

# Obesity paradox in patients with reduced ejection fraction eligible for device implantation – an observational study

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## Abstract

**Aims** Patients with obesity have an overall higher cardiovascular risk, at the same time obesity could be associated with a better outcome in a certain subgroup of patients, a phenomenon known as the obesity paradox. Data are scarce in candidates for cardiac resynchronization therapy (CRT). We aimed to investigate the association between body mass index (BMI) and all-cause mortality in patients eligible for CRT.

**Methods** Altogether 1,585 patients underwent cardiac resynchronization therapy between 2000–2020 and were categorized based on their BMI, 459 (29%) patients with normal weight (BMI < 25 kg/m<sup>2</sup>), 641 (40%) patients with overweight (BMI 25–< 30 kg/m<sup>2</sup>) and 485 (31%) with obesity (BMI ≥ 30 kg/m<sup>2</sup>). The primary endpoint was all-cause mortality, heart transplantation, and left ventricular assist device implantation. We assessed periprocedural complications and 6-month echocardiographic response.

**Results** Normal-weight patients were older compared to patients with overweight or obesity (70 years vs. 69 years vs. 68 years; *P* < 0.001), respectively. Sex distribution, ischaemic aetiology, and CRT-D implantation rates were similar in the three patient groups. Diabetes mellitus (BMI < 25 kg/m<sup>2</sup> 26% vs. BMI 25–< 30 kg/m<sup>2</sup> 37% vs. BMI ≥ 30 kg/m<sup>2</sup> 48%; *P* < 0.001) and hypertension (BMI < 25 kg/m<sup>2</sup> 71% vs. BMI 25–< 30 kg/m<sup>2</sup> 74% vs. BMI ≥ 30 kg/m<sup>2</sup> 82%; *P* < 0.001) were more frequent in patients with overweight and obesity.

During the mean follow-up time of 5.1 years, 973 (61%) reached the primary endpoint, 66% in the BMI < 25 kg/m<sup>2</sup> group, 61% in the BMI 25–< 30 kg/m<sup>2</sup> group and 58% in the BMI ≥ 30 kg/m<sup>2</sup> group (log-rank *P* < 0.05). Patients with obesity showed mortality benefit over normal-weight patients (HR 0.78; 95%CI 0.66–0.92; *P* = 0.003). The obesity paradox was present in patients free from diabetes, atrial fibrillation, and ischemic events. Periprocedural complication rates did not differ in the three groups (BMI < 25 kg/m<sup>2</sup> 25% vs. BMI 25–< 30 kg/m<sup>2</sup> 28% vs. BMI ≥ 30 kg/m<sup>2</sup> 26%; *P* = 0.48). Left ventricular ejection fraction improved significantly in all patient groups (BMI < 25 kg/m<sup>2</sup> median Δ-LVEF 7% vs. BMI 25–< 30 kg/m<sup>2</sup> median Δ-LVEF 7.5% vs. BMI ≥ 30 kg/m<sup>2</sup> median Δ-LVEF 6%; *P* < 0.0001) with a similar proportion of developing reverse remodeling (BMI < 25 kg/m<sup>2</sup> 58% vs. BMI 25–< 30 kg/m<sup>2</sup> 61% vs. BMI ≥ 30 kg/m<sup>2</sup> 57%; *P* = 0.48); *P* = 0.75).

**Conclusions** The obesity paradox was present in our HF cohort at long-term, patients underwent CRT implantation with obesity and free of comorbidities showed mortality benefit compared to normal weight patients. Patients with obesity showed similar echocardiographic response and safety outcomes compared to normal weight patients.

**Keywords** obesity paradox; heart failure; mortality; cardiac resynchronization therapy

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## Introduction

Heart failure affects 1–2% of the general population, reaching up to 10% in the elderly.<sup>1</sup> Populations with obesity have a higher risk of acquiring heart failure (HF),<sup>2</sup> however, these patients tend to have more favourable outcomes, a phenomenon known as the obesity paradox.<sup>3,4</sup> Its pathophysiology remains unidentified as mainly hypotheses emerged, including obesity's protective factor against protein energy malnutrition and the activation of inflammatory cytokines.<sup>5</sup> At the end-stage of heart failure, a catabolic state occurs often paired with malnutrition.<sup>6,7</sup> Other hypothesis mention changes in lipid metabolisms (higher cholesterol levels and lipoproteins), lower prothrombotic agents levels, an increased ghrelin production (as it may improve cardiac contractility) and elevated cytokine/adipokine production that may have cardioprotective properties.<sup>8</sup>

Within the subset of heart failure patients, those with reduced ejection fraction (HFrEF) have the highest risk for adverse clinical outcomes, the rate of all-cause mortality of HF can reach 50% in five years.<sup>9–11</sup> Cardiac resynchronization therapy (CRT) is known as an effective device treatment, which reduces mortality in a well-selected HFrEF patient population.<sup>12,13</sup> The incidence of obesity in CRT candidates is high, approximately 36% have a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> defined as obese, whereas the mean BMI of the population ranges between 26.5–31.2 kg/m<sup>2</sup>.<sup>12–14</sup> A few data elucidated that obesity does not decrease the clinical benefit of CRT,<sup>15</sup> or may even have a positive effect on the outcome.<sup>16,17</sup> However, data are incomprehensive on the association between the optimal BMI range and such patients' survival benefit.

Our aim was to examine the association of obesity classified by BMI with all-cause mortality, periprocedural complications, and echocardiographic response at long-term in HF patients undergoing CRT.

## Methods

### Study population and categorization by body mass index

Altogether 2,656 HF patients underwent CRT implantation at the Semmelweis University, Heart and Vascular Center, between June 2000 and August 2020. Indication for CRT implantation was set up based on current ESC guidelines (symptomatic heart failure patients on optimal medical treatment, LVEF  $< 35\%$  and QRS  $> 130$  ms).<sup>18</sup> Patients' data were collected retrospectively into our registry „Biobankok" via hospital records. The registry consists of medical history, clinical and echocardiographic parameters, laboratory tests, and parameters of the procedures. Finally, 1,585 patients were enrolled in our

study that had their weight and height available at baseline. To quantify obesity, we calculated their BMI as the ratio of weight in kilograms to the square of height in meters (BMI = kg/m<sup>2</sup>). Patients were then categorized into three patient groups based on the WHO classification, underweight and normal weight (further mentioned as normal weight group [BMI  $< 25$  kg/m<sup>2</sup>]), patients with overweight (BMI 25.0– $< 30$  kg/m<sup>2</sup>) and patients with obesity (BMI  $\geq 30$  kg/m<sup>2</sup>).<sup>19,20</sup> Obese patients were additionally categorized into three obesity groups, also based on the WHO classification: obese I (BMI 30– $< 34.9$  kg/m<sup>2</sup>), obese II (BMI  $\geq 35$ – $< 40$  kg/m<sup>2</sup>) and obese III (BMI  $\geq 40$  kg/m<sup>2</sup>). Survival analyses were also conducted without underweight patients, added as supplementary material.

The study complies with the Declaration of Helsinki and was approved by the Regional and Institutional Committee and Research; No. 161–0/2019.

### Outcomes

The main outcomes were the composite endpoint of all-cause mortality, heart transplantation, or left ventricular assist device (LVAD) implantation. The date of death was retrieved via the National Health Insurance Fund of Hungary, updated in December 2021. The mean follow-up time was 5.1 years, calculated from the enrolment date into this observational study, that was defined as the date of the CRT implantation to the date of death, heart transplantation or LVAD implantation.

Secondary outcomes were periprocedural complications (bleeding, pneumothorax, haemothorax, coronary sinus dissection, pericardial tamponade, pocket infection/decubitus, infective endocarditis, lead dislodgement, lead dysfunction or phrenic nerve stimulation).

Tertiary outcomes were echocardiographic response and the development of reverse remodeling, defined as a relative increase of 15% or more in left ventricular ejection fraction (LVEF) within 6 months after CRT implantation.

### Procedures

Device implantation was carried out under X-ray, and leads were implanted through the cephalic or subclavian veins. Right ventricular leads were implanted preferably in a septal position. The optimal coronary sinus side branch was chosen by venogram routinely, left ventricular leads were preferably implanted into the lateral or posterolateral vein. Left ventricular lead implantations, if failed by the coronary sinus, were carried out by epicardial or transeptal approach. Electrical parameters such as sensing values, pacing threshold, impedance, RV-LV activation delay were evaluated intraoperatively.

## Statistical analysis

Continuous variables were described as median and interquartile range (25<sup>th</sup>–75<sup>th</sup> percentile), after Shapiro–Wilk normality test and categorical variables as numbers and percentages. Patient characteristics were compared amongst categories using chi-squared tests for categorical variables and the Mann–Whitney and the Kruskal–Wallis tests for continuous variables, as appropriate. Kaplan–Meier estimates and log-rank tests were used to evaluate unadjusted event-free survival in each patient category. Cox multivariate regression analysis was used to assess the association between BMI status and outcomes after CRT implantation. Statistical analysis was performed using GraphPad Prism, version 8.4.2 (San Diego, CA, USA, GraphPad Software) and IBM SPSS Statistics, version 26 (Armonk, NY, USA, IBM Corp). A *P*-value of less than 0.05 was considered statistically significant.

## Results

### Baseline clinical characteristics of the study cohort

Altogether 1,585 patients were included in our study, 459 (29%) patients were in the normal weight group (BMI < 25 kg/m<sup>2</sup>) of which 23 (5%) patients were underweight (BMI ≤ 18.5 kg/m<sup>2</sup>), 641 (40%) patients were in the overweight category (BMI 25– < 30 kg/m<sup>2</sup>) and 485 (31%) were patients with obesity (BMI ≥ 30 kg/m<sup>2</sup>). Patients with obesity were further categorized, of these 361 (74.4%) belonged to the obese I patient group (BMI 30–<34.9 kg/m<sup>2</sup>), 94 (19.4%) in the obese II group (BMI ≥ 35–<40 kg/m<sup>2</sup>) and 30 (6.2%) in the obese III group (BMI ≥ 40 kg/m<sup>2</sup>).

Normal-weight patients were older compared to patients with overweight or obesity (70 years vs. 69 years vs. 68 years; *p* < 0.001), respectively. Sex distribution, ischaemic aetiology, and CRT-D implantation rates were similar in the three patient groups. Diabetes mellitus (DM) (normal weight 26% vs. patients with overweight 37% vs. patients with obesity 48%; *p* < 0.001) and hypertension (normal weight 71% vs. patients with overweight 74% vs. patients with obesity 82%; *p* < 0.001) were more frequent in patients with overweight and obesity.

Patients had a comparable renal function (normal weight eGFR 64 mL/min/1.73m<sup>2</sup> vs. patients with overweight eGFR 63 mL/min/1.73m<sup>2</sup> vs. patients with obesity eGFR 66 mL/min/1.73m<sup>2</sup>; *P* = 0.25) and similar N-terminal pro-B-Type natriuretic peptide (NT-proBNP) levels (normal weight 3,000 pmol/l vs. patients with overweight 2,498 pmol/l vs. patients with obesity 2,488 pmol/l; *P* = 0.21).

Regarding echocardiographic parameters, patients with overweight and obesity had significantly higher left ventricular ejection fractions (LVEF) (patients with obesity 30% vs. patients with overweight 28% vs. normal weight 27%; *p* < 0.001).

Patients were on comparable medical treatment, but digoxin was used more in normal weight patients (normal weight 24% vs. patients with overweight 17% vs. patients with obesity 16%; *P* = 0.003), respectively and oral anticoagulant was used most in overweight patients (normal weight 27%, patients with overweight 33%; patients with obesity 27%; *P* = 0.03). (Table 1.)

## Outcomes

### Main outcomes

During our mean follow-up time of 5.1 years, 973 (61%) reached the primary endpoint, 302 (66%) in the BMI < 25 kg/m<sup>2</sup> group, 389 (61%) in the BMI 25– < 30 kg/m<sup>2</sup> group and 282 (58%) in the BMI ≥ 30 kg/m<sup>2</sup> group (log-rank *p* < 0.05). Absolute mortality rates were the lowest in the 35– < 40 kg/m<sup>2</sup> BMI range, depicting a J-shaped curve (Figure 1.). Altogether 29 (2%) patients underwent orthotopic heart transplantation, 8 (2%) patients with normal weight, 16 (2%) patients with overweight and 5 (1%) patients with obesity. 4 (0.2%) patients reached the primary endpoint by the implantation of an LVAD, 1 (0.2%) patient with normal weight, 1 (0.1%) patient with overweight and 2 (0.4%) patients with obesity.

Patients with obesity had a significantly lower risk of all-cause mortality compared to normal-weight patients (HR 0.78; 95% CI 0.66–0.92; *P* = 0.003) and patients with overweight showed a trend compared to normal-weight patients (HR 0.86; 95% CI 0.74–1.00; *P* = 0.05). (Table 2.) (Figure 2.)

Patients in the obese II group were more likely to survive than patients in the obese III group (HR 0.51; 95% CI 0.26–1.00; *P* = 0.017). Survival in other patient groups did not differ significantly [obese I vs. obese II (HR 1.26; 95%CI 0.90–1.75; *P* = 0.20) and obese I vs. obese III (HR 0.66; 95% CI 0.37–1.20; *P* = 0.10)].

When underweight patients were excluded from the studied patients, statistical results did not differ notably, the risk of the primary endpoint in patients with a BMI 18.5– < 25 kg/m<sup>2</sup> vs. overweight patients was similar (HR 0.87; 95% CI 0.75–1.02; *P* = 0.08) and was significantly greater compared to obese patients (HR 0.79; 95% CI 0.67–0.94; *P* = 0.006). (Supplementary Table S1 and Figure S3).

At multivariate analysis, patients with a BMI < 25 kg/m<sup>2</sup> showed a 25% higher risk of all-cause mortality compared to patients with overweight and obesity (HR 1.25; 95% CI 1.06–1.47; *P* = 0.006) after adjusting for age, sex, NYHA class, diabetes, hypertension, myocardial infarction, and atrial fibrillation.

**Table 1** Baseline clinical characteristics of patients by BMI groups

Baseline variables	All patients (n = 1,585)	BMI < 25 kg/m <sup>2</sup> (n = 459)	BMI 25- < 30 kg/m <sup>2</sup> (n = 641)	BMI ≥ 30 kg/m <sup>2</sup> (n = 485)	p-value
Age (yrs; median/IQR)	69 (61–75)	70 (62–76)	69 (61–76)	68 (60–73)	<0.001
Sex (female; n; %)	395 (25)	144 (31)	136 (21)	115 (24)	0.17
NYHA III/IV (st; n; %)	802 (50)	238 (52)	313 (49)	251 (52)	0.49
Ischaemic aetiology (n; %)	832 (52)	232 (50)	354 (55)	246 (51)	0.20
CRT-D (n; %)	863 (54)	238 (52)	350 (55)	275 (57)	0.32
BMI (kg/m <sup>2</sup> ; median/IQR)	27.4 (24.6–30.8)	22.9 (21.1–24.2)	27.4 (26.2–28.5)	32.5 (31.0–35.1)	NA
QRS (ms; median/IQR)	160 (140–180)	160 (140–177)	160 (140–178)	160 (140–180)	0.83
<b>Medical history</b>					
Atrial Fibrillation (n; %)	618 (39)	162 (35)	257 (40)	199 (41)	0.15
Diabetes mellitus (n; %)	594 (37)	118 (26)	241 (37)	235 (48)	<0.001
Hypertension (n; %)	1,200 (76)	328 (71)	474 (74)	400 (82)	<0.001
Prior MI (n; %)	654 (41)	186 (40)	276 (43)	192 (39)	0.47
Prior PCI (n; %)	520 (33)	141 (31)	228 (35)	151 (31)	0.15
Prior CABG (n; %)	226 (14)	56 (12)	100 (16)	70 (14)	0.28
Prior COPD (n; %)	250 (16)	74 (16)	88 (14)	88 (18)	0.13
<b>Laboratory parameters</b>					
Serum urea (μmol/l; median/IQR)	381 (310–469)	409 (304–518)	412 (333–491)	406 (342–468)	0.93
Serum creatinine (μmol/l; median/IQR)	110 (89–145)	99 (79–127)	102 (84–133)	98 (82–128)	0.09
Serum cholesterol (mmol/l; median/IQR)	4.3 (3.5–5.1)	4.3 (3.4–5.1)	4.2 (3.5–5.1)	4.0 (3.3–5.0)	0.27
eGFR (ml/min/1.73m <sup>2</sup> ; median/IQR)	64 (48–81)	64 (49–82)	63 (47–78)	66 (48–83)	0.25
NT-proBNP (pmol/l; median/IQR)	1,332 (509–3,365)	3,000 (1,380–4,434)	2,498 (1,573–3,434)	2,488 (1,270–3,045)	0.21
<b>Echocardiographic parameters</b>					
LVEF (%; median/IQR)	28 (24–33)	27 (23–30)	28 (24–33)	30 (25–35)	<0.001
LVEDV (ml; median/IQR)	208 (154–271)	198 (168–244)	225 (159–225)	205 (150–277)	0.63
LVESV (ml; median/IQR)	153 (113–209)	150 (117–207)	167 (117–211)	142 (99–212)	0.51
LVEDD (mm; median/IQR)	63 (57–69)	63 (57–68)	63 (57–70)	63 (57–70)	0.30
LVESD (mm; median/IQR)	53 (47–60)	53 (47–59)	53 (46–60)	53 (46–60)	0.87
<b>Medical treatment</b>					
Beta blocker (n; %)	1,349 (85)	404 (88)	538 (84)	407 (84)	0.12
ACE-I/ARB (n; %)	1,385 (87)	403 (88)	549 (86)	433 (89)	0.18
MRA (n; %)	1,000 (63)	308 (67)	393 (61)	299 (62)	0.11
Furosemid (n; %)	1,192 (75)	362 (79)	471 (73)	359 (74)	0.09
Digoxin (n; %)	296 (19)	109 (24)	110 (17)	77 (16)	0.003
Amiodarone (n; %)	401 (25)	124 (27)	164 (25)	113 (23)	0.41
Oral anticoagulant therapy (n; %)	469 (29)	123 (27)	213 (33)	133 (27)	0.03

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker, BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-Terminal pro-B-Type Natriuretic Peptide; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention.

### Subgroup analyses

Patients with a BMI ≥ 25 kg/m<sup>2</sup> show survival benefit over patients with a BMI of <25 kg/m<sup>2</sup> in non-ischaemic patients (HR 0.67; 95% CI 0.53–0.84; p < 0.001), obesity did not protect patients with ischaemic aetiology (HR 0.94; 95% CI 0.78–1.13; P = 0.51). (Figure S1.) Non-diabetic patients with overweight or obesity show the best probability of survival, the lowest survival was seen in diabetic patients with a BMI <25 kg/m<sup>2</sup> (p < 0.001). Diabetic patients did not show the obesity paradox (HR 0.85; 95% CI 0.66–1.10; P = 0.20). (Figure S2.) Both male (HR 0.87; 95% CI 0.70–0.97; P = 0.02) and female (HR 0.72; 95%CI 0.54–0.97; P = 0.02) patients experienced the obesity paradox. We did not observe survival gain in patients with overweight or obesity with atrial fibrillation (HR 0.89; 95% CI 0.77–1.11; P = 0.30). Patients with overweight or obesity had the lowest risk of all-cause mortality with a CRT-D device, the highest was in normal-weighted patients

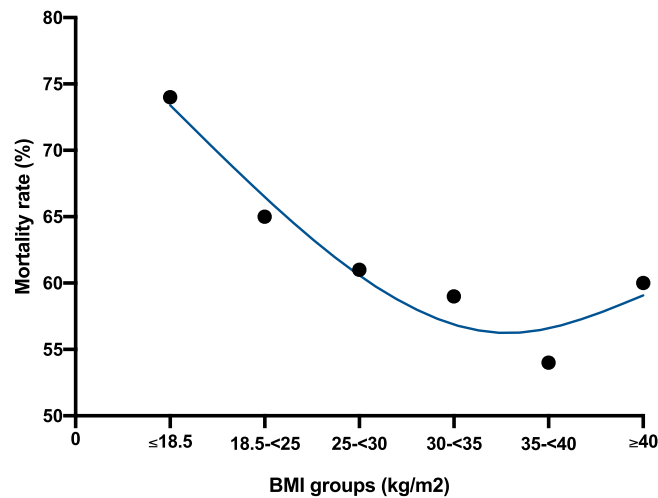
with a CRT-P device (P = 0.005), but we did not find a significant difference between patients with a BMI ≥ 25 kg/m<sup>2</sup> and patients with a BMI <25 kg/m<sup>2</sup> after CRT-D implantation (HR 0.89; 95%CI 0.73–1.09; P = 0.28).

Regarding age, young (age <65 years) patients with obesity were most likely to survive and elderly (age ≥65 years) patients had the highest risk of all-cause mortality (p<0.001); obesity did not provide survival benefit in the elderly (HR 1.01; 95% CI 0.86–1.20; P = 0.86). (Figure 3.)

### Periprocedural complications

An equal distribution of periprocedural complications was observed, none of the examined complications occurred more frequently in any of the patient groups (BMI < 25 kg/m<sup>2</sup> 25% vs. BMI 25- < 30 kg/m<sup>2</sup> 28% vs. BMI ≥ 30 kg/m<sup>2</sup> 26%; P = 0.48). (Table 3.) At the same time, bleeding (P = 0.81), pneumothorax (P = 0.19), haemothorax (P = 0.25), coronary

**Figure 1** Cumulative rate of mortality by BMI groups.

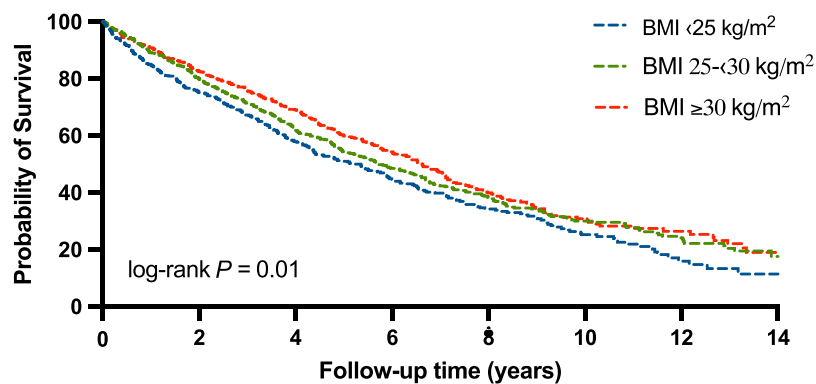


**Table 2** The associations of the BMI with the risk of all-cause mortality

Comparison of different BMI groups			
Endpoint	All-cause mortality		
	Hazard ratio	95% CI	p-value
BMI 25- $<30$ kg/m <sup>2</sup> vs. BMI $<25$ kg/m <sup>2</sup>	0.86	0.74–1.00	0.05
BMI 25- $<30$ kg/m <sup>2</sup> vs. BMI $\geq 30$ kg/m <sup>2</sup>	1.10	0.95–1.29	0.19
BMI $\geq 30$ kg/m <sup>2</sup> vs. BMI $<25$ kg/m <sup>2</sup>	0.78	0.66–0.92	<b>0.003</b>

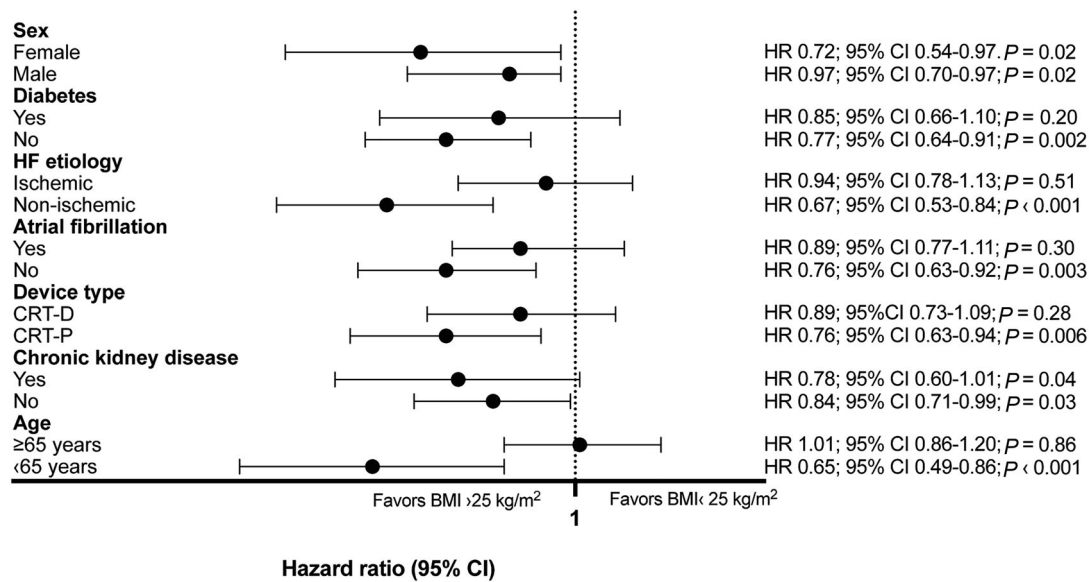
BMI, body mass index; CI, confidence interval.

**Figure 2** Kaplan-Meier estimates of the probability of survival after CRT implantation by BMI groups. Patients with overweight and obesity show survival benefit compared to patients with normal weight at long-term (log-rank  $P < 0.01$ ).



Patients at risk

BMI $<25$ kg/m <sup>2</sup>	459	340	242	151	88	45	14	5
BMI 25- $<30$ kg/m <sup>2</sup>	641	503	350	229	127	74	41	8
BMI $\geq 30$ kg/m <sup>2</sup>	485	397	298	198	105	50	26	12

**Figure 3** Subgroup analyses of enrolled patients. Dominantly patients with obesity (BMI > 25 kg/m<sup>2</sup>) and free of comorbidities gain survival benefit.**Table 3** Perioperative complications divided by BMI groups

Complications	All patients (n = 1,585)	BMI <25 kg/m <sup>2</sup> (n = 459)	BMI 25- < 30 kg/m <sup>2</sup> (n = 641)	BMI ≥30 kg/m <sup>2</sup> (n = 485)	p-value
All complications (n; %)	420 (26)	115 (25)	180 (28)	125 (26)	0.48
Bleeding (n; %)	24 (1.5)	8 (1.7)	10 (1.6)	6 (1)	0.81
Pneumothorax (n; %)	22 (1.4)	10 (2)	8 (1.2)	4 (0.8)	0.19
Haemothorax (n; %)	4 (0.2)	2 (0.4)	0 (0)	2 (0.4)	0.25
Coronary sinus dissection (n; %)	13 (0.8)	2 (0.4)	6 (1)	5 (1)	0.55
Pericardial tamponade (n; %)	6 (0.4)	1 (0.2)	2 (0.3)	3 (0.6)	0.57
Pocket infection/decubitus (n; %)	39 (2)	8 (1.7)	18 (3)	13 (3)	0.49
Infective endocarditis (n; %)	6 (0.4)	2 (0.2)	3 (0.5)	1 (0.2)	0.75
Lead dislodgement (n; %)	112 (7)	33 (7)	54 (8)	35 (7)	0.10
Lead dysfunction/fracture (n; %)	30 (2)	6 (1.3)	13 (2)	11 (2)	0.53
Phrenic nerve stimulation (n; %)	94 (6)	27 (6)	34 (5)	33 (7)	0.57

BMI, body mass index

sinus dissection (P = 0.55), pericardial tamponade (P = 0.57), pocket infection (P = 0.49), infective endocarditis (P = 0.75), lead dislodgement (P = 0.10), lead dysfunction/fracture (P = 0.53) and phrenic nerve stimulation (P = 0.57) occurred evenly across the patient groups. (Table 3.)

#### Echocardiographic response

A significant improvement in LVEF over the course of 6 months was seen in all patient categories. The mean of  $\Delta$ -LVEF was 7% in the normal weight group (p < 0.001),  $\Delta$ -LVEF was 7.5% in patients with overweight (p < 0.001) and 6% in patients with obesity (p < 0.001) (Table 4.). A similar proportion of reverse remodeling was observed across the patient groups, 58% in the normal weight, 61% in the overweight and 57% in the obese groups (P = 0.75). (Table 5.)

## Discussion

In this large-scale retrospective, observational study, heart failure patients with obesity free of comorbidities and selected for CRT implantation showed survival benefit compared with normal-weight CRT candidates. Additionally, among all BMI groups the proportions of patients with reverse remodeling were similar, the incidence of peri- and postprocedural complications did not differ.

Based on previous observational studies, the association between obesity and a beneficial outcome in heart failure patients was partly described.<sup>21</sup> However, this phenomenon was uncertain in the most severe subset of heart failure patients, those undergoing CRT implantation.<sup>17,22,23</sup> In previous trials, the association of obesity with all-cause mortality has

**Table 4** Change of left ventricular ejection fraction 6 months after CRT implantation across patient groups

	BMI <25 kg/m <sup>2</sup> (n = 105)	BMI 25- < 30 kg/m <sup>2</sup> (n = 167)	BMI ≥30 kg/m <sup>2</sup> (n = 111)
Baseline LVEF (%; median/IQR)	27 (23–30)	28 (24–33)	30 (25–35)
6 months LVEF (%; median/IQR)	33 (25–40)	34 (29–40)	37 (30–41)
Δ-LVEF (%; median/IQR)	7 (0–12)	7.5 (1–13)	6 (0.75–11)
p-value	<0.001	<0.001	<0.001

BMI, body mass index; IQR, interquartile range; LVEF, left ventricular ejection fraction

**Table 5** The rate of reverse remodeling across patient groups

	BMI <25 kg/m <sup>2</sup> (n = 105)	BMI 25- < 30 kg/m <sup>2</sup> (n = 167)	BMI ≥30 kg/m <sup>2</sup> (n = 111)	p-value
Reverse remodeling (n; %)	61 (58)	102 (61)	63 (57)	0.75

BMI, body mass index

been described as a J-shaped curve in HF patients with the lowest mortality at a BMI of 25 kg/m<sup>2</sup>.<sup>24</sup> Others associated being overweight (BMI 25- < 30 kg/m<sup>2</sup>) with a more beneficial outcome compared to normal weight.<sup>25</sup> Despite these incomprehensive data in the literature; as some showed mortality benefit with overweight,<sup>22</sup> some with obesity in heart failure patients,<sup>17</sup> altogether higher BMI was described to associate with mortality benefit compared to normal weight or particularly with cachexia, therefore obesity may refer to a better metabolic reserve.<sup>26</sup>

The heterogeneity of findings of previous studies might be explained by the patient selection or the time of enrolment in their course of the disease.

In the current analysis, the characteristics of our cohort are similar to prior milestone trials that enrolled HFrEF patients eligible for device implantation.<sup>12,27</sup> Patients with obesity were generally younger<sup>22,26</sup> and frequently have concomitant diseases such as diabetes,<sup>22,26</sup> hypertension<sup>16,28</sup> and are more likely to have higher LVEF than normal-weighted patients,<sup>3,16</sup> which might also be associated with a better outcome. Moreover, the type of CRT device can also influence the risk of mortality when adding a defibrillator (CRT-D) to further reduce the risk of sudden cardiac death. However, few data described a higher incidence of CRT-D implantations in those with overweight or obesity,<sup>22,29</sup> in our entire study population the proportion of CRT-D implantation did not differ across BMI groups.

The length of the follow-up time may also influence the result. Grandin *et al.* investigated the ten-year survival free from all-cause death, orthotopic heart transplantation, or ventricular assist device implantation, which was found to be the highest in patients with obesity (36.3%), lower in overweight ones (19.2%), and the lowest in normal weight patients (12.1%).<sup>17</sup>

Notably, we cannot know whether patients in the normal BMI group represent an end stage heart failure patient with unintentional weight loss or a normal weight one at an earlier stage of the disease. Moreover, intentional

weight loss by diet or new antidiabetic drugs (e.g., GLP-1 analogues) and its effect on outcomes is scarcely investigated in patients with device therapy, therefore further trials are warranted to investigate the effect of such new treatments on the outcome of heart failure patients selected for device implantation. As the global burden of cardiovascular diseases attributed to high BMIs is significant, acting upon prevention strategies is necessary to navigate patients into optimal BMI ranges and to avoid obtaining comorbidities.<sup>30</sup>

Findings about the obesity paradox are influenced by several other covariates. In a recently published article, using novice anthropometric measures to define obesity, the beneficial effect could not be detected on heart failure hospitalization or all-cause mortality. However, the protective factor could be observed when adjusted for conventional risk variables, it diminished to insignificance after adding log NT-proBNP,<sup>31</sup> a biomarker known to be influenced by obesity.

The presence of concomitant diseases may have a severe influence on the outcome. Based on our analyses, only patients free of co-morbidities gained survival benefit with obesity. The obesity paradox was present in both sexes, in patients without diabetes, without atrial fibrillation, without ischaemic aetiology, and in younger ones. In the literature, the presence of the phenomenon in the subgroup of diabetic patients is questionable. In previous studies, obesity did not provide survival benefit in patients with DM,<sup>32–34</sup> while others found that irrespective of DM status, those with obesity showed mortality benefit after CRT implantation.<sup>17</sup> At the same time, DM is linked to a higher burden of comorbidities and poorer outcomes in HF patients,<sup>35,36</sup> possibly mitigating obesity's protective factor. The other relevant concomitant disease, that might have influence on the presence of obesity paradox is the ischaemic aetiology.<sup>17</sup> Zamora *et al.*, similarly to our findings, only observed the obesity paradox in non-ischaemic HF.<sup>37</sup>

As obesity's prevalence and the number of device implantations rises,<sup>38</sup> safety assessment is crucial in this patient group. Complication rates increase with the complexity of the devices and are also influenced by individual covariates.<sup>18</sup> In our analysis, periprocedural complications did not occur more frequently in patients with obesity. Device-related complications did not differ among patient groups in a prior analysis, within 90 days after CRT-D implantation in elderly patients.<sup>16</sup> But patients with obesity might face a higher rate of failed left ventricular lead placement (in patients with extreme obesity) or lead dislodgement.<sup>39,40</sup> Generally CRT implantation is considered a safe and well endured procedure in patients with higher BMIs.<sup>41</sup>

Evaluating the response to CRT therapy within 6–12 months is essential, as positive response, the development of reverse remodeling is correlated with long-term survival.<sup>42</sup> A few studies with CRT patients showed that those with obesity can experience the same or even more significant improvements in LVEF and left ventricular end-diastolic diameter.<sup>23,29,43</sup> We found similar improvement in LVEF and an even proportion of developing reverse remodeling across patient groups.

## Limitations

Our study has a few limitations. First, this is a single-centre, retrospective, observational study. Second, BMI is a standardized method to quantify obesity, but it does not consider body composition nor fitness, while the fit or physically active patients with obesity show better prognosis than sarcopenic ones,<sup>44,45</sup> which was not specified in the current analysis. Third, our patient population lacked underweight or cachectic patients, who show the worst outcome.<sup>46</sup> Also, we do not have data on the use of drugs such as sodium glucose co-transporter 2 inhibitors or angiotensin receptor-neprilysin inhibitor that may influence the outcome and missed to have data on laboratory parameters (such as e.g., NT-proBNP levels).

## Conclusions

In the subset of heart failure patients eligible for cardiac resynchronization therapy implantation, those with obesity and free of comorbidities showed mortality benefit compared to normal-weighted patients, which proved that the obesity paradox was present in our cohort.

Additionally, obesity did not infer higher rates of periprocedural complications and did not affect the efficacy of the device treatment.

## Authors contributions

Study design and conceptualization: EDM, AK, BM. Data collection: WRS, AB, EDM. Data analyses: EDM, AK. Results interpretations: all authors. Manuscript writing: all authors. Manuscript proofing: all authors.

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## Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Kaplan Meier estimates of the probability of survival after CRT implantation by BMI groups and diabetes

status. Non-diabetic patients with overweight or obesity show the best probability of survival, the lowest survival was seen in diabetic patients with a BMI <25 kg/m<sup>2</sup> (log-rank  $p < 0.001$ ). Diabetic patients did not experience the obesity paradox (HR 0.85; 95% CI 0.66–1.10;  $P = 0.20$ ).

**Figure S2.** Kaplan Meier estimates of the probability of survival after CRT implantation by BMI groups and heart failure aetiology. Patients with a BMI  $\geq 25$  kg/m<sup>2</sup> show survival benefit over patients with a BMI of <25 kg/m<sup>2</sup> in non-ischaeamic patients (HR 0.67; 95% CI 0.53–0.84;  $p < 0.001$ ), obesity did not protect patients with ischaemic aetiology (HR 0.94; 95% CI 0.78–1.13;  $P = 0.51$ ).

**Figure S3.** Kaplan Meier estimates of the probability of survival after CRT implantation by BMI groups, underweight patients excluded.

**Table S1.** The associations of the BMI with the risk of all-cause mortality.

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