nutritional markers: anthropometric measurements and blood samples

TS, BS, SS, and SIS were measured to the nearest 0.1 mm three times with a skinfold caliper (Lange, Cambridge Scientific Instruments, Cambridge, MA, USA) with patient in a relaxed position. Thickness of the skinfold was defined as the mean of the sum of the three values. A single observer performed all measurements according to standard techniques. Arm muscle circumference (AMC) was calculated by the following formula: AMC (cm) = arm circumference (cm) − [0.314 × TS (mm)]. Lower limits of anthropometry parameters normal values were calculated with the 5th percentile for each age and sex group [19] of the reference population [20].

Blood samples were drawn by venipuncture between 09:00 and 14:00 h with the patient at rest. The nutritional markers albumin levels and total lymphocyte count were measured. The albumin and total lymphocyte counts thresholds for malnutrition were the Spanish Society of Parenteral and Enteral Nutrition limits: albumin < 35 g/L and total lymphocyte count $\leq 1.2 \times 10^9$). N-terminal pro-B-type **natriuretic** peptide (NTproBNP) levels were also measured.

### 2.4. Undernourishment definition

We used two nutritional assessments (Fig. 1):

**Definition 1**. recently reported by Gastelurrutia et al.[11] in a pilot study with HF patients, is derived from a consensus of the nutritional markers used most in the literature: albumin (a biochemical indicator of protein reserves), total lymphocyte count (an immunological parameter related to protein depletion and loss of immune defense), and anthropometry markers, including TS and SS (which measure subcutaneous fat reflecting the caloric aspect of malnutrition), and AMC (which estimates muscularity). Undernourishment was defined as the presence of $\geq$2 of these variables below the normal values [11,21].

**Definition 2**. proposed for the first time by Gassull et al. [19], uses TS as a measure of fat, AMC as a measure of muscle, and albumin as a visceral protein indicator. Undernourishment was defined as the presence of $\geq$1 of these variables below the normal values. This definition allowed us to classify the type of undernourishment (kwashiorkor-like, marasmus, or mixed) based on the type of deficit (fat, muscle, or visceral protein).

### 2.5. Statistical analysis

Frequencies and percentages described categorical variables. Mean ± standard deviation (SD), or median and 25th–75th percentiles (P25–P75) in the case of skewed distribution, described continuous variables. Normal Q–Q plots were used to assess normal distribution. Statistical differences between groups were assessed with the chi-square test for categorical variables and Student's *t*-test for continuous variables if normally distributed or Mann–Whitney U-test if non-normally distributed. Kappa values were obtained from the WHO definition of BMI and the Gallagher percentage of fat strata. Univariate Cox survival curves were plotted to ascertain the relationship between the presence of undernourishment (by both definitions) and our composite endpoint. To identify independent predictors of the primary endpoint, multivariable Cox proportional hazards models (backward step method) were performed, adjusting for the following classical confounders: age, sex, New York Heart Association functional class, etiology of HF, LVEF, BMI, hemoglobin, estimated glomerular filtration rate (CKD-EPI equation), treatment with beta-blockers and angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), NTproBNP levels, percentage of fat, and undernourishment. To fulfill the assumption of linearity for the covariables, the logarithmic function of NT-proBNP levels was used. Adjusted Cox survival curves were also plotted. Statistical analyses