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Clinical significance of nutritional status in patients with chronic heart failure—a systematic review

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Abstract

Chronic heart failure (CHF) and nutritional disorders are recognized as major challenges for contemporary medicine. This study aims to estimate the role of nutritional disorders as risk factors for CHF development and prognostic factors for CHF patients and the outcome of nutritional intervention in CHF. Full-text English articles published between January 2013 and February 2019 available in the PubMed and Scopus databases were considered. Seventy-five prospective, retrospective, and cross-sectional studies as well as meta-analyses on patients with CHF, reporting correlation of their nutritional status with the risk and prognosis of CHF and the outcome of nutritional interventions in CHF were all included. Higher BMI increases the risk of CHF by 15–70%, especially when associated with severe, long-lasting and abdominal obesity. Overweight and obesity are associated with the reduction of mortality in CHF by 24–59% and 15–65%, respectively, and do not affect the outcome of invasive CHF treatment. Malnutrition increases the risk of mortality (by 2- to 10-fold) and the risk of hospitalization (by 1.2- to 1.7-fold). Favorable outcome of nutritional support in CHF patients was reported in a few studies. Nutritional disorders are prevalent in patients with CHF and play a significant role in the incidence, course, and prognosis of the disease. The existence of an "obesity paradox" in patients with CHF was confirmed. Further studies on the effect of nutritional support and body weight reduction in patients with CHF are necessary.

Keywords Chronic heart failure · Malnutrition · Nutritional status · Obesity · Prognosis · Intervention

Introduction

Chronic heart failure (CHF), as well as nutritional disorders, is recognized as being among the major challenges for contemporary medicine. The most recent data show that about 26 million people worldwide suffer from CHF [1] and, in developed countries, CHF affects 1–2% of adults [1, 2]. In the USA, the medical costs of treatment due to CHF amount to approximately $30–40 billion (absorbing over 10% of medical expenditures) [1, 3, 4]. The prognosis are also poor—mortality rate is higher for patients with CHF in comparison with cancerous diseases (apart from lung cancer) [5]. The probability of survival is estimated at 50% up to 5 years after CHF diagnosis and 10% after 10 years [6]. It is assumed that both these unfavorable outcomes are linked to patients' nutritional status, mainly due to epidemiological associations [7–14]. The term "inappropriate nutritional status" covers two different and broad groups: (1) excessive nutrition, i.e., overweigh and obesity, primarily defined with a body mass index (BMI) due to the World Health Organization (WHO) classification (the most common way to measure excessive fat accumulation) and (2) malnutrition (a condition resulting from energy, proteins, and other macro- and micronutrient deficiencies, leading to measured clinical effects being a consequence of changes in the body's tissues and functions). This two types of nutritional disorders frequently affects patients with CHF. Current research indicates that about 38–58% of patients with CHF are obese. What is more, more than one third of these patients are

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severely obese [15]. The incidence of malnutrition among CHF patients is also disturbing. About 75–90% of patients with exacerbation or an advanced stage of the disease are undernourished and at least 10–15% will suffer from cardiac cachexia (defined as a drop in body weight due to wasting, decreased muscle mass and significant depletion of adipose tissue) [16]. However, the authors of the current paper have also assumed that the relationship between CHF and nutritional status may depend on pathophysiological interrelationships (Fig. 1) in addition to epidemiological associations.

We formulated the following hypotheses: (1) nutritional status affects the development of CHF; (2) both malnutrition and excessive nutrition determine the course of disease, the severity of symptoms, the effectiveness of the therapy, mortality rates and frequency of complication in CHF; and (3) correction of nutritional status in patients with CHF improves the course of the disease and reduces complications as well as decreases mortality rate.

The aim of this review is to present the most recent data concerning the relationship between nutritional status and the development and course of CHF, in relation to the hypotheses mentioned and with precise objectives described below.

Methods

Search strategy

A search covering the period from January 2013 to February 2019 was conducted using the PubMed and Scopus databases according to pre-specified inclusion criteria protocol and following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement" (PRISMA). The search terms applied were "chronic heart failure" combined with (body mass OR overweight OR obesity OR adiposity OR underweight OR obesity paradox OR weight loss OR malnutrition OR undernutrition OR nutritional status) AND (clinical study OR clinical trial OR comparative study OR controlled clinical trial OR meta-analysis OR observational study OR randomized controlled trial OR review OR systematic review OR prospective study OR cohort study OR retrospective study

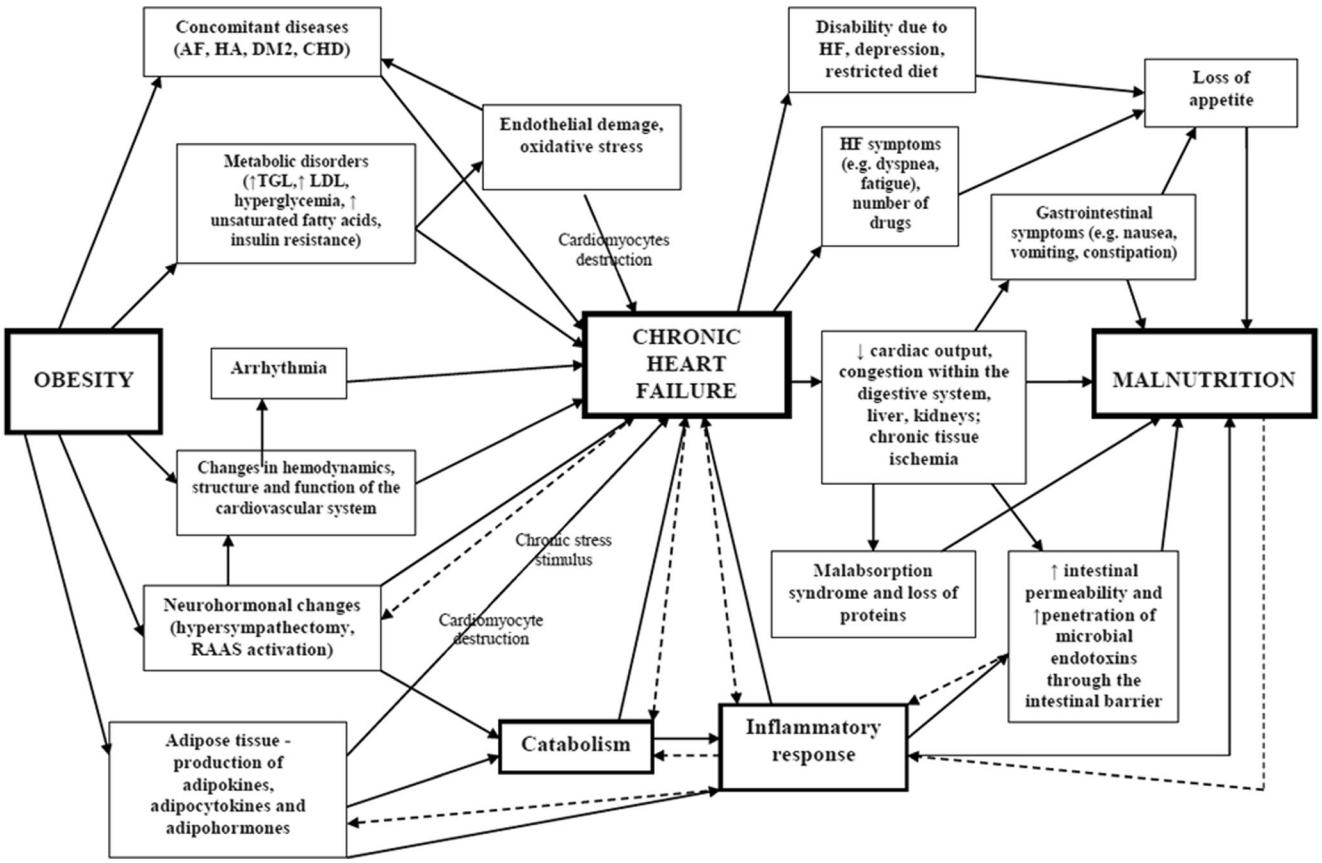

Fig. 1 Pathophysiological mechanisms linking CHF with nutritional status. Relationship between CHF and nutritional status (obesity and malnutrition) depends mainly on pathophysiological interrelationships. The mechanisms of these conditions mutually intertwine and interact with each other and are based on the principle of a "vicious circle."

Abbreviations: AF, atrial fibrillation; CHD, coronary heart disease; CHF, chronic heart failure; DM2, type 2 diabetes mellitus; HA, hypertension arterialis; HF, heart failure; LDL, low-density lipoprotein; RAAS, renin-angiotensin system; TGL, triglycerides

Or interventional study) AND (prognosis OR mortality OR progression OR quality of life OR symptom burden OR outcome OR hospitalization). Some of the references obtained from the publications retrieved were searched manually for additional studies and reviews. A number of research papers were excluded from the analysis. For example, papers concerning genetically determined heart failure or postoperative exacerbations of the disease—with the detailed reasons included in a flow diagram in Fig. 2. Only English language articles were taken into consideration. Abstracts only were not included. The last search was performed on the 18th of February 2019. This systematic review is not registered.

Eligibility criteria

The studies were included according to five components of the PICOS process: (1) studies carried out on human adults of more than 18 years of age with the CHF diagnosis and studies on general population without history of cardiovascular diseases (CVD), in order to assess the prognosis factor for CHF (P) with comparison to healthy population or CHF patients with an appropriate nutritional status (C) defined with different tools due to the constant lack of the "gold standard" in diagnosing malnutrition and some doubts concerning the inaccuracy of using BMI to define obesity in CHF; (2) studies assessing nutritional interventions (I) in CHF patients (supportive nutritional and dietary treatment in terms of malnutrition, as well as weight reduction in the cases of excessive nutritional status, with the exception of bariatric surgery as an intentional weight-loss intervention in obese patients) as well as observational studies without intervention; (3) studies with the assessment of hard or surrogate endpoints (O), e.g., mortality rate, frequency of complication (like hospitalizations, severity of symptoms and effectiveness of CHF therapy) being evaluated with evidence-based medicine (EBM) parameters (i.e., relative risk estimates—hazard ratio (HR), risk ratio (RR), and odds ratio (OR)) or log-rank test with the 95% confidence intervals (CIs) and/or associated p values); (4) studies performed in following design (S): prospective, retrospective, cross-sectional, interventional, and clinical trials, as well as meta-analysis of a full-length publication in English reporting the association of nutritional status and nutritional disorders (i.e., malnutrition and obesity or overweight) with the CHF prognosis and course evaluation, as well as the CHF treatment outcome, including specific cardiac implantable electronic devices therapy (excluding heart transplantation).

Outcomes measured

The primary outcome of interest was CHF mortality (cardiac, all-cause, and sudden death), CHF incidence, CHF hospitalizations, the severity of symptoms, response to invasive treatment, complication after implantation of invasive tools, and the effectiveness of intervention in patients' nutritional status.

Secondary outcome measures were quality of life, symptoms improvement, changes in cardiac parameters and functional improvement, such as exercise capacity (particularly for interventional studies).

Data extraction

Data were extracted and eligibility assessment were performed independently by three reviewers (AW, AW, MA) and checked for accuracy by another reviewer (JB). Discrepancies between reviewers were resolved by consensus. Information was extracted according to five components of the PICOS process: (1) the characteristics of study participants (the patients and the control group), including, for example, age, gender, percent of ejection fraction (EF), CHF diagnosis assessment, percent of malnutrition among patients in the related studies, type of tool used for nutritional status assessment and comparison; (2) CHF treatment type and/or nutritional intervention type in the related studies; (3) the follow-up period; (4) type of outcome and summary effect measure; and (5) study design.

Results

Study selection

The process of the article selection based on PRISMA guidelines is presented in Fig. 2. A preliminary literature search in the PubMed and Scopus databases yielded 4037 papers published between 1st January 2013 and 18th February 2019. After excluding the duplicates, 1691 articles remained and were then screened based on the assessment of the abstracts and titles. After excluding the inappropriate papers (with the reasons specified in Fig. 2), 95 full-text articles were evaluated according to the inclusion criteria. From these articles, 20 articles were deemed as irrelevant. Finally, the remaining 75 articles were included in this systematic review.

Baseline characteristics

The baseline characteristics of the included studies (e.g., sample size, patients' age, follow-up, etc.) are summarized in Tables 1, 2, 3, and 4. Among the included articles, 10 were related to assessment of nutritional status as a risk factor in CHF [3, 17–25] (Table 1), the other 60 papers assessed the relationships between CHF patients' nutritional status and their prognosis, as well as the outcome of invasive treatment of the disease [26–85] (Tables 2 and 3), and only 5 studies

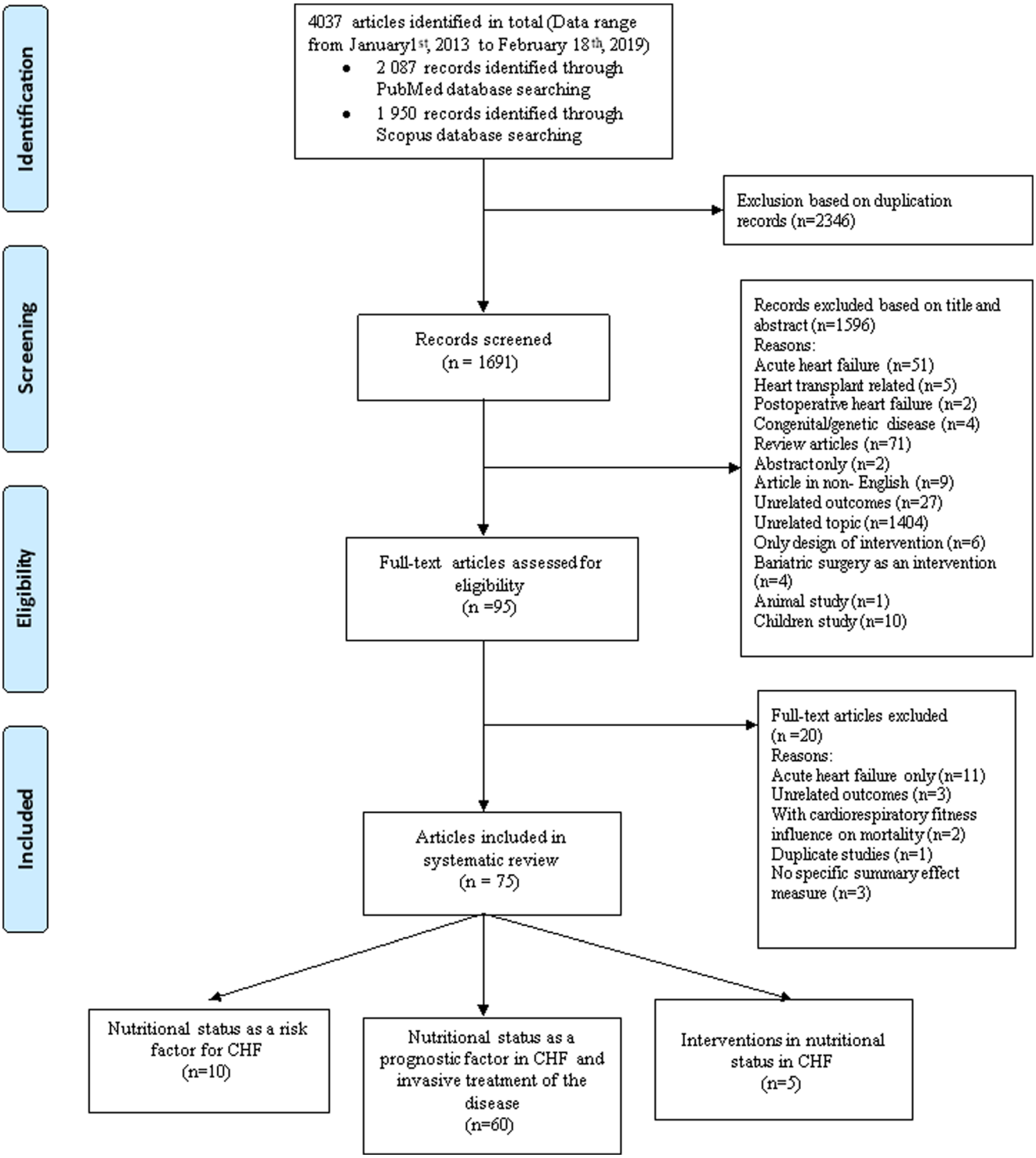

Fig. 2 The flow diagram of selecting eligible articles based on PRISMA. Abbreviations: CHF, chronic heart failure

evaluated the interventions in nutritional status in CHF [13, 86–89] (Table 4).

This systematic review includes 39 prospective studies, 20 retrospective studies, 2 cross-sectional studies, and 8 meta-analysis as well as 7 interventional studies (among which, 5 were directly related to nutritional intervention, with only 3 placebo-controlled randomized trials).

The geographic distribution of the studies was predominantly in North America and Europe (24 papers on studies from the USA, 24 from Europe, and 11 from Asia). Six papers were based on international studies (not including the eight

Table 1 Nutritional status as a risk factor for CHF

No.	Author/country	Study design	Patients	No. of pts.	Age[a]	Gender	Follow-up	Tools	Endpoint	Outcome/effect measure
1.	Ho Je et al. [17]/USA	FHS (prospective cohort study)	No history of prevalent CHF at the moment of diagnosis	6340 (512, 8.1% developed CHF)	60 ± 12 years	Males, 46%	Up to 8 years; mean, 7.7 ± 1.7 years	BMI	Incident HF	Higher BMI was a stronger predictor for risk of incident HFpEF (EF > 45%) vs. HFrEF (≤ 45%); BMI (per 4.7 kg m^{-2}): HR 1.41 (95% CI, 1.23–1.61; $p < 0.001$).
2.	Mørkedal et al. [18]/Norway	Population-based prospective cohort study, HUNT-2 (Nord-Trøndelag health study)	Men and women free of CVD, classified according to BMI and metabolic status at baseline; age at baseline ≥ 20 years	61, 299 (1201 HF cases, 2%)	44.3–60.1 years	Males, 28.8–54.9%	Median 12.3 years	BMI	Incident HF	BMI ≥ 30 vs. BMI < 25 at baseline, for MH: HR 1.7 (95% CI, 1.3–2.3), for MUH: HR 1.7 (95% CI, 1.4–2.2). BMI 35–39.9 vs. BMI < 25: MH: HR 0.9 (95% CI, 0.5–1.9), MUH: HR 2.5 (95% CI, 1.9–3.4). BMI ≥ 40 vs. BMI < 25: MH: HR 5.0 (95% CI, 2.5–9.7), MUH: HR 4.9 (95% CI, 3.1–7.7). Long-term (> 30 years) BMI ≥ 30 MUH: HR 2.2 (95% CI, 1.7–2.9), recently developed BMI ≥ 30 MUH: HR 1.3 (95% CI, 0.8–2.1).
3.	Schmidt et al. [19]/Denmark	Population-based prospective cohort study	Men undergoing examination for military service in Denmark (at the age of 18 years or shortly thereafter; median age 19 years at baseline), who survived until their 22nd birthday (start of follow-up)	12,850; 107, 0.8% pts. with CHF		Males, 100%	Median, 26 years; maximum, 36 years	BMI	Occurrence of CHF	Young adulthood obesity is an important risk factor for CHF without pre-existing IHD. 36-year risk of CHF without pre-existing IHD: normal weight (BMI 18.5–25) 0.8% (95% CI, 0.6–1.1), obesity (BMI > 30) 4.0% (95% CI, 1.5–8.6). Obesity vs. normal weight: HR 6.68 (95% CI, 2.85–15.66).
4.	Del Gobbo et al. [3]/USA	Prospective study	Pts. from CHS (community-based prospective cohort of older adults ≥ 65 years without HF)	4490; 1380, 31% cases HF	72 years	Males, 49%	Maximum, 21.5 years	BMI	Incident HF	Maintaining BMI < 30, independently associated with decreased risk of CHF; BMI < 30 vs. BMI ≥ 30: HR 0.66 (95% CI, 0.62–0.82).
5.	Chahal et al. [20]/USA	Multicenter observational prospective cohort study (MESA)	Pts. free of clinical CVD at baseline	6814; 176, 2.6% HF cases	62.1 ± 10 years	Males, 47.2%	Median, 4.7 years	BMI	Incident HF	BMI an independent predictor of CHF: HR 1.40 (95% CI, 1.10–1.80) per 5 kg m^{-2}.
6.	Yang et al. [21]/ International	Meta-analysis and systematic	15 observational studies in	456,850; 11,467, 2.5% cases		Males, 32–100%	Mean, 4–29 years	BMI	Incident HF	

Table 1 (continued)

No.	Author/country	Study design	Patients	No. of pts.	Age[a]	Gender	Follow-up	Tools	Endpoint	Outcome/effect measure
	(America, Europe)	review of prospective studies	unselected community populations		21–81 (weighted range, 42 ± 13 years)					BMI (per 5 kg m^{-2}): incident HF (HR = 1.15; 95% CI, 1.06–1.25).
7.	Krishnamoorthy et al. [22]/USA	Retrospective analysis of data from prospective epidemiologic study	Community sample of African Americans participating in the Jackson Heart Study without HF at baseline	5292; 214, 4% HF cases	Median age, 53.3–58.1 years		Median, 4.8–9 years (different period for the outcomes)	BMI	HF prevalence; HF hospitalization	Obesity (higher BMI) associated with HF prevalence ($p < 0.001$) and HF hospitalizations (especially for morbid obesity ≥ 35 kg m^{-2} (9.0%; 95% CI, 7.6–11.7) vs. normal weight (6.3%; 95% CI, 4.7–8.4]). Each 1-point ↑ in BMI: risk of CHF (HR 1.05; 95% CI, 1.03–1.06; $p < 0$ .001); risk of HF hospitalization (for BMI > 32 kg m^{-2}: HR 1.05; 95% CI, 1.03–1.07; $p < 0.001$).
8.	Aune et al. [23]/ International (USA, Europe, Asia, Australia)	Meta-analysis and systematic review of prospective studies	27 prospective studies (23 connected with incident HF), 4 with HF mortality	647,388; 15,905, 2.5% HF (for BMI analysis); 362,450; 9865, 2.7% HF cases (for WC analysis)	Median age, 19–84 years		Different (from < 1 to 27 years)	BMI, WC, WHR	Incident HF	RR for a 5-unit ↑ in BMI, 1.41 (95% CI, 1.34–1.47; I^2 = 83%) for HF incidence; RR for a 10-cm ↑ in WC, 1.29 (95% CI, 1.21–1.37; I^2 = 89%) and per 0.1-unit ↑ in WHR, 1.29 (95% CI, 1.13–1.47; I^2 = 82%) for HF incidence.
9.	Ho et al. [24]/ International (USA/ Netherlands)	4 prospective, observational community-based cohort studies: FHS, CHS, PREVEND, MESA.	Participants from four community-based cohorts without HF at baseline examination; age ≥ 30 years	28,820 individuals; 982, 3.4% HFpEF (> 45%) and 909, 3.2% HFrEF (≤ 45%); across the studies	49–73 years	Males, 43–50%	Up to 15 years; median, 12 years	BMI	First HF event occurring up to 15 years after baseline examination	BMI: significant risk factor and predictor of incident. (1) Derivation set, sex, and age adjusted: BMI per 4 kg m^{-2}: HFpEF: HR 1.33 (95% CI, 1.25–1.41; $p < 0.0001$), BMI per 4 kg m^{-2}: HFrEF: HR 1.26 (95% CI, 1.18–1.35; $p < 0.0001$). (2) Multivariable model risk of HFpEF per 4 kg m^{-2} BMI (HR 1.28; 95% CI, 1.21–1.37; $p < 0.0001$), risk of HFrEF per 4 kg m^{-2} BMI (HR 1.19; 95% CI, 1.11–1.28; $p < 0.0001$).
10.	Crump et al. [25]/Sweden	National cohort prospective study	Military conscripts in Sweden during (1969–1997)	1,330,610; 11,711, 9% with HF; only men	Age at baseline (97–98%), 18 years; at diagnosis: mean, 48.0 ± 7.4 years	Males, 100%	Mean, 28.2 years; end in 2012	BMI	Incidence of HF	High BMI at the age of 18 years = higher risk of HF in adulthood (vs. normal BMI, < 25.6 kg m^{-2}); overweight at the age of 18 years

Table 1 (continued)

No.	Author/country	Study design	Patients	No. of pts.	Age[a]	Gender	Follow-up	Tools	Endpoint	Outcome/effect measure
										(≥25.6–28.9 kg m^{-2}): adjusted HR 1.48 (95% CI. 1.38–1.58), obesity at the age of 18 years (≥29 kg m^{-2}) adjusted HR 2.06 (95% CI, 1.90–2.24), per 1 BMI unit (trend test) adjusted HR 1.06 (95% CI, 1.06–1.07), $p < 0.001$ for all)

Abbreviations: *BMI*, body mass index (kg m^{-2}); *CHF*, chronic heart failure; *CHS*, Cardiovascular Health Study; *CI*, confidence interval; *CVD*, cardiovascular disease; *EF*, ejection fraction; *FHS*, Framingham Heart Study; *HF*, heart failure; *HFpEF*, heart failure with preserved ejection fraction; *HFrEF*, heart failure with reduced ejection fraction; *HR*, hazard ratio; *IHD*, ischemic heart disease; *MESA*, Multi-Ethnic Study of Atherosclerosis; *MH*, metabolically healthy; *MUH*, metabolically unhealthy (which means: elevated waist circumference (> 94 cm for men, > 80 cm for women) or BMI ≥ 30 kg m^{-2} in addition to ≥ 2 of: ↑ nonfasting triglycerides (≥ 1.7 mmol l^{-1}), ↓ high-density lipoprotein cholesterol (< 1.03 mmol l^{-1} for men, < 1.29 mmol l^{-1} for women), ↑ blood pressure (≥ 130 85 mmHg^{-1}) or use of blood pressure medication, ↑ nonfasting glucose (≥ 11.1 mmol l^{-1}), or diabetes diagnosis); *PREVEND*, Prevention of Renal and Vascular Endstage Disease; *pts.*, patients; *RR*, relative risk; *WC*, waist circumference; *WHR*, waist-to-hip ratio

[a] Mean ± SD unless it was showed different

meta-analyses). The sample size of studies varied from 54—in the study of Huang et al. [69] to 11,711—in the study of Crump et al. [25]. However, in the interventional studies, the quantity of patients included was smaller (ranging from 13 to 622) and in meta-analyses, the number of participants was between 23,967 to 647,388.

In the majority of the articles (which presented the data for a whole sample), the study groups primarily consisted of men, with the proportion of male participants from 19 to 98–100% (three studies only on men [19, 25, 37], not including meta-analyses and with exception of one small study with almost only women—12 of 13 participants [87]). The reported range of mean age of participants was from 48 to 78 years old (some studies did not disclose the ages for the entire group, others used median values). The follow-up range was from 21 days for interventional study of Mathew et al. [87] to maximum 36 years in the study of Schmidt et al. [19] (in almost every analyzed study, the duration of follow-up was longer than 1 year, excluding two prospective studies [63, 74] and all the interventional studies [86–89]).

Most patients with CHF in eligible studies were mainly diagnosed with European Society of Cardiology (ESC) criteria and Framingham criteria or with the left ventricular ejection fraction (LVEF) measurement associated with the clinical evaluations of experienced cardiologists. The mean range of reported ejection fraction (EF) was 16.7% (in the study related to LVAD patients [84]) to 61.6% (in the interventional study [89]).

Since the study designs, participants, methods of nutritional status assessment, and reported outcome measures varied significantly in extracted publications, we focused on describing the reviewed studies and their results as well as limitations, rather than quantitative synthesis.

Nutritional status as a risk factor in chronic heart failure

Publications on the relationships between nutritional status and risk of CHF are presented in Table 1 [3, 17–25]. The reviewed material included 44,564 CHF incident cases among 2,560,753 participants. All the presented studies consistently communicate a strong association between HF occurrence and obesity (a BMI > 30 kg m^{-2}) or overweight (a BMI range, 25–29.9 kg m^{-2}): a higher BMI increases the risk of disease by 15–70%, up to a 3- to 5-fold increase for morbid obesity (BMI ≥ 40 kg m^{-2}), which underlines the significance of obesity degree, as the poorest prognosis is presented for patients with severe obesity (BMI ≥ 35 kg m^{-2} [21]). In the studies analyzed, excessive nutrition is mostly defined using BMI values (considered to be an independent variable of HF incidence [20, 21]). Similar relationships are demonstrated for other nutritional indicators, such as waist circumference (WC) or waist-to-hip ratio (WHR), which highlight the negative impact

Table 2 Nutritional status as a prognostic factor in CHF

No.	Author/country	Study design	Patients	No. of pts.	Age[a]	Gender
Obesity as a prognostic factor in CHF						
1.	Farrell et al. [26]/USA	CCLS prospective observational cohort study	Men without a history of CVD, BMI < 18.5 kg m^{-2}	44,674	43.4 ± 9.2 years	
2.	Nagarajan et al. [27]/USA	Retrospective study	Advanced HF referred for heart transplantation; BMI < 18.5 kg m^{-2} excluded	501	Median age, 55–57 years (across BMI groups)	Males, 74.3%
3.	Stavrakis et al. [28]/USA	Retrospective cohort study	Pts. with HFpEF; EF > 45%	150	69 ± 11 years	Male, 98%
4.	Tavazzi et al. [29]/Italy	Multicenter, nationwide, prospective observational trial	3755 outpts. with CHF (EF, 38 ± 11%); 1855 pts. with AHF (EF, 38 ± 14%)	5610	CHF, 69 ± 12 years; AHF, 72 ± 12 years	CHF (men), 76%; AHF (men), 60%
5.	Barlera et al. [30]/Italy	Data from GISSI-HF trial: multicenter, randomized, double-blind, placebo-controlled study	CHF survivors/nonsurvivors: EF: 34 ± 8.1/32 ± 9.3%	6975	Survivors/nonsurvivors: age, 65.5 ± 10.8/71.4 ± 9.2 years	
6.	Huxley et al. [31]/Asia/Australia	Overview (meta-analysis) of prospective cohort studies (32)—data from the APCSC	Pts. from different studies with and without a medical history of CVD at baseline (general population)	543,694 (85% Asian)	Age at baseline (across the studies), 42–79 years	Males, 33–100%
7.	Glogner et al. [32]/Sweden	Prospective population-based cohort study (data from Swedish National Diabetes Registry)	Pts. with DM2 without a diagnosis of HF at baseline ≥ 18 years	83,021; number of cases, 10,969, 13%	Age at baseline, 65.8 ± 11.7 years	Males, 55.3%
8.	Cui et al. [33]/Japan	Data from Japan Collaborative Cohort (JACC) study (prospective)	Subjects aged 40–79 years from general population; mean age at baseline for HF, 67.7 years (40–79); at the endpoint, 79.7 years (46–100)	61,571		Males, 42%
9.	Khalid et al. [34]/USA	Community-based prospective cohort study: ARIC	With incident HF; average age at the moment of diagnosis, 67 years	1487		Males, 54%
10.	Padwal et al. [35]/International	Subanalysis of the MAGGIC meta-analysis of prospective studies	With HF (NYHA II, III), pts. from 14 studies. Analysis of differences between HFpEF (EF, ≥ 50%) vs. HFrEF	23,967 subjects	66.8 years	Males, 68%
11.	Puig et al. [36]/Spain	Prospective observational study, data from REDINSCOR (Spanish Heart Failure Network) Registry	CHF (NYHA II-IV), BMI < 18.5 kg m^{-2} excluded; EF, ≥ 45–22%	2254	Age 66.3 ± 12.8 years	Males, 70%
12.	Wannamethee et al. [37]/UK	Prospective study	Men aged 60–79 years with (1) no HF or CHD, (2) CHD but no HF, or (3) HF	4046	For CHF (across BMI groups), 69.5–72.3 years	Males, 100%
13.	Cioffi et al. [38]/Italy	Prospective study	CHF (also HFpEF) NYHA II or III, with the highest risk of all-cause death predicted with cardiac and comorbid conditions HF (3C-HF) score	1777; 246 subgroup of the highest risk; EF 37 ± 16%	80 ± 8 years	Males, 66%
14.	Pinho et al. [39]/Portugal	Retrospective cohort study	Ambulatory systolic HF pts.; EF, ≤ 50%	503	Median age, 69.4 years (IQR, 56.9–77.7)	Males, 68%
15.	Vest et al. [40]/USA	Retrospective analysis of cohort study design, differential impact of BMI on mortality in males vs. females ($p < 0.0001$).	Advanced HF pts. with EF ≤ 40%; BMI < 18.5 kg m^{-2} excluded; median EF, 20% (IQR, 15–25%)	3811	54.1 ± 11.6 years	Males, 75%
16.	Shadman et al. [41]/International	5 prospective cohort studies: PRAISE, Val-HeFT, Italian HF Registry, COMET, University of Washington cohort	Ambulatory pts. with HF with predominantly systolic (EF < 40%) dysfunction without ICDs; EF, 27 ± 11%	9885	64 ± 15 years	Males, 79%
17.	Pozzo et al. [42]/France	Prospective study	Nonischemic HF with systolic dysfunction (EF, ≤ 45%); EF, 26.8 ± 5%	222	55.4 ± 13.9 years	Males, 76%
18.	Ford et al. [43]/France/Sweden	Retrospective analysis of data from the SHIFT trial (double-blind,		6390	60.9 ± 11.4 years	Males, 58%

Table 2 (continued)

		placebo-RCT in pts. with moderate to severe HF and LVSD)	CHF with EF ≤ 35% and ↑ heart rate (≥ 70 bpm in sinus rhythm); EF, 29.0 ± 5.2%			
19.	Sharma et al. [44]/International	Meta-analysis	CHF	6 reports for final analyses (n = 22,807)	Mean age in studies: 66–72 years	Males: 60–81%
20.	Dalos et al. [45]/Austria	Prospective cohort study (observational)	HFpEF; EF, > 50%; EF, 58.9 ± 7.0%	193	68.6 ± 9.4 years (NYHA II); 72.3 ± 8.3 years (NYHA III, IV)	Males, 31%
21.	Zamora et al. [46]/Spain	Prospective cohort study	Ambulatory pts. with CHF; EF, 38 ± 16%	2527	69 ± 12.3 years	Males, 66.3%
22.	Heo et al. [47]/USA	Cross-sectional correlational study (using baseline data from observational study)	HF	247	Age, 61 ± 11.6 years	Males, 67.2%
23.	Qin et al. [48]/International (Europe, Asia, America)	Dose-response meta-analysis of prospective cohort studies (14 studies)	With HF; EF, < 45%	46,794; 13,508 death cases	Mean age 52.59–71.21 years across studies	
24.	Vlaras et al. [49]/Greece	Retrospective cohort study	Pts. with chronic HF (EF, ≤ 45%); EF, 31.1 ± 0.7%	112	62.8 ± 1.1 years	Males, 79.5%
25.	Tsujimoto et al. [50]/International (USA, Canada, Argentina, Brazil, Russia, Georgia)	Post hoc analysis of data from the TOPCAT trial: international, multicenter, RCT, double-blinded, placebo-controlled	With HFpEF EF ≥ 45%, age > 50 years; median EF, 56% (IQR, 51–61)	3310; 2413 pts. with abdominal obesity (AO)	Median age, 68.7 years (IQR, 60.7–75.5)	Males, 48.4%
26.	Chioncel et al. [51]/International (European and Mediterranean countries)	Prospective, observational study; European Society of Cardiology Heart Failure Long-Term Registry	HF classified according to LVEF: 1. HFrEF (EF, < 40%) 2. With mid-range EF HFmrEF (EF, 40–50%) 3. With preserved EF (EF, > 50%)	9134; EF, 37.6 ± 13.5	64.8 ± 13.3 years	Males, 71.8%
27.	Milajerdi et al. [52]/International	A dose-response meta-analysis of 16 observational studies (6 pre-diagnosis and 10 postdiagnosis BMI)	With HF (6 studies: pre-diagnosis, 2 with healthy population and 2 with CVD risk; 6 studies: postdiagnosis of HF)	258,379 subjects	From 40 to 74.47 years	Males, 37.6–100% (2 studies men only)
28.	Streng et al. [53]/Scotland	Scottish BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) multicenter, prospective observational study	With CHF	1479	75 ± 11 years	Males, 67%
29.	Thomas et al. [54]/USA	Prospective study	Outpatients with CHF; mean EF, 38 ± 16%	359	56 ± 14 years	Males, 72.4%
30.	Zhang et al. [55]/International (USA/Canada/Israel)	Dose–response meta-analysis of 10 prospective studies	HFrEF (LVEF < 40%) or HFpEF (LVEF ≥ 50%)	96,424; HFpEF, 59,263; HFrEF, 37,161	HFpEF (mean age), 68 years; HFrEF (mean age), 60 years	HFpEF (males), 62%; HFrEF (males), 83%
Malnutrition as a prognostic factor in CHF						
1.	Melenovsky et al. [56]/Chech Republic	Prospective study	Chronic (> 6 months) HF, EF < 50%, EF, 25 ± 6%	408	59 ± 11 years	Males, 84%
2.	Nochioka et al. [57]/Japan	Data from CHART-2 Study (Chronic Heart Failure Analysis and Registry in the Tohoku District-2 Study)—prospective study	Asymptomatic pts. with structural and/or functional heart diseases, classified as stage B in the ESC/AHA/ACC chronic HF guidelines	3421	66.9 ± 12.7 years	Males, 71.6%
3.	Narumi et al. [58]/Japan	Prospective study	CHF; EF, 50.3 ± 17.2%	388	69.6 ± 12.3 years	Males, 60%
4.	Zuchinali et al. [59]/Brazil	Prospective cohort study	CHF outpts. with EF < 50%; EF, 32 ± 9%	344	59 ± 13	Males, 65%
5.	Gouya et al. [60]/Austria	Prospective observational cohort study	Stable pts. with HF; EF, 35% (IQR, 25–45%)	137	Median age, 60 years (IQR, 49–68)	Males, 80%
6.	Rossignol et al. [61]/Italy/International	Post hoc retrospective analysis of 2 large cohorts from 2 trials: GISSI-HF (Italy) and Val-HeFT (international)	With CHF	GISSI-HF (n = 6820); EF, 33 ± 8.5%; Val-HeFT (n = 4892); EF, 27%	GISSI-HF, 67 ± 11 years; Val-HeFT, 62 years	GISSI-HF (males), 77.8%; Val-HeFT (males), 80%
7.	Gastelurrutia et al. [62]/Spain		Ambulatory HF pts.; EF, 36.7 ± 12.7%	214	68.7 ± 11.4 years	Males, 75.2%

Table 2 (continued)

		Prospective cohort study (PLICA study; Nutritional Status and Prognosis in Heart Failure)				
8.	Narumi et al. [63]/Japan	Prospective study with control group	With CHF; mean EF, 50 ± 18%	267	Mean age, 71 ± 12 years	Males, 60%
9.	Tevik et al. [64]/Norway	Cross-sectional study	CHF EF ≤ 50% and NYHA II-IV.	131	Median age, 78 years (37–95)	Males, 58%
10.	Song et al. [65]/South Korea	Prospective study	Chronic HF; EF, 34.4 ± 13.0%	232	66 ± 8 years	Males, 66.4%
11.	Tevik et al. [66]/Norway	Prospective observational study	CHF, EF, ≤ 50%; II, III, IV NYHA class; EF, 30–33%	131	Median age, 78 years (37–95)	Males, 58%
12.	Nakagomi et al. [67]/Japan	Prospective observational study	Outpts. with chronic HF (II or III NYHA), EF, ≤ 45%; EF, 26.0 ± 6.4%	114	66.0 ± 11.3 years	Males, 746%
13.	Sargento et al. [68]/Portugal	Prospective study	Stable geriatric outpts. > 65 years with HFrEF (EF, < 40%); EF, 26.6 ± 3.8%	143	75.4 ± 6.5 years	Males, 69.9%
14.	Huang et al. [69]/Singapore	Observational prospective cohort study	HFpEF (EF, ≥ 45%); mean EF, 52 ± 7.67%	54	Mean age, 75.13 ± 10.72 years	Males: 42.59%
15.	Zhao et al. [70]/China	Retrospective study	With CHD and HF (LVEF < 45%); EF, 39.5 ± 4.0%	118	58.6 ± 10.9 years	Males, 64.4%
16.	La Rovere et al. [71]/Italy	Retrospective analysis of prospectively collected data	Hospitalized HF patients able to complete 6MWT, mostly with CHF (118 with decompensation); mean EF 34 ± 11%	466	61.3 ± 11 years	Males, 86%
17	Joaquin et al. [72]/Spain	Prospective study	HF outpatients	151	68.6 ± 10.9 years	Males, 72.2%

No.	Follow-up	Tools	Endpoint	Outcome/effect measure	Obesity paradox/% of malnutrition
Obesity as a prognostic factor in CHF					
1.	19.8 ± 10.4 years; minimum, 1 years	BMI	HF mortality	HR for NW (BMI, 18.5–24.9), overweight (25–29.9), and obesity (≥ 30), 1.0, 1.56, 3.71, respectively (p for trend < 0.0001)	Not confirmed
2.	Maximum, 3.8 years	Nonobese: BMI, < 30 kg m^{-2}; obese: BMI, 30–39.9 kg m^{-2}; morbidly obese: BMI, ≥ 40 kg m^{-2}	1. Event-free survival; 2. Primary: all-cause mortality or transplantation.	1. For BMI groups: 48.4% = nonobese, 57.4% = obese, 28.6% = morbidly obese. 2. Nonobese vs. obese: HR 1.44 (95% CI, 1.09–1.91; p = 0.01); morbidly obese vs. obese: HR 2.46 (95% CI, 1.40–4.30; p = 0.002).	Confirmed; however, not for severe obesity
3.	Median, 16.3 months (range, 0.3–69.1 months)	BMI	All-cause mortality	Compared with BMI < 25 kg m^{-2}; BMI, 25–29.9: HR 0.32 (95% CI, 0.14–0.70; p = 0.005); BMI ≥ 30: HR 0.47 (95% CI, 0.26–0.85; p = 0.01); BMI > 40 HR 0.35 (95% CI, 0.16–0.81; p = 0.01).	Confirmed
4.	1 year	BMI	All-cause death	Higher BMI = significant independent predictor of lower mortality only in CHF: BMI (per 1-kg m^{-2} increase): HR 0.96 (95% CI, 0.92–0.99; p = 0.015)	Confirmed for CHF
5.	Median, 3.9 years (range, 3–4.5) follow-up	BMI	All-cause mortality	↑ BMI (per 1 kg m^{-2}): HR 0.98 (95% CI, 0.97–0.99; p = 0.0003); ↑ by 2% in risk per 1 kg m^{-2} ↓ in BMI	Confirmed
6.	3,793,229 person years	BMI	Mortality from HF	Compared with normal weight (BMI 18.5–21.9): underweight: HR 1.68 (95% CI, 1.34–2.11); obesity: HR 1.69 (1.17–2.43).	Not confirmed
7.	Median, 7.2 years	BMI	Hospitalization for HF	Compared with BMI 20 to < 25: higher BMI = higher risk of hospitalization for HF. BMI < 20: HR 1.07 (95% CI, 0.91–1.26), BMI 25 to < 27.5: HR 1.04 (95% CI, 0.98–1.11), BMI 27.5 to < 30: HR 1.22 (95% CI, 1.15–1.30), BMI 30 to < 35: HR 1.54 (95% CI, 1.45–1.63), BMI 35 to < 40: HR 2.16 (95% CI, 2.00–2.33), BMI ≥ 40: HR 3.22 (95% CI, 2.88–3.60).	Not confirmed
8.	20 years (median, 19.2 years, for HF pts., 11.7 years)	BMI weight changes (± 10.0 kg or more) vs. weight at 20 years old	Mortality from HF (605)		Confirmed

Table 2 (continued)

				HR for weight loss of ≥ 10.0 kg, 1.57 (95% CI, 1.20–2.05, $p < 0.01$); HR for weight gain of ≥ 10.0 kg, 0.91 (95% CI, 0.69–1.20, $p < 0.001$)	
9.	10 years after incident HF	BMI	Long-term mortality after incident HF	Compared with BMI 18.5 to < 25: BMI 25 to < 30: HR 0.72 (95% CI, 0.58–0.90; $p = 0.004$); BMI ≥ 30: HR 0.70 (95% CI, 0.56–0.87; $p = 0.001$).	Confirmed
10.	3 years	BMI	Total mortality	HFrEF (vs. BMI 22.5–24.9 kg m^{-2}): BMI < 22.5: HR 1.31 (95% CI, 1.15–1.50); BMI 25.0–29.9: HR 0.85 (95% CI, 0.76–0.96); BMI 30.0–34.9 kg m^{-2}: HR 0.64 (95% CI, 0.55–0.74); BMI ≥ 35: HR 0.95 (95% CI, 0.78–1.15). HFpEF (vs. BMI 22.5–24.9): BMI < 22.5: HR 1.12 (95% CI, 0.80–1.57); BMI 25.0–29.9: HR 0.74 (95% CI, 0.56–0.97); BMI 30.0–34.9: HR 0.64 (95% CI, 0.46–0.88); BMI ≥ 35: HR 0.71 (95% CI, 0.49–1.05).	Confirmed for HFrEF and HFpEF
11.	Maximum: 4 years; median: 21 months	BMI: WC (central obesity WC ≥ 88 cm for women, and ≥ 102 cm for men)	1. Total mortality 2. Cardiac mortality	1.Higher BMI: HR 0.84 (95% CI, 0.76–0.93; $p < 0.001$); higher WC: HR 0.97 (95% CI, 0.95–0.99; $p = 0.01$) 2. Higher BMI: HR 0.84 (95% CI, 0.75–0.93; $p < 0.001$); higher WC: HR 0.97 (95% CI, 0.94–0.99; $p = 0.01$).	Confirmed but not for severe obesity
12.	Up to maximum 20 years; mean, 11 years	BMI; WC; MUAC; MAMC	Mortality	For HF group: BMI 25–29.9 vs. BMI 18.5–24.9: HR 0.57 (95% CI, 0.28–1.16; $p = 0.04$); BMI ≥ 30 vs. BMI 18.5–24.9: HR 0.41 (95% CI, 0.16–1.09; $p = 0.04$).	Confirmed; depends mostly on fat mass (WC)
13.	Median, 21 months (12–40), at least 1 years	BMI	All-cause death-free survival	BMI: HR 1.08 (95% CI, 1.01–1.15; $p = 0.02$)	Confirmed
14.	5 years	BMI	All-cause mortality	Higher BMI (continuous variable) = better survival: for whole sample and for subgroup of nondiabetic vs. diabetic: HR 0.93 (95% CI, 0.89–0.98 per kg m^{-2}; $p = 0.003$) vs. HR 0.99 (95% CI, 0.94–1.04; $p = 0.70$; p for interaction = 0.009). BMI < 25 kg m^{-2} for nondiabetic vs. diabetic: HR 1.90 (95% CI, 1.23–2.94; $p = 0.004$) vs. HR 0.80 (95% CI, 0.46–1.39; $p = 0.43$; p for interaction = 0.012).	Confirmed but not for DM2
15.	Median, 6.2 years	BMI	All-cause mortality	For all: unadjusted BMI ≥ 30: HR 0.91 (95% CI, 0.87–0.96); after adjustment: BMI ≥ 30: HR 1.09 (95% CI, 1.04–1.14); females: overweight vs. normal weight: HR 0.84 (95% CI, 0.77–0.93; $p = 0.0005$); males: HR 1.12 (95% CI, 1.06–1.18).	Obesity paradox not confirmed (only in unadjusted data, or for overweight women)
16.	Average, 2.3 years	BMI	Sudden death	Proportional risk of sudden death increases by 24% for every 5 kg m^{-2} increase in BMI (sudden vs. nonsudden death multivariate OR, 1.24; $p < 0.001$).	Not confirmed for sudden death
17.	4 years	BMI	Mortality	BMI ≥ 30 vs. < 30, 11.1 vs. 26.4% ($p = 0.009$); obesity: HR 0.52 (95%CI, 0.28–0.99; $p = 0.048$)	Confirmed
18.	Median, 22.9 months (IQR, 18–28)	BMI; TC	1. Primary outcome: composite of cardiovascular death or HF hospitalization 2. All-cause mortality 3. Cardiovascular mortality 4. HF hospitalization	BMI 1 kg m^{-2} decrease < 27.5: (1) HR 1.07 (95% CI, 1.05–1.09; $p < 0.001$); (2) HR 1.06 (95% CI, 1.03–1.09; $p < 0.001$); (3) HR 1.08 (95% CI, 1.05–1.10; $p < 0.001$). Lower TC (≤ 3.4 vs. ≥ 4.5 mmol l^{-1}), (1) HR 1.46 (95% CI, 1.26–1.57; $p < 0.001$); (2) HF hospitalization HR 1.69 (95% CI, 1.41–2.01; $p < 0.001$).	Confirmed
19.	Mean period, 2.85 years	BMI	All-cause mortality; cardiovascular (CV) mortality; hospitalization	BMI < 20 kg m^{-2}: total mortality: RR 1.27 (95% CI, 1.17–1.37); CV mortality: RR 1.20 (95% CI, 1.01–1.43); hospitalization RR 1.19 (95% CI, 1.09–1.30). BMI 25–29.9 kg m^{-2}: CV mortality: RR 0.79 (95% CI, 0.70–0.90); hospitalization: RR 0.92 (95% CI, 0.86–0.97). BMI ≥ 35:kg m^{-2}: hospitalization: RR 1.28 (95% CI, 0.88–1.87)	Confirmed but not for hospitalization of severely obese
20.	Median follow-up, 21.9 ± 13.1 months	BMI			Not confirmed

Table 2 (continued)

			Combined: cardiac death and/or HF hospitalization; association between BMI level and NYHA class	Increasing BMI vs. outcome: HR 1.030 (95% CI, 0.995–1.066; $p = 0.090$). Increasing BMI vs. NYHA class (III or IV): OR 1.096 (95% CI, 1.035–1.161; $p = 0.002$).	
21.	Mean, 4.3 ± 3.0 years (up to 10 years)	BMI	Long-term mortality; all-cause and cardiovascular death	Nondiabetic CHF: BMI < 20.5: HR 2.04 (95% CI, 1.50–2.78; $p < 0.001$); BMI ≥ 30: HR 0.76 (95% CI, 0.58–0.99; $p = 0.04$); in diabetic CHF: BMI < 20.5: HR 1.30 (95% CI, 0.77–2.19; $p = 0.32$); BMI ≥ 30: HR 0.99 (95% CI, 0.78–1.26; $p = 0.95$).	DM2-reduced obesity paradox
22.	–	BMI	Symptom Status Questionnaire-Heart Failure, score range, 0–24 points	In males, BMI ≥ 35 kg m^{-2} associated with more severe symptoms ($R^2 = 0.568$; $p < 0.001$)	Not confirmed
23.	Mean, 3.73 years	BMI	All-cause mortality	U-shaped nonlinear relationship of BMI and mortality (p nonlinearity = 0.0025); HR (per 5 units ↑ in BMI) 0.95 (95% CI, 0.92–0.97) with high heterogeneity ($I^2 = 90.10\%$, $p < 0.00001$).	Confirmed but not for severe obesity (BMI > 37 kg m^{-2})
24.	2 years	BMI	1- and 2-years mortality	Obese vs. normal BMI values: after 1 year (13 vs. 34.6%, $p = 0.039$); after 2 years (4 vs. 21.4%, $p = 0.022$)	Confirmed but not for CHD
25.	Mean follow-up, 3.4 ± 1.7 years	BMI; WC (≥ 102 cm in men and ≥ 88 cm in women).	Primary outcome: (1) all-cause mortality; secondary: (2) cardiovascular; and (3) noncardiovascular death	AO vs. no-AO: 1. Adjusted HR 1.52 (95% CI, 1.16–1.99; $p = 0.002$); 2. Adjusted HR 1.50 (95% CI, 1.08–2.08; $p = 0.01$); 3. Adjusted HR 1.58 (95% CI, 1.00–2.51; $p = 0.04$). 1. vs. BMI 18.5–24.9: BMI 25–29.9: HR 0.55 (95% CI, 0.41–0.74; $p < 0.001$); BMI ≥ 30: HR 0.52 (95% CI, 0.38–0.72; $p < 0.001$).	Confirmed but not for abdominal obesity (with WC)
26.	1 year	BMI	All-cause mortality	BMI an independent predictor of mortality in HFpEF and HFrEF (higher BMI = lower mortality) HFrEF: OR 0.958 (95% CI, 0.937–0.979; $p = 0.0001$); HFpEF: OR 0.938 (95% CI, 0.896–0.983; $p = 0.0071$. Lower BMI = significantly higher mortality in HFrEF 8.8% vs. HFpEF 6.3% HFmrEF 7.6%.	Confirmed
27.	1.30–30 years	BMI	HF mortality (13,201, 5.1% deaths due to HF)	Pre-diagnosis BMI: nonlinear U-shaped association (p nonlinearity < 0.0001). Higher for BMIs < 25 and > 29 kg m^{-2}, underweight: higher risk than others. Postdiagnosis BMI: no significant association with outcome (p nonlinearity = 0.41).	Not confirmed
28.	Median, 21 months	Waist-to-hip ratio (WHR); obesity diagnosed on BMI (≥ 30 kg m^{-2}) and WHR (≥ 0.90 for men, ≥ 0.85 for women)	All-cause mortality	Women: higher WHR = higher mortality risk HR 2.23 (95% CI, 1.37–3.63; $p = 0.001$), no significant association for men (HR 0.87; 95% CI, 0.63–1.20; $p = 0.409$). Strong association between a higher WHR and elevated markers of inflammation	Not confirmed (for abdominal obesity)
29.	Over 5 years	Bioelectrical impedance analysis of body composition (BIA); body fat and lean mass indexed by height (m^2): body fat mass index (BFMi); lean body mass index (LBMi)	Death; 5-year survival	Multivariable analysis: higher BFMi = improved survival (HR 0.89 per kg m^{-2} increase in BFMi; $p = 0.044$) but attenuated after adjustment for diabetes. No significant association for LBMi, High BFMi vs. low = better survival (90.2 vs. 80.1%; $p = 0.008$). Univariate HR 2.3 (95% CI, 1.2–4.5). High vs. low LBMi = better survival (89.3 vs. 80.9%; $p = 0.036$). Univariate HR 1.9 (95% CI, 1.0–3.7). Combination low BFMi and low LBMi vs. high BFMi and LBMi (HR of 4.67; $p = 0.02$).	Confirmed (depends mainly on fat mass)
30.	0.8–7.5 years	BMI	All-cause mortality	For HFpEF and HFrEF, the relationship: BMI and mortality: U-shaped with a similar nadir of risk at a BMI of 32–33 kg m^{-2}. HFpEF: summary HR 0.93 (95% CI, 0.89–0.97)	Confirmed (not for morbid obese)

Table 2 (continued)

				per 5 units increase in BMI; HFrEF: summary HR 0.96 (95% CI, 0.92–0.99) per 5 units increase in BMI.	
Malnutrition as a prognostic factor in CHF					
1.	Median, 541 days (IQR, 254–873 days)	- Weight loss (> 5% within 6 months) - Cardiac cachexia, defined as significant weight loss + simultaneous abnormal biochemistry (CRP > 5 mg l^{-1} or hemoglobin < 120 g l^{-1} or albumin < 32 g l^{-1}) - BMI and others	Combined endpoint (death without transplantation, urgent heart transplantation, or implantation of LVAD)	1. Cachexia: HR 2.90 (95% CI, 2.00–4.12; $p < 0.0001$). 2. Weight loss: HR 1.85 (95% CI, 1.32–2.59; $p = 0.0005$). 3. Increased BMI: HR per kg m^{-2}, 0.92 (95% CI, 0.88–0.96; $p < 0.001$); this protection mediated by higher fat mass: HR 0.91 (95% CI, 0.87–0.96; $p < 0.001$) but not a fat-free mass index: HR 0.97 (95% CI, 0.92–1.03; $p = 0.40$).	OP confirmed (dependent mostly on fat mass) 19% cachexia and 33% W-LOSS
2.	3 years; median, 2.89 years	CONUT score (0–1, 2, ≥ 3 points)	1. All-cause death 2. HF hospitalization	1. HR 1.27 per point ↑ (95% CI, 1.16–1.39; $p < 0.001$). 2. ↑ 17% in HF hospitalization in pts. ≥ 70 years (HR 1.17; 95%CI, 1.0–1.38; $p = 0.049$) but not in those aged < 70 years (HR 0.7; 95% CI, 0.51–0.97; $p = 0.03$).	Moderate or severe undernutrition (≥ 3 points of CONUT score)—17.74%
3.	28.4 months (range, 11.8–51.8)	CONUT (0–1 = normal), PNI (> 38 = normal), GNRI (> 98 = normal)	Cardiovascular events: death (due to a cardiovascular event) and/or hospitalization	CONUT score (9–12): HR 9.4 (95% CI, 4.8–18.3; $p < 0.001$); PNI score (< 35): HR 3.8 (95% CI, 2.1–6.8; $p < 0.001$); GNRI score (< 82): HR 6.0 (95% CI, 3.2–11.5; $p < 0.001$).	60–69% depending on nutritional tool
4.	Mean, 30 ± 8.2 months	TSF, body surface area, BMI (WHO and PAHO), WC, AC, AMC	All-cause mortality; HF hospitalizations	TSF ≥ 20 mm: HR 0.36 (95% CI, 0.13–0.97; $p = 0.03$). HF hospitalizations: TSF non significant ($p = 0.69$).	Underweight (BMI < 18.5 kg m^{-2}), 17%; TSF ≥ 20 mm, 20%
5.	Median, 31 months (IQR, 28–34)	NRI; cardiac cachexia: unexplained W-LOSS of ≥ 7.5%/minimum 6 months	All-cause mortality; HF-related hospitalization	A baseline NRI of < 113 was associated with a higher risk of all-cause mortality (log-rank = 0.033) and HF hospitalization (log rank = 0.034).	32%
6.	1 year (clinical visit at 1, 3, 6, and 12 months)	Both trials: at least 1 episode of ≥ 5% weight loss during the first year of follow-up; GISSI-HF only: self-reported unintentional weight loss ≥ 2 kg between 2 consecutive clinical visits within 1 year	Mortality (all-cause, cardiovascular and noncardiovascular)	1. Weight loss frequency in CHF: 16.4% (GISSI-HF) and 15.7% (Val-HeFT) and unintentional ≥ 2 kg weight loss 18.9% (in GISSI-HF). 2. All-cause mortality: GISSI-HF weight loss ≥ 5%: HR 1.20 (95% CI: 1.05–1.36; $p = 0.007$); GISSI-HF unintentional weight loss ≥ 2 kg: HR 1.22 (95% CI: 1.08–1.37; $p = 0.002$); Val-HeFT weight loss ≥ 5%: HR 2.52 (95% CI, 2.05–3.08; $p < 0.0001$).	15.7–18.9% (depending on criterion)
7.	2 years	2 definitions of undernourishment: 1. Included: albumin, TC, TSF, subscapular skinfold, and AMC measurements (≥ 2 below normal); 2. Included: TSF, AMC and albumin (≥ 1 below normal considered undernourishment).	All-cause death or HF hospitalization (primary endpoint).	Definitions 1 and 2, respectively: multivariable model: HR ± 95% CI, 2.25 ± 1.11–4.56; 2.24 ± 1.19–4.21. BMI and body fat percentage do not predict the outcome.	Definition 1, 12.2%; definition 2, 20.6%
8.	Median, 10.7 months (IQR, 3.0–20.3 months)	Fat-free mass index (FFMI) (marker of sarcopenia)	Cardiac events: death due to cardiac event (death due to progressive CHF, MI or sudden cardiac death)or/and hospitalization for worsening of CHF.	Adjusted HR for FFMI (1 kg m^{-2} increase): 0.68 (95% CI, 0.47–0.98; $p = 0.038$). FFMI in pts. with cardiac events compared with those without (17.0 vs. 17.6 kg m^{-2}; $p = 0.045$). In the Kaplan-Meier analysis, higher cardiac event rate in the low-FFMI group (log-rank test, $p = 0.017$).	60–69%
9.	During hospitalization	NRS-2002 (NRS-2002 ≥ 3; nonrisk pts. = NRS-2002 < 3)	1. In-hospital complications 2. LOS	1. NRS-2002 ≥ 3 vs. < 3, 12.0 vs. 0.0%; $p = 0.01$. 2. For longer LOS NRS-2002 ≥ 3, OR 2.99 (95% CI, 1.33–6.73).	57%
10.	2 years	Tools: Patient Health Questionnaire 9 (PHQ-9): to measure depressive symptoms; 3-day food diary: to	Primary outcome: composite of time to first cardiac-related emergency	Higher micronutrient deficiency (≥ 5): HR for outcome 1.68 (95% CI, 1.05–2.67; $p = 0.03$). Risk of cardiac events ↑ by 13% for each	Underweight < 18.5 kg m^{-2} = 11.2%

Table 2 (continued)

		determine the number of micronutrient deficiencies (0–15, cut-off point 5)	department (ED) visit, hospitalization or death	additional micronutrient deficiency in the diet (95% CI, 1.04–1.22; $p = 0.003$)	
11.	3 years	NRS-2002 (score ≥ 3 = nutritional risk)	Long-term mortality (from any cause)	NRS-2002 score ≥ 3: HR 2.78 (95% CI, 1.53–5.03); HR (95% CI) for components: weight loss (> 5% in last 1–3 months): 2.66 (1.09–6.48; $p = 0.031$), BMI ≤ 20.5: HR 5.25 (2.23–12.35; $p < 0.001$); nutritional status: HR 1.82 (95% CI, 1.03–3.22; $p = 0.039$).	57%
12.	Median, 67.5 months (range, 12–180 months)	CONUT score (categories, 0–1, 2, ≥ 3)	Incidence of cardiac events (cardiac death or hospitalization due to worsening CHF)	CONUT score of ≥ 3: HR 11.97 (95% CI, 2.21–64.67; $p = 0.004$)	40%
13.	3 years	GNRI (GNRI, ≤ 98 = risk of malnutrition)	All-cause death	Survival: ↑ GNRI (HR 0.93; 95% CI, 0.90–0.95; $p < 0.001$); GNRI > 98 (HR 0.29, 95% CI, 0.15–0.57; $p < 0.001$). Deceased pts.: lower GNRI vs. survivors (105.6 ± 9.2 vs. 113.6 ± 9.1; $p < 0.001$). GNRI is better discriminator of death than weight or albumin.	11.2%
14.	At least 3 years (median, 1124 days)	BMI	Death on follow-up; hospitalization at 1 year	Low BMI < 18.5 associated with earlier mortality over the 3-year period (HR 4.30, 95% CI, 1.25–14.78; $p = 0.020$).	–
15.	–	BMI, albumin level, TC, HDL-C, CRP	Combined: hospitalization for HF, symptom deterioration and all-cause mortality	Poor prognosis connected with lower BMI, albumin level, TC: OR 0.97 (95% CI, 0.92–0.99); lower HDL-C: OR 0.95 (95% CI, 0.90–0.98); and higher CRP ($p < 0.05$ for all).	–
16.	1 year	CONUT score; BMI (and MAGGIC score and 6MWT)	All-cause mortality	Deceased vs. survivors worse nutritional status: higher CONUT score 2.8 ± 1.5 vs. 1.7 ± 1.3, $p < 0.0001$ and lower BMI (25.1 ± 4.4 vs. 27.4 ± 4.5; $p = 0.003$); CONUT score: HR 1.701 (95% CI, 1.363–2.122; $p < 0.0001$); CONUT added significant predictive value to combination of MAGGIC and 6MWT a (c-index 0.82 (95% CI, 0.75–0.88).	54% mild or moderate undernourishment
17	2 years	MUST, MNA-SF, MST, SGA, MNA	All-cause mortality	MNA an independent predictor of mortality: HR 4.55 (95% CI, 1.55–13.37; $p = 0.006$). (MNA-SF the best sensitivity 71%)	15.9% SGA; 25.1% MNA

BMI standard values according to WHO categories unless stated otherwise (kg m^{-2})

Abbreviations: *AC*, arm circumference; *AHF*, acute heart failure; *AMC*, arm muscle circumference; *APCSC*, Asia Pacific Cohort Studies Collaboration; *ARIC*, Atherosclerosis Risk in Communities; *BMI*, body mass index; *bpm*, beats per minute; *CCLS*, Cooper Center Longitudinal Study; *CHD*, coronary heart disease; *CHF*, chronic heart failure; *CI*, confidence interval; *COMET*, Carvedilol or Metoprolol European Trial; *CONUT*, Controlling Nutritional Status; *CRP*, C-reactive protein; *CVD*, cardiovascular disease; *DM2*, type 2 diabetes mellitus; *EF*, ejection fraction; *ESC/AHA/ACC*, European Society of Cardiology/American Heart Association/American College of Cardiology; *GISSI-HF*, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure trial; *GNRI*, Geriatric Nutritional Risk Index; *HDL-C*, high-density lipoprotein cholesterol; *HF*, heart failure; *HFmrEF*, heart failure with mid-range ejection fraction; *HFpEF*, heart failure with preserved ejection fraction; *HFrEF*, heart failure with reduced ejection fraction; *HR*, hazard ratio; *ICD*, implantable cardioverter defibrillator; *IQR*, interquartile range; *LOS*, length of stay (in hospital) stay; *LVAD*, left ventricular assist device; *LVEF*, left ventricle ejection fraction; *LVSD*, left ventricular systolic dysfunction; *M*, multivariate; *MAMC*, mid-arm muscle circumference; *MI*, myocardial infarction; *MNA*, Mini Nutritional Assessment; *MNA-SF*, Mini Nutritional Assessment—Short Form; *MST*, Malnutrition Screening Tool; *MUAC*, mid-upper arm circumference; *MUST*, Malnutrition Universal Screening Tool; *NRI*, Nutritional Risk Index; *NRS-2002*, Nutritional Risk Score; *NW*, normal weight; *NYHA*, New York Heart Association; *OP*, obesity paradox; *OR*, odds ratio; *PRAISE*, Prospective Randomized Amlodipine Survival Evaluation; *pts*., patients; *RCT*, randomized controlled trial; *RR*, risk ratio; *SD*, standard deviation; *SGA*, the Subjective Global Assessment; *SHIFT*, systolic heart failure treatment with the IF inhibitor ivabradine Trial; *TC*, total cholesterol; *TOPCAT*, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial; *TSF*, triceps skinfold thickness; *Val-HeFT*, Valsartan Heart Failure Trial; *WC*, waist circumference; *WHO*, World Health Organization; *WHR*, waist-to-hip ratio; *W-LOSS*, loss in body weight; *6MWT*, 6-min walk test; *PAHO*, Pan American Health Organization criteria for the elderly: underweight (< 23 kg m^{-2}; normal weight (23–28 kg m^{-2}), and overweight (> 28 kg m^{-2}))

[a] Mean ± SD unless it was showed different

Table 3 Nutritional status as a prognosis factor in invasive treatment of CHF

No.	Author/country	Study design	Patients	No. of pts.	Age[a]
1.	Hsu et al. [73]/USA	Retrospective study—data from National Cardiovascular Data Registry-ICD Registry	First-time ICD recipients	83,312	61.4–66.4 years
2.	Cai et al. [74]/China	Prospective study	Pts. with CRT; EF, 28 ± 7%	247	59.2 ± 10.7 years
3.	Aktas et al. [75]/USA	Prospectively collecting data from study: MADIT-CRT	Pts. with CRT-D, mild symptoms of HF (NYHA I or II); EF, < 30%	994; nonobese EF, 28.8 ± 3.5%; obese EF, 29 ± 3.3%	Nonobese, 61.1 ± 10.7 years; obese, 66.6 ± 10.1 years
4.	Yanagisawa et al. [76]/Japan	Retrospective study	HF after CRT-D implantation; EF, ≤ 35%	125; EF, 26.1 ± 6.8%	67.7 ± 10.9 years
5.	Mohamedali et al. [77]/USA	Retrospective study	HeartMate II and HeartWare (HVADs) who underwent LVAD placement as a bridge to transplantation (BTT) and destination therapy (DT). Obese/nonobese: EF, 20.4 ± 8.7/18.3 ± 6.7%	288	Obese/nonobese, 55.1 ± 12.7/62.4 ± 12.4 years
6.	Imamura et al. [78]/Japan	Retrospective study	Pts. who had received CF LVAD; EF, 19 ± 8%	57	40 ± 12 years
7.	Grandin et al. [79]/USA	Retrospective study	HF after CRT-D implantation; EF, 20 ± 8%	113	Age at implant, 66 ± 11 years
8.	Daimee et al. [80]/International (USA, Canada, Europe)	Retrospective study (MADIT-CRT)	With HF receiving CRT-D therapy; EF, ≤ 30%	993	Age at implantation, 64 years
9.	Volkovicher et al. [81]/USA	Single-center retrospective analysis	CHF patients with continuous-flow left ventricular assist device (CF-LVAD) implantation (BMI < 18.5 excluded); EF, 21.7 ± 3.6%	526	54.7 ± 13.5 years
10.	Yost et al. [82]/USA	Retrospective study	Patients after CF-LVAD implantation; median PNI for all 30.0; mean PNI was 30.05. PNI < 30–44.1%	288	Group1/2: 60.25 ± 12.41 years/59.8 ± 9.80 years
11.	Critsineli et al. [83]/USA	Single-center retrospective analysis	CHF patients with continuous-flow left ventricular assist device (CF-LVAD) implantation; EF, 21.7 ± 3.6%	526	54.7 ± 13.5 years
12.	Hullmann et al. [84]/USA	Single-institution retrospective chart review	136 patients with HF, who underwent LVAD implantation; EF, 16 ± 7%/17 ± 8%	136	Obese/nonobese, 53.1 ± 10.9 years/57.5 ± 3.2 years
13.	Uribarri et al. [85]/Germany	Retrospective study	Who underwent CF-LVAD implantation	279	Across NRI groups, 50.7–55.1 years

No.	Gender	Follow-up	Tools	Endpoint	Outcome/effect measure
1.	Males, 53.9–73.4%	Until hospital discharge	BMI < 18.5; 18.5–29.9, ≥ 30 kg m^{-2}	1. In-hospital complications 2. Length of hospital stay (> 3 or ≤ 3 days) 3. In-hospital mortality	BMI ≥ 30: no meaningful differences. BMI < 18.5: more complications vs. normal weight: in-hospital complications (OR 2.15 (95% CI, 1.68–2.75); $p < 0.0001$; hospital stay > 3 days (OR 1.62 (1.38–1.89), $p < 0.0001$; in-hospital death (OR 2.27 (1.21–4.27); $p = 0.011$.
2.	Males, 67.2%	6 months	BMI	1. All-cause mortality 2. Combined endpoint of death or HF hospitalization	1. Higher BMI in multivariate model: HR 0.88 for every 1-kg m^{-2} increase in BMI; 9; 95% CI, 0.77–0.99; $p = 0.040$.

Table 3 (continued)

				3. Clinical and ECHO improvement 4. Response rate to CRT	2. Higher BMI in multivariate model: HR, 0.87 for every 1-kg m^{-2} increase in BMI; 95% CI, 0. 80–0.94; $p = 0.001$. BMI 24–28 and ≥ 28 vs. BMI < 18.5 and 18.5–24 = stronger improvement ($p < 0.05$) and higher response to CRT ($p < 0.001$), lower all-cause mortality ($p = 0.015$) and combined endpoint ($p = 0.001$)
3.	Nonobese males, 77%; obese males, 74%	1 year	Weight loss of ≥ 2 kg 1 $year^{-1}$; BMI ≥ 30 vs. nonobese	1. Primary endpoint: episode of HF or death. 2. Secondary endpoint: risk of all-cause death alone.	Weight loss vs. no weight loss: 1. HR 1.82 (95% CI, 1.26–2.63; $p = 001$); 2. HR 1.79 (95% CI, 1.16–3.34; $p = 0.01$). Obese vs. nonobese: no difference in cumulative probability of HF or death ($p = 0.74$) and death alone ($p = 0.94$). BMI ≥ 30 vs. < 30: 1. HR 1.10 (95% CI, 0.81–1.50; $p = 0.54$); 2. HR 1.34 (95% CI, 0.82–2.19; $p = 0.24$).
4.	Males, 73%	3.1 ± 1.8 years	BMI	1. Composite: all-cause death and appropriate shock therapy. 2. All-cause death	1. BMI ≥ 25 vs. normal weight, multivariate model: HR 0.27 (95% CI, 0.08–0.91; $p = 0.034$) ≥ only in nonresponders (log rank $p = 0.04$), no differences among the responders (log rank $p = 0.60$); BMI < 18.5 kg m^{-2}: pts. poorer prognosis compared with others. 2. BMI ≥ 25 vs. normal weight, multivariate model: HR 0.15 (95% CI, 0.02–1.14; $p = 0.07$).
5.	Obese/nonobese males, 76.8/78.8%	3 years	BMI ≥ 30 vs. BMI < 30	3-year survival hospitalization; length of hospitalization	Obese vs. nonobese survival, 20 vs. 20%; $p = 0.97$. Hospitalizations, 4.2 vs. 3.4; $p = 0.03$. HF hospitalizations, 29 vs. 16%; $p = 0.009$, OR 2.47 (95% CI, 1.15–5.32; $p = 0.02$). Median total length of stay after LVAD implantation: 28 vs. 14 days; $p = 0.05$.
6.	Males, 79%	Median, 530 days	Albumin concentration; BMI; the New Score	Hospitalization due to DLI (device-specific infection)	Independent predictors of DLI hospitalization: lower S-ALB: HR 0.144 (95% CI, 0.026–0.804; $p = 0.027$) and lower BMI: HR 0.843 (95% CI, 0.711–0.998; $p = 0.048$). The New Score significantly stratifies 2-year hospitalization-free rate ($p = 0.008$).
7.	Males, 86%	10 years; median, 4.5 years (IQR, 1.9–8.7 years)	Pre-implant BMI	10-year survival free from primary endpoints of: heart transplant or ventricular heart device	BMI ≥ 30, 36.3%; BMI 25–29, 19.2%; BMI < 25, > 12.1% (log-rank p trend = 0.004). BMI (↑per 1 kg m^{-2}) adjusted HR 0.92 (95% CI, 0.88–0.97; $p = 0.002$).
8.	Males, 74.7%	1 year	Weight change at 1 year: weight loss (≥ 5%), weight gain (≥ 5%), and stable weight	1. Primary: inappropriate ICD therapy 2. Secondary: inappropriate ICD therapy related to SVAs	1. Weight loss vs. stable weight: HR 2.35 (95% CI, 1.39–3.98; p = 0.001) or vs. weight gain: HR 2.27 (95% CI, 1.18–4.38; $p = 0.014$). 2. Weight loss vs. stable weight: HR 2.16 (95% CI, 1.18–3.95; $p = 0.013$) or weight gain: HR 2.02 (95% CI, 0.95–4.29; $p = 0.068$).
9.	Males, 78.1%	Max 24 months	BMI 4 groups: underweight (< 18.5 kg m^{-2}), normal-weight (18.5–25 kg m^{-2}), overweight (25–30 kg m^{-2}), obese (> 30 kg m^{-2})	Postoperative adverse events and short- (1 month), mid- (6 and 12 months), and long-term survival (24 months)	Obesity not a significant predictor of mortality HR 0.98 (95% CI, 0.77–1.28; $p = 0.13$). No difference in survival (1, 6, 12, and 24 months) across BMI groups. Kaplan–Meier analysis: higher mortality for morbid obesity (BMI > 38.5 kg m^{-2}; $p = 0.049$).

Table 3 (continued)

10.	Males, 78.9/78.3%	1 year	Prognostic nutritional index (PNI) 2 groups of analysis: 1. With PNI < 30 and 2. With PNI ≥ 30	1 year survival	Multivariate model: PNI < 30, 12.2% reduction in postoperative survival: HR: 0.89 (95% CI, 0.80–0.99; $p = 0.037$).
11.	Males, 78.1%	Max 24 months	Pre-operative serum albumin levels hypoalbuminemia (< 3.5 g dl^{-1}, moderate: 2.5–3.5 g dl^{-1} or severe: < 2.5 g dl^{-1}); 38.8% hypoalbuminemia	Postoperative adverse events and short- (1 month), mid- (6 and 12 months), and long-term survival (24 months)	Decreased survival vs. normal pre-operative albumin level ($p < 0.001$). Albumin < 3.5 g dl^{-1}: HR 1.61 (95% CI, 1.21–2.13; $p < 0.001$). Higher incidences of postoperative infection, gastrointestinal bleeding, neurological dysfunction, and acute kidney injury ($p < 0.01$ for all)
12.	Obese/nonobese males, 85.2%/74.4%	1 year; average, 508 days; max. 2461 days	BMI; comparison of 2 groups: nonobese (18.5 < BMI < 30.0; $n = 82$) and obese (BMI > 30.0; $n = 54$)	Heart transplantation, recovery or ongoing LVAD support at 1 year	No significant differences between 2 groups (obese vs. nonobese) for rates of ongoing device support (50/48.8%, $p = 0.89$), orthotopic heart transplant (27.8/26.8%, $p = 0.90$), and death (20.4/23.2%, $p = 0.70$). Obesity and mortality: HR 1.05 (95% CI, 0.51–2.13, $p = 0.90$).
13.	Across NRI groups males, 73.3–90.0%	1 year	Pre-operative nutritional risk index (NRI); nutritional risk NRI < 100 = 36.2%	All-cause mortality; postoperative clinical events	A normal NRI = lower risk of death aHR per 1 unit, 0.96 (95% CI, 0.94–0.98; $p < 0.001$), lower risk of postoperative infections aOR, 0.97 (95% CI, 0.97–0.99; $p = 0.007$), respiratory failure aOR, 0.96 (95% CI, 0.94–0.99; $p = 0.004$), and right heart failure aOR, 0.96 (95% CI, 0.93–0.99; $p = 0.014$).

The New Score = 7 × (S-ALB (g dl^{-1})) + (BMI) stratified hospitalization-free rate into three groups (low- (> 50 pt.), intermediate- (44–50 pt.), and high-risk groups (< 44 pt.))

Abbreviations: *aOR*, adjusted odds ratio; *BMI*, body mass index; *CF LVAD*, continuous flow left ventricular assist device; *CHF*, chronic heart failure; *CI*, confidence interval; *CRT*, cardiac resynchronization therapy; *CRT-D*, cardiac resynchronization therapy with defibrillator; *DLI*, driveline infection; *ECHO*, echocardiography; *EF*, ejection fraction; *HF*, heart failure; *HR*, hazard ratio; *ICD*, implantable cardioverter defibrillator; *IQR*, interquartile range; *LVAD*, left ventricular assist device; *MADIT-CRT*, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; *NYHA*, New York Heart Association; *OR*, odds ratio; *pt.*, points; *pts.*, patients; *S-ALB*, serum albumin concentration; *SVAs*, supraventricular arrhythmias

[a] Mean ± SD unless it was showed different

Table 4 Interventions in nutritional status in CHF

No.	Author/ country	Study design	Patients	No. of pts.	Age[a]	Gender	Intervention	Follow-up	Endpoint	Outcome/effect measure
1.	Wu et al. [86]/USA	Randomized double-blind, placebo-controlled trial	CHF pts. (age > 45 years, EF, ≤ 35%); EF, 28.1%	31	At baseline, 59 ± 2 years	Males, 84%	L-Alanyl-L-glutamine (8 g day^{-1}) and PUFA (6.5 g day^{-1}) or placebo (safflower oil and milk powder) for 3 months	3 months	Primary: exercise function (CPET, SMWT and muscle functional testing). Secondary: skeletal muscle metabolism and mass (DXA scanning), echocardiography parameters, inflammatory serum markers. QoL (Kansas City Cardiomyopathy Questionnaire (KCCQ) and MLHF).	Active vs. placebo group: improvement in QoL: KCCQ 73 ± 19 to 83 ± 12; $p = 0.04$; MLHF 36 ± 22 to 24 ± 16; $p = 0.02$; increase in absolute lean body mass (54.4 ± 2.8 to 56.1 ± 2.5 kg at 3 months; $p = 0.04$) and lean body mass corrected for BMI (19.7 ± 0.6 to 20.2 ± 0.5 kg m^{-2} at 3 months; $p = 0.04$)
2.	Mathew et al. [87]/USA	Interventional Dietary Approaches to Stop Hypertension in Diastolic Heart Failure (DASH-DHF) study (without control group)	With treated hypertension and stable HFpEF	13	72 ± 10 years	12/13 females	Sodium-restricted (50 mmol day^{-1}) DASH/SRD diet for 21 days	21 days	Changes in metabolism; changes in cardiac function	24-h ambulatory systolic blood pressure reduction (130 ± 4 to 123 ± 4 mmHg; $p = 0.02$), improvement of ventricular diastolic stiffness and relaxation (*k:* 252 ± 115 to 170 ± 37 g s^{-2}; $p = 0.03$ and *c:* 24.3 ± 5.3 to 22.7 ± 8.1 g s^{-1}; $p = 0.03$), increased ventricular contractility($d\sigma^*/dtmax$, 1.6 ± 0.5 to 1.8 ± 0.5 s^{-1}; $p = 0.01$) and ventricular-arterial coupling ratio (*Ees:Ea*, 1.5 ± 0.3 to 1.7 ± 0.4; $p = 0.04$).
3.	Deutz et al. [88]/USA	Multicenter, randomized, placebo-controlled, double-blind trial. NOURISH study	Pts. ≥ 65 years, malnourished (SGA class B or C) hospitalized for different reasons, including congestive HF	309 (placebo) + 313 (HP-HMB) = 622	Placebo/HP-HMB: mean age (SD), 78.1(8.6)/ 77.7(8.2)	Males, 48.2/47.6%	Standard-of-care + high-protein oral supplement HMB, twice/ day (in-hospital and during 90-day follow-up).	30, 60, and 90 days postdischarge	Primary composite: 90-day death or nonelective hospitalization. + 30- and 60-day death or hospitalization, LOS, SGA class, body weight, activities of daily living (ADL).	Primary composite endpoint similar: HP-HMB (26.8%) and placebo (31.1%). 90-day mortality significantly lower with HP-HMB vs. placebo (4.8 vs. 9.7%; RR 0.49; 95% CI, 0.27–0.90; $p = 0.018$). HP-HMB group: improvement in nutritional status at day 90 (SGA class, OR 2.04; 95% CI, 1.28–3.25; $p = 0.009$)

Table 4 (continued)

No.	Author/ country	Study design	Patients	No. of pts.	Age[a]	Gender	Intervention	Follow-up	Endpoint	Outcome/effect measure
										and ↑ in body weight at day 30 ($p = 0.035$).
4.	Kitzman et al. [89]/USA	Randomized, attention-controlled, 2 × 2 factorial trial	Obese (BMI ≥ 30 kg m^{-2}); older (≥ 60 years) pts. with chronic, stable HFpEF (EF, ≥ 50%); EF, 61 ± 6%	100	Mean age, 67 ± 5 years	Males, 19%	20 weeks of hypocaloric diet and/or exercise; body weight ↓ by both diet and exercise. Exercise main effect: − 3 kg; 95% CI, − 5, − 1; $p < 0.0001$; diet main effect, − 7 kg 95%CI: − 9, −5; $p < 0.0001$	Telephone calls every 2 weeks of study period	Primary: exercise capacity (peak oxygen consumption (VO_2, ml kg^{-1} min^{-1})); co-primary: QoL measured by the MLHF total score (score range, 0–105, higher scores indicate worse HF-related QoL). Exploratory outcomes: body composition, leg muscle function, cardiac function, inflammation.	Peak VO_2 ↑: exercise main effect: 1.2 ml kg^{-1} min^{-1} (95% CI, 0.7–1.7; $p < 0.001$); diet main effect, 1.3 ml kg^{-1} min^{-1} (95% CI, 0.8–1.8; $p < 0.001$); exercise+diet joint effect, 2.5 ml kg^{-1} min^{-1}. Change in MLHF total score nonsignificant with exercise (main effect, − 1 unit; 95% CI, − 8 to 5; $p = 0.70$) and with diet (main effect, − 0.6 units; 95% CI, − 12 to 1; $p = 0.078$). Change in peak VO_2 positively correlated with change in % lean body mass ($r = 0.32$; $p = 0.003$) and in thigh muscle/ intermuscular fat ratio ($r = 0.27$; $p = 0.02$).
5.	Babb et al. [13]/USA	Retrospective study (with control group)	HF inpts.	570	68.4 ± 14.2 years	Males, 56.5%	High-calorie ONS, at least twice daily, with a total daily, 660 kcal, 58 g carbohydrate, 26 g protein, 22 g fat, and essential vitamins and minerals.	Data collected during hospitalization	LOS	ONS use = higher LOS (OR 2.43; 95% CI, 1.34–4.41; $p = 0.0033$).

Abbreviations: *c*, damping constant, diastolic function component, yields ventricular relaxation; *CHF*, chronic heart failure; *CI*, confidence interval; *CPET*, cardiopulmonary exercise test; *DXA*, dual-energy X-ray absorptiometry; *dσ*/dtmax,* maximal rate of change of pressure-normalized wall stress–cardiac index of left ventricular contractility; *Ees:Ea*, ventricular–arterial coupling ratio (ratio between arterial elastance (EA) and end-systolic elastance (EES) of the left ventricle); *EF*, ejection fraction; *HF*, heart failure; *HFpEF*, heart failure with preserved ejection fraction; *HMB-beta*, hydroxy-beta-methylbutyrate; *k*, spring constant, diastolic function component, yields ventricular stiffness; *LOS*, length of stay (in hospital); *MLHF*, Minnesota Living with HF Questionnaire; *NOURISH study*, Nutrition effect on Unplanned Hospitalization and Survival in Hospitalized pts.; *ONS*, oral nutritional supplement; *OR*, odds ratio; *pts.*, patients; *PUFA*, polyunsaturated fatty acid; *QoL*, quality of life; *SD*, standard deviation; *SGA*, Subjective Global Assessment; *SMWT*, 6-min walk test

[a] Mean ± SD unless it was showed different

of visceral (abdominal) obesity on HF occurrence (see a meta-analysis of 27 prospective studies [23]).

Moreover, the period of excessive nutritional status is also important, as presented in a study conducted by Mørkedal et al. [18]. Chronic obesity (a BMI ≥ 30 kg m^{-2} for more than 30 years) doubles the risk of CHF compared with recently developed obesity. Other long-term analyses also confirm these results (with a median follow-up period of 12–36 years [3, 19, 24, 25]). A population-based cohort study by Schmidt et al. [19] is particularly notable, as the relation between obesity in young adulthood (defined using BMI) and HF incidence was confirmed by an almost 7-fold increased risk of developing HF. Crump et al. [25] established a similar association in national cohort prospective study in Sweden, but the risk of HF incidence for obese men at 18 years old (with a BMI > 29 kg m^{-2}) was only 2-fold higher. Obesity also accelerates the development of HF, and studies confirm that younger patients with CHF have a higher BMI. In the CHARM study, Wong et al. [90] (not include in the table) find that a BMI ≥ 35 kg m^{-2} was observed in 23% of younger patients (20–39 years old) in comparison with 6% of older patients (≥ 70 years old; $p < 0.0001$). Moreover, in their two studies [17, 24], Ho et al. are the only ones to confirm earlier observations that obesity (defined only by a higher BMI) shows slightly more predisposition to the development of HF with preserved left ventricular ejection fraction (HFpEF) than with reduced fraction (HFrEF). Recently, attention has also been paid to the metabolic status of patients with CHF and "metabolically neutral obesity". By classifying patients as metabolically healthy or unhealthy, Mørkedal et al. [18] confirm that excessive body weight has more important implications for the occurrence of HF than metabolic status. According to the authors, their finding dispels previous doubts about recommending weight reduction for the general population.

Nutritional status as a prognostic factor in CHF

Severity of the disease and mortality risk

Table 2 [26–72] presents studies analyzing the relationship between the course of CHF (which was measured by the severity of symptoms, mortality rate and risk of hospitalization) and nutritional status. Only two papers focus on the relation between nutritional status and the severity of symptoms [45, 47]. There is a trend suggesting that both obesity and overweight are associated with more severe symptoms, defined primarily as a higher New York Heart Association (NYHA) class [45]. However, in a cross-sectional study by Heo et al. [47], the above relationship applies only to male patients. The most severe symptoms (assessed using a different scale—the Symptom Status Questionnaire-Heart Failure) were shown only by men in the II/III class of obesity (BMI ≥ 35 kg m^{-2}; $p < 0.001$). However, the methodology of these studies is based mainly on the analysis of clinical symptom classification, and objective methods, e.g., spiroergometry, were not used. In the study by Dalos et al. [45], in which the analysis of pulmonary vasculature, invasive hemodynamic measurements from cardiac catheterization and pulmonary parameters such as vital capacity and forced expiratory volume in 1 s (FEV_1) were taken into consideration; however, cardiac assessment was not performed during cardiopulmonary exercise.

Most of the studies focus on the assessment of the relationship between nutritional status and mortality (35 papers). The vast majority of them focus on evaluating excessive nutrition (overweigh and obesity defined mostly in terms of BMI values due to the WHO classification), as a good prognostic marker in CHF [27–30, 33–39, 42–44, 46, 48, 49]. The prevalence of obesity among studies varies from 20 to 54% and overweight from 19 to 52%. Principally, the studies describe a higher BMI as having a protective effect on the survival of patients with CHF and lower BMI as a poor prognosis marker. The risk of all-cause mortality for obese and overweight patients decreased by 24–59% and by 15–65%, respectively (and by 2–16% with increasing BMI when it was considered a continuous variable). This phenomenon shows that obesity, in spite of being a risk factor in CHF development, may be a favorable prognostic factor: the so-called "obesity paradox." This relationship was shown for long-term mortality (in follow-up studies of 1 to 20 years). However, Milajerdi et al. [52] in the meta-analysis of six observational studies concerning relationship of pre-diagnosis BMI and HF mortality, illustrate a nonlinear U-shaped association with a higher mortality for both BMI > 29 kg m^{-2} as well as BMI < 25 kg m^{-2}, with no significance for the postdiagnosis BMI and the outcome (there were ten studies included in the analysis). The obesity paradox does not depend on the type of CHF. In two different meta-analysis [35, 55], it is reported that, for both HFrEF and HFpEF, the relationship between BMI and mortality takes the shape of a U curve (as for the general population with CHF [48]), with obese patients having the best prognosis (for BMI 30.0–34.9 kg m^{-2} [35] and with nadir of risk for BMI of 32–33 kg m^{-2} [55]).

A potential explanation of the obesity paradox in patients with CHF could be obtained through a comparison of mortality between obese patients and malnourished patients. However, exploration of this topic is difficult because many studies exclude patients with a BMI < 18.5 kg m^{-2} from their analysis. Only one study by Huang et al. [69] confirms that a low BMI, of less than 18.5 kg m^{-2}, is associated with a 4-fold increase in mortality rate over a 3-year period. Furthermore, malnutrition diagnosis still constitutes a challenge for clinicians and researchers, as there is no universal standard for nutritional assessment, especially in CHF—a chronic disease associated with body wasting and fluid retention. The analysis of the studies relating to malnutrition in CHF is difficult, due

to the different nutritional tools used to determine malnutrition and an insufficiency of BMI in diagnosis of this nutritional status, questioning the comparison with studies pertaining only to BMI. In the reviewed papers [56–72], the degree of malnutrition found in patients with CHF is significant (in the range of 12 to 69%), which is an indication of the scale of the problem. All the studies unequivocally reveal that inadequate nutritional status is associated with worse prognosis and may indicate the progression of the underlying disease. The studies analyzed focus only on long-term mortality (from 10 months to 4 years depending on the study) showing that malnutrition is associated with an increased risk of death. The risk of death increases from 2- to over 10-fold (for cardiac mortality being an element of composite endpoint), depending on the nutritional tools used, especially when questionnaires such as the Nutritional Risk Score 2002 (NRS-2002) and Mini Nutritional Assessment (MNA) or composed definitions or multifactor scores like Controlling Nutritional Status (CONUT) score are used to analyze the nutritional risk (as these tools take into consideration multiple aspects of malnutrition). Moreover, La Rovere et al. [71] emphasize that evaluation of undernourishment in CHF patients is extremely important. They submit that the nutritional status (assessed with CONUT score) improves the 12-month mortality prediction, as an additive to the information provided by clinical evaluation (e.g., using Meta-Analysis Global Group in Chronic Heart Failure score (MAGGIC score)) and functional capacity measured with, e.g., 6-Min Walk Test (6MWT).

Obesity paradox

Recent research on the obesity paradox in CHF has shown that the occurrence of this phenomenon is not as clear as was thought in earlier studies. This observation was also noted and confirmed in the articles analyzed in this review (Tables 1 and 2). There are many factors affecting a favorable prognostic effect of obesity on CHF survival that are not taken into account in a number of studies, such as the stage of obesity, CHF etiology, and the patient's metabolic status, age, and fitness. First, as presented in the study by Qin et al. [48], the obesity paradox has limitations and does not apply to patients with a BMI > 37 kg m^{-2} (or even BMI ≥ 35 kg m^{-2} [9, 27, 36]), with the exception of one study [28], in which lower by 65% mortality was also indicated for morbid obesity (BMI > 40 kg m^{-2}) compared with normal weight.

Several studies point out that the etiology of CHF is critical to the existence of a protective effect of obesity in this disease. For patients with an ischemic etiology of CHF, the paradox effect disappears [49, 91]. Furthermore, metabolic state is crucial. For obese patients with CHF and concomitant diabetes, there is a lower probability of survival in comparison with obese CHF patients without diabetes [39, 46]. Zamora et al. [46] explain that, in type 2 diabetes, more abdominal fat is observed, which does not promote the metabolic profile of the body (e.g., by causing insulin resistance and increased inflammatory response), whereas not having diabetes is metabolically healthier, which offers an advantage for survival.

Recently, Thomas et al. [54] have revealed, by using bioelectrical impedance analysis (BIA) to examine body composition, that low lean body mass also has an influence on mortality, despite the fact that, in their study, a better prognosis was primarily associated with body fat mass. In this work, a combination of low fat mass and low lean mass was associated with an almost 5-fold increase in 5-year mortality. More studies focusing on the significance of fat mass in CHF prognosis are needed. Zuchinali et al. [59] use the triceps skinfold (TSF), an anthropometric measurement of subcutaneous fat, and one of the best parameters referring to total body fat percentage. They report that the TSF is a better predictor of mortality in CHF than BMI, pointing out the significance of fat mass in obesity paradox (TSF ≥ 20 mm is a strong independent predictor of all-cause mortality, connected with a 44% lower risk of death). Moreover, recent distinctions between the various types of obesity, including, for example, sarcopenic obesity, confirm that the adipose tissue distribution is important for CHF prognosis [50]. The results of studies concerning the role of visceral fat in CHF are both ambiguous and contradictory [36, 37, 50, 53]. Some papers [36, 37] prove its protective role in CHF (with WC measurement) [36, 37], but Puig et al. [36] indicate that this relationship disappears for extreme values of WC (> 120 cm). In a different study, the obesity paradox is not observed after considering visceral obesity [50, 53]. What is more, Streng et al. [53] demonstrate a more than 2-fold higher risk of mortality for women with abdominal obesity (WHR ≥ 0.85). Also, lower biochemical parameter values connected with fat mass, i.e., total cholesterol (TC), can be appropriate markers of poor prognosis in CHF [43, 70].

Hospitalizations

The most challenging problem associated with HF therapy is recurrent hospitalization. Unfortunately, there are only a few studies that analyze the relationship between nutritional status and relapse leading to hospitalization [32, 43, 44, 57, 59, 60] and most reports use combined endpoint (death and hospitalization), thereby limiting separate evaluations of these events [45, 58, 62, 63, 65, 67, 70]. The results show that the problem of hospitalization concerns about 3.4 [51]–25% [58] of patients. The material available shows unambiguous data on the impact of nutritional status on the frequency of hospitalizations, which probably arise from the use of different nutritional assessment tools (BMI, TSF, CONUT score, TC, prealbumin level). Some of the studies [43, 44, 57] show that poor nutritional status can increase the risk of hospitalization from 1.2- to 1.7-fold. On the other hand, the report by Zuchinali et al. [59] do not show significant associations

between different nutritional tools (mainly the measurement of TSF) and CHF exacerbations requiring hospitalization. Tevik et al. [64] underline another factor, in that patients with CHF at risk of malnutrition (with ≥ 3 points on the NRS-2002 questionnaire) face further complications during hospitalization and their LOS is also longer. The role of BMI values to predict hospitalization rate in CHF is doubtful, as meta-analysis by Sharma et al. [44] shows that both too low BMI (< 20 kg m^{-2}) as well as a morbidly high (≥ 35 kg m^{-2}) BMI are related to an increase risk of hospitalization by 19–28%. In contrast, Dalos et al. [45] do not find any relationship between BMI and the composite endpoint (including hospitalization due to HF and/or cardiac death).

Nutritional status as prognosis factor for invasive treatment of CHF

Nutritional status is also crucial to the effectiveness of invasive methods of CHF therapy, such as: cardiac resynchronization therapy (CRT), implantable cardioverter-defibrillator (ICD) implantation, heart transplantation, and left ventricular assist device (LVAD) placement. As illustrated in Table 3 [73–85], there are only a few studies concerning the relation between nutritional status and the outcome of invasive CHF treatment and they provide conflicting conclusions. Most of them indicate that obesity [74, 79] or overweight [74, 76] defined using different BMI values: 24–28 kg m^{-2} or ≥ 25 kg m^{-2}, is protective and improves prognosis after using supportive devices and electrotherapy, thus confirming the theory of the obesity paradox in CHF. Grandin et al. [79] reported that the probability of 10-year survival free from postimplantation complications was greater for patients with a higher BMI before CRT-D implantation (an independent effect of BMI on survival). They indicate a further favorable impact on successful invasive therapy in the case of metabolic disorders such as diabetes. However, Yanagisawa et al. [76] demonstrate that an association between BMI and prognosis was only found for nonresponders to CRT-D, which suggests that effective electrotherapy delivers the greatest benefits for CHF prognosis, improves the function of the heart and body weight has minor significance.

Other studies conclude that higher BMI and even obesity do not significantly affect prognosis after invasive treatment [75], including LVAD placement [70, 78, 84]. However, Volkovicher at al. [81] report worse prognoses for patients with morbid obesity (≥ 38.5 kg m^{-2}). On the other hand, Aktas et al. [75] emphasize that a weight loss of ≥ 2 kg during the annual follow-up is more important, as it increases the risk of death for any reason in patients with CRT-D by 79%.

Furthermore, the effect of malnutrition on the outcome of invasive CHF therapy is dependent on a proper diagnosis of malnutrition [73, 78, 82, 83, 85]. Imamura et al. [78] find that lower BMI and albumin levels at discharge were associated with an increased risk of hospitalization due to infections linked with the implanted device (driveline infection (DLI); device-specific infection), similar to the increased risk of post-operative infection in the case of malnutrition. Using these parameters (BMI and albumin levels at discharge), they created a new prognosis index (New Score) to define more accurately the risk of hospitalization due to the above-mentioned complications within 2 years of using a device (LVAD). Lower BMI also means a higher risk of hospital complications after ICD implantation [73] (mainly infections). In addition, weight loss of ≥ 5% $year^{-1}$ after ICD implantation is associated more frequently (2-fold increase) in the device not working appropriately [80].

Interventions in nutritional status in CHF

Correction of nutritional status in patients with CHF may involve a reduction in body mass or nutritional support as a part of malnutrition treatment or multidisciplinary approach in CHF. In the guidelines of cardiac societies, there are currently no recommendations regarding supportive nutritional and dietary treatment for CHF (other than to restrict the amount of fluids and sodium consumed, which is not, however, supported by scientific research [44, 92] or for the treatment of malnutrition and cachexia in this group of patients [61]. There are also barely a few clinical trials analyzing the importance of diet in the treatment of CHF [13, 86, 87] and assessing dietary intervention in malnourished patients [88]. What is more, this small number of studies describe little or heterogeneous groups of patients [88] and only analyze substitute endpoints, such as improvement in physical fitness, quality of life, changes in the structure and function of the heart, and length of stay (LOS) in hospital [13, 86, 87, 89].

An analysis of the literature suggests that for patients with CHF, a high-protein diet seems to be promising because of its contribution to increasing lean body mass, preventing muscle loss, and regulating metabolism not only among malnourished patients but also for those who are obese or overweight [93]. Unfortunately, only one study related to the importance of nutritional interventions in the form of protein-rich supplements, have been found [88]. For a group of over 600 elderly patients with cardiopulmonary diseases (including CHF), Deutz et al. [88] find that immediate implementation (within 72 h of admission to hospital) and continuation (for 3 months) of nutritional treatment in patients in class B or C according to Subjective Global Assessment (SGA) had a positive effect on prognosis (a 2-fold reduction in mortality, improvement in SGA class and weight gain). We are well aware of the limitations of aforementioned trial, due to the study population and difficulties in generalizing the conclusions to CHF patients, therefore, more well-designed studies are needed. Babb et al. [13] also indicate the necessity for individually adjusted dietary intervention since the routine use of commercial oral

nutritional supplements was associated with a more than 2-fold higher risk of longer hospitalization.

Our review also presents other studies on CHF treatment outcomes with different diet therapy, such as the Dietary Approaches to Stop Hypertension (DASH) diet [87], a sodium-restricted diet [87, 92], and nutritional supplements in patients with CHF such as polyunsaturated omega-3 fatty acids (PUFAs) [86]. However, the available studies show a positive influence of aforementioned dietary patterns, but they do not provide strong evidence for their efficacy, as only substitute endpoints were evaluated: improvement in cardiac function, better LVEF and improved quality of life, with their role as prognostic markers for clinically significant primary endpoints in CHF not being confirmed. However, Song et al. [65] underline the significance of micronutrients in the course of CHF, demonstrating that the higher the deficiencies (≥ 5 substances), the greater the risk of an adverse cardiac event (1.7-fold higher).

Very small amount of studies focus on the issue of body weight reduction recommendations for obese or overweight patients with CHF. Only one paper in our review was directly related to intentional weight reduction in obese patients [89]. In the study of Kitzman et al., on the group of obese older patients with clinically stable heart failure and preserved ejection fraction, both caloric restriction diet and aerobic exercise training, increased exercise capacity measured with oxygen consumption, and the effects may be additive. Surprisingly, they found also that more benefits can be achieved by a hypocaloric diet than by physical activity, what is inconsistent with an analysis of the literature suggesting that better physical fitness means better prognosis because it is an independent predictor of mortality [9, 39, 91, 94, 95]. This is confirmed in the ESC guidelines as they encourage the introduction of individually matched physical training for CHF patients [2].

Discussion

Summary of evidence

The findings of this systematic review demonstrate significance of nutritional status in CHF. To the best of our knowledge, it is the first systematic review of multiple associated factors relating to nutritional status and CHF, with a complex analysis of both excessive nutrition as well as malnutrition in CHF (together with invasive therapy) and a summary of nutritional interventions, all in one paper. Previous reviews and meta-analyses largely analyzed these two nutritional disorders separately, with the majority predominantly concerning the role of obesity or obesity paradox within this group of patients, using mainly BMI values [15, 21, 23, 31, 35, 44, 48, 52, 55, 96–102]. Only a small number of articles described malnutrition or the use of different nutritional status assessment tools [16, 95, 103] and the outcomes of nutritional interventions in CHF [104–106].

First of all, the results of our review confirmed that both excessive nutrition status and undernourishment are common phenomena in CHF, and the prevalence of these two disorders (19–54% for obesity or overweight and 12–69% for malnutrition) is similar to data previously presented in other reviews or meta-analyses [100, 101, 103, 104].

Secondly, we confirmed (Table 1) that obesity is recognized as a risk factor for developing CHF [3, 17–25]. It has been revealed the dose-dependent relationship with a 5% increase in CHF risk for men and 8% for women with each single-unit increase in BMI [96, 100, 107], and the CHF risk was increased by 49% for overweight participants and even 180% for obese individuals [100, 102]. In this review, we note that the aforementioned relationship is especially evident in the case of severe [18, 19], abdominal [23], and long-lasting obesity (with diagnosis in adolescence) [18, 19, 25]. However, the most important conclusion arising from the association of obesity and CHF is that, this relationship was independent of the metabolic consequences of overnutrition and was mainly related to excessive body weight, but not to the pre-diagnosis metabolic status [18, 100].

Thirdly, our review demonstrates a significant role of nutritional status in the course and prognosis of CHF (Table 2). For the most part, our analysis and recently performed review [105] unequivocally confirm that malnutrition is certainly a bad prognostic marker of CHF, with a similar impact on mortality (from a 2- to 10-fold increase of death). By contrast, the precise prognostic role of excessive nutrition in CHF still remains unresolved issue with many doubts and questions. The conclusions of currently analyzed papers are divergent as it was presented in former reviews. Yet, in the vast majority of studies, the obesity paradox was confirmed [27–30, 33–39, 42–44, 48–51, 54–56], meaning that obesity can be recognized, on the one hand as a risk factor for CHF, and, on the other hand, as a favorable prognostic factor associated with reduction in a long-term mortality by 24–59% [9, 99, 102]. However, a small amount of studies of this review, state that relationship between obesity and mortality is U-shaped [35, 48, 52, 55], as it was revealed earlier [99, 102], concluding that extensive obesity (with different cut off BMI values, e.g., > 37 kg m^{-2} [48] or ≥ 35 kg m^{-2} [44]) does not have a protective value. What is more, a very important direction and design of researches are observed, as more precise analysis of the obesity paradox have been recently performed with many confounders taking into consideration. Also in this review, the most important additional factors were assessed, in order to appropriately evaluate the positive impact of obesity on mortality, such as the stage of obesity, body composition, CHF etiology, patient's metabolic status (similar to previous reviews [9, 99–101] which also included fitness [101], obesity phenotype [101], gender [9, 94, 99], and age [94]). This

adjustment for confounders causes that survival paradox of high BMI to disappear, what is still unresolved and unexplained matter [96]. Moreover, an analysis of the recent literature demonstrates, that another phenomenon, known as the "lean paradox" [96], is discussed and could be responsible for a better prognosis for obese patients with CHF. It is suggested that normal weight or BMI do not reflect an appropriate nutritional status in every case. The association of normal weight with a worse prognosis is in fact the result of weight loss throughout CHF and is related to disease progression and ongoing malnutrition, or even the beginning of cardiac cachexia (malnutrition-inflammation syndrome) [73, 96, 99]. Furthermore, more studies suggest that different phenotypes of obesity should be distinguished in the analysis of the influence of obesity on the course of CHF. There are different types of obesity, depending on the metabolic profile or physical capacity of the patient, such as fat and fit, normal weight obesity and metabolically healthy obesity (MHO) [96], or sarcopenic obesity [101], which cannot simply be defined with only a BMI measurement. The BMI values are not directly related to body composition (such as body fat mass or fat distribution, these being the most significant element of obesity definition). Although the observations concerning obesity, mentioned in this and former reviews, were mainly based on studies in which a BMI ≥ 30 kg m^{-2} was used as a cut-off value for obesity diagnosis. It is known that this threshold underestimates obesity prevalence and BMI does not measure fluid retention or adiposity distribution, and it is mainly appropriate for general population study group [96]. Therefore, further studies are needed to evaluate links between obesity and the prognosis of patients with CHF based on modern methods for nutritional status assessment. In many more studies, different body components are included in the assessment (to start with, the simple measurement of WC, WHR or triceps skinfold, to even usage of more precise methods of BIA [36, 37, 50, 53, 54]). Unfortunately, the available data has not pointed out which body component is the most significant in survival for CHF so far. This leads towards the conclusion that achieving and maintaining a balance between lean body mass and fat mass is the most appropriate goal in terms of nutritional treatment in CHF. On the other hand, although the use of BMI in order to assess adiposity is flawed, it is a good marker of excess body weight which can predict cardiovascular risk or incidence of CHF and all-cause survival in CHF in a way better than more expensive and precise measurements (Table 2). It should still be widely used, especially in medical practice and at general population level [96, 101].

Fourthly, in this systematic review, we emphasize the effectiveness of the invasive methods of CHF treatment in obese patients (Table 3). Numerous studies have shown that obesity does not affect the risk of complications after invasive treatment of CHF, as it often improves prognosis [74, 76, 77, 79]. Therefore, obesity should not disqualify a patient from more aggressive, advanced methods of treatment. However, morbid obesity is still a contraindication for heart transplants, with the need to achieve a BMI < 35 kg m^{-2} before being placed on a waiting list [2]. Prior to a recommendation for invasive therapy, it is more important to focus on patients at risk of malnutrition and to implement proper nutritional intervention.

Fifthly, in this review, we found out that role of malnutrition in CHF, despite being a poor prognosis marker, is still not suitable explored (Table 2). Available studies are heterogeneous, mainly due to different methodologies or the various nutritional status assessment methods, as well as the lack of universal guidance concerning the diagnosis of malnutrition in CHF. Also, in the majority of studies on patients with CHF, a BMI < 18.5 kg m^{-2} is used as an exclusion criterion. The discrepancies mentioned above do not allow a precise presentation of the seriousness of the malnutrition problem, and make the comparison of the studies rather difficult. This illustrates the necessity for further studies of the role of malnutrition in CHF which should also plan to identify a "gold standard" for diagnosing malnutrition in patients with CHF. Recent studies have indicated more significant nutritional tools being a candidate to the best method of undernourishment diagnosis, like the MNA questionnaire [72, 103] (which can also be used as a recommended pattern to evaluate the specificities and sensitivities of different tools in future research with CHF patients, until a general consensus is reached [103]), the GNRI [58, 68, 108] or CONUT score (used mainly in our review) [57, 67, 71]. What is more, the analysis of most current and previous papers demonstrates that the best means of evaluating nutritional status and of accurately performing screening of malnutrition in CHF is to use multidimensional tools, as they reduce interference from confounding variables such as fluid retention or hypoalbuminemia being a part of CHF. Difficulties in defining malnutrition unambiguously cause another problem for clinical practice which was emphasized in reviewed studies—malnutrition is an undervalued condition which is very often overlooked and nutritional support is introduced in only 2 to 13.3% [88] of malnourished individuals.

Sixthly, this review indicates that there is also a lack of interventional studies on nutritional status correction in CHF, and because of this, we also include observational studies to this part of the review (Table 4). Available studies are designed with improper methodology as they are related to the relatively small and heterogeneous groups of patients, very often lacking randomization, or only substitute endpoints are analyzed, with the follow-up period being very short. Most of the available studies focus on nutritional support in CHF treatment, but the results are ambiguous. As the analysis of actual data and previous reviews shows, the most successful dietary patterns in secondary prevention of CHF seems to be: the DASH Diet (also in our review [87]), the Hyperproteic Diet

[105], and the Mediterranean diet [105]. These mainly result in improving functional capacity and cardiac function. Our review also includes studies on dietary supplements. And among them also PUFAs were included with successful impact on measure outcome, but without strong evidence of efficacy. It is similar with previously performed reviews and studies, where the most promising approach was also the use PUFAs, which were associated with a decrease in mortality and frequency of hospitalization [79, 86, 94, 109–111]. However, the European Society of Cardiology (ESC) has withdrawn its recommendation for PUFA supplementation in patients with cardiovascular diseases due to methodological shortcomings in the GISSI-Prevenzione study. Additionally, the role of Coenzyme Q10, iron, vitamin D or L-carnitine in the course of CHF was also analyzed in previous reviews [106, 112] (also with disappointing results). However, the available studies do not provide a strong evidence for the efficacy of the aforementioned supplements, as only substitute endpoints were evaluated: an improvement in NYHA class, better LVEF and improved quality of life, and their role as prognostic markers for clinically significant primary endpoints in CHF were not confirmed [106, 112]. We did not found any eligible study related to micronutrient supplementation (perhaps mainly due to the disappointing results of previous studies), so the nutritional support in CHF is still unresolved issue.

Moreover, studies assessing various types of dietary intervention in the case of malnutrition in CHF are lacking and necessary (only one paper [88] included in this review and to the best of our knowledge any previous review on this issue). The treatment of malnutrition and improvement of nutritional status in the case of undernourishment risk in CHF is still an unresolved problem. The lack of a universal nutritional tool and gold standard in order to diagnose malnutrition does not help to design appropriate interventional studies. More precise recommendations would be helpful to conduct these necessary clinical trials. Also, more adequate and multidisciplinary clinical approaches in daily practices, based on individually matched nutritional support in the case of identification of malnutrition risk would add many important information for further studies. More valuable and promising trials on nutritional interventions (analyzing hard endpoints) concern only to the patients with exacerbations of the CHF. The PICNIC study is worthy of mention [113], as the researchers demonstrate that individually prescribed 6-month food interventions (optimized diet and nutritional supplements) in malnourished patients with acute heart failure (MNA score < 17 points) reduce the mortality rate (by more than 2-fold) and risk of readmission due to exacerbation of the disease. Similar trials are needed for patients with CHF.

Furthermore, studies evaluating intentional weight reduction in obese patients are also needed. The phenomenon of the obesity paradox calls this into question. Also, a lack of clear recommendations for obese patients does not help to conduct these studies. It is responsible for "vicious circle," as properly designed trials will clarify the recommendations of cardiological societies and improve the multidisciplinary approach to CHF patients. The premises for such studies are data showing an unfavorable prognosis associated with unintentional weight loss in patients with CHF [56, 61, 75, 80]. Recently, some reviews have shown that clinical trials relating to weight reduction in CHF are promising, mainly due to the improvement of LVEF and exercise capacity, but the results are equivocal (e.g., for improvement of quality of life) [89, 96, 104]. An equally important matter is to answer the question—who will benefit most from weight reduction and what is the best way to achieve it? ESC guidelines advise considering it only for patients with a BMI ≥ 35 kg m^{-2} [2]. The results of some studies also show a favorable effect of weight loss in patients with CHF, especially for morbidly obese patients (BMI > 40 kg m^{-2}), and also for individuals with a BMI > 35 kg m^{-2} [27, 94, 95]). The importance of weight reduction in other BMI ranges is not clear. However, there are indications that weight loss can improve the severity of symptoms and NYHA class for less extreme obesity (< 35 kg m^{-2}) and overweight (but more studies are still needed [94, 95]). In particular, moderate (5–10%) intentional weight loss appears to be important [93] especially when achieved through a properly balanced diet and physical exercise [91, 109]. This procedure is particularly recommended when the metabolic profile of an obese patient is disturbed (metabolic syndrome) [93]. In contrast, a calorie-restricted diet alone is not recommended (as this primarily causes a loss of lean body mass, which is important for the overall fitness of the body) [9, 91, 94, 95], although one study included in our review by Kitzman et al. [89] indicates that more benefits can be achieved by a hypocaloric diet than by physical activity. As far as nutritional correction in CHF is still an unexplored issue and remains a challenge for both researchers and clinicians.

Limitations

Our review has several limitations. First of all, the analyzed data is extensive with many screened and finally included articles, due to the important nature of the describing subject. That could be overwhelming and make the readers confused and not focus on the matter of the article and to overlook the most crucial points of the review. The eligibility criteria of the included studies could be more precise. However, the aim of this article was to present the most complex and multi-factorial analysis of nutritional status in CHF and put the most important and recent findings in one place. Unfortunately, the second limitation of the search strategy, such as reviewing only two databases and

restricting to English-language publications, could result in overlooking some crucial information which could have an influence on the final conclusions of the article (selection bias). Thirdly, the interventional studies were carried out on relatively small samples size with short follow-up period and, what is more, some of them did not comply with the randomization process, thus the comparison of these studies are lacking in reliability. However, the inclusion of these papers to analysis arises from deficiency of studies on nutritional interventions in CHF. The last, but the most important limitation of this paper, as with any overview, is that the patient population, sample size, study design, definitions of the CHF diagnosis, nutritional tools and outcomes are not identical across all of the studies. Mainly, the methods of nutritional status measurement and the definitions of undernourishment vary significantly in the papers as the result of the absence of precise universal guidelines and a gold standard for define nutritional status of CHF patient, as we have mentioned previously.

Conclusions

Both obesity and malnutrition are common phenomena in the nutritional status of patients with CHF and have a significant impact on the prevalence, course, and prognosis of this disease. Obesity is recognized, on the one hand, as a risk factor for CHF and, on the other, as a favorable prognostic factor associated with reduction in mortality (the obesity paradox), including patients with invasive treatment of CHF. Therefore, obesity should not disqualify a patient from receiving more aggressive, advanced methods of CHF treatment. Further studies are needed to evaluate links between obesity and risk and the prognosis of patients with CHF based on modern methods, as BMI underestimates obesity prevalence and seems to be unreliable as a parameter of nutritional status assessment in patients with CHF as it does not provide measurement of fluid retention and adiposity distribution. Further researches focusing on the identification of malnutrition biomarkers in patients with CHF, as well as with plan to evaluate the effectiveness of the intervention in CHF patient's nutritional status, both being obese and malnourished, are also needed.

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Compliance with ethical standards

The manuscript does not contain clinical studies or patient data.

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Ethical approval This article does not contain any studies with animals performed by any of the authors.

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